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Contenido

Artículos originales

Effect of dexpanthenol on wound healing in penile fracture model: An experimental study

Efecto del dexpantenol en la cicatrización de heridas en un modelo de fractura de pene: un estudio experimental

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Abstract

Objectives: *In the present study, we aimed to investigate the effect of dexpanthenol on wound healing at the histopathological level on cavernous tissue.* **Materials and methods:** *Forty-four Wistar albino rats weighing 220-250 g were used. The rats were randomly divided into four groups as Group B, Group S, Group LD, and Group SD. In Group B, the incision was not repaired and left to secondary healing. In Group S, the incision line was repaired with 5/0 polyglactin suture. In Group LD, 0.25 mg/kg dexpanthenol was applied subcutaneously below the repaired wound region once a day during 14 days. In Group SD, 500 mg dexpanthenol was applied intraperitoneally once a day during 14 days.* **Results:** *No fibrosis was observed in 8 (80%) rats in group SD. Fibrosis rates were significantly lower in Group SD compared to Group B, Group S, and Group LD (p = 0.013, p = 0.005, and p = 0.003, respectively).* **Conclusion:** *Systemic dexpanthenol administration significantly decreased fibrosis in penile fracture model on rats.*

Keywords: *Dexpanthenol. Fibrosis. Penile fracture. Rat.*

Resumen

Objetivo: *En el estudio actual nuestro objetivo fue investigar el efecto del dexpantenol en la cicatrización de heridas a nivel histopatológico en el tejido cavernoso.* **Métodos:** *se utilizaron 44 ratas Wistar albinas con un peso de 220-250 g. Las ratas se dividieron aleatoriamente en 4 grupos como grupo B, grupo S, grupo LD y grupo SD. En el grupo B, la incisión no se reparó y se dejó para la cicatrización secundaria. En el grupo S, la línea de incisión se reparó con sutura de poliglactina 5/0. En el grupo LD, se aplicaron 0.25 mg/kg de dexpantenol por vía subcutánea debajo de la región de la herida reparada una vez al día durante 14 días. En el grupo SD se aplicaron 500 mg de dexpantenol por vía intraperitoneal una vez al día durante 14 días.* **Resultados:** *No se observó fibrosis en 8 (80%) ratas del grupo SD. Las tasas de fibrosis fueron significativamente más bajas en el grupo SD en comparación con el grupo B, el grupo S y el grupo LD (todos p < 0.05).* **Conclusión:** *La administración sistémica de dexpantenol disminuyó significativamente la fibrosis en el modelo de fractura de pene en ratas.*

Palabras clave: *Dexpantenol. Fibrosis. Fractura de pene. Rata.*

Introduction

Penile fracture (PF) is defined as a traumatic rupture of the tunica albuginea of the corpora cavernosa during penile erection. Although vaginal intercourse is the most common reason for PF, penile manipulation and masturbation have also been shown to be responsible in the etiology[1]. The recommended treatment of surgery has excellent long-term results[1-3]. Although complications such as penile curvature, penile deformity, fibrosis, and sexual dysfunction are less common following surgical treatment, overall morbidity rates remain high due to inflammatory and fibrotic processes[2-4].

Dexpanthenol has been used in clinical practice for many years as it promotes wound healing[5,6]. Dexpanthenol is the molecule that is the alcohol form of pantothenic acid and accelerates anti-inflammatory effects by increasing mitotic activity. In the body, it transforms to pantothenic acid, which is a molecule that assists the coenzyme A structure, and by decreasing myeloperoxidase secretion from granulocytes, it halts the formation of free oxygen radicals, while also increasing mitotic activity which results in an anti-inflammatory effect[5,7].

The aim of this study was to investigate the effect of dexpanthenol on wound healing at the histopathological level on cavernous tissue. To the best of our knowledge, this is the first study to have examined the use of dexpanthenol in penile cavernous tissue.

Materials and methods

The study was conducted in the Experimental Animals Laboratory of Ankara Training and Research Hospital. Approval for the study was granted by the Local Ethics Committee (approval number: 0055-17.09.19). The study sample was formed of a total of 44 Wistar albino rats, each weighing 220-250 g. Both pre- and postoperatively, all the rats were housed in separate cages at 22°C and 50% humidity with free access to food and water.

On the day of the study, all the rats were administered anesthesia of 50 mg/kg ketamine under sterile conditions. At 1 h before the procedure, a single prophylactic dose of 20 mg/kg ceftriaxone was injected intramuscularly. Then, the rats were positioned supine, the genital area was shaved, and the penis area was wiped with 10% povidone iodine. A 3 Fr urethral catheter was inserted from the external meatus up to the mid-urethral level at approximately 2 cm. The experimental model of PF was created with a number 15 lancet as previously described literature[8,9] (Fig. 1). After the interventions, the rats were randomly separated into four study groups as Group B, Group S, Group LD, and Group SD, and a reference group of Group A.

Group A was the reference group with no PF applied. In Group B, the incision was made, then left for secondary healing with no repair. In Group S, the incision line was repaired with 5/0 polyglactin suture. In Group LD, the incision line was repaired with 5/0 polyglactin suture, then 0.25 mg/kg dexpanthenol was applied subcutaneously below the repaired wound region once a day for 14 days. In Group SD, the incision line was repaired with 5/0 polyglactin suture, then 500 mg dexpanthenol was applied intraperitoneally once a day for 14 days.

Six weeks later, all the rats were sacrificed using the cervical dislocation method. The penectomy was performed from proximal of the repaired region using a lancet. The penectomy material obtained from each group was placed in a 10% formaldehyde solution for pathological examination.

Histopathological evaluation using a light microscope was performed by a single independent pathologist blinded to the study groups. The penectomy material of each rat was fixed in 10% formaldehyde until macroscopic examination. Circles of tissue were cut at 4-mm intervals and then embedded in paraffin blocks, from which slices 4 micron in thickness were cut and stained with hematoxylin and eosin (HE) and with Masson trichrome for histopathological examination. Light microscopy examination was made of the preparates at ×20 and ×40 magnification. Fibrosis was evaluated as follows: 0: none, *Mild*: fibrosis in the focal area or ≤10% of the cavernous body, *Moderate*: fibrosis in >10%-≤30% of the included cavernosal tissues, and *Severe*: fibrosis in > 30% of the included cavernosal tissues. Inflammation was evaluated according to the presence of inflammatory cells such as neutrophils, lymphocytes, and monocytes. The groups were compared according to fibrosis and inflammation parameters.

Data obtained in the study were analyzed statistically using PASW 18 software (SPSS/IBM, Chicago, IL, USA). Categorical data were stated as number and percentage. Categorical variables were analyzed using the Pearson Chi-square test. A value of $p < 0.05$ was considered statistically significant.

Figure 1. *Using a number 15 lancet to create a penile fracture model.*

Table 1. Fibrosis rates of the groups

Fibrosis	Group B	Group S	Group LD	Group SD	p-value
None (n %)	1 (10%)	0	0	8 (80%)	0.001*
Mild (n %)	5 (50%)	6 (66.7%)	6 (60%)	2 (20%)	
Moderate (n %)	3 (30%)	2 (22.2%)	1 (10%)	0	
Severe (n %)	1 (10%)	1 (11.1%)	3 (30%)	0	

Table 2. Inflammation rates of the groups

Inflammation	Group B	Group S	Group LD	Group SD	p-value
None (n %)	3 (30%)	6 (66.7%)	5 (50%)	8 (80%)	0.13
Observed (n %)	7 (70%)	3 (33.3%)	5 (50%)	2 (20%)	

Results

One rat in Group S died 12 h after anesthesia, possibly due to anesthesia complications. The most common complications of infection and urinary retention were not observed in any rat.

No severe fibrosis was observed in any rat in Group SD and was determined in one rat in Group B, in one rat in Group S, and in three rats in Group LD (p = 0.001). No fibrosis was observed in 8 (80%) rats in Group SD. The fibrosis rate was significantly lower in Group SD compared to Group B, Group S, and Group LD (p= 0.013, p = 0.005, and p = 0.003, respectively) (Table 1) (Fig. 2). In Group SD, total healing was observed in 8 (80%) rats.

When the groups were evaluated in terms of inflammation, the lowest inflammation rate was observed in Group SD (2 rats, 20%), with no statistically significant difference determined between the groups (p = 0.13) (Table 2) (Fig. 3). In the control groups (Groups B and S), fibrosis and inflammation were predominant features of the healing. More extensive fibrosis was observed in these groups than in Group SD.

Discussion

With the occurrence of PF, there can be a sudden cracking or popping sound, pain, and immediate detumescence. There is rapid local swelling of the penile shaft due to a growing hematoma, because PF includes rupture of the tunica albuginea and the enclosed corpus cavernosum[10]. When PF is diagnosed, the recommended treatment is surgical repair with closure of the tunica albuginea. Negative long-term complications such as penile curvature and deformity are kept to a minimum with this repair and the psychological well-being of the patient is not negatively affected[11]. Other complications may also be observed such as painful coitus, penile nodule formation, priapism, wound infection, and penile abscess, but the incidence rates of these can be decreased with delicate surgery.

Dexpanthenol was investigated in this study due to its well-known anti-inflammatory, wound healing, and epithelization properties. It also has the advantages of low cost and few side-effects[12,13]. The role of inflammation in wound healing is a matter of debate since excessive inflammation affects this process negatively. In the present study, fibrosis was not observed in 8 (80%) rats in Group SD. Compared to other groups, these rates were statistically significant and only two rats had mild fibrosis. Similarly, inflammation was not detected in 8 (80%) rats in Group SD, but this was not statistically significant. Interestingly, the fibrosis rate was higher in Group LD. Although mostly mild (60%), fibrosis was observed in all rats in Group LD. This could be explained by different reasons, the first being possibly the microtrauma caused by the subcutaneous application of dexpanthenol for 2 weeks, and the second reason might be that a sufficient concentration of the subcutaneously administered dexpanthenol could not reach the tunica and cavernous tissue.

A previous study by the current author group investigated the effect of intraurethral dexpanthenol in
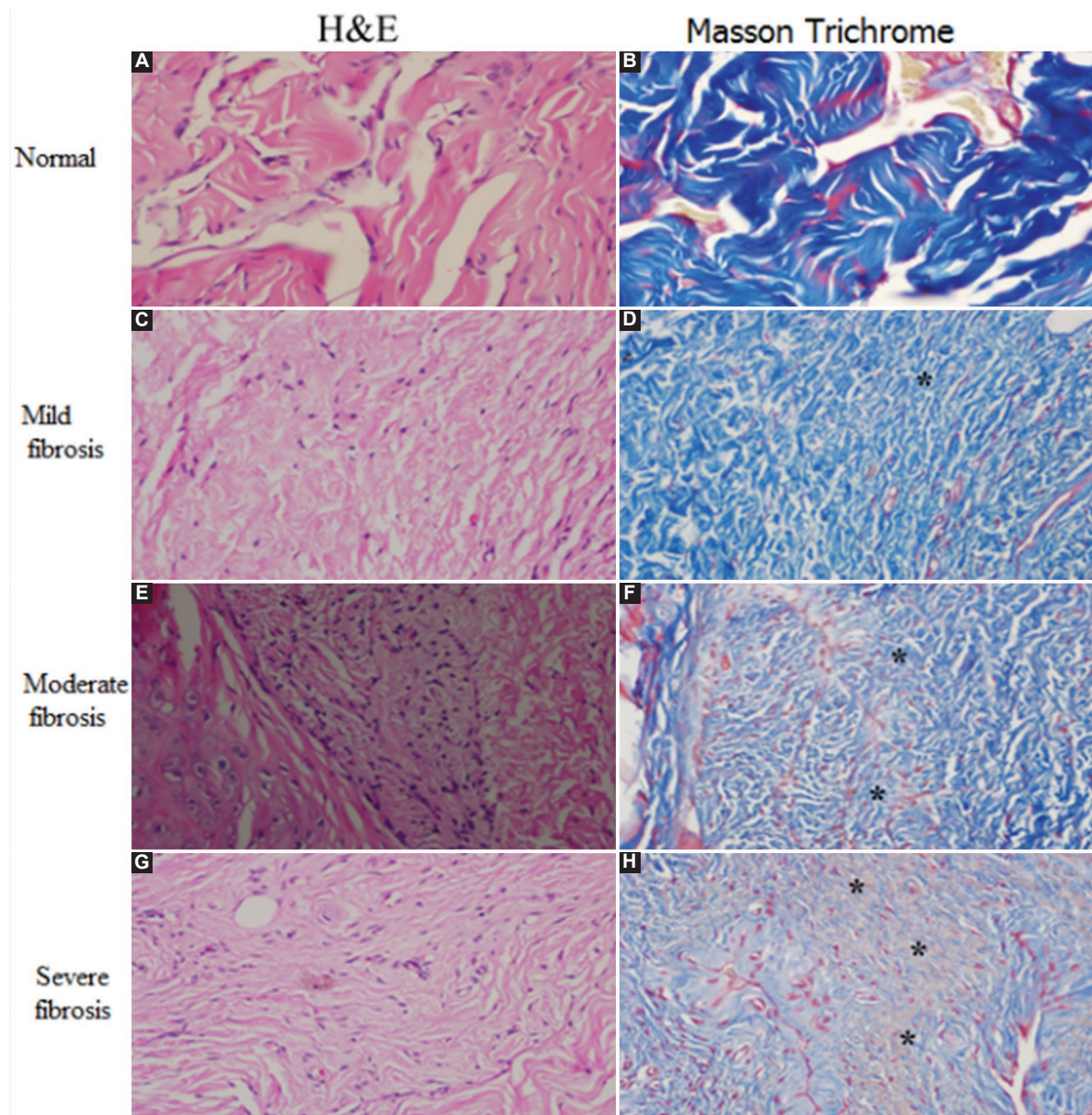
Figure 2. *Sections of rat penis (×40).* **A:** *H&E image of a normal rat penis in Group A.* **B:** *Masson trichrome image of the same rat penis in Group A.* **C:** *H&E image of mild fibrosis in Group S.* **D:** *Masson trichrome image of mild fibrosis in the same rat penis in Group SD.* **E:** *H&E image of moderate fibrosis in Group S.* **F:** *Masson trichrome image of moderate fibrosis in the same rat penis in Group S.* **G:** *H&E image of severe fibrosis in Group LD.* **H:** *Masson trichrome image of severe fibrosis in the same rat penis in Group LD. (*: areas of fibrosis).*

hypospadias repair and intraurethral dexpanthenol administration was found to significantly decrease inflammation and fibrosis. Similarly, in another study by the same group, intraurethral dexpanthenol was used in post-traumatic urethral stricture and was shown to reduce both inflammation and fibrosis[14,15]. The promising results of those two studies encouraged the current research of the effect of dexpanthenol on wound healing in a PF model. Several studies have shown that dexpanthenol accelerates wound healing after surgery and can successfully prevent scar formation[16,17]. To the best of our knowledge, this is the first study to have investigated the effect of dexpanthenol on wound healing in an experimental animal model of PF. However, the fact that it was an experimental model is a limitation of the study and there is a need for further advanced clinical studies to confirm these findings.

H&E
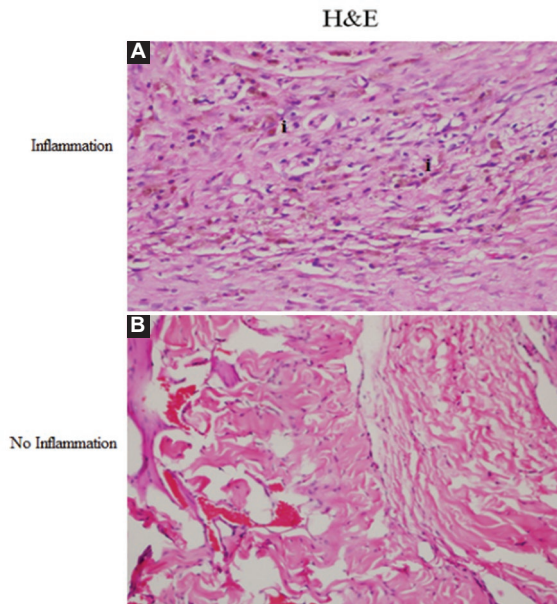
Figure 3. A: *Appearance of inflammation in Group S (×40) and* **B:** *image without inflammation in Group SD. (i: inflammatory cells).*

Conclusion

Systemic dexpanthenol administration was seen to significantly decrease fibrosis in a rat model of penile fracture. Further studies are needed to evaluate the effects of dexpanthenol therapy.

Funding

Conflicts of interest

The authors have no conflicts of interest to declare that is relevant to the content of this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Effect of Re-TUR time on recurrence and progression in high-risk non-muscle-invasive bladder cancer

Efecto del tiempo de Re-TUR en la recurrencia y progresión en cáncer de vejiga no músculo invasivo de alto riesgo

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Abstract

Objective: *We aimed to investigate the significance of time to re-staging transurethral resection (re-TUR) on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer as a prospective randomized study.* **Methods:** *The patients were randomly separated into three groups according to Re-TUR timing. In Groups 1, 2, and 3, the time interval between initial and re-TUR was 14-28 days, 29-42 days, and 43-56 days, respectively. Cox regression analysis was used to assess the effect of time from initial TUR to re-TUR on oncological outcomes.* **Results:** *Twenty patients in Group 1 (14-28 days), 22 patients in Group 2 (29-42 days), and 29 patients in Group 3 (43-56 days) completed the study. Kaplan–Meier plots showed no differences in recurrence-free survival (RFS) and progression-free survival (PFS) rates between the three groups. Cox regression analysis demonstrated that only tumor number was found to be a prognostic factor on RFS rates.* **Conclusion:** *Our prospective study demonstrated that time laps from initial TUR to re-TUR did not significantly affect on RFS and PFS rates.*

Keywords: Non-muscle invasive bladder cancer. Restaging transurethral resection. High grade. Oncological outcomes.

Resumen

Objetivo: *Nuestro objetivo fue investigar la importancia del tiempo para volver a estadificar la resección transuretral (re-RTU) en las tasas de recurrencia y progresión en pacientes con cáncer de vejiga no músculo invasivo de alto riesgo como un estudio prospectivo aleatorizado.* **Método:** *Los pacientes se separaron aleatoriamente en 3 grupos de acuerdo con el tiempo de Re-TUR. En el grupo 1, 2 y 3, el intervalo de tiempo entre la RTU inicial y la nueva fue de 14 a 28 días, 29 a 42 días y 43 a 56 días, respectivamente. Cox para evaluar el efecto del tiempo desde la RTU inicial hasta la nueva RTU sobre los resultados oncológicos.* **Resultados:** *Veinte pacientes del grupo 1, 22 pacientes del grupo 2, 29 pacientes del grupo 3 completaron el estudio. Los gráficos de Kaplan-Meier no mostraron diferencias en las tasas de SLR y SLP entre los tres grupos. El análisis de regresión de Cox demostró que solo se encontró que el número de tumores era un factor pronóstico en las tasas de RFS.* **Conclusión:** *Nuestro estudio prospectivo demostró que los lapsos de tiempo desde la RTU inicial hasta la nueva RTU no afectaron significativamente las tasas de SLR y SLP.*

Palabras clave: Cáncer de vejiga no músculo invasivo. Reestablecimiento de la resección transuretral. Alto grado. Resultados oncológicos.

Introduction

Bladder cancer (BC) is the 11th most commonly diagnosed cancer worldwide[1]. Non-muscle invasive bladder cancer (NMIBC) accounts for approximately 75% of the cases. Despite advanced treatment methods, the recurrence and progression rates of NMIBC are still high (70-75% and 10%, respectively)[2]. To reduce the risk of recurrence and progression, re-staging transurethral resection (Re-TUR) of high risk bladder tumor and application of intravesical immunotherapy with Bacillus Calmette-Guerin (BCG) to that tumor are recommended by uro-oncology guidelines[1,3].

European Association of Urology (EAU) guidelines recommend that Re-TUR should be performed within 2-6 weeks after initial TUR[1,4]. Nevertheless, these recommendations are based on low levels of evidence[4]. To the best of our knowledge, there are no prospective studies in the literature addressing that issue. Therefore in this prospective, randomized controlled study, we aimed to investigate the significance of time to re-TUR on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer.

Materials and methods

This study was performed between August 2016 and December 2020 after obtaining the approval of local ethics committee (0651-5479). Clinical Trials Registration ID of the present study is NCT04768894. Patients diagnosed with primary high risk non-muscle-invasive bladder cancer at our clinic as well as the patients who were referred to our clinic with the same diagnosis were included to the study. All patients gave their written informed consent. The patients were randomly separated into three groups according to Re-TUR timing with the random number table envelope method. The names of the groups were written on small papers with the same size, they were folded, put in an envelope, and drawn by the doctors. In Groups 1, 2, and 3, the time interval between initial and re-TUR were 14-28 days, 29-42 days, and 43-56 days, respectively. Separate analysis was also performed for patients who had Re-TUR at ≤ 42 and > 42 days. All patients received six weekly instillations of BCG therapy, and at least 1 year of maintenance BCG therapy (3 weekly instillations administered at 3, 6, and 12 months).

Patients with a tumor pathology other than transitional cell carcinoma, incomplete resection at initial TUR, who cannot complete 1 year of maintenance BCG treatment, did not attend their regular cystoscopic control or wanted to leave from the study voluntarily and finally, with a diagnosis of muscle-invasive cancer on Re-TUR were excluded from the study. Inclusion criteria were having a high grade Ta or T1 transitional cell carcinoma with or without carcinoma *in situ* (CIS) after a complete initial TUR of bladder carcinoma, and receiving 6 weekly induction BCG therapy with at least 1 year maintenance.

Re-TUR contained resection of all visible tumor, deep resection of previously resected areas and adequate sampling of muscle layers. Cystoscopic control was performed according to EAU guideline recommendations for high-risk non-muscle-invasive bladder cancer[5,6]. Progression was defined as an increase in the pathological stage (Ta-T1 or T1-T2).

Demographic data of the patients such as age, gender, and parameters related to bladder cancer such as tumor grade, T stage, concomitant CIS, number of tumors, main tumor size, application of early single dose chemotherapy, recurrence, and progression were noted. Primary end point of the current study was recurrence and progression free survival rates. Pathologic investigations were made by single expert uropathologist at our hospital.

Statistical analysis

The data analyses were performed with PASW 18 (SPSS, IBM, Chicago, IL) software. Kolmogorov-Smirnov and P-P plot were used to verify the normality of the distribution of continuous variables. The results were reported as means standard deviations, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were given as percentages. For parameters that did not show normal distribution, the nonparametric Kruskal–Wallis One-Way analysis of variance and Mann–Whitney U test were used to compare them. Multivariable semi-parametric Cox regression analysis was used to evaluate predictors of recurrence-free survival (RFS) and progression-free survival (PFS) rates. Kaplan–Meier curves were constructed for RFS and PFS and groups were compared with the long-rank test. The study power and sample size were calculated with G power 3.1.9.7 version (A priori). When effect size is set to 0.33 (medium size) with 80% power, the total number of
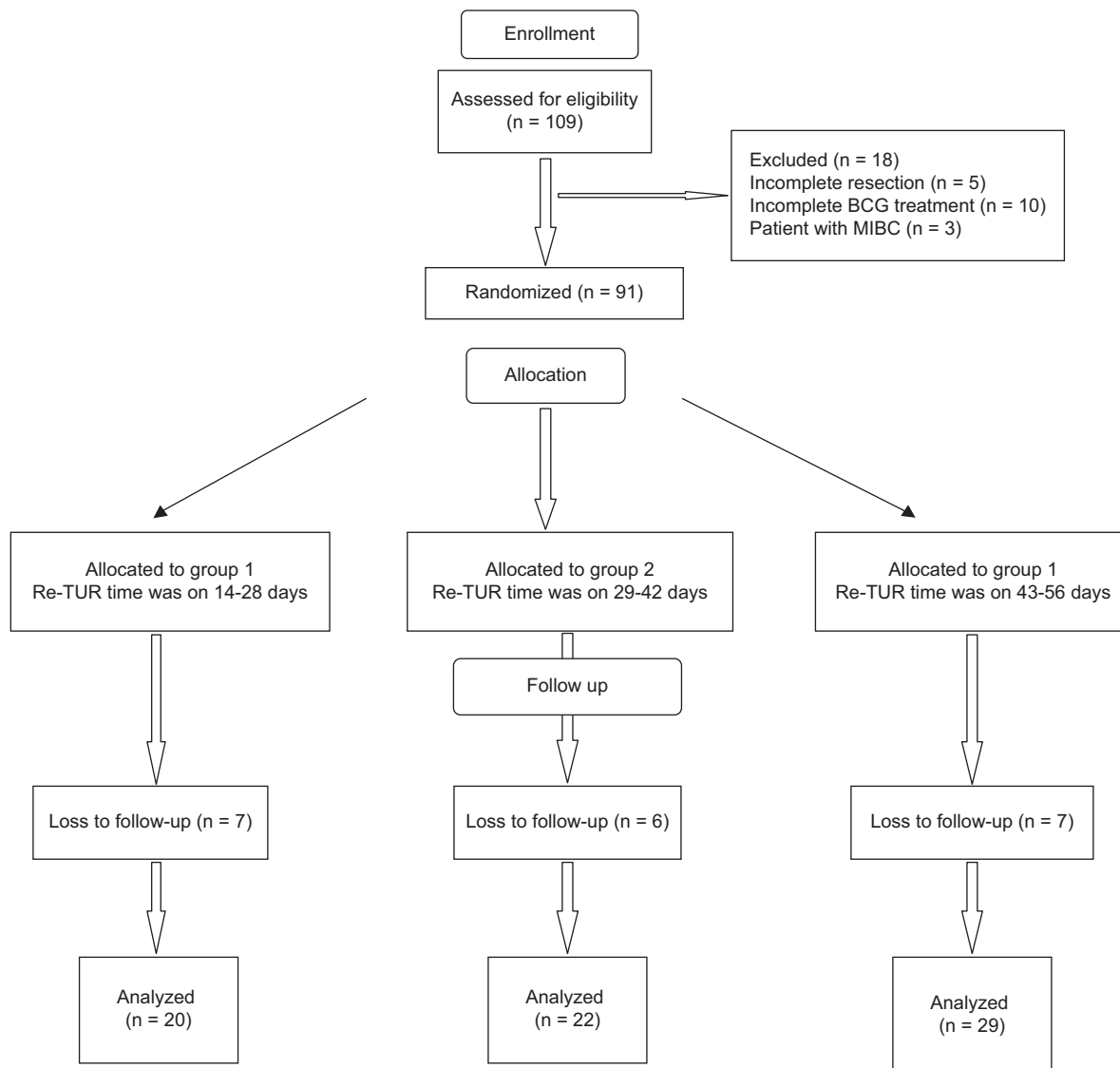
Figure 1. *Flow charts.*

patients required to be included in the study was 73. $p < 0.05$ was considered as statistically significant.

Results

A total of 109 patients with primary high risk non-muscle-invasive bladder cancer were randomly divided into three groups. Twenty patients were excluded because of loss to follow-up. Five patients with incomplete resection at initial TUR, ten patients who could not complete 1 year of maintenance BCG treatment, and three patients with a diagnosis of muscle-invasive cancer on re-TUR were excluded from the study. Twenty patients in Group 1 (14-28 days), 22 patients in Group 2 (29-42 days), and

29 patients in Group 3 (43-56 days) completed the study (Fig. 1).

The mean age of the study population was 64.5 ± 8.7 years and the mean follow-up was 20 ± 8.9 months. Of our patients 58 (81.7%) male and 13 (18.3%) were female. All tumors in this study were high grade. Stage Ta and T1 tumors were present in 14 (19.7%) and 57 (80.3%) patients, respectively. Concomitant CIS was present in 7 (9.9%) patients. Residual tumors were detected in 9 of 71 (12.6%) patients. No T2 tumor was detected in any patient after the re-TUR. There were no differences between the groups in age, sex, T stage, concomitant CIS, largest tumor diameter, tumor numbers, and instillation of immediate post-operative intravesical chemotherapy (Table 1). In the

Table 1. Baseline patients characteristics of groups

Variable	Group 1: 14-28 days, n (%)	Group 2: 29-42 days, n (%)	Group 3: 43-56 days, n (%)	p
Number of patients	20	22	29	
Age, median (minimum-maximum)	65 (49-86)	65 (44-83)	63 (46-77)	0.48
Gender				0.62
Female	5 (25)	3 (13.6)	5 (17.2)	
Male	15 (75)	19 (86.4)	24 (82.8)	
Stage				0.36
Ta	6 (30)	4 (18.2)	4 (13.8)	
T1	14 (70)	18 (81.8)	25 (86.2)	
Concomitant CIS	2 (10)	2 (9.1)	3 (10.3)	0.98
Tumor size (mm), median (minimum-maximum)	40 (15-100)	40 (20-100)	30 (15-75)	0.34
Number of initial tumors, median (minimum-maximum)	1 (1-5)	1 (1-5)	1 (1-5)	0.89
Immediate post-operative intravesical chemotherapy	17 (85)	20 (91)	27 (93)	0.63
Smoking	16 (80)	17 (77)	23 (79)	0.97
Progression rate	0	1 (4.5)	3 (10)	0.36

CIS: Carcinoma *in situ*
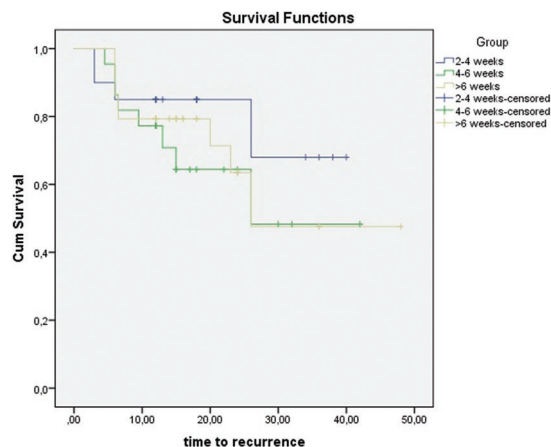
Figure 2. *Recurrence-free survival rates of the three groups at a mean follow-up of 20 months (14-28 days, 29-42 days, and 43-56 days).*

follow-up period, 4 (5.6%) patients underwent radical cystectomy. One patient had been administered radiation therapy with chemotherapy.

Recurrence-free survival rates of the patients were 80 %, 63.6%, and 69% in Groups 1, 2, and 3, respectively, at a mean follow-up of 20 months (p = 0.56). When we performed a separate analysis by dividing patients into two groups based on the interval between initial and Re-TUR (≤ 42 days and > 42 days), we did not also detect statistically different RFS rates (71.4% and 69%, respectively, p = 0.85) (Figs. 2 and 3). The progression

rate in group > 42 days was similar to that of group ≤ 42 days (2.4% and 10.3% p = 0.20, respectively) (Table 2).

The progression was observed in 0, 1 (4.5%), 3 (10%) patients in groups 1, 2, and 3, respectively, at a mean follow-up of 20 months (p = 0.36). PFS was found as 100%, 95.5%, and 89.7% in Groups 1, 2, and 3 at a mean follow-up of 20 months (Fig. 4) (p = 0.36). According to the cox regression analysis, only number of tumors was found to be a prognostic factor on RFS rates (Table 3).

Discussion

A complete resection is vital to achieve a good prognosis in non-muscle invasive bladder cancer[7,8]. The goal of TUR of bladder cancer in NMIBC is to achieve the correct diagnosis and completely remove all visible lesions and it is an essential procedure in the management of NMIBC. The absence of muscularis propria in the specimen is associated with a significantly higher risk of residual tumor, early recurrence, and tumor understaging[9]. The significant risk of residual disease after initial TURB of NMIBC has been demonstrated[8,10]. Especially high-grade T1 bladder cancer has a high recurrence and progression rate.

A Re-TUR of bladder cancer can increase RFS, improve outcomes after BCG treatment and provide prognostic information[11-14]. Therefore, a Re-TUR is

Table 2. Baseline patients characteristics of groups according to ≤ 42 days and > 42 days

Variable	Group 1: ≤ 42 days, n (%)	Group 2: > 42 days, n (%)	p
Number of patients	42	29	
Age, median (minimum-maximum)	65 (44-86)	63 (46-77)	0.29
Gender			
Female	8 (19)	5 (17.2)	0.84
Male	34 (81)	24 (82.8)	
Stage			
Ta	10 (23.8)	4 (13.8)	0.3
T1	32 (76.2)	25 (86.2)	
Concomitant CIS	4 (9.5)	3 (10.3)	0.91
Tumor size (mm), median (minimum-maximum)	40 (15-100)	30 (15-75)	0.17
Number of initial tumors, median (minimum-maximum)	1 (1-5)	1 (1-5)	0.66
Immediate post-operative intravesical chemotherapy	37 (88.1)	27 (93.1)	0.49
Smoking	33 (78.6)	23 (79.3)	0.94
Progression rate	1 (2.4)	3 (10.3)	0.20

CIS: Carcinoma *in situ*

Figure 3. *Recurrence-free survival rates of the two groups at a mean follow-up of 20 months (≤ 42 and > 42 days).*

Table 3. Cox regression analysis of clinical factors potentially affecting oncological results

Covariate	Recurrence free survival		
	HR	95% CI	p
Age	1.05	0.99-1.1	0.07
Tumor size	1.1	0.26-4.72	0.87
Number of initial tumors	1.5	1.01-2.34	0.04
Concomitant CIS	0.47	0.08-2.5	0.38
Time to re-TUR (days)			
14-28	Ref		
29-42	0.98	0.26-3.6	0.97
43-56	1.96	0.64-5.9	0.23

HR: hazard ratio, CI: confidence interval, re-TUR: re-staging transurethral resection, CIS: carcinoma *in situ*

Figure 4. *Progression-free survival rates of the three groups at a mean follow-up of 20 months.*

recommended in patients with high risk NMIBC. Although Re-TUR is mostly recommended within 2-6 weeks after initial TUR in the recent EAU guideline, review of the literature regarding the timing of a Re-TUR arises a large range from an immediate second TUR to 3 months after the initial TUR[14,15]. This recommendation to perform Re-TUR 2-6 weeks after initial TUR is based on a retrospective study recently performed by Baltaci et al.[4]

To the best of our knowledge, the present study is the first prospective, randomized, and controlled study evaluating the time lapse from initial TUR to Re-TUR and its association with RFS rates and progression rates. Our results revealed that the RFS rates of the Groups 1, 2, and 3 were 80%, 63.6%, and 69%, respectively, at a mean follow-up of 20 months (p = 0.56). These rates were not statistically significant. Similarly, PFS was found as 100%, 95.5%, and 89.7% in Groups 1, 2, and 3 at a mean follow-up of 20 months, respectively, and these results were also not statistically significant. When we divide the patients into two groups, we found

that the progression rate in group > 42 days was also similar to that of group ≤ 42 days. To the best of our knowledge, there are three retrospective studies evaluating the role of time from initial TUR to Re-TUR[4,16,17]. Two of them are multicentric studies. Calo et al. investigated the timing from initial TUR to Re-TUR in patients with high grade NMIBC. The authors divided the patients into three groups (A, B, and C) based on time to Re-TUR in their study. In Group A, B, and C, Re-TUR times are determined as within 6 weeks, > 6-12 weeks, and > 12-18 weeks, respectively. They found that recurrence rate was 38.3%, 24.8%, and 28.3% in Groups A, B, and C, respectively. Kaplan–Meier plots showed that such differences were not statistically significant (p = 0.1). They also found that progression rates between the groups were also not statistically significant. The authors thought that biological tumor characteristics might be more relevant than the "traditional" clinical and pathological characteristics in predicting the oncological outcomes. Similarly, we could not detect any significant effect of time from initial TUR to Re-TUR on PFS and RFS rates. In the present study, residual tumor was detected in 9 of 71 (12.6%) patients after the Re-TUR. This finding is lower than the results of previous studies, as residual cancer can be found in 20-78% of cases on a Re-TUR[3,12,18]. Therefore, this may be one reason why we could not find any effect of time from initial TUR to Re-TUR on RFS and PFS rates in the current study.

Baltaci et al. showed that second TUR performed 14-42 days after initial resection yielded longer RFS and PFS rates compared to a second TUR performed after 43-90 days[4]. Specifially, the 3-year RFS rates were 73.6% versus 46.2% (p < 0.001) and the 3-year PFS rates were 89.1% versus 79.1% (p = 0.006) for those having a second TUR 14-42 days and 43-90 days after initial TUR, respectively. This study is a valuable study, but because of it is multi-centric, it is a disadvantage that the second TURs were performed by different surgeons and the pathology results were evaluated by different pathologists, which might have caused interobserver differences. At present, interobserver differences are common in reporting tumor grade and stage.

Another recently published study by Krajewski et al. demonstrated that a second TUR performed within 6 weeks was associated to better RFS, PFS and CSS rates[17]. There was a great heterogeneity in BCG treatment in this study as it included patients who received al least 7 BCG instillations. Studies have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC. Studies have also demonstrated that BCG therapy delays and potentially lowers the risk of tumor progression[19-22]. For this reason, it is important for such study that patients must receive BCG treatment for a similar time and similar dose to avoid bias.

The relatively low number of patients and the short follow-up period are the main limitations of the present study. However, to the best of our knowledge, this is the first prospective, randomized, and controlled study evaluating the time lapse from initial TUR to Re-TUR and its association with RFS rates and progression rates in a single tertiary center.

Conclusions

Our prospective study demonstrated that time lapse from initial TUR to Re-TUR did not significantly affect RFS and PFS rates. Further prospective randomized larger sample studies are needed to confirm these findings.

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Changing characteristics of emergency surgery during COVID-19 pandemic: a retrospective cohort study

Cambio en las características de las cirugías de emergencia en la pandemia de COVID-19: estudio de cohorte retrospectiva

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Abstract

Background: *In other countries, researchers have noticed diverse variations in the features of patients undergoing emergency surgery during the COVID-19 pandemic. In Mexico, there is not information about this issue.* **Methods:** *Workers of the Mexican Government, who required emergency surgeries were studied by the general surgery service of a General Hospital administered by the Institute of Social Security and Services for State Workers Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), through the periods from March-August 2019 (non-exposed) and March-August 2020 (exposed). The analysis included: demographic data, laboratory information, post-operative diagnoses, symptoms' length, days of emergency stay, and post-operative stay.* **Results:** *One hundred and ninety-three emergency surgeries were analyzed; 106 in 2019 and 87 in 2020 (a decrease of 18%). Throughout the pandemic, the number of days between the symptoms' onset and surgery was greater: 2019, 7.6 ± 4.6 days; 2020, 14 ± 6.7 days (p < 0.0001). In addition, cases of acute appendicitis decreased (2019-60.3%; 2020-42.5%), and those of acute calculous cholecystitis increased (2019-12.2%; 2020-24.1%).* **Conclusion:** *Through the COVID-19 pandemic, there were notable changes in the characteristics of Mexican Government's workers who warranted emergency surgery.*

Keywords: *Abdominal pain. Abdominal surgery. COVID-19. Emergency. Lockdown.*

Resumen

Antecedentes: *En otros países, han notado diversos cambios en las características de los pacientes sometidos a cirugía de emergencia durante la pandemia de COVID-19. En México no existe información sobre este tema.* **Método:** *Estudiamos a los trabajadores del gobierno mexicano que requirieron tratamiento quirúrgico de emergencia por el servicio de cirugía general de un Hospital General del Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado (ISSSTE), durante los periodos de marzo-agosto de 2019 (no expuestos) y marzo-agosto de 2020 (expuestos). El análisis incluyó: datos demográficos, datos de laboratorio, diagnósticos postoperatorios, duración de los síntomas, días de estancia en emergencias y estadía postoperatoria.* **Resultados:** *Se analizaron 193 cirugías de emergencia; 106 en 2019 y 87 en 2020 (una disminución del 18%). En la pandemia, el número de días entre el inicio de los síntomas y la cirugía fue mayor: 2019, 7.6 ± 4.6 días; 2020, 14 ± 6.7 días (p < 0.0001). Además, disminuyeron los casos de apendicitis aguda (2019-60,3%; 2020-42,5%) y aumentaron los de colecistitis litiásica aguda (2019-12,2%; 2020-24,1%).* **Conclusión:** *Durante la pandemia de COVID-19, hubo cambios notables en las características de los trabajadores del gobierno mexicano que ameritaron cirugías de emergencia.*

Palabras clave: *Cirugía abdominal. Confinamiento. COVID-19. Dolor abdominal. Emergencia.*

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, generated notable changes in all human activities[1,2]. Therefore, medical and surgical practice also had great modifications[2]. The pandemic transformed the functioning of general surgery services worldwide[3]; while elective surgeries were suspended, emergency surgeries had to continue[4].

In other countries, most researchers have noticed diverse changes in the features of cases that warrant emergency surgery during the 2020 COVID-19 pandemic[5]. In Mexico, there is no information about this issue. The study was carried out to evaluate the features of the Mexican Government's workers who required emergency surgery in the general surgery service at a General Hospital administered by the Institute of Social Security and Services for State Workers Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) during the 2020 COVID-19 pandemic compared to a non-exposed group in 2019.

Methods

It was a retrospective cohort study. This investigation was approved by the institutional Research and Education Division. All procedures performed and studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We analyzed the medical records of Mexican Government's workers, or their relatives, undergoing emergency surgery during the periods from March-August 2019 and from March-August 2020 (COVID-19 pandemic), at the Hospital General Tacuba. From March-2020, our institution was adapted in a COVID-19 hospital. Patients undergoing surgery outside the hospital were excluded, and cases with insufficient information or lost records were eliminated.

Initially, at the emergency department, all cases were assessed with a full clinical history and a thorough physical examination. Their evaluation included complete blood count, glucose, urea, creatinine, and activated partial thromboplastin time. Besides, abdominal, or pelvic ultrasound, and chest X-rays were done. According to individual clinical data, the evaluation was extended to thoracic, or abdominopelvic computed tomography (CT scan). With the diagnosis of an abdominal emergency, the staff of the general surgery department evaluated the patients, determining the diagnosis, and the surgical management.

From all medical files, the following variables were analyzed: demography (age, gender), anthropometry (weight, height, and body mass index), biochemical (hemoglobin, hematocrit, leukocytes, platelets, glucose, urea, and creatinine), and comorbidity (diabetes, metabolic syndrome, arterial hypertension, obesity, and so on) that were registered upon admission to the emergency service. In addition, post-operative diagnoses (acute appendicitis, acute calculous cholecystitis, intestinal occlusion, and etcetera), days of stay in the emergency room before surgery, days from the onset of symptoms until emergency surgery, post-surgery stay, and post-surgical complications were examined.

Continuous variables were expressed as absolute values or their mean with standard deviation. The categorical variables were presented in numbers with their percentage. The analysis of the continuous variables, with normal distribution, was performed with the two-tailed student's t-test for independent samples. The categorical variables' analysis was carried out with the "X^2" test, or Fisher's exact test; the latter, if any of the values in the 2×2 table were ≤ 5. For all assessments, the statistic program OpenEpi version 3 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open-Source Epidemiologic Statistics for Public Health, Versión. www.OpenEpi.com. USA) was used. All values of $p < 0.05$ were considered statistically significant.

Results

Two hundred and fourteen patients undergoing emergency surgery were identified; however, 21 cases were excluded from the study. Finally, 193 patients were analyzed: 106 from 2019 and 87 from 2020 (Table 1). This represented a decrease of 18% in surgical emergencies. Both groups were similar (Table 1).

In the pandemic, the days elapsed between the onset of symptoms, and the emergency surgery increased (Table 1). Meanwhile, the days spent in the emergency room were reduced. In addition, the number of cases of appendicitis decreased 29.6% (Table 2). While an increased by 97.8% occurred for the surgeries for acute calculous cholecystitis (Table 2). Only five patients had an emergency surgery and simultaneously COVID-19 infection (two

Table 1. Demography, anthropometry, comorbidities, and pre-post-operative information

Characteristic	2019 (n = 106)	2020 (n = 87)	p
Age	47.5 ± 19.7	51.4 ± 18.2	0.15#
Women, n (%)	53 (50)	87 (60)	0.11$
Body mass index	27.2 ± 5	28.3 ± 5.6	0.15#
Patients without comorbidity, n (%)	55 (51.8)	42 (48.2)	0.97$
Days of stay in the emergency room	1.5 ± 0.6	1.3 ± 0.6	0.02#
Days from the onset of symptoms to surgery	7.6 ± 4.6	14 ± 6.7	< 0.0001#
Days of post-operative stay	5.2 ± 8.6	5.2 ± 5.4	> 0.99#

#Statistical test used: Two-tailed student's t-test for independent samples, $The "χ²" test, &Fisher's exact test

Table 2. The most frequent surgical pathologies

Characteristic	2019 (n = 106), n (%)	2020 (n = 87), n (%)	p
Acute appendicitis	64 (60.3)	37 (42.5)	0.007$
Acute calculous cholecystitis	13 (12.2)	21 (24.14)	0.02$
Complicated abdominal wall hernias	13 (12.2)	9 (10.3)	0.34$
Bowel occlusion due to adhesions	3 (2.8)	3 (3.4)	> 0.99&
Intestinal volvulus	3 (2.8)	1 (1.1)	0.47&
Mesenteric thrombosis	1 (0.9)	1 (1.1)	> 0.99&

#Statistical test used: Two-tailed student's t-test for independent samples, $The "χ²" test, &Fisher's exact test. All values of p <0.05 were considered statistically significant.

Table 3. Acute appendicitis cases

Characteristic	2019 (n = 64)	2020 (n = 37)	p
Age	39.1 ± 17.5	44.7 ± 17.7	0.12#
Patients without comorbidity, n (%)	41 (64)	19 (51.3)	0.69$
Body mass index	24.6 ± 9.3	24 ± 9.6	0.76#
Initial leukocytes	15.8 ± 4.7	15.1 ± 6	0.54#
Days of stay at the emergency room	1.4 ± 0.5	1.3 ± 0.5	0.33#
Days of symptom onset to surgery	2.6 ± 1.4	3.5 ± 1.4	0.002#
Days of post-operative stay	3 ± 1.3	2.9 ± 1.2	0.7#
Grade IV appendicitis, n (%)	16 (25)	11 (29.7)	0.30$

#Statistical test used: Two-tailed student's t-test for independent samples, $The "χ²" test, &Fisher's exact test

Table 4. Acute calculous cholecystitis cases

Characteristic	2019 (n = 13)	2020 (n = 21)	p
Age	61.9 ± 14.1	48.9 ± 15.1	0.01#
Patients without comorbidity, n (%)	4 (30.7)	9 (42.8)	0.51&
Body mass index	26.2 ± 3.5	29 ± 2.5	0.01#
Initial leukocytes	9.6 ± 3.6	13.6 ± 6.1	0.02#
Days of stay at the emergency room	1.8 ± 0.5	1.3 ± 0.6	0.001#
Days of symptom onset to surgery	17.5 ± 5.3	35.5.1 ± 8.9	< 0.0001#
Patients with gangrenous cholecystitis, n (%)	1 (7.6)	9 (42.8)	0.03&

#Statistical test used: Two-tailed student's t-test for independent samples, $The "χ²" test, &Fisher's exact test. All values of p <0.05 were considered statistically significant.

acute appendicitis and three acute calculous cholecystitis); no one died. From the 87 cases attended in the pandemic, just six had a pre-operative COVID-19 test, all done outside the hospital.

In cases of appendicitis, during the pandemic, the days elapsed between the onset of symptoms, and the surgery increased (Table 3). Just six cases were managed with laparoscopic appendectomy. In the cases of acute calculous cholecystitis, during the pandemic, the patients age, and the days of stay in the emergency room decreased (Table 4). However, the body mass index, the days elapsed between the onsets of symptoms until the surgery, leukocytes and

cases with gangrenous cholecystitis increased (Table 4). Just six cases were managed with laparoscopic cholecystectomy.

Discussion

In this investigation, notable changes were identified in emergency surgeries during the 2020 COVID-19 pandemic at a general hospital that insured workers of the Mexican Government: these surgeries decreased. In other parts of the world, the behavior of these operations was heterogeneous. While, in few countries these surgeries were maintained with the same

frequency[5-8], in most reports, a reduction was described[3,9-16]. This diverse conduct was due to the heterogeneous manner of the pandemic in the different countries[7].

In this research, it was identified that the number of days between surgery, and the onset of the surgical disease increased. This finding is like the reports from other regions of the World[9,15,17]. Authors agree that this circumstance was by several factors, including the "stay at home" recommendation from authorities or the patients' fear of going to hospitals, delaying their timely management[3,9-16].

Herein, a decrease in the number of cases of acute appendicitis was found. In other parts of the world, the behavior of this disease was also heterogeneous. A few medical units identified an increase in these cases[16,18,19]; however, most hospitals recognized a reduction[20-23]. This diverse conduct was also due to the heterogeneous behavior of the pandemic in the World[7].

In a singular way, in our work an increase in cases of acute calculous cholecystitis was identified. Meanwhile, few authors did not detect changes in the frequency of this disease[5,20]; most centers noticed a decline in cases of cholecystitis[9,10,21,22]. In our cholecystitis cases, a significant increase in their body mass index, initial leukocytes, cases with gangrenous cholecystitis, as well as in the number of days between the onset of symptoms and cholecystectomy were identified. This was consistent with what happened with appendicitis, where patients did not go to hospitals in a timely manner due to the "stay at home" recommendation from authorities or the patients' fear of contracting COVID-19[3,9-16].

Alike all studies this one has limitations. This work is the result of a single urban hospital population. Our patients were exclusively workers of the Mexican Government or their relatives. In addition, retrospective cohort studies have intrinsic limitations due to their design. Notwithstanding the former data, our findings are consistent with other surveys.

Conclusion

During the COVID-19 pandemic in 2020, in our patients the cases that warrant emergency surgery decreased. The number of days between the symptoms' onset and surgery was greater. Cases of acute appendicitis diminished, and those of acute calculous cholecystitis increased.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Common bile duct pressure after open intraoperative instrumentation in patients with uncomplicated choledocholithiasis

Presión del conducto biliar común después de instrumentación transoperatoria abierta en pacientes con coledocolitiasis no complicada

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Abstract

Background: *Common bile duct pressure (CBDP) after surgical exploration has not been fully detailed. The objective was to describe the changes of CBDP after open surgical exploration in patients with choledocholithiasis, considering clinical scenarios in remote locations.* **Material and methods:** *A before-after study was designed. Patients with choledocholithiasis who required an open cholecystectomy with exploration of bile ducts were included in the study. Open cholecystectomy was performed and perioperative T-tube CBDP was registered immediately after the procedure and weekly thereafter, with a 6 week follow-up. Control T-tube cholangiogram was performed at week 6 to exclude residual stones. Data were analyzed with T test for paired samples.* **Results:** *Thirteen patients were included (age range, 17-69 years; 38.69 ± 17.97). Mean CBDP (cm H_2O) registered were as follows: Initial = 19.5, week 1 = 16.2, week 2 = 14.3, week 3 = 13.0, week 4 = 12.1, week 5 = 11.1, and week 6 = 9.7. There were significant differences shown when comparing week 2 ($p = 0.05$), week 3 ($p = 0.036$), week 4 ($p = 0.023$), week 5 ($p = 0.010$), and week 6 ($p = 0.004$) with the initial value.* **Conclusions:** *CBDP decreases between 2nd and 3rd post-operative weeks. The use of choledochomanometry is useful in clinical scenarios with no access to imaging or interventionism facilities as in remote populations or rural locations.*

Keywords: Choledocholithiasis. Cholecystectomy. Common bile duct. Common bile duct pressure. Cholangiography. Common bile duct stones.

Resumen

Antecedentes: *La presión del conducto biliar común (PCBC) después de exploración quirúrgica no ha sido totalmente detallada. El objetivo fue describir los cambios de la PCBC tras exploración por coledocolitiasis.* **Material y métodos:** *Estudio de antes y después, en pacientes con coledocolitiasis, que requirieron colecistectomía con exploración de vías biliares, registrando la PCBC por 6 semanas. Con colangiografía por sonda en T en la semana seis. Análisis con T de Student para muestras pareadas.* **Resultados:** *Se incluyeron 13 pacientes (rango 17-69 años; 38,69 ± 17,97). Las presiones medias del CBC fueron: Inicial = 19.5, semana 1 = 16.2, semana 2 = 14.3, semana 3 = 13.0, semana 4 = 12.1, semana 5 = 11.1 y semana 6 = 9.7. Se mostraron diferencias significativas al comparar la semana 2 ($p = 0.05$), la semana 3 ($p = 0.036$), la semana 4 ($p = 0.023$),*

la semana 5 (p = 0.010) y la semana 6 (p = 0.004) contra el valor inicial. **Discusión:** *La PCBC disminuye entre la segunda y la tercera semana posoperatoria. La coledocomanometría muestra ser útil en escenarios clínicos sin acceso a intervencionismo como en poblaciones remotas o localidades rurales.*

Palabras clave: *Coledocolitiasis. Colecistectomía. Colédoco. Presión del colédoco. Colangiograma. Litos en conducto biliar común.*

Introduction

Choledocholithiasis is a condition in which one or more gallstones are present in the common bile duct (CBD). Its prevalence is 10% to 20% in those with cholelithiasis, although the natural history of CBD stones is not well understood. Bile stones can be divided into two separate entities in relation to their site of origin; primary (bile ducts) and secondary (gallbladder). Secondary stones are by far the most common in America, including Mexico. These stones originate in the gallbladder and migrate to the CBD by means of the cystic duct[1,2]. The prevalence in Mexico was reported in the 1990's to be 14.3% (8.5% for men and 20.4% for women) in a large necropsy study[3], and in a more recent study it was reported to be 13.2%[4].

The goal of its management consists of clearing the CBD of stones by either endoscopy or surgery. Actual treatment options include endoscopic retrograde cholangiopancreatography (ERCP) with laparoscopic cholecystectomy (LC) or laparoscopic common bile duct exploration (LCBDE) with LC. Nevertheless, in developing countries it is not always a possibility, being forced to resort to open exploration of the CBD, which implies temporary CBD drainage by means of a T tube[2].

However, after intraoperative exploration of the CBD, inflammatory changes secondary to manipulation could happen, and they may alter CBD pressure. In a study conducted in the late 1980s, it was found a fell from an initial CBD pressure value of 17.2 ± 1.9-9.1 ± 0.9 cm bile on the seventh post-operative day, but exploration with metal instruments was avoided, and stone extraction was effected by irrigation and biliary balloon catheters[5].

The aim of this study is to describe the behavior of the intraluminal CBD pressure after open surgical instrumented exploration (Randall forceps) of the bile ducts in patients with uncomplicated choledocolithiasis.

Materials and methods

A double blinded nonrandomized before-after trial was designed for common bile duct (CBD) pressure measurement during and after open surgical management of uncomplicated choledocolithiasis at Hospital General de México "Dr. Eduardo Liceaga".

All patients gave their informed consent to be included in the study to be managed by elective open cholecystectomy and operative exploration of the common bile duct. Two patients were eliminated because they did not complete the follow-up period. The authors declare that the study was registered and authorized by the institution's research ethics committee in accordance with the 1975 Helsinki Declaration and its subsequent revisions (including the emanating from the 64th general assembly in Fortaleza, Brazil, in October 2013) in accordance with good clinical practices[6], and was registered at ClinicalTrials.gov (NCT04968873).

During elective open cholecystectomy, a basal CBD manometry was obtained immediately after cholecystectomy, with a 10 Fr. silicone tube introduced into the cystic duct and connected to a glass manometer. The zero reference was set as the level of the cystic-choledochal junction. Pressure was expressed in cm H_2O. After registering the baseline CBD pressure, a careful CBD intraluminal exploration (CBDE) was carried out with Randall forceps. A Foley catheter (12 Fr. Silicone-coated Foley catheter) was introduced into the cystic duct and saline water infusion was performed for lavage. Then, a T-tube (14 Fr, Kerr latex T-tube) was introduced into the CBD and the proximal end was externalized through an independent skin incision and fixed as routine.

A post-operative cholangiogram was obtained through the T tube and an initial CBD pressure was immediately registered after verifying no residual intraluminal stones, with the zero reference taken at the cystic-choledochal junction, in the mid axillary line. Thereafter a weekly follow-up was carried out for a period of 6 weeks (for study purposes) by another surgeon, totally blinded to the aim of the study and to the initial CBD lecture, adhering to the described method. Finally, liver function tests and a T-tube cholangiogram were carried out on all patients at week 6.

Statistical analysis

The sample size (n = 15) was calculated to reach a confidence level of 95% with a power of 90% for an expected difference of 4.2 (standard deviation of 4.8), based on the study reported by Csendes[7]. Accepting an alpha risk of 0.05 and a beta risk of 0.1 in a two-sided contrast, 15 subjects are required to detect a difference equal to or > 4.2 units. A standard deviation of 4.8 is assumed. A tracking loss rate of 5% has been estimated.

Values were expressed as mean and standard deviation (SD) of the mean. For statistical evaluation, T test for parametric values was employed, considering significance at 5% level.

Results

Twelve patients were female (92.6%) and one was male (7.6%), with a mean age of 38.69 years (SD ± 17.75) (Table 1). Initial liver function tests were abnormal in all 13 patients, with increased values of total and direct bilirubin, alkaline phosphatase, AST, and gamma-glutamyl transpeptidase.

Among the 13 patients studied, no complications were reported, but one maintained a high CBD pressure during all follow-up period because of residual choledocolithiasis. In the final T tube cholangiogram at week 6, a residual stone was evidenced and extracted through the existing fistula by an interventional radiologist. CBD pressure was monitored again, decreasing to normal parameters by week 8. Thus, it was excluded from the statistical analysis to assess the behavior of CBD pressures in the rest of the group.

Values of the CBD pressure evolution of all cases are shown in table 1. Initial mean CBD pressure was 19.5 cm H_2O (highest value 38 cm H_2O). Weekly mean values were decreasing constantly, at a mean rate of 1.59 cm H_2O/per week. Mean CBD pressures at weeks 1 and 2 were 16.21 cm H_2O and 14.33 cm H_2O, and when compared to mean CBD initial pressure, no significant differences occurred (week 1, $p < 0.134$; and week 2, $p < 0.05$). Meanwhile, the mean CBD pressures during weeks 3-6 were significantly low when compared to the mean initial CBD pressure (Table 2).

Values of the CBD pressure evolution for the case with the residual stone are shown in table 3, depicting a similar decrease as with the other cases, once the residual stone was removed at week 6, to reach a normal value after week 9.

Final liver function tests were completely normal in all 13 patients, as well as final T tube cholangiogram (at week 6) in all cases but the one previously described to have had a residual stone.

Discussion

At present, open choledochotomy still plays a role in cases diagnosed with choledocholithiasis with or without cholangitis, while endoscopic, percutaneous, or laparoscopic approaches failed, or are not available, as in remote populations or rural locations. Furthermore, it could also be used in the case of a preexisting open surgery that limits the application of endoscopic approaches, as in Roux-en-Y enteral reconstruction after gastrectomy[8].

The residual stone rate of routine CBDE is about 7-11% and in recent studies < 6%. In addition, stones proximal to the cystic duct-CBD junction can be extracted in only 40% of cases, requiring either a laparoscopic or open choledochotomy[9-11].

Thus, the results of the present study lead to a series of clinical relevant observations.

First, CBD pressure after open surgical exploration significantly decreased week by week, being the first significant decrease near the 3rd week. Apparently, surgical manipulation (Randall forceps exploration) causes CBD intraluminal inflammatory changes that tend to maintain a high CBD pressure, reaching its peak by the end of the 2nd week. Then, the inflammation progressively decreased to permit intraluminal pressure to reach physiologic parameters. Thus, CBD intraluminal manometry could be used to indirectly monitor the inflammatory process of the ampulla of Vater.

Second, the previous studies have described that CBD pressure was higher in patients with CBD stones compared to patients without them[4,6,12]. In this study, one patient maintained high CBD pressure values during the entire evaluation period. At the end of follow-up period, the T tube cholangiogram demonstrated the presence of a residual stone, which was successfully removed by the endoscopist after which the same pattern of decreasing CBD pressure was observed. During the post-operative period, findings of CBD pressure values higher than 20 cm H_2O[7,12] suggest the possibility of a persistent inflammatory process or an obstruction of the lumen (residual stone). Again, it allows us to assume that the use of choledochomanometry can be useful, mostly in clinical

Table 1. Demographic characteristics and individual common bile duct pressure by week

Age	Sex	Surgery	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 9	Week 12
51	Male	38.0	19.7	18.2	15.7	13.7	13.1	9.5	NA	NA
54	Female	17.3	13.0	12.7	11.6	10.6	9.7	9.2	NA	NA
61	Female	15.3	13.8	11.0	10.2	8.5	9.2	8.7	NA	NA
52	Female	16.9	14.7	13.3	8.0	8.0	9.0	9.3	NA	NA
17	Female	19.2	15.8	13.2	12.2	11.7	10.1	9.0	NA	NA
18	Female	20.5	20.2	17.3	14.6	13.3	12.6	10.2	NA	NA
34	Female	16.1	13.9	11.3	10.8	10.4	10.2	9.8	NA	NA
19	Female	18.7	16.4	13.1	14.4	17.0	12.8	10.3	NA	NA
32	Female	21.6	21.0	20.0	17.6	15.8	14.0	11.6	NA	NA
18	Female	21.6	18.7	17.1	18.0	16.2	13.3	12.0	NA	NA
69	Female	17.8	14.3	12.8	11.3	10.1	9.6	9.4	NA	NA
36	Female	11.0	13.0	12.0	11.6	9.7	9.4	8.0	NA	NA
42	Female	21.1	23.5	24.0	22.2	23.3	21.6	19.8	15.6	9.1

NA: not available

Table 2. Mean common bile duct pressure by week

Moment	n	Mean CBDP (cm H_2O)	Range (cm H_2O)	Statistical comparison (p)
Surgery	12	19.50	11–38	-
Week 1	12	16.21	13–21	Initial versus week 1 (0.134)
Week 2	12	14.33	11–20	Initial versus week 2 (0.050)
Week 3	12	13.00	8–18	Initial versus week 3 (0.036)*
Week 4	12	12.08	8–17	Initial versus week 4 (0.023)*
Week 5	12	11.08	9–14	Initial versus week 5 (0.010)*
Week 6	12	9.75	8–12	Initial versus week 6 (0.004)*

*Significant (T-test for one sample). CBDP: Common bile duct pressure, n: sample

Table 3. Common bile duct pressure of patient with residual stone

Moment	CBDP (cm H_2O)
Intraoperative	21.10
Week 1	23.50
Week 2	24.00
Week 3	22.20
Week 4	23.30
Week 5	21.60
Week 6	19.80
Week 9	15.60
Week 12	9.10

CBDP: common bile duct pressure

scenarios with no access to imaging or interventionism facilities as in remote populations or rural locations. Furthermore, it is a usual practice in Mexico, that senior residents serve in rural hospitals at least during a 4-month period, where there is a lack of facilities for this kind of surgical procedures, making this practice to become a feasible option.

Thus, in countries where there is a lack of medical funding in public medical care services, this procedure could be an alternative in the follow-up period.

Finally, surgeons must provide different alternatives in therapeutic and diagnostic approaches to the patient. Cholangiomanometry proves to be a complimentary, accessible, inexpensive, safe, and efficient method for patients with choledocolithiasis.

Conclusions

The common bile duct pressure decreases between the second and third postoperative weeks. Choledochomanometry let us monitor CBD pressure

and is a useful approach in clinical scenarios as remote populations or rural locations with no access to endoscopic facilities.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/ or subjects referred to in the article. This document is in the possession of the corresponding author.

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Comparison of wire versus Nylon in Bonny-Mallet Finger treated with pull-out surgery

Comparación de alambre y nailon en Bonny-Mallet Finger tratado con cirugía de pull-out

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Abstract

Introduction: *Zone I extensor tendon lesion accompanies an avulsion fracture of the bone insertion. A common complication of traditional pull-out is the necrosis of the site of the button in the finger pad. Zhang described an alternative way of anchoring the cerclage to the Kirschner Wire (K-wire) to relieve the pressure in the finger pad. He describes the use of wire cerclage, for fracture reduction. The objective of this paper is to perform a comparison between wire and nylon using Zhang pull-out technique.* **Material and methods:** *We performed a cohort study comparing Nylon versus Wire in Zhang technique. Comparing cosmetic satisfaction, stiffness, residual pain, and Crawford scale.* **Results:** *When comparing the outcomes between both groups, we found no statistical difference in cosmetic satisfaction (p = 0.285), stiffness (p = 0.460), and residual pain (p =1.000), overall complications (p = 1.000), or Crawford scale (p = 1.000). We only found a significant statistical difference in pain when removing the cerclage, being greater in Group B (p = 0.008).* **Conclusions:** *We found no significant outcome difference between nylon and wire cerclage. However, at the time of removing it, patients experience less pain.*

Keywords: *Mallet-finger. Pull-out. Hand surgery. Tendon surgery.*

Resumen

Introducción: *Una complicación común del pull-put tradicional es la necrosis del sitio del botón en la yema del dedo. Zhang describió una forma alternativa de anclar el cerclaje al clavo de Kirschner para aliviar la presión en la yema del dedo. Describe el uso de cerclaje de alambre para la reducción de fracturas. El objetivo de este trabajo es realizar una comparación entre el alambre y el nailon utilizando la técnica de extracción de Zhang.* **Material y métodos:** *Realizamos un estudio de cohorte comparando la técnica de nailon versus alambre en Zhang. Comparación de satisfacción cosmética, rigidez, dolor residual y escala de Crawford.* **Resultados:** *Al comparar los resultados entre ambos grupos, no encontramos diferencias estadísticas en la satisfacción cosmética (p = 0.285), rigidez (p = 0.460) y dolor residual (p = 1.000), complicaciones generales (p = 1.000) o escala de Crawford (p = 1.000). Solo encontramos una diferencia estadística significativa en el dolor al retirar el cerclaje, siendo mayor en el Grupo B (p = 0.008).* **Conclusiones:** *No encontramos diferencias significativas en los resultados entre el cerclaje de nailon y el cerclaje con alambre. Pero, al momento de retirarlo, los pacientes experimentan menos dolor. Tipo de estudio: terapéutico Nivel de evidencia III.*

Palabras clave: *Dedo en martillo. Pull-out. Cirugía de la mano. Cirugía del tendón.*

Introduction

The Bony-Mallet finger (BMF) is a widespread synonym for a Zone I extensor tendon lesion. It accompanies an avulsion fracture of the bone tendon insertion[1]. It is a frequent lesion among athletes, and it represents 2% of all hand injuries[2]. When this lesion does not receive adequate treatment, it can result in loss of distal extension, chronic finger pain, subluxation of the distal phalange, deformity of inter-phalangeal articulations, among others[3].

The actual recommendation for surgical treatment is when 30% of the articulation is involved[3]. Several techniques for reduction and fixation have been described, with advantages and disadvantages, in each case[1,3-9]. The most common techniques used are the pull-out and pull-in, with multiple variants among them. Today, there is no consensus or evidence to recommend one over the other[10]. Pull-out technique appears to need minor dissection, and it may be more replicable[11]. A usual complication of traditional pull-out is the necrosis of the site of the button in the finger pad. Zhang et al.[11] described an alternative way of anchoring the cerclage to the Kirschner Wire (K-wire) to relieve the pressure in the finger pad. In his technique, it describes the use of wire cerclage for fracture reduction[11]. In our experience, wire removal can be laborious. Therefore, we choose nylon as an alternative to our procedures.

To the best of our knowledge, there is no prior evidence comparing wire versus nylon in the pull-out technique and therefore, no evidence of the advantages and disadvantages among them. We found this topic to be, feasible, noteworthy, novel, ethical, and relevant. This paper aims to perform a comparison between wire and nylon in patients with BMF using Zhang pull out technique.

Materials and methods

It was performed a prospective experimental study with simple randomization. For sample calculation, the following epidemiologic data were used. The Institutional Review Board approved the study, and each patient signed a consent report. Every year there is an incidence of hand injury of 1500 cases in 100,000 inhabitants[12]. Mallet's fingers are 2%, around 30 cases for 100,000 inhabitants[2,8]. In Mexico City are 8.9 million people and 365,000 inhabitants in the Miguel Hidalgo municipality[13]. From those data, it can be assumed that 90 cases/year could be reported with mallet finger. With the prior data, and after applying a confidence interval of 95% with an interval of confidence of ± 5, our objective sample was 21 cases. The population is, patients with BMF derived to our center in a period of 3 months[14].

Inclusion criteria were patients with BMF with 30% or more articular compromise. Exclusion criteria were patients with no fracture, patients that did not accept to be included in the study, and patients with another lesion representing confounding factors (phalangeal fractures, a neurovascular compromise, and among others). The elimination criteria were also patients that failed to return to follow-up for data collection. Simple randomization was made to form two groups of 11 patients each. Group A, corresponding to a cerclage with nylon, and Group B to cerclage with wire.

The variables included were: age, gender, comorbidities, occupation, hand dominance, hand affected, finger injured, mechanism of the lesion, Doyle classification, Wehbe classification, articular compromise percentage, time of injury, surgical time, nylon/wire, functional conformity, cosmetic conformity, residual pain, residual stiffness, complications, pain referred at the moment of removing cerclage, and Crawford scale.

Surgical technique

The technique was standardized to have high reproducibility in each step. The surgeons involved in this study had prior training in performing this particular procedure; described as follows:

A tourniquet was applied on the fingers to the patient positioned with the hand placed palm down. A procedure was performed under a digital nerve block, with 3 mL 2% lidocaine injection. The distal interphalangeal (DIP) joint was exposed through a dorsal incision over the DIP joint and care to avoid extension above the germinal matrix. The fragment connected with the extensor tendon was released and retracted proximally after that fracture surface site was exposed. The hematoma was removed as well as the interposed soft tissue to inspect the articular surface better (Fig. 1A). Two drill holes were then made, one needle distal to the bony fragment and one proximal to it and both through the distal phalanx using a 14 G needle (Fig. 1B). A 3-0 nylon (or a 0.016" surgical wire) was passed, anchoring the bony fragment with the extensor tendon, and passed through the needle, and adequate reduction of the bony fragment is ensured
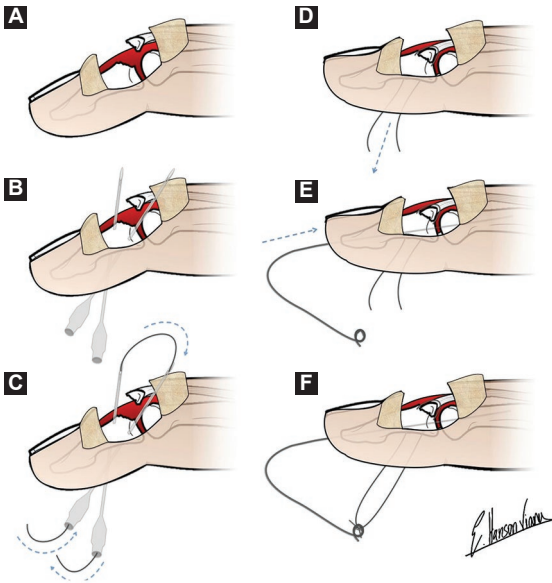
Figure 1. A-D: *surgical incision description.* **A:** *bone fragment and angulation for nylon/wire fixation.* **D-F:** *surgical technique. Traction during K-wire fixation through the joint. This traction ensures perfect reduction of the bone fragment.*

(Fig. 1C and D). At this moment, the K-wire (0.035") was passed through the DIP with the distal phalanx in 0-5° degrees extension. After the DIP is locked, 1 cm distal to the finger, the K-wire was bent, in the volar direction at 45° until reaching the end of the cerclage (Fig. 1E). It is then essential to pull the nylon or wire at a 45° in a volar direction to ensure a 100% fracture reduction (Fig. 1F). The surgical technique is schematized afterward (Fig. 2A-H). In figure 3 and 4, we show example cases of nylon and wire (Figs. 3 and 4).

Statistical methods

We used an Excel data sheet for data collection and R-studio® and StatGraphics® centurion for statistical analysis. The statistical formulas were X2, T-student, No inferiority test, and equivalence analysis with $p < 0.05$.

Results

Ninety-eight patients with **BMF** were received, and only 25 were with insertion site fracture > 30%. A total of 22 patients were randomized into two groups of 11 patients, Group A, corresponding to a cerclage with nylon, and Group B to cerclage with wire.

The mean age was 44 years (IC 95%, 44 ± 17.74). Males accounted for 73% (n = 16), most common comorbidity diabetes mellitus in three patients, followed by hypertension in 2. Most predominant occupation was construction worker with 32% (n = 7). In 86% of cases (n = 19), the right hand was dominant, and the most injured in 55% (n = 12) of the cases. The most injured finger was the second in 32% (n = 7) of the cases, followed by the thumb and third finger with 23% (n = 5) each. The mechanism of injury most prevalent was crush injury in 41% (n = 9). The most prevalent Doyle classification was IV B, with 59% (n = 13). Whereas, the most common Wehbe-Schneider classification was III with C subtype in 36% (n = 8). The open injury was the most common in 64% (n = 14) of the patients. The time of injury had a mean of 5.27 h with a minimum of 2 and a maximum of 10 (IC 95%, 5.12 ± 1.57). The percentage of articular injury was 30-50% in 59% (n = 13), and 41% of them had an articular injury grater of 50%.

Outcome statistics

When evaluated the survey, the patients referred a cosmetic satisfaction in 95% (n = 23). No patient was referred to as residual pain after surgery. And only 23% (n = 5) referred residual stiffness of the articulation at the third moth after K-wire extraction. Only one patient presented with infection and partial dehiscence, secondary to poor patient hygiene. When evaluating the Crawford scale, 55% showed excellent results, 41% good, and only one case presented a fair result, secondary to infection complications. Moreover, among the patients with a III C Wehbe-Schneider classification (n = 8); two patients showed excellent results, 5 good and 1 fair results in the Crawford scale. When removing the cerclage, the pain ranged from 2 to 8 on a visual analog pain scale with a mean of 4.9, Group B with an average of 6.7, and 3.0 in Group A.

When comparing the outcomes between both groups no statistical difference was found between duration of the procedure (p = 0.20), cosmetic satisfaction (p = 0.68), stiffness (p = 0.363) and residual pain (p = 0.6895), overall complications (p = 6,895), or Crawford scale (p = 0.19). We only found a significant statistical difference in pain when removing the cerclage, greater in patients with wire cerclage (p = 0.00015) (Fig. 5).
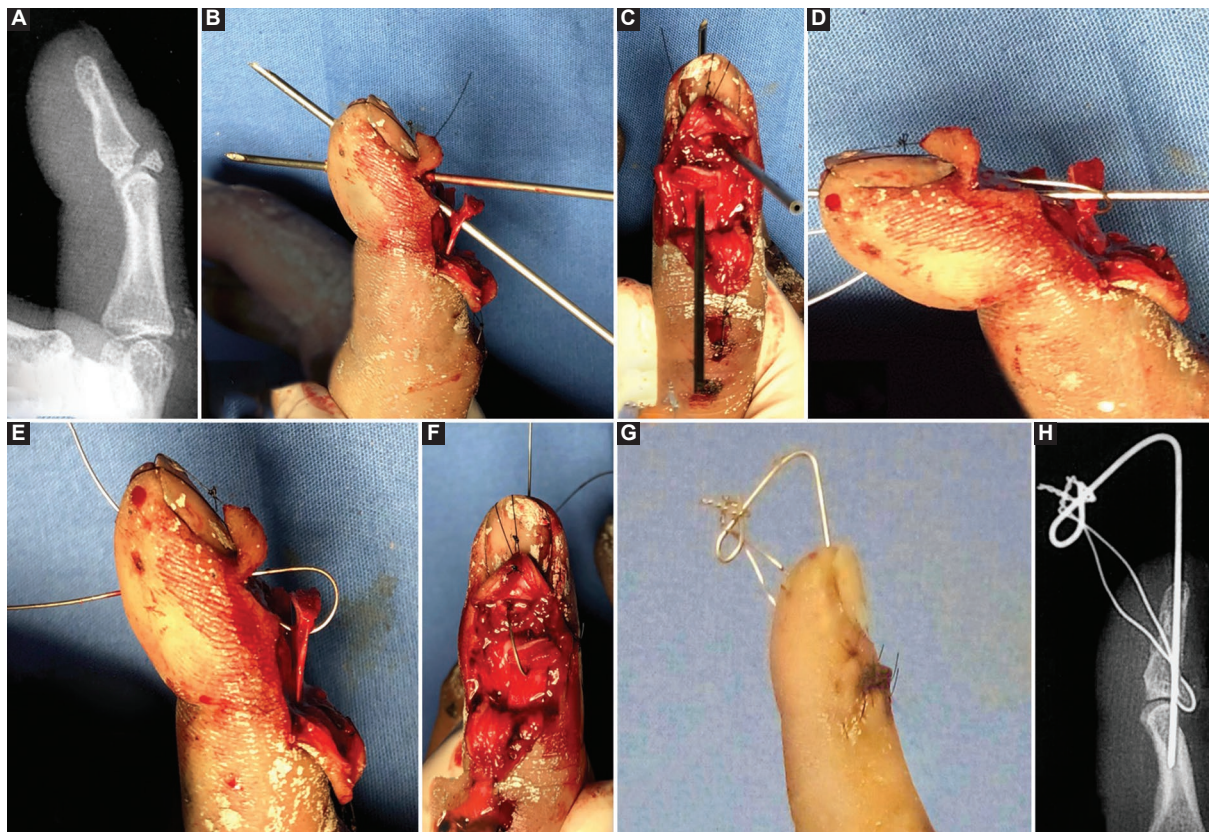
Figure 2. *Case example showing the technique.* **A:** *radiograph.* **B:** *the two trochars on the respective place.* **C:** *dorsal view of trochar placement.* **D:** *lateral view.* **E:** *The bony fragment.* **F:** *dorsal view.* **G:** *7 days after surgery.* **H:** *control radiograph.*
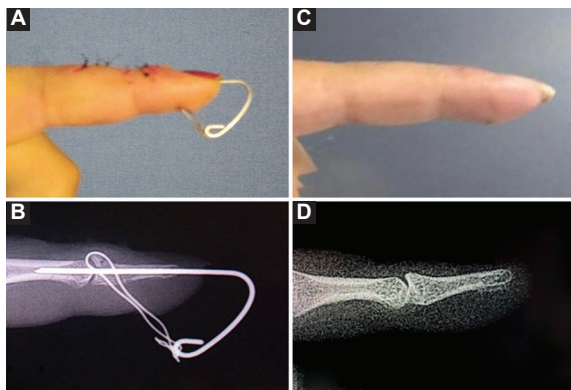
Figure 3. *Example case of wire.* **A:** *postoperative lateral view.* **B:** *postoperative lateral radiograph.* **C:** *lateral view 15 days after removing wire and K-wire.* **D:** *radiograph follow-up.*

Discussion

We described some benefits in executing the previously described technique by Zhang et al.[11]. We consider that nylon cerclage is an adequate substitute to the wire. Furthermore, nylon handling is uncomplicated to control the given tension to the cerclage, without apparent tension loss in the time needed. Further, patients experience less pain when removing the cerclage, resulting in a much better alternative since nylon is cheaper with easy access in most centers.

Zhang et al.[11] previously described a replicable technique with a successfully controlled direction of the bony fragment reduction, based on wire fixation. While this present work could corroborate those results, it is recommended to use nylon as a substitute for the wire.

Prior papers had evaluated the tensile force of nylon available in the United States of America[15]. And they proved that there is a small variability between brands, but we consider that the percent of elongation and failure is far from *in vivo* scenarios, and it is useful in cerclage fixation.

Several authors had described an extensive range of surgical and orthopedical solutions for bony mallet fingers. Minimal invasive procedures such as Ishiguro´s et al.[16] blocking technique had been suggested. In that specific technique, the surgeon uses a dorsal blocking pin with flexion of the distal phalange to trap the bony fragment, and then another pin is used with an extension of the same phalange to reduce the fragment.
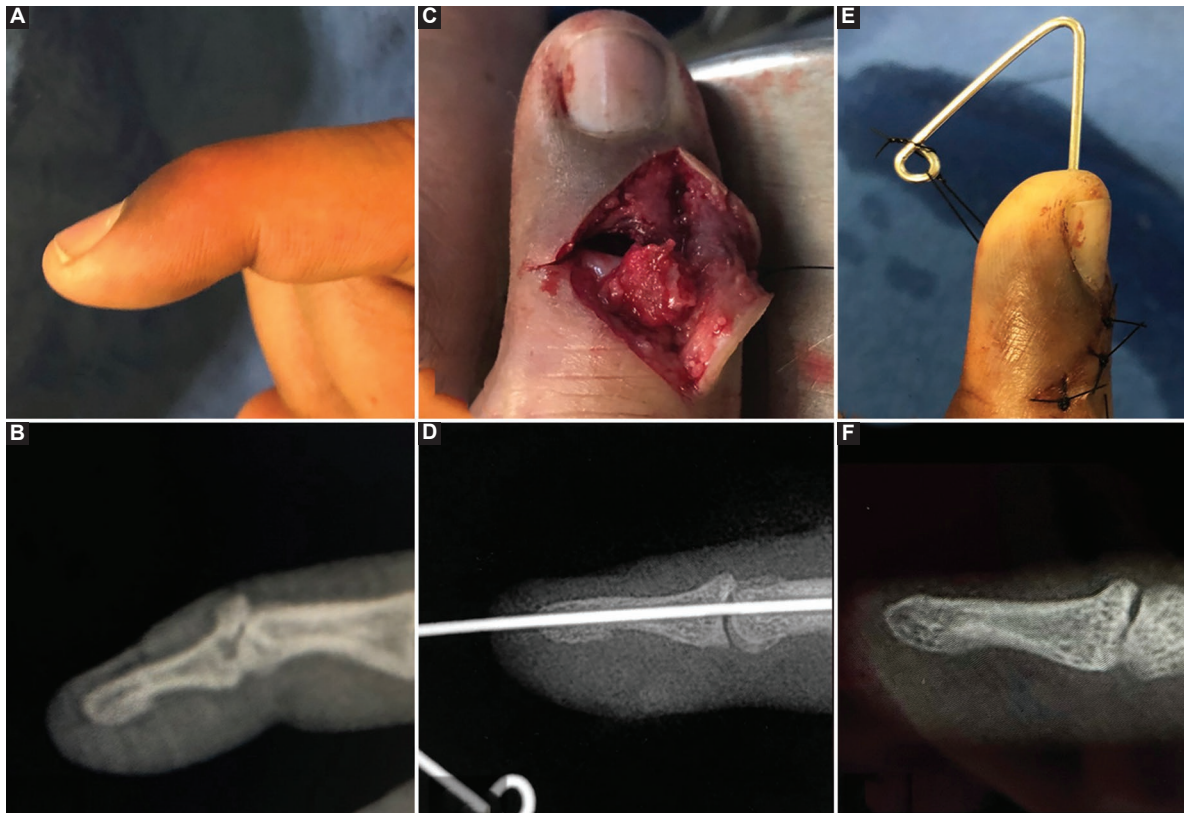
Figure 4. *Example case of wire.* **A:** *preoperative image.* **B:** *lateral view.* **C:** *surgery.* **D:** *lateral view immediate radiograph.* **E:** *lateral view the immediate photograph.* **F:** *follow up without K-wire and nylon.*
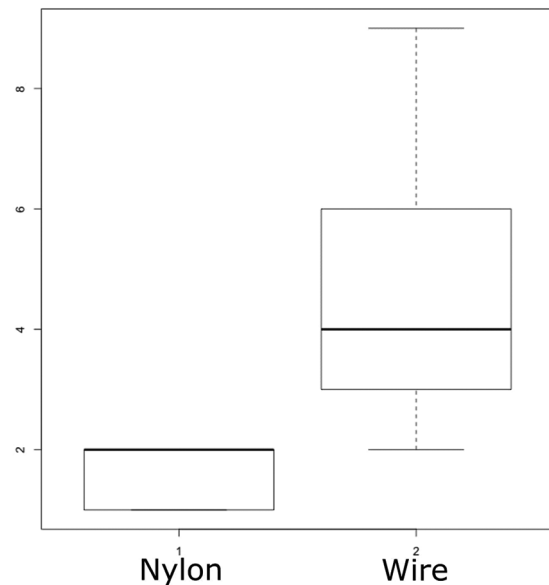
Figure 5. *The histogram representing difference in pain at the moment of removing the wire or nylon.*

present work performed a prospective randomized trial, comparing both therapeutical procedures, which is mandatory to reach such conclusions.

Consequently, we cannot suggest that Zhang's technique is superior to Ishiguro´s. Nevertheless, we can at least expose the advantages and disadvantages of both. Zhang´s advantages are that the volar pulp skin is under no pressure, and the bony fragment has constant reduction and compression. Its disadvantages are that it requires a dorsal surgical approach with skin scars and articular stiffness resulting in higher relative risk. Ishiguro´s, on the other hand, it is a simple technique with no surgical dissection, providing constant reduction and compression. On the other hand, no direct fragments visualization and imaging studies is mandatory during the procedure, potentially requiring multiple attempts.

Conclusions

We found no significant differences between nylon and wire cerclage. However, at the time of removing it, patients experience less pain. Furthermore, it

They concluded that this procedure is straightforward with better results than open surgical approach. The

appears to be easier to control nylon tension and is overall more available. Therefore, nylon appears to be a more appropriate substitute for wire fixation.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Atherectomy followed by drug-coated balloon angioplasty for below knee lesions in diabetic patients

Aterectomía seguida de angioplastia con balón recubierto de fármaco para lesiones debajo de la rodilla en pacientes diabéticos

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Abstract

Objective: *The aim of this study was to compare the long-term outcomes of below the knee revascularization with percutaneous atherectomy followed by drug-coated balloon and revascularization with drug-coated balloon alone for symptomatic diabetic patients with peripheral arterial disease.* **Patients and methods:** *Between April 2015 and January 2020, total of 128 patients and 228 below the knee procedures were enrolled into this retrospective study. Sixty-five patients were treated with atherectomy followed by drug-coated balloon and 63 patients were treated solely with drug-coated balloon.* **Results:** *Technical success rates were similar in the AT+DCB group and DCB group. Target lesion revascularization (TLR) was found similar in both groups at 6-month follow-up. Clinically, driven repeat endovascular and surgical limb revascularization rates were also significantly lower at 12 and 24 months.* **Conclusion:** *Combined usage of rotational atherectomy and drug-coated balloons for the treatment of diabetic patients with below-the knee arterial lesions and critical limb ischemia is associated with reduced long-term TLR rates and improved the long-term outcomes.*

Keywords: Atherectomy. Below the knee peripheral artery disease. Chronic limb-threatening ischemia.

Resumen

Objetivo: *El objetivo de este estudio fue comparar los resultados a largo plazo de la revascularización por debajo de la rodilla con aterectomía percutánea seguida de balón recubierto de fármaco y revascularización con balón recubierto de fármaco solo en pacientes diabéticos sintomáticos con arteriopatía periférica.* **Métodos:** *Entre abril de 2015 y enero de 2020, un total de 128 pacientes y 228 procedimientos por debajo de la rodilla se inscribieron en este estudio retrospectivo. Sesenta y cinco pacientes fueron tratados con aterectomía seguida de balón recubierto de fármaco y 63 pacientes fueron tratados únicamente con balón recubierto de fármaco.* **Resultados:** *Las tasas de éxito técnico fueron similares en el grupo AT+DCB y DCB. La revascularización de la lesión diana fue similar en ambos grupos a los 6 meses de seguimiento. Las tasas de revascularización endovascular y quirúrgica de las extremidades también fueron significativamente más bajas a los 12 y 24 meses.* **Conclusión:** *El uso combinado de aterectomía rotacional y balones recubiertos de fármaco para el tratamiento de pacientes diabéticos con lesiones arteriales por debajo de la rodilla e isquemia crítica de las extremidades se asocia con tasas reducidas de revascularización de la lesión diana a largo plazo y mejores resultados a largo plazo.*

Palabras clave: Aterectomía. Enfermedad arterial periférica debajo de la rodilla. Isquemia crónica que amenaza las extremidades.

Introduction

Infra-popliteal (or below-the-knee [BTK]) atherosclerosis is the most common cause of critical limb ischemia (CLI). The pathology is associated with increased morbidity, mortality, and amputation rates[1]. The mortality rates of patients with peripheral arterial disease (PAD), especially in the presence of CLI, are approximately 20% in 6 months and may be more than 50% within 5 years from the first diagnosis[2,3]. Endovascular interventions are more frequently preferred in the current era with respect to the low success rates of open surgical revascularization in the infra-popliteal lesions[1]. However, despite advances in endovascular procedures, the restenosis and revascularization necessities are still challenging[4,5].

Percutaneous transluminal angioplasty (PTA) alone is widely used for the treatment of infra-popliteal atherosclerosis. It may be performed with standard or drug-coated balloons. However, the long-term patency of the technique is suboptimal[6]. The calcification, which frequently persists in tibial arteries, limits the efficacy of PTA leading to vessel recoil, dissection, and increased target lesion revascularization (TLR)[7,8].

At present, there is no approved stent available for the treatment of infra-popliteal revascularization. On the other hand, atherectomy provides atherosclerotic plaque removal from the arterial wall and may be used as a sole therapy or applied in combination with balloon angioplasty[9].

The symptomatic PAD is seen in approximately 21% of the patients with diabetes mellitus[10]. The infra-popliteal lesions generally consist of heavy and circumferential calcifications. These characteristic features of the BTK lesions complicate revascularization and cause endovascular interventions to become more challenging[11]. Diabetes mellitus may lead to chronic kidney disease which in combination significantly increases incidence of PAD[12]. Percutanous transluminal angioplasty of complex and calcified lesions may result in the early recoiling and dissections in patients with diabetes mellitus and end-stage renal disease. Furthermore, the primary and secondary patency rates are lower in these cases and bailout stenting may be required in up to 50% of the cases[13].

Patients with CLI generally have transatlantic intersociety consensus D lesions, total occlusions, and/or advanced calcified lesions, and these lesions are not fully suitable for interventional therapies. Surgical treatment is superior to PTA (with or without stenting) in the presence of a suitable ipsilateral saphenous vein and an appropriate non-calcified artery[6]. However, the patients with CLI, especially those with infra-popliteal lesions, sometimes do not have an appropriate saphenous vein as a graft or a non-calcified bypass-able patent artery. Besides, these patients may have multiple comorbidities, that the open surgical treatment may have higher risk for the occurrence of major adverse events[6].

Preparation of the vessels before PTA in complex lesions increases the success rates of PTA. For instance, the increased lumen diameter before angioplasty could enable lesion crossing and provide higher long-term patency rates[13]. The atherectomy prepares vessels by debulking the plaque burden and requires lower pressures of PTA for revascularization; presenting decreased risk of intimal hyperplasia and dissection[14].

The aim of the present study was to compare the long-term results of rotational atherectomy followed by drug-coated balloon angioplasty (AT+DCB) with sole drug-coated angioplasty (DCB) for the treatment of infra-popliteal PAD in patients with diabetes mellitus.

Patients and methods

This retrospective study included 128 diabetic patients with symptomatic PAD patients secondary to infra-popliteal lesions who underwent endovascular interventions with drug-coated balloon alone or in combination with atherectomy between April 2015 and January 2020. Due to the retrospective nature of the study, the ethical approval was not required. The patients older than 18 years of age, who had severe claudication (Rutherford 3) or CLI (Rutherford 4-6) were investigated retrospectively if they had at least 70% stenosis in a lower extremity, confirmed by angiography. Patients with concomitant femoropopliteal disease and in-stent restenosis were excluded from the study. The 128 patients and a total of 218 BTK interventions were categorized into two groups according to use of rotational atherectomy followed by drug-coated balloon (AT+DCB) or drug-coated balloon (DCB) alone.

All of the patients had diabetes mellitus with the mean HbA1c levels of 8.9. Mean age of the patients were 66.4 ± 10.7 years and 67.1% (n = 86) of the patients were male. About 76.5% (n = 98) of patients consisted of past and current smokers. Hypertension and hyperlipidemia were the most frequently seen comorbidities in our cohort, found in 75.8% (n = 97) and 73.4% (n = 94),

respectively; followed by 71.1% (n = 91) of the patients with coronary artery disease. About 29.2% (n = 19) of patients had a history of myocardial infarction, while 32% (n = 41) of the patient population had coronary artery revascularization either percutaneously or with coronary artery bypass surgery. About 11.7% (n = 15) of the patients had prior amputations.

Percutaneous interventions were performed with standard techniques as femoral ante- and retrograde approach. Dual antiplatelet therapy including 300 mg aspirin and 300 mg or 600 mg clopidogrel were initiated in all patients before the procedures. Heparin (100 units/kg) was administered for periprocedural anticoagulation. Drug-coated balloon was applied with (Bio-Path™ 035 paclitaxel-eluting balloon dilatation catheter) balloon diameters of 80-90% of reference vessel with low pressure and 60 s inflation time. Additional inflations were not hesitated if necessary. Phoenix rotational atherectomy device (Volcano Corporation, San Diego, California) was utilized in this study. Distal protection systems were not used. The interventions with a result of postprocedural TIMI 3 flow, without dissection, and residual stenosis were defined as successful intervention.

The primary endpoints of this study were determined as primary patency rates, clinically driven repeat endovascular and surgical limb revascularization (CD-TLR). The change in ankle brachial index (ABI) and Rutherford classification at 1 and 2 years were also evaluated. The secondary endpoints included 1-year all-cause mortality, major and minor amputations, and peri-procedural complications such as perforation, dissection, and distal embolization.

All the patients were prescribed 40 mg/day atorvastatin and dual antiplatelet therapy with clopidogrel (75 mg) and acetylsalicylic acid (100 mg) once a day. Dual antiplatelet therapy was used to prevent the risk of acute or subacute thrombosis originating from the intima-media exposure of reticulocytes after atherectomy[15].

Statistical analysis

All the statistical analysis was performed with SPSS 18.0 software (Statistical Package for the Social Sciences Inc., Chicago, Ill, US). Data are expressed as mean ± SD for continuous variables and as counts for categorical variables. Categorical variables are presented as percentages. Comparisons of clinical, angiographic, and procedural characteristics were performed with the Fisher exact test for categorical variables and Mann–Whitney U-test for non-parametric continuous variables. Odds ratio and 95% confidence interval were calculated with univariate logistic regression. Variables with $p \leq 0.2$ in the univariate model or known to be significantly associated were entered into a multivariate logistic regression model. The target vessel revascularization, primary, and secondary patency rates during the follow-up were presented with Kaplan–Meier event-free survival curves. A value of $p < 0.05$ was described statistically significant.

Results

The features of patients and characteristics of the lesions are described in Table 1. A total of 228 BTK procedures were performed in 128 patients. The AT+DCB group consisted 50.7% (n = 65) of the interventions and 49.3% (n = 63) of the patients were treated only with DCB. Clinical characteristics of the patients were similar in both groups. An indication for the treatment of CLI was present in 74.2% (n = 95) of the patients.

The characteristics of the lesions such as the location and the morphology of the segments and the number of total chronic occlusions were similar in both groups. The pre-operative ABI and Rutherford classification data did not significantly differ between the two groups (p = 0.28). The mean lengths of the lesions were also similar (47.12 ± 24.03 mm in AT+DCB vs. 42.26 ± 26.5 mm in DCB, p = 0.47). Vessel calcifications (75.4% in AT+DCB vs. 69.1% in DCB) were comparable between two groups.

The location of the lesion was primarily the anterior tibial artery both in AT+DCB and DCB alone group (43.2%, n = 51 vs. 42.7%, n = 47). The mean time of inflation duration, length, and diameter of balloon angioplasty among two intervention groups were similar ([2.8±1.3 min vs. 3.1±1.5 min [p = 0.63], 3.2±0.9 mm vs. 3.4±1.1 mm [p = 0.33], and 12.3±8.2 cm vs. 11.9±6.7 cm (p = 0.47]). However, inflation pressures required for sufficient arterial patency were higher in DCB alone group (6.2±3.9 vs. 8.9±4.1 atmospheres [p = 0.001]).

Technical success rates were similar in the AT+DCB group (Fig. 1) and DCB alone group (98.4% vs. 96.8%, p = 0.228). The adverse events did not differ between two groups; however, bailout stenting was more common in the PTA alone group (DCB, 11.1% [n = 7] vs. AT+DCB, 1.5% [n = 1], p < 0.001) as a result of flow-limiting dissection. The periprocedural complications are presented in Table 2.

Table 1. Baseline characteristics and risk factors

Variables	Total (n = 128)	RA-DCB (n = 65)	DCB (n = 63)	p-value
Mean age, years	66.4 ± 10.7	68.6 ± 12.4	63.2 ± 11.3	0.528
Male, gender	67.1% (86/128)	67.6% (44/65)	67.8% (42/63)	0.423
Diabetes Mellitus	100% (128/128)	100% (65/65)	100% (63/63)	1.000
HbA1c (SD)	8.9 (1.6)	9.2 (1.3)	8.7 (1.8)	0.758
Hypertension	75.8% (97/128)	87.5% (48/65)	77.8% (49/63)	0.856
Hyperlipidemia	73.4% (94/128)	73.5% (49/65)	71.4% (45/63)	0.793
Smoking				
Current smoker	46.1% (59/128)	46.1% (30/65)	46.0% (29/63)	0.563
Past smoker	30.4% (39/128)	32.3% (21/65)	25.6% (18/63)	0.647
Never smoker	21.7% (30/128)	27.7% (18/65)	19.0% (12/63)	0.452
BMI (kg/m^2)	32.3 ± 6.7	32.7 ± 6.8	31.7 ± 6.4	0.482
CAD	71.1% (91/128)	78.5% (51/65)	63.4% (40/63)	0.453
History of stroke	10.1% (13/128)	12.3% (8/65)	7.9% (5/63)	0.352
History of MI	29.2% (19/128)	18.4% (12/65)	11.1% (9/63)	0.567
CHF	14.1% (18/128)	16.9% (11/65)	11.1% (7/63)	0.752
CABG or PCI	32.0% (41/128)	33.8% (22/65)	30.1% (19/63)	0.468
CRD	20.3% (26/128)	21.5% (14/65)	19% (12/63)	0.355
ESRD	21% (21/128)	20% (13/65)	12.6% (8/63)	0.582
COPD	28.2% (36/128)	32.3% (21/65)	23.8% (15/39)	0.498
Aspirin	94.45% (121/128)	95.3% (62/65)	93.6% (59/63)	0.454
Clopidogrel	96.1% (123/128)	96.9% (63/65)	95.2% (60/63)	0.328
Statin	85.9% (110/128)	83.1% (54/65)	88.8% (56/63)	0.256
Prior amputation	11.7% (15/128)	13.8% (9/65)	9.5% (6/63)	0.228

TLR at 6 months was not different in both groups (DCB, 6.3% [n = 4] vs. AT+DCB, 3.1% [n = 2], p = 0.224). However, it was more frequent in the DCB only group at 12 months follow-up (DCB, 17.4% [n = 11] vs. AT+DCB, 6.1% [n = 4], p = 0.001) and 24 months follow-up (DCB, 30.1% [n = 7] vs. AT+DCB, 10.7% [n = 7], p < 0.001) (Fig. 2). CD-TLR rate was detected significantly lower at 1 and 2 years with the use of AT+DCB when compared with DCB (6.1% vs. 17.4%; p < 0.001) in Kaplan-Meier analysis. The rate of CD-TLR decreased by 64% at 1 year and 65% in 2 years with AT+DCB when compared with DCB only group in the adjusted Cox proportional hazard model (HR 0.23, 95% CI 0.32-0.78; p < 0.01; HR 0.23, 95% CI 0.27-0.76; p < 0.01). The values are presented in Figure 2.

The minor amputation rates at 6-12- and 24-months follow-ups were lower in AT+DCB compared to DCB
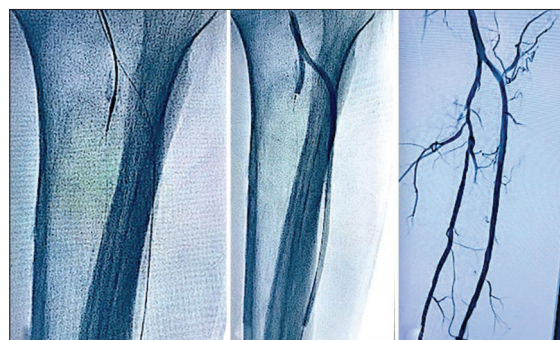
Figure 1. *Atherectomy followed by drug-coated balloon angioplasty.*

only group (3.1%, n = 2 vs. 9.5%, n = 6, p = 0.08; 6.1%, n = 4 vs. 12.6%, n = 8, p = 0.07; 7.6%, n = 5 vs. 15.8%, n = 10, p = 0.58), while the major amputation rates were similar between groups. At 6 months follow-up,

Table 2. Peri-procedural complications

Complication	RA + DCB	DCB only	p-value
Distal embolism (clinically significant)	1.5% (1/65)	9.5% (6/63)	0.05
Dissection-grade C/D or greater	1.5% (1/65)	11.1% (7/63)	< 0.001
Vessel recoil	1.5% (1/65)	4.7% (3/63)	< 0.001
Arterial perforation	1.5% (1/65)	3.1% (2/63)	0.638
Arteriovenous fistula	0	1.6% (1/63)	0.623
Pseudoaneursysm	0	0	1.000
Hematoma	3% (2/65)	3.1% (2/63)	0.476
Total number of events	5	18	< 0.001

Figure 2. *Target lesion revascularization.*
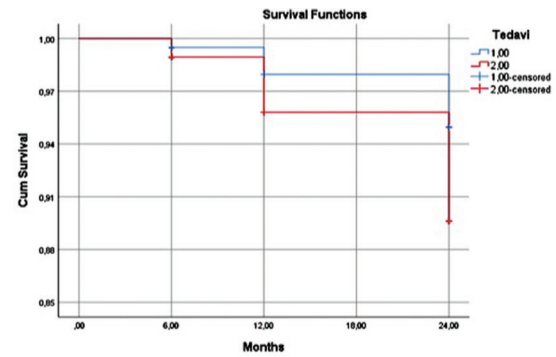
Figure 3. *Major amputation-free survival.*

there were two patients (3.1%) with below the knee + Syme amputations in DCB group and one patient (1.5%) with Syme amputation in RA+DCB (p = 0.57). At 12-month follow-up, three patients (4.7%) treated with DCB alone had above the knee amputation and two of the patients (3.1%) in AT+DCB group had Syme amputations (p = 0.64). At 24-month follow-up, four patients (6.3%) in DCB only group and two patients (3.1%) in AT+DCB group required below the knee amputations (p = 0.58) (Fig. 2). The all-cause mortality rates at 6, 12, and 24 months were also similar (Fig. 3). At 6-month follow-up, two patients (3.1%) in DCB alone group and one patient in (1.5%) AT+DCB group; at 12 months follow-up, three patients (4.7%) in DCB alone group and two patients (3.1%) in AT+DCB group; and at 24 months follow-up, four patients (6.3%) in DCB alone and two patients (3.1%) in AT+DCB group were deceased (p = 0.25; p = 0.23; p = 0.44). Finally, distal embolization rates were significantly lower in the AT+DCB group when compared with DCB only group (1.5%, n = 1 vs. 9.5%; n = 6, p = 0.05). The amputation free survival and all-cause mortality are presented in Figures 3 and 4.

Figure 4. *All-cause mortality-free survival.*

Discussion

Patients with diabetes mellitus often experience atherosclerotic peripheral arterial lesions in the course of the disease. Advanced infra-popliteal atherosclerosis is associated with severe lower extremity ischemia[16]. The comorbidities such as older age, diabetes mellitus, and end-stage renal disease are associated with high risk of complex and highly calcified lesions which increase the risk of amputation and mortality. Even at a rate as high as 67% amputation is performed as an initial therapy without diagnostic angiography or further vascular interventions in this particular patient population with CLI[17].

Atherectomy has been shown to be a useful adjunctive therapy in the long term, especially in the long and calcified lesions. While directional atherectomy

devices are generally used in short or chronic totally occluded lesions, rotational atherectomy devices are more effective in long, highly calcified lesions. The improved luminal gain and decreased requirement for stenting are the main advantages of atherectomy when compared with PTA. These advantages allow inflation of the balloon at lower pressures providing lower dissection rates[18-20].

Atherectomy provides a reduction in plaque burden and facilitates PTA. Such an advantage has proven superior to PTA alone treatment in patients with CLI due to complex infra-popliteal diseases[21]. The patency rates and patient outcomes have been improved parallelly with increased clinical experience for the use of atherectomy as an alternative or additive technique for the treatment of PAD[22].

According to the randomized trial in 2005, amputation-free survival at 6 months was similar between the infra-inguinal saphenous vein bypass and PTA at the above-knee or below-knee segments (BASIL). Since then, endovascular interventions decreased morbidity, lowered the costs, and provided sufficient quality of life outcomes for the patients equal to the surgery[23].

The DEBATE-BTK trial included 132 diabetic patients with CLI. The study compared drug-eluting balloon (In. Pact Amphirion, Medtronic Cardiovascular) and PTA in 158 infra-popliteal lesions. The mean length of lesion was 129 ± 83 mm and this was longer than other randomized trials with drug-eluting stents for the treatment of the infra-popliteal lesions. The restenosis rate and target vessel occlusion were higher in PTA group at 1 year, and major adverse events were less often in the drug-eluting balloon group. However, amputation, limb salvage, and mortality rates were similar between the two groups[24].

In another study, the results of atherectomy were compared on patients with diabetes mellitus and non-diabetic patients with PAD. The TLR, amputation, or death rates were not significantly different between the groups. In addition, there was no statistically significant difference in the time to TLR, amputation or death in Kaplan–Mayer analysis in this particular research[25].

Stavroulakis et al.[25] compared drug-coated balloon angioplasty with directional atherectomy with anti-restenotic therapy in popliteal artery lesions. The freedom from TLR was similar between two groups (82% vs. 94%, p = 0.072), while the primary patency rates were found significantly higher in the DAART group (p = 0.021) at 12-month follow-up. Secondary patency rates were similar (96% vs. 96%) between two groups at 12 months. Bailout stenting was more often following DCB angioplasty (p = 0.13) and aneurysmal degeneration was more common after DAART (p = 0.25)[26].

In another recent meta-analysis, there was no significant benefit associated with single use of atherectomy compared to balloon angioplasty[27]. Atherectomy was typically used for highly calcified lesions that were challenging for stent or balloon expansion, or in the regions that are risky for stent fracture (common femoral and popliteal arteries). Despite more often occurrence of distal embolization in the registry data, it was found lower in the contemporary non-randomized DEFINITIVE-LE study[28]. Literature lacks information about the use of distal protection for atherectomy; however, it is generally applied in the existence of poor or single-vessel distal run-off[29].

Severity of illness, amputation level, gender, and comorbidities may influence the amputation rates. The amputation rates were higher in male and diabetic patients in the reported analysis and the procedure types (DCB or PTA alone vs. atherectomy-PTA or atherectomy-DCB) were not found superior to one another in terms of amputation rates in the multivariate analysis[30]. Among the included studies, all-cause mortality rates did not differ between both groups at 12 and 24 months. The patients with more advanced diseases had higher mortality rates[22,31].

In our study, although the major amputation rates were similar between two groups, minor amputation rates were lower in the AT+DCB group. CD-TLR rate was significantly lower in AT+DCB group and the rate of CD-TLR was decreased by 64% at 1-year and 65% at 2-year with AT+DCB when compared with DCB alone, in the adjusted Cox proportional hazard model. The all-cause mortality rates and adverse events did not differ significantly between two groups; however, bailout stenting and distal embolization rates were lower in AT+DCB group.

Conclusion

Combined usage of rotational atherectomy and drug-coated balloons reduce the long-term TLR rates and improve the long-term outcomes, especially in diabetic patients with heavily calcified below-the knee lesions and CLI.

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Conflicts of interest

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Gastric cancer: histological response of tumor and metastatic lymph nodes for perioperative chemotherapy

Cáncer gástrico: respuesta histológica del tumor y los ganglios linfáticos metastásicos para la quimioterapia perioperatoria

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Abstract

Background: *Gastric cancer is the fourth cancer most common in the world and the second cause of cancer-related deaths. Perioperative chemotherapy may reduce tumor burden and decrease lymph node invasion, improving R0 resections rates. On the other hand, administered before surgery, chemotherapy may cause fibrosis and tissue edema, with potential increase of surgical difficulty and in the number of post-operative complications. Therefore, we aim to investigate the effect of perioperative chemotherapy for tumor burden and metastatic lymph nodes of gastric cancer.* **Methods:** *Retrospective analysis of all patients submitted to perioperative chemotherapy and surgery, between January 2010 and June 2020, which showed lymph node regression and tumor regression (Becker's classification).* **Results:** *A total of 112 patients with an average age of 61.9 years were analyzed. About 90.2% completed three cycles of perioperative chemotherapy. Good tumor response to chemotherapy (<10% residual tumor) was achieved in 21.3% of patients. Only three patients obtained a complete pathological response. A median lymph node response of 33.3% was achieved in our series.* **Conclusion:** *Despite no evident outstanding regression rate was observed, perioperative chemotherapy seems to be useful in obtaining a R0 resection in gastric cancer, even in advanced gastric cancer.*

Keywords: Gastric cancer. Histological response. Perioperative chemotherapy.

Resumen

Introducción: *El cáncer de estómago es el cuarto tipo de cáncer más común y la segunda causa de muerte relacionada con el cáncer. La quimioterapia perioperatoria puede reducir la carga tumoral y disminuir la invasión de los ganglios linfáticos. Por otro lado, administrada antes de la cirugía, la quimioterapia puede causar fibrosis y edema tisular, aumentando potencialmente la dificultad quirúrgica y el número de complicaciones posoperatorias. Nuestro objetivo es investigar el efecto de la quimioterapia perioperatoria sobre la carga tumoral y los ganglios metastásicos en el cáncer gástrico.* **Métodos:** *Análisis retrospectivo de todos los pacientes sometidos a quimioterapia y cirugía, entre enero de 2010 y junio de 2020.* **Resultados:** *Se analizaron 112 pacientes con una edad media de 61.9 años. El 90.2% completó 3 ciclos de quimioterapia perioperatoria. Se logró una buena respuesta tumoral a la quimioterapia (< 10% de tumor residual) en el 21.3% de los pacientes. Tres pacientes lograron una respuesta patológica completa. En nuestra serie se logró una mediana de respuesta de los ganglios linfáticos del 33.3%.* **Conclusión:** *Aunque no se observó una tasa de regresión manifiesta, la quimioterapia perioperatoria parece ser útil para lograr una resección R0 en el cáncer gástrico, incluso en el cáncer gástrico avanzado.*

Palabras clave: Cáncer gástrico. Respuesta histológica. Quimioterapia perioperatoria.

Introduction

Gastric cancer is the fourth most prevalent cancer worldwide[1], right after lung, breast and colorectal cancers; and the second leading cause of cancer-related deaths[2]. Despite a major decline observed in incidence and mortality over the past several decades[2], mortality remains considerably high even after surgery, which is the only curative therapy for gastric cancer[3]. In 2006 Cunningham et al. demonstrated that perioperative chemotherapy improves overall and progression-free survival when compared to surgery alone[4-6]. Historically, most gastric cancers are diagnosed at locally advanced stages; therefore. standard treatment was no longer unimodal (surgery-based), but the use of perioperative chemotherapy regimens was implemented[7-9]. This combined therapy has shown benefits on curative resection rates, disease-free survival, and overall survival[7,10]. Different studies examined the use of perioperative chemotherapy. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[11] showed that the 5-year survival for patients randomized to perioperative epirubicin, cisplatin, and fluorouracil (ECF), was significantly improved compared to those undergoing surgery alone[12]. Even though perioperative chemotherapy may reduce tumor burden, eradicate possible lymph node metastasis[10,13] and improve R0 resection rates[4,13], case series demonstrated that it may cause fibrosis and tissue edema, leading to more complicated surgical procedures and higher post-surgical morbidity[4]. In contrast, a meta-analysis[14] found no significant difference in perioperative or postoperative complication rates between a group of patients submitted to preoperative chemotherapy and surgery versus to surgery alone. Schuhmacher et al.[15] challenges the contribution of perioperative chemotherapy in a patient with a more extensive lymphadenectomy[16].

In the literature, it is widely accepted that gastric adenocarcinoma with signet ring cells is less responsive to chemotherapy when compared to intestinal gastric cancer type[17,18]. However, Rougier et al.[19] and Lemoine et al.[17] found no differences in survival in signet ring cell adenocarcinoma, despite a lower response rate to chemotherapy. This difference may be explained by a higher peritoneal involvement, with requirement of higher concentrations of chemotherapy[17]. Therefore, signet cells gastric adenocarcinoma patients seem to benefit less from perioperative

chemotherapy, raising the need to consider and evaluate drugs with better response in intraperitoneal disease or drugs with higher peritoneal cavity penetration. Zurlo et al. suggest that the intestinal histotype might have a better response to a perioperative regime when compared to diffuse type to whom an adjuvant chemotherapy approach might ensure better survival[20].

In this study, we aimed to investigate the rate of histological tumor regression and metastatic lymph nodes response to perioperative chemotherapy in gastric cancer patients and factors associated with this response.

Material and methods

Retrospective, transversal, and observational study of consecutive patients diagnosed with gastric cancer who underwent perioperative chemotherapy followed by gastrectomy, between January of 2010 and June of 2020. Exclusion criteria included: age under 18 years and insufficient clinical data. A total of 112 patients were included. Socio-demographical characteristics (age, gender, and BMI), pre-operative clinical information, treatment, and outcomes were obtained from the hospital database.

Chemotherapy regimen was chosen by the Oncologist, after discussion of every case on MDT meeting, and included mainly regimes such as EOX (IV administration of 50 mg/m^2 epirubicin and 130 mg/m^2 oxaliplatin on day 1, and 625 mg/m^2 capecitabine *per os* twice a day on days 1-14, this regimen was repeated every 21 days), Folfox (IV administration of 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin and IV push administration of 400 mg/m^2 fluorouracil, and 2400 mg/m^2 fluorouracil IV continuous infusion for 46 h, this regimen was repeated every 14 days), FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 100 mg/m^2, and 5-fluorouracil 2600 mg/m^2 as a 24 h infusion, all given on day 1 and administered every 2 weeks) and mDCF (docetaxel 40 mg/m^2, cisplatin 40 mg/m^2, and IV push administration of 400 mg/m^2 fluorouracil, and 2000 mg/m^2 fluorouracil IV continuous infusion for 46 h, administered every 21 days). Options for surgical resection included subtotal and total gastrectomy.

Histopathological tumor regression was evaluated in the 112 surgical resection specimens, based on estimation of residual tumor tissue percentage at the primary tumor site in comparison to the identifiable former tumor bed, according to the Becker's criteria[21]. Tumor bed was identified by flattening/ulceration of

the mucosa, fibrosis, necrosis, and presence of macrophages. Regression was graded into the following categories: G1a (no residual tumor cells); G1b (< 10% residual tumor cells); G2 (10-50% residual tumor cells); and G3 (> 50% residual tumor cells). Lymph nodes without any signs of metastatic involvement were regarded to be tumor free. Fibrosis and xanthomatous macrophages were considered regression changes in lymph nodes.

Statistical analysis was performed using SPSS 26.0®. All continuous variables were assessed for normality and described accordingly. For comparative analysis, parametric and non-parametric tests were used when needed. $p < 0.05$ was considered statistically significant.

Results

A total of 112 patients, 58% males, with a mean age (SD) of 61.9 (10.1) y.o., were included in our study. Clinico-pathological features are described on table 1. Accounting for 56.5% of cases, antrum was the most common anatomic location of the tumor.

The majority (90.2%) completed at least three cycles, with a 56,5-day median duration. While intestinal type neoplasm was the most observed histological type, with 43.6% of cases.

Good tumor response to chemotherapy (< 10% residual tumor) was achieved in 21.3% of patients, but in 50.9% only regression of < 50% could be obtained – table 2 (n = 108, four cases omitted due to lack of information in the histological report). Age, gender, and patient's BMI presented no statistical association with the tumor response. Furthermore, neither tumor location nor chemotherapy regime or duration showed significant difference in tumor response to chemotherapy.

Regarding lymph node response, 11 patients achieved complete regression, while 28 patients presented no lymph node response at all – table 2 (n = 85, due to lack of information in the clinical process). Median lymph node response was 33.3%. As with the age, gender, BMI, and chemotherapy regime and duration did not present any statistical association with lymph node response to chemotherapy.

A total of 3222 lymph nodes were removed (median of 26.5 lymph nodes per patient, min = 6, max = 72). In G1a staging patients, (n = 3), 88 nodes were removed, none of which with metastatic involvement, 10 lymph nodes with complete response to chemotherapy (LNR 100%). In G1b patients (n = 20), 459

nodes were removed, 56 of which with metastatic involvement, 57 presented a good response to chemotherapy. In G2 staging patients (n = 30), 808 nodes were removed, 186 with metastatic involvement, and only 121 responded to chemotherapy. In G3 staging patients (n = 55), 1743 nodes were resected, 445 with metastatic involvement, and only 131 responded to chemotherapy.

Lymph node regression was higher among patients with better tumoral response to chemotherapy with G1b patients presenting 63.57% median lymph node regression while G2 and G3 presented significantly lower response rates, 33.92% and 30.78%, respectively ($p = 0.009$) (Table 3). A significant negative correlation

Table 1. Sample descriptive statistics (n = 112)

Demographic and tumor data	n
Age, mean (SD)	61.9 (10.1)
BMI, mean (SD)	25 (4.99)
Gender, n (%)	
Male	65 (58)
Female	47 (42)
Chemotherapy duration (median days, P5-P95)	56.5 (24.7-127.5)
Chemotherapy regime, n (%)	
EOX (Epirubicin, oxaliplatin, capecitabine) EOX (Epirubicin, oxaliplatin, capecitabine)	47 (42.3)
FOLFOX (Folinic acid, 5-FU, oxaliplatin)	8 (7.1)
mDCF (Docetaxel, levofolinate, 5-FU, cisplatin)	20 (17.9)
FLOT (5-FU, folinic acid, oxaliplatin, and docetaxel)	29 (25.9)
Other	8 (7.1)
Anatomic location (%)	
Antrum	56.5
Body	35.2
Fundus	8.3
Lauren classification (%)	
Intestinal type	43.6
Diffuse type	15.4
Unclassified	41
Operative procedure, n (%)	
Distal gastrectomy	47 (42)
Total gastrectomy	65 (58)
Pre-therapeutic staging	
cStage II	52 (46.4)
cStage III	50 (44.6)
cStage IV	10 (9)
Post-therapeutic staging	
ypStage 0 (complete response)	3 (2.7)
ypStage I	19 (17)
ypStage II	33 (29.5)
ypStage III	39 (34.8)
ypaStage IV	18 (16)

SD: standard deviation, BMI: body mass index

Table 2. Tumoral and lymph node regression

Tumor and lymphatic regression	n (%)
Becker - Tumoral regression*	
G1a	3 (2.7)
G1b	20 (18.6)
G2	30 (27.8)
G3	55 (50.9)
Lymph node regression**	
Complete regression	11 (12.9)
Parcial regression	46 (54.1)
Stable disease	28 (32.9)

*n = 108, **n = 85

Table 3. Comparison between tumoral regression and lymph node regression

Becker (tumoral regression)	Lymph node regression (%)	p
G1a	100	0.009
G1b	63.57	
G2	33.92	
G3	30.78	

was found between lymph node regression and post-chemotherapy histological stage (p < 0.001).

As for signet ring cell tumors (n = 37), 363 (33.2%) lymph nodes presented metastatic involvement of a total of 1093 lymph nodes resected, but only 156 (14.3%) of them shows signals of regression. Regarding intestinal type, there were 81 (6.5%) metastatic lymph nodes of 1239 resected, having 87 (7.0%) of these regressed. Curiously, signet ring cell tumors seem to have significantly higher lymph node regression (p = 0.041). Still, no significant differences were found between different chemotherapy schemes and the rate of tumoral and lymph node regression.

Although the follow-up time of 19 patients is < 1 year, we can say that there is a positive correlation between lymph node regression and survival length (p = 0.018).

Discussion

There is no consensus on most appropriate approach to the management of localized gastric adenocarcinoma. Gastrectomy with D2 lymphadenectomy has been generally regarded as the standard treatment for achieving cure[22]. An D2 lymphadenectomy is recommended in all patients with a resectable gastric tumor, as we know this procedure is associated with lower locoregional recurrence[13]. Recently, perioperative chemotherapy has gained an increasingly important role in the treatment of advanced gastric cancer, by contributing to reduce tumor burden and decrease lymph node invasion. However, there are not enough studies about the effects in metastatic lymph nodes or if it is possible to limit lymph node resection in patients submitted to chemotherapy preoperatively.

In spite of only three cases resulting in complete histological tumoral regression and eleven in total regression in metastatic lymph nodes, we noticed a correlation between chemotherapy response in lymph nodes invaded and primary tumor. Spiegel et al.[12] suggested that neoadjuvant chemotherapy, besides disease downstaging before attempted surgical resection, also allows selection of patients for surgery based on disease biology. This means that those who did not present disease progression during perioperative period will be better candidates for surgery, whereas those who do develop overt metastasis can be spared the morbidity of surgery. Thus, perioperative chemotherapy should be considered as a selection method for surgery, enabling better outcomes of both R0 resection rate and disease-free survival time. As opposed to our results, Kinoshita et al. showed that even metastatic lymph nodes clinically exhibiting favorable response to chemotherapy also presented an unsatisfactory histological response[13]. As of these incongruous results, a D2 lymphadenectomy should be performed even in patients with a good objective response of the primary tumor and metastatic lymph nodes[6].

As signet ring cells tumors show worse prognosis and response to chemotherapy, it is emphasized the importance of early diagnosis and treatment and more effective agent and chemotherapy administration routes should also be further considered and evaluated. Interestingly and contrary what was reported by Lemoine et al.[17], we have concluded that patients with gastric cancer with signet ring cells seemed to have a slight better lymph node regression with chemotherapy when compared with intestinal type, perhaps due to the use of more aggressive and more prolonged schemes. Perioperative chemotherapy was found to be an independent predictor of poor survival and it was suggested that neoadjuvant treatment toxicity was correlated with worse outcome[23,24]. On the other hand, whereas signet ring cells gastric adenocarcinoma is thought to be less chemosensitive than intestinal type, recent reports suggest it could have a

specific sensitivity profile and be more sensitive to taxane-based chemotherapy or antiangiogenics[24]. However, this has yet to be confirmed in a specific prospective trial.

In our sample, survival is correlated with metastatic regression of the lymph nodes in response to perioperative chemotherapy. Lymph node dissection is an important part of the surgical treatment of advanced gastric cancer due to the high incidence of lymph node metastasis. The appropriate lymphadenectomy associated with ganglion regression, may be the reason why perioperative chemotherapy in gastric cancer plays a role in increasing the survival of patients with advanced gastric cancer, allowing the reduction of lymph nodes metastases, more important than the reduction of tumor mass.

Notably, this was a retrospective study, based on a limited number of patients, not all patients completed the perioperative treatment and we included cases with advanced disease.

Conclusion

While this study did not present an outstanding lymph node regression rate, an important decrease in tumor burden (we observed a pathological complete response in three cases) and number of invaded lymph nodes was observed. In addition, we found a correlation between lymph node regression and tumor regression. Nonetheless, for now we must not neglect that an adequate tumor resection and D2 lymphadenectomy must always be performed to obtain R0 resections. Further prospective studies should be carried out to evaluate the effect of perioperative chemotherapy on survival and to compare the combined effect with lymphadenectomy in both early and advanced stages of gastric cancer. Maybe in the future, we can consider the hypothesis of a conservative approach in cases with the evidence of clinic complete regression after adequate chemotherapy regimens.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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ORIGINAL ARTICLE

Clinical prediction rules in acute appendicitis: which combination of variables is more effective at predicting?

Escalas de predicción diagnóstica en la apendicitis aguda: que combinación de variables es más eficiente?

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Abstract

Background: Clinical prediction rules have been designed to reduce variability and improve the diagnostic process. However, there are no unanimous criteria regarding which of them is the most efficient for the diagnosis of acute appendicitis. **Aim:** The primary aim of this study was to assess the diagnostic efficacy of the most commonly used clinical prediction rules. The second aim was to identify the combination of the smallest number of clinical and analytical variables that would allow a cost-effective diagnostic approach. **Methods:** A retrospective observational study was conducted of 458 patients who were evaluated for right iliac fossa pain between January 2010 and December 2016. The scores tested were Alvarado, AIR, RIPASA, and AAS. Univariate and multiple regressions were used for validation. **Results:** Alvarado one was the most efficient to establish a positive diagnosis of acute appendicitis. However, the most simplified and predictive combination variables included anorexia, white blood cell count > 8275 leukocytes/μL, neutrophilia (> 75%), abdominal pain < 48 h, migrating pain, and temperature out the range of 37-39ºC. **Conclusions:** A new and effective CPR (HMC score) for predicting appendicitis in patients presenting with the right iliac fossa pain has been established.

Keywords: Acute appendicitis. Appendicitis diagnosis score. Laparoscopic appendectomy. Clinical prediction rules.

Resumen

Introducción: Las escalas de predicción diagnóstica (EPD) se han diseñado con el objetivo de reducir la variabilidad y mejorar el proceso de diagnóstico. Sin embargo, no existen criterios unánimes sobre cuál de ellas es la más el más eficiente para el diagnóstico de apendicitis aguda. **Objetivo:** El objetivo principal de este estudio fue evaluar la eficacia diagnóstica de las escalas de predicción diagnóstica más utilizadas. El segundo objetivo fue identificar la combinación del menor número de variables clínicas y analíticas que permitieran un enfoque diagnóstico más eficiente. **Métodos:** Se realizó un estudio observacional retrospectivo de 458 pacientes que fueron evaluados por dolor en la fosa ilíaca derecha entre enero de 2010 y diciembre de 2016. Las escalas evaluadas fueron las de Alvarado, AIR, RIPASA y AAS. Se utilizaron la regresion univariada y la múltiple para la validación de los resultados. **Resultados:** la escala de Alvarado fue la más eficiente para establecer un diagnóstico de apendicitis aguda. No obstante, la combinación de las siguientes variables: anorexia, recuento de leucocitos > 8275 leucocitos/μL, neutrofilia (> 75%), dolor abdominal < 48 horas, dolor migratorio y temperatura fuera del rango de 37-39ºC, demostró ser la más eficiente para establecer un diagnóstico positivo de apendicitis aguda. **Conclusiones:** Se ha

desarrollada una nueva EPD (escala HMDC) para determinar la presencia de apendicitis en pacientes evaluados por dolor en la fosa ilíaca derecha.

Palabras clave: Apendicitis aguda. Escalas de predicción diagnósticas. Apendicectomía laparoscópica.

Introduction

Acute appendicitis (AA) is one of the most common surgical pathologies in emergence departments, with a lifetime risk between 7% and 9%[1-3]. It is more frequent between children and young adults. Its incidence seems to be conditioned by different factors such as sex, age, ethnicity, and the season of the year[2,4]. However, most of the patients who present with acute right iliac fossa pain (RIFP) do not have appendicitis. The differential diagnosis can be difficult and remains a clinical challenge[3].

Traditionally considered as a progressive disease whose natural evolution is toward perforation, early diagnosis and treatment are necessary to reduce morbidity and mortality[5,6], and surgery is the gold standard of treatment[7,8]. The etiology and pathogenesis of AA remain poorly understood and predicting its evolution towards a mild or complicated form of the disease is difficult. However, recent studies suggest that with a logistic regression model, this could be predicted[6]. At present, two types of appendicitis are thought to exist: uncomplicated (non-perforating) and complicated (perforating) appendicitis[6]. Regardless of its presentation, the concept of early diagnosis and treatment remains in force[8-11].

Diagnosis is based on the clinical assessment, and laboratory and imaging tests[12].

Ultrasonography (US), abdominal computed tomography (CT), and magnetic resonance imaging (MRI) are most commonly used to reduce the negative appendectomy rate, which has been reported to be as high as 15%[13].

US is noninvasive, not expose to ionizing radiation and is associated with a sensitivity rate between 71% and 94% and a specificity rate between 81% and 98%[14,15]. It is efficient to confirm the presence of appendicitis, but not to exclude the presence of it, being also operator dependent[3]. The lack of conclusive findings, either due to non-visualization of the appendix or due to specific technical difficulties (obese or obstetric patients), makes necessary to implement second-line imaging studies. Abdominal CT for suspected appendicitis has sensitivity and specificity rates between 76% and 100% and 83-100%, respectively[15,16]. However, the radiation exposure is a concern, particularly in children and pregnant women[16]. In these cases, MRI is another option[5].

There is an evident lack of uniformity between the different guidelines regarding diagnosing and managing AA[7]. In an attempt to standardize the diagnostic approach to this pathology, clinical prediction rules (CPRs) have been introduced, seeking to provide a more objective approach to diagnosing RIFP and avoiding unnecessary operations[12,17].

Both clinical and biochemical variables have been used in CPRs to increase the value of individual variables. Since the initial proposal of Alvarado[18], there are currently approximately 12 CPRs available for AA diagnosis[12].

The most tested one is the Alvarado score, introduced in 1986[8]. This score has proven to be very efficient at "ruling-out" appendicitis with an overall sensitivity and specificity of 96% and 81%, respectively[17]. However, of the eight variables used in the initial scale of Alvarado, new variables and weightings have been added to the successive scales developed, leading to a progressive complexity of CPRs and, therefore, making their use less efficient[12].

Despite that, the use of these scores seems to be useful to determine the low, medium, or high likelihood of AA. Furthermore, they allow identifying the cases in which image methods must be implemented[14]. The systematic clinical evaluation of patients with RIFP can be done efficiently with the use of CPR, but the simplification of these tools can make them more useful and easier to apply.

The aim of this study was to validate the effectiveness of the currently available CPRs in performing a correct diagnosis and to develop a new simplified and efficient scoring system.

Methods

A retrospective observational study was conducted. The clinical records of 458 patients who were evaluated for suspected AA from January 2010 to December 2016 were reviewed. All patients underwent surgery using an open (25) or a laparoscopic (433) approach. Before surgery, informed consent was obtained from all subjects or legal guardian.

Diagnostic confirmation was obtained through the anatomopathological report, which indicated AA by the presence of inflammatory cells (leukocytes, lymphocytes, or plasma cells) in the surgical specimen or indicated negative appendectomy (NA) in the absence of these cells[19].

The information collected included demographic and personal data, clinical features, and analytical data at admission, as well as interventional reports, and post-operative outcomes. With this information, the Alvarado, Raja isteri pengiran anak saleha appendicitis (RIPASA), appendicitis inflammatory response (AIR), and adult appendicitis score (AAS) scores were established for the selected patients.

The data obtained were entered into an anonymized database created in Microsoft Excel (Microsoft Corporation. Redmond, WA 98052. USA) and were analyzed using IBM SPSS Statistics version 20.0 (IBM Corporation Armonk, New York 10504. USA). In the descriptive analysis, the quantitative variables are reported as the median and the interquartile range (IQR). The qualitative variables are reported as frequencies and percentages of the total number of patients (N, %). Associations between the qualitative variables were analyzed by the Pearson Chi-square (χ^2) test. Comparisons of the quantitative values were carried out using the nonparametric Mann–Whitney U test. To determine the diagnostic efficiency of these scales, an analysis was performed using receiver operating characteristic (ROC) curves, with a calculation of the area under the curve (AUC) for each scale. Then, the scores were stratified according to a low, medium, or high probability of presenting AA according to established literature guidelines the Alvarado[17,18], RIPASA[20], AIR[21], and AAS[22] scales.

To elaborate a new score Hospital Medina del Campo score (HMC score), a univariate logistic regression was performed for each variable incluidas en los items de las escalas. In addition, the white blood cell count (WBCC) was categorized to establish a cut-off point. A univariate binary logistic regression was performed with each decile of leukocytes, being considered significant if p < 0.05. The lowets data who fullfilled the condition was considered the cut-off point since it included a greater number of patients. With this aim, the variables with p < 0.1 in the univariate analysis were included in a multivariate logistic regression analysis using "the enter method" and "the Wald method."

With those variables that reached statistical value a new AA diagnostic probability scale was designed,

Table 1. Multivariate logistic regession

Variable	Coefficient β	Score	p
Anorexia	0.825	8	0.039
WBCC ≥ 8.275	1.640	16	0.001
NTF > 75%	1.157	12	0.002
Pain migration to RIF	0.861	9	0.021
Pain evolution < 48 h	0.745	7	0.028
T - > 37°C, < 39°C	−0.873	−9	0.013

Wald method for calculating the HMC score. NTF: Neutrophilia, RIF: Right iliac fossa, T: temperature, WBCC: white blood cell count, HMC: Hospital Medina del Campo

calculating its Area Under the Curve. To score this new scale, whole number was calculated from the coefficient B of the Wald method, multiplying it by 10 and eliminating the decimals (Table 1).

This is a retrospective study which involved using data from clinical records. To guarantee the adequate treatment of the information and its confidentiality, the data were treated confidentially and anonymously according to the provisions of Spanish Organic Law 15/1999 of December 13 of the Personal Data Protection (LOPD). All methods were performed in accordance with the guidelines and regulations established by the Declaration of Helsinki (1964/Revised in 1983) on biomedical research in humans and Spanish Royal Decree 1090/2015, of December 4, which regulates clinical trials with drugs, the Research Ethics Committees with drugs and the Spanish Registry of Clinical Studies.

Ethical approval through the Clinical Trials and Ethics Committee of Valladolid University was granted in January 2017.

Results

We analyzed 458 patients who fulfilled the inclusion criteria: abdominal pain with suspected AA and underwent an appendectomy. Of these, 404 (88.2%) patients had a histological confirmation of appendicitis, and 54 (11.8%) had a normal appendix. In 36 patients, the intraoperative appearance of the appendix was considered normal; however, in ten of these patients (27.8%), the histological report confirmed the presence of AA. The median age of all patients was 31 years (IQR: 18.0-48.0 years). In the distribution by sex, a male predominance was observed (266 patients: 58.1%), and 60.9% of the patients with histologically confirmed appendicitis were males (p < 0.001). US

was performed in all cases and was suggestive of AA in 260 (60%) patients, including 243 patients with histological confirmation of AA (sensitivity 63.8% and specificity 67.3%).

The scales under investigation were applied to all patients in our cohort, and all scales showed statistically significant results in terms of predictive ability and diagnostic performance (Table 2).

The AUC of each CPR based on the probability of AA diagnosis is shown in table 3, and the ROC curves are shown in figure 1.

Of the 4 CPRs, the Alvarado score presented the most accurate diagnosis when the scores were high, assigning a high probability of AA to 206 patients, with diagnostic confirmation of 96.6%. In addition, the Alvarado score places fewer patients in the intermediate probability of having AA (37,6%). In the low probability group, the AAS score was the most efficient, with 81.91% confirmed cases of AA.

On the other hand, the multivariate analysis identified the following variables as independent factors of confirmed diagnosis of AA: anorexia (increased the risk by 2.28 times [p = 0.039]), WBCC $\geq$ 8.275 leukocytes/μL (increased the risk by 5.16 times [p < 0.001]), neutrophilia (NTF) > 75% (increased risk of 3.18 times [p = 0.002]), migrating pain to the RIF (increased the risk by 2.37 times [p = 0.021]), and abdominal pain for < 48 h of evolution (increased the risk of AA by 2.11 times [p = 0.028]).

In contrast, a temperature between 37°C and 39°C was associated with a lower risk of AA than that in patients with a temperature out of that range (OR = 0.42 [p = 0.013]).

The novel CPR built with these six variables was able to establish three levels of risk among our cohort: low probability ($\leq$ 25 points): 24.9% of patients, medium probability (26-40 points): 47.9% of patients, and high probability ($\geq$ 41 points): 27% of patients (Fig. 2). The AUC was 0.81 (CI 95%: 0.74-0.87 [p < 0.001]). This score has a sensitivity of 60.91% (CI 95%: 53.85-67.98) and a specificity of 90% (CI 95%: 79.45-100).

Discussion

To improve the effectiveness of the diagnostic process, the ideal scoring system should work as an effective and accurate tool that accelerates and improves the decision-making process and simultaneously reduces the need for complementary imaging studies[22].

Table 2. Results of predictive ability and diagnostic performance of clinical prediction rules tested for acute appendicitis

Score	Total (n = 458)	NA (n = 54; 11.8%)	AA (n = 404; 88.2%)	p
Alvarado	6.00 (5.00-8.00)	5.00 (4.00-6.00)	6.00 (5.00-8.00)	< 0.001
RIPASA	7.50 (6.50-9.00)	7.00 (5.50-8.00)	7.50 (6.50-9.00)	< 0.001
AIR	5.00 (4.00-7.00)	4.00 (2.00-5.00)	5.00 (4.00-7.00)	< 0.001
AAS	11.00 (9.00-13.00)	9.00 (7.00-11.00)	11.00 (9.00-13.50)	< 0.001

AA: Histological confirmation, NA: No histological support for AA. AA: Acute appendicitis, RIPASA: Raja isteri pengiran anak saleha appendicitis, AIR: appendicitis inflammatory response, AAS: Adult appendicitis score

Table 3. Area under the curve of the scales according to the histological confirmation of acute appendicitis in our cohort

Score	AUC	95% CI	p
Alvarado	0.74	0.67-0.80	< 0.001
RIPASA	0.63	0.56-0.71	< 0.001
AIR	0.70	0.62-0.78	< 0.001
AAS	0.70	0.62-0.78	< 0.001

RIPASA: Raja isteri pengiran anak saleha appendicitis, AIR: appendicitis inflammatory response, AAS: adult appendicitis score, CI: confidence interval, AUC: area under the curve

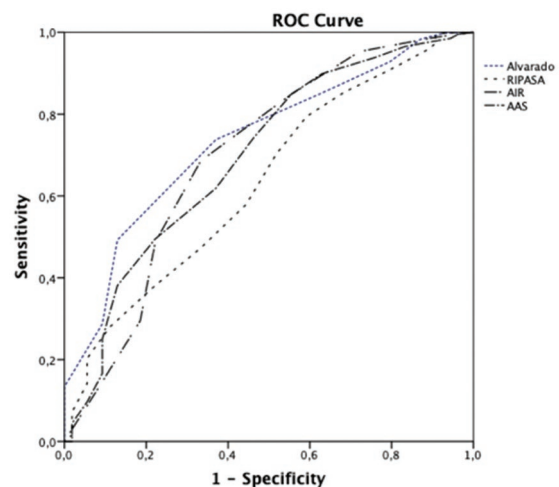**Figure 1.** *Receiver operating characteristic curves of the clinical prediction rule tested.*

The aim of this study was to validate the effectiveness of the most commonly used CPRs and to develop a new streamlined and efficient scoring system.

In this sense, the most efficient of the CPRs evaluated was the Alvarado score, which has been confirmed in multiple previous studies[3,17]. This score enables risk stratification in patients with RIFP with the quantification of eight variables. The other CPRS shows a lower diagnostic efficiency with an increase in the number of variables evaluated.

The newly developed CPR (HMC score) included six variables: anorexia, abdominal pain with < 48 h of evolution, migratory pain to the RIF, WBCC > 8.275 leukocytes/µL, NTF > 75%, and axillary temperature between 37°C and 39°C. The score performs well as a predictor of AA with an area under the ROC curve of 0.81 (p < 0.001), with an improved diagnostic performance over the other scales (Fig. 3).

It is composed of three symptoms and three clinical data categories, which are easily identifiable by the patient and the evaluator, respectively. The HMC score has the advantage of being simpler (with fewer items) than the previous ones (Alvarado, RIPASA, AIR, and AAS), eliminating subjective data such as the degree of defense/rebound in the abdominal exploration (AIR and AAS), and data that are not always collected in the patient's medical records.

This score established a cutoff point for the leukocyte count. Although it has already been shown that individual or combined analytical tests have limited or little specific value when predicting AA, their simultaneous negativity allows practically negating the diagnosis of AA[23]. In a prospective study of 1032 patients, Lau[24] concluded that the elevation of the WBCC and the percentage of neutrophils simultaneously increased the diagnostic specificity for AA. In another study, Atema[25] found that a WBC count of > 20,000 associated with symptoms for more than 48 h was associated with a positive predictive value of 100%.

Among patients with AA, the reported sensitivity and specificity rates of leukocyte counts were 60-87% and 53-100%, respectively[26], with different leukocyte cut-off points: 11,000 leukocytes/µL in the study of Bilic[27] and 10,400 leukocytes/µL reported by Narci[28]. Our leukocyte cutoff point was 8275 leukocytes/µL, which increased the sensitivity of the test and, when combined with NTF (> 75%), the specificity was also increased. The percentage of neutrophils is by itself considered the best diagnostic marker for AA and is also related to its severity[25].

Another aspect introduced by the HMC scale is in reference to body temperature. Fever is one of the variables present in most of the RIFP diagnostic scales (Alvarado, RIPASA, and AIR). However, many
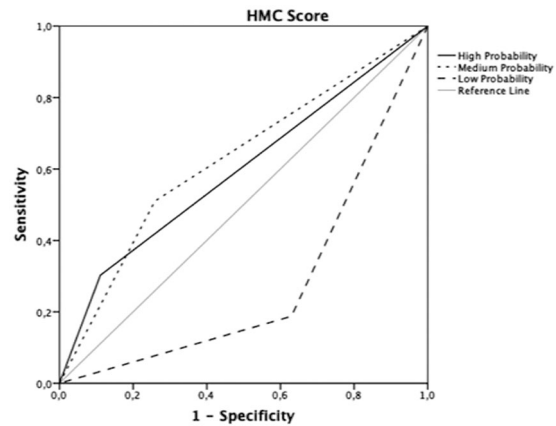
Figure 2. *Stratification of the Hospital Medina del Campo score: low probability (≤ 25 points); medium probability (26-40 points); high probability (≥ 41 points).*
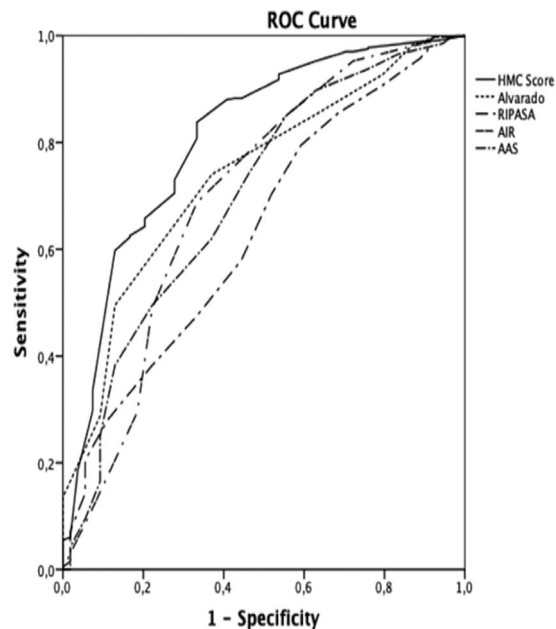
Figure 3. *Comparative receiver operating characteristic curves of the clinical prediction rules tested versus Hospital Medina del Campo score (HMC score): HMC (AUC: 0.81); Alvarado (AUC: 0.74); appendicitis inflammatory response (AUC: 0.70); adult appendicitis score (AUC: 0.70); Alvarado, Raja isteri pengiran anak saleha appendicitis (AUC: 0.63).*

authors believe that the predictive value of fever for AA is limited[29,30]. Andersson[31], in a study of 496 patients, demonstrated that a temperature > 37.7°C had a sensitivity and specificity of 70% and 65%, respectively, for the diagnosis of AA. In a later study, Andersson found that the mean temperature in nonsurgical abdominal pathology was 37.7°C, and

only its persistence in serial physical evaluations would indicate the presence of complicated AA[32]. Therefore, temperature, as an independent variable, is not as useful[3,29]. In our scale, an axillary temperature between 37°C and 39°C was associated with a lower risk of AA. For that reason, and in agreement with these authors, our data support the idea that temperature is not a good predictive value of AA pathology. Its presence in patients evaluated for RIFP should alert clinicians to the possible existence of other intra-abdominal pathologies, such acute gastroenteritis and pelvic inflammatory disease.

It is well established that the diagnostic approach to RIFP is conditioned by certain characteristics of the patient, such as age and sex[2,4]. When comparing the global cohort of female patients with AA, we found that the HMC scale presented an AUC = 0.84 (0.77-0.90) (p < 0.001), which was higher than the AUC of the other CPRs. The data were even more obvious when we analyzed the group of women between the ages of 15 and 64 with an AUC of 0.86 (0.78-0.93) (p < 0.001). In addition, the diagnostic approach in women of childbearing age is particularly difficult because of the overlap of gynecological symptoms with those of AA itself, causing an increase in NA due to diagnostic errors[33]. It has been postulated that CPR scores fail to properly evaluate this subgroup of patients because the scores cannot adequately exclude the presence of gynecological pathologies. In fact, a diagnostic scale has been developed for the management of acute abdominal pain in women of reproductive age[34].

When we applied the HMC score to women between 15 and 64 years old, we obtained a very high degree of success for the diagnosis of AA because of the 44 patients in this age subgroup with an HMC score ≥ 41, only one of them had a diagnosis recorded as AN, which improves the data provided by other authors[35]. However, female patients with a score ≤ 25 had the highest rate of NA (20 out of 44). These results support those collected in other studies that also showed high rates of NA in women of childbearing age[29,36] and support the early implementation of imaging tests in these patients[37].

Another group of patients with specific characteristics is the pediatric group. In this subgroup, the diagnosis of AA is a challenge both for the presence of nonsurgical pathologies that resemble appendicitis and for the difficulties of the anamnesis and exploration of these patients[14]. The rate of diagnostic errors increases as age decreases, and children 3 under 3 years of age have up to 5 times more risk of complicated AA[38]. Unable to provide data on patients under 5 years of age, our results show that NA was more frequent in pubescent girls between 10 and 14 years old (60% in our cohort), which are similar results to those found by Güller in a retrospective study of 7452 cases[39].

The HMC scale was shown to be an acceptable predictor of AA in pediatric patients, with an AUC = 0.74 (0.59-0.90; p = 0.019), a result not achieved when applying the other scales. A high score on this scale was 100% diagnosed by AA, which could have avoided the use of ultrasound, a conclusion similar to that derived from the study of Blitman in which the Alvarado score was applied[14]. On the other hand, authors such as Fleischman[40] showed that low scores of the appendicitis scales in children had good sensitivity to rule out AA and, therefore, to save diagnostic imaging tests with certainty and avoid unnecessary radiation risks.

Consequently, we believe that imaging tests improve the diagnostic accuracy, avoid errors and delays in definitive treatment, and should be performed in the diagnostic workup of doubtful diagnoses (intermediate scores) followed by CT scan when needed, a strategy supported by other authors[41,42].

Finally, in elderly patients, the AA rate is approximately 10%, although with the aging of the population, these figures are increasing[43]. Comorbidities, the insidious onset of the disease and the delay in diagnosis with the high rate of perforations make AA pathology with high using and mortality rates in elderly patients[44]. The diagnostic scales for AA were designed with a young population, so their effectiveness in an elderly age group is not well documented[45]. For all this, and in the same way as other authors[44], we recommended the early use of imaging tests in these patients, especially in the presence of inconclusive clinical data.

In our study, 11.1% of the patients were within this age group, with only 3 results of NA. None of the CPRs tested were statistically significant when applied to this group to discriminate between AA and NA. Nevertheless, the HMC scale was statistically significant, with the best AUC for elderly patients out of all the scores (0.86), showing that it was also a good predictive model for these patients. However, this sample size seems to be too small to make suitable comparisons with other published data.

The major weaknesses of this study are its retrospective nature, which increases the potential for bias and that it is a single center study. Among the strengths, it stands out that all patients have been treated by a small number of surgeons, with an adequate level of

criteria uniformity and that in more than 95% of the cases, the clinical data were complete. Obviously, the score developed requires a validation that is currently being implemented in our center.

Conclusion

We can affirm that the diagnostic probability scales for AA are useful tools to evaluate patients with RIFP, which can facilitate the diagnostic approach during emergency situations and save time and unnecessary tests. The diagnostic accuracy for AA can be increased, in probable or inconclusive cases in which the diagnoses are based on clinical data, with the implementation of US and CT studies.

Obviously, in western countries, access to image studies is relatively easy. However, frequently, this supposes an overload for the radiological services as in our center. The implementation and proper use of these tools in emergency services can help to select those patients who truly need an extension of the clinical evaluation with complementary imaging studies.

Finally, our data allow us to affirm that the HMC score improves the diagnostic effectiveness in the population groups studied with respect to the other scales that have been evaluated and previously validated and supported by the literature.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Use of enhanced recovery after surgery protocol in laparoscopic cholecystectomy in patients with symptomatic cholelithiasis

Uso de protocolo de recuperación acelarada después de cirugía en colecistectomía laparoscópica para pacientes con colelitiasis sintomática

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Abstract

Objective: The objective of the study was to determine the success rate of ambulatory laparoscopic cholecystectomy with an enhanced recovery after surgery (ERAS) protocol, in patients with symptomatic cholelithiasis. **Materials and methods:** Prospective cohort of patients with symptomatic cholelithiasis underwent elective surgery at the General and Endoscopic Surgery Division of the General Hospital "Dr. Manuel Gea González" from July 2015 to September 2017. **Results:** 160 patients were included, the mean age was 36.8 years (15-73 years), and 83.7% were women. We obtained a success rate of 95.6% with this protocol. Two patients required postoperative unplanned hospitalization (1.2%), one of them had surgical treatment (0.6%). Five patients presented post-operative complications (3.1%): one with acute pancreatitis (0.6%) and four (2.5%) were diagnosed with surgical site infection. Overall satisfaction with procedure was close to 99%. **Conclusion:** The performance of ambulatory laparoscopic cholecystectomy with an ERAS protocol in patients with symptomatic cholelithiasis has an adequate success rate, as well as postoperative evolution. Our study shows its safety, reliability, and possibility for routinely implementation without presenting a significant number of complications.

Keywords: Ambulatory laparoscopic cholecystectomy. Enhanced recovery after surgery. Accelerated postoperative recovery protocol. Symptomatic cholelithiasis.

Resumen

Objetivo: Determinar la tasa de éxito de la colecistectomía laparoscópica ambulatoria con un protocolo de recuperación acelerada después de la cirugía (ERAS por sus siglas en inglés), en pacientes con colelitiasis sintomática. **Materiales y métodos:** Cohorte prospectiva de pacientes con colelitiasis sintomática sometidos a cirugía electiva en la División de Cirugía General y Endoscópica del Hospital General "Dr. Manuel Gea González "de julio de 2015 a septiembre de 2017. **Resultados:** Se incluyeron 160 pacientes, la edad media fue de 36,8 años (15-73 años), el 83,7% eran mujeres. Obtuvimos una tasa de éxito del 95,6% con este protocolo. Dos pacientes requirieron hospitalización postoperatoria no planificada (1.2%), uno de ellos recibió tratamiento quirúrgico (0.6%). Cinco pacientes presentaron complicaciones postoperatorias (3.1%): uno con pancreatitis aguda (0.6%) y cuatro (2.5%) fueron diagnosticados de infección del sitio quirúrgico. La satisfacción general con el procedimiento fue cercana al 99%. **Conclusión:** La realización de colecistectomía laparoscópica ambulatoria con protocolo ERAS en pacientes con colelitiasis sintomática tiene una adecuada tasa de éxito, así como de

evolución postoperatoria. Nuestro estudio muestra su seguridad, confiabilidad y posibilidad de implementación rutinaria sin presentar un número significativo de complicaciones.

Palabras clave: *Colecistectomía laparoscópica ambulatoria. Recuperación acelarada después de la cirugía. Protocolo de recuperación posoperatoria acelerada. Colelitiasis sintomática.*

Introduction

Symptoms due to gallstone disease are a leading gastrointestinal cause for hospitalization and healthcare utilization[1].

Definitive treatment consists of performing cholecystectomy, since the risk of developing recurrent symptoms or complications rises to 70% 2 years after the initial presentation. Whenever possible, the laparoscopic approach is preferable over open surgery. Although there are no differences in terms of mortality and complications, the laparoscopic approach reduces hospital stay and shortens the period of convalescence. The complication rate is approximately 5% and includes bile duct injury, bile leakage, hemorrhage, and infection of the surgical wound. The operative mortality rates between 0% and 0.3%[2].

Outpatient surgery, defined as one in which the patient may be discharged 12 h after the surgical act, requires clinical practice guidelines that allow the current surgeon to begin or improve their practice[3].

In 1995, Dr. Kehlet's group published the results of a multimodal perioperative care protocol in patients undergoing elective colectomy[4], which was later called enhanced recovery after surgery (ERAS)[5]. Since then, this multimodal approach has been applied in other types of elective surgeries, including cholecystectomy[6].

The ERAS protocol includes a combination of techniques in pre-operative management in elective surgery, aimed to attenuating surgical stress and improving postoperative recovery. It consists of optimizing pre-operative preparation for surgery, reducing stress response, avoiding post-operative ileus, accelerating recovery with return to normal function, as well as an early recognition of recovery failure and intervention if necessary[7].

Our aim was to evaluate the success rate of ambulatory laparoscopic cholecystectomy with an ERAS protocol in a prospective cohort of patients with symptomatic cholelithiasis.

Materials and methods

We performed a prospective cohort of patients with symptomatic gallstones who underwent elective surgery on an outpatient basis at the General and Endoscopic Surgery Division of the General Hospital "Dr. Manuel Gea González" from July 2015 to September 2017.

Patients with a diagnosis of symptomatic gallstones treated with ambulatory laparoscopic cholecystectomy with an ERAS protocol of any sex, aged between 15 and 75 years, with an American Society of Anesthesiologists (ASA) classification I or II were included in the study. Pregnant women, foreign patients, those with uncontrolled comorbidities, anticoagulant's user and poor family support were excluded from the study. Elimination criteria included those who retract their consent or did not have post-operative follow-up.

The primary end point was the success rate of ambulatory laparoscopic cholecystectomy, defined as in which the patient was able to be discharged on an outpatient basis (within 12 h), without hospital readmission and no post-operative complications at 30 days follow-up. Secondary end points studied were intraoperative complications, post-operative complications, duration of post-operative hospital stay, unplanned hospital admission, and patients' satisfaction.

Laparoscopic cholecistectomy with ERAS protocol

PRE-OPERATIVE CARE

Information about the principles of ERAS protocol was given to patients and their caregiver.

An exhaustive pre-operative evaluation by the anesthesiology group was performed for all patients. Patients were admitted on the morning of the surgery. Pre-operative treatment with crystalloid isotonic solution (calculated according patient's requirements), antibiotics (cefalotine 1 g intravenous [IV]), standard gastric prophylaxis (omeprazole 40 mg IV), and opioid-sparing analgesia (acetaminophen 1 g IV and ketorolac 30 mg IV) were applied.

INTRA-OPERATIVE CARE

Balanced general anesthesia, strict control of fluid therapy, prevention of hypothermia, and adequate

analgesia were given to all patients to reduce metabolic stress response.

The surgical technique included three trocars. All port sites were infiltrated before incision using 0.5% bupivacaine. Nasogastric tubes or drains were not inserted. Anti-emesis prophylaxis was achieved with dexamethasone (4 mg IV) and ondansetron (8 mg IV).

POST-OPERATIVE CARE

Patients were taken to a recovery area adjacent to the operating room, where they were monitored and recordings of their vital signs and pain using the visual analog scale (VAS) was obtained. At this stage, antibiotics were suspended and opioid-sparing multimodal analgesia was given (acetaminophen 1 g IV and ketorolac 30 mg IV); in cases of post-operative nausea and vomiting ondansetron was administrated. After reaching a satisfactory level of consciousness, patients were encouraged to walk around freely and start oral intake with clear liquids.

Discharge criteria included pain controlled with oral analgesics (VAS < 4), adequate tolerance to oral intake, ambulation, capacity of micturation, hemodynamic stability, fully mental recovery, surgeon's approval, and absence of nausea and vomiting. Patients were reviewed and given home post-operative instructions, with special emphasis on alarm symptoms.

Follow-up

All patients were followed up with a phone call on post-operative day 3 and clinical appointments on post-operative days 7 and 30. Post-operative complications, readmissions, and reoperations were recorded if they presented during the 30-day follow-up period.

Sample size

A power calculation was performed using a ninety percent of expected success rate of ambulatory laparoscopic cholecystectomy, with and alpha error = 0.05 and precision of 5%. One hundred and thirty-eight patients were calculated, with a 10% of expected loss, 152 patients were obtained.

Our data were summarized as the means (with minimum and maximum values) or number of patients (percentages).

SPSS version 18.0 for MAC (SPSS Inc. Chicago, IL, USA) was used for analyzing data.

Table 1. Patients baseline characteristics

Characteristics	n (%)
n (patients)	160 patients
Sex (female:male)	134 (83.7):26 (16.2)
Mean age (years)	36.8 (15-73)
ASA I	150 (93.7)
ASA II	10 (6.2)
Abdominal surgery history	89 (55.6)
Medical history	
Diabetes	2 (1.25)
Hypertension	5 (3.12)
Other	4 (2.5)
None	149 (93.1)

ASA: American Society of Anesthesiologists

Table 2. Surgical findings and characteristics

Characteristics	n (min-max)
Duration of surgery (minutes)	63.8 (25-150)
Bleading (ml)	30.1 (5-100)
Mean postoperative VAS	4.1 (0-10)
Mean postoperative stay (hours)	4.6 (1-95)
Surgical findings	**n (%)**
Cholelithiasis	135 (84.3)
Unexpected Acute Cholecystitis	15 (9.3)
Empyema	6 (3.75)
Gallbladder Hydrops	4 (2.5)

Results

From July 2015 to September 2017, a total of 174 patients with symptomatic cholelithiasis were evaluated, 14 patients were also eliminated because they did not have postoperative follow-up. Therefore, we continued the study with 160 patients, of which 134 were women (83.7%) and 26 (16.2%) were men. Baseline demographic data are shown in table 1.

Intraoperative findings were: 135 patients with cholelithiasis (84.3%), 15 patients with unexpected acute cholecystitis (9.3%), six patients with empyema (3.7%), and four patients with gallbladder hydrops (2.5%). The average post-operative hospital stay in hours was 4.6 ± 7.3 (SD) (Table 2).
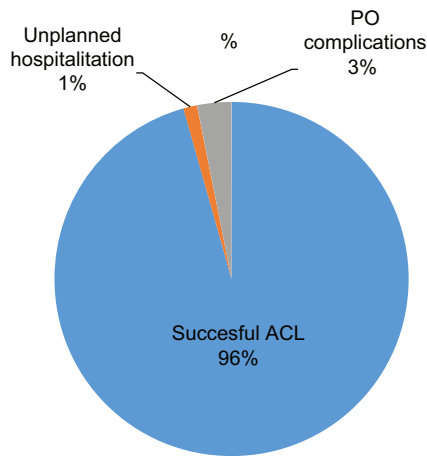
Figure 1. *Success rate of ambulatory laparoscopic cholecystectomy (ALC). Unplanned hospitalization rate account for 1.2% and post-operative complications for 3.12% of our sample. Successful ACL was feasible in 96% of our patients.*

On the other hand, unplanned hospital admission was reported in two patients (1.2%), 1 who underwent pain that did not subside with oral medication and 1 (0.6%) patient required surgical management due to bleeding (0.6%); both patients were diagnosed with gallbladder empyema during surgery. Post-operative complications were seen in 5 (3.1%) patients: 4 (2.5%) of these patients had a diagnosis of residual abscess and 1 (0.6%) patient developed acute pancreatitis. Thus, a success rate of 95.6% (153 patients) was obtained in this protocol (Fig. 1). Other points analyzed were intraoperative complications, which were not found in this protocol, reporting a total of zero cases (0%). Conversion to open surgery was not registered in this protocol.

Furthermore, we evaluated patients' satisfaction with medical care, hospital length stays, and information received by our team. All of them showed a rate close to 99%.

Discussion

Successful ambulatory laparoscopic cholecystectomy (ALC) is one in which the patient can be discharged within 12 h post-operative period, without hospital readmission and no postoperative complications at 30 days. In our study, unplanned admission (1.2%), intraoperative complication including conversion rate to open surgery (0%) and postoperative complication, including surgical site infection and acute pancreatitis (3.1%), account for a total of 4.3% of our sample,

achieving a success rate of 95.6% for ambulatory cholecystectomy using an ERAS protocol.

Several studies mention their success rate for this procedure[8-12] (Table 3). For instance, Jiménez and Costa[11] described their experience with 100 cases of outpatient laparoscopic cholecystectomy subjected to a protocolized anesthesia that included intraperitoneal and parietal use of local anesthesia achieving excellent pain control, the main cause of hospitalization. The frequency of outpatient discharge was 96%. The mean hospital stay of the patients was 7.4 h (7-9.6 h). The morbidity and mortality of the series were 0%; and conversion rate to laparotomy in the series was 0%. No patient required readmission after discharge, and 97% of the patients were very satisfied with the procedure.

Tang and Dong[13] performed a meta-analysis comparing short-stay surgery versus night-stay surgery in patients with lithiasic cholecystitis after laparoscopic cholecystectomy. It included 12 studies, with a total of 1,430 patients, 650 were classified as ambulatory cholecystectomy and 780 as overnight stay surgery. Within the results they reported morbidity of 5.2% and 6% for the group of short stay surgery and night stay surgery, respectively, being statistically not significant. Regarding prolonged stay or unplanned hospital admission, they found 13.1% in the ambulatory surgery group. The main causes were conversion to open surgery, nausea or vomiting that did not give way to medications, pain, and use of drainage. While in the overnight stay group, a 12.1% length of hospital stay was found for the same reasons, being statistically not significant between groups. The percentage of readmission once hospital discharge was 0-4.8% in the short stay group, while in the overnight stay group it was 0-5.2%, the main diagnoses in both groups being infections, pancreatitis, and biliary leak. However, this was also not statistically significant. Other points that were analyzed were the quality of life on the day of surgery and the time of return to work activities; however, the differences were not statistically significant. The authors concluded that outpatient laparoscopic cholecystectomy is safe, effective and cheaper and can be performed without major problems in selected patients.

Lezana et al.[9] analyzed the effectiveness and quality of outpatient cholecystectomy versus conventional laparoscopic cholecystectomy management. In this study, no intervention was performed regarding pain control. The overall satisfaction index was 82% and the satisfaction indicator for the care received was 81%, both above the previously set standard. Regarding the other

Table 3. Several studies were success rate and degree of satisfaction of ambulatory laparoscopic cholecystectomy was reported

Study (year)	Number of patients	Success rate of ALC (%)	Unplanned hospitalization (%)	Readmission (%)	Reintervention (%)	Conversion to open surgery	Degree of satisfaction at 7th day post-operative
Akoh et al.[8]	258	69.0	31.0	5.0	-	-	-
Lezana-Pérez et al.[9]	141	82.0	18.4	3.5	1.4	0.7	82
Soler-Dorda and Marton-Bedia[10]	511	70.0	30.0	2.8	1.2	3.3	-
Jiménez and Costa[11]	100	96.0	4.0	0.0	-	0	97
Sala-Hernández et al.[12]	164	92.8	5.5	1.8	-	1.2	87.10
Mendoza-Velez et al.	160	95.6	1.2	0.0	0.6	0	99

ALC: ambulatory laparoscopic cholecystectomy

parameters analyzed (mortality, morbidity, reinterventions, readmissions, and stay) there was no difference between the two groups as in other studies cited.

In our study, the degree of satisfaction expressed was either excellent or very good in 99% of our sample on the 7th post-operative day. We valued medical care (99.3%), hospital stay length (99.3%), and information received before procedure (98.7%), achieving a great acceptance between our patients.

Based on this study, we intend to carry out new prospective studies to assess outpatient management with ERAS protocol in patients with symptomatic cholelithiasis.

Conclusion

The performance of ALC with an accelerated post-operative recovery protocol in patients with symptomatic gallbladder lithiasis has a significant success rate in the period investigated and similar to the reported in international literature. Our study supports the safety, reliability, and possibility for implementation of routine ALC with ERAS protocol, with a demonstrated high degree of patient satisfaction. Our data advocate the inclusion of ALC as a treatment of choice for symptomatic cholelithiasis that minimizes hospitalizations. However, our sample is limited to one center and no control group was followed.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Mentoring: ¿qué esperamos en Colombia de nuestros profesores de cirugía? Un ejemplo latinoamericano

Mentoring: what to expect from our surgical mentors in Colombia? A Latin American example

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Rsumen

Objetivo: *Identificar el alcance del mentoring quirúrgico en la Facultad de Medicina de la Pontificia Universidad Javeriana y comparar las percepciones de docentes y estudiantes, con el fin de reconocer características y competencias de dicha práctica y necesidades a futuro.* **Método:** *Se diseñaron dos encuestas para evaluar la existencia y la importancia del proceso de mentoring e indagar acerca de las características, las cualidades y las competencias esperadas de los mentores.* **Resultados:** *Ambos grupos coinciden en la importancia de contar con un mentor. El 84.2% de los docentes consideran ser mentores, pero solo el 38.6% de los estudiantes los consideraron a ellos como tales. Las cualidad más relevantes del mentor reconocidas por los estudiantes fueron la disposición y la habilidad para enseñar, mientras que para los docentes fue el respeto. Para los estudiantes, la competencia más importante fue la capacidad de explicar y enseñar sobre los procedimientos a realizar, mientras que para los docentes fue la capacidad de brindar confianza y seguridad.* **Conclusiones:** *Existe un comportamiento paradójico, pues los estudiantes no consideraron contar con un mentor mientras que los docentes sí estimaron serlo. Se identificó la necesidad de ampliar la literatura respecto al mentoring en Colombia, específicamente en el ámbito quirúrgico.*

Palabras clave: *Mentoring. Cirugía. Educación médica. Mentor. Aprendiz.*

Abstract

Objective: *Identifying the scope of surgical mentoring at Pontificia Universidad Javeriana and compare the perceptions of teachers and students to recognize characteristics and competences of such practice and future needs.* **Method:** *Two surveys were designed to evaluate the existence and importance of mentoring and inquire about the characteristics, qualities and skills expected on mentors.* **Results:** *Both groups agree on the importance of having a mentor. 84.2% of teachers consider themselves mentors, however, only 38.6% of students considered them as such. The most relevant quality of the mentor recognized by students was the willingness and ability to teach, while for teachers it was respect. For the students, the most important competence was the ability to explain and teach about the procedures to be performed, while for teachers it was the ability to provide confidence and security.* **Conclusions:** *There is a paradoxical behavior, most students consider they do not have a mentor while most teachers consider to be such. The need to expand the literature regarding mentoring in Colombia specifically in the surgical field was identified.*

Keywords: *Mentoring. Surgery. Medical education. Mentor. Mentee*

Introducción

En el contexto médico, el Standing Committee on Postgraduate Medical (and Dental) Education (SCOPME) del Reino Unido define el *mentoring* como «el proceso por el cual una persona experimentada, altamente respetada y empática (el mentor), guía a otro individuo (el aprendiz) en el desarrollo de sus propias ideas, aprendizaje y desarrollo personal y profesional»[1]. Según Entezami et al.[2], además de impartir las técnicas de atención clínica, los mentores son responsables de instruir a los alumnos en aspectos vitales de la vida diaria, como son la compasión, la comunicación, el profesionalismo y la ética de la atención al paciente.

El *mentoring* ha demostrado tener un impacto positivo no solo en el ámbito académico, sino también en el ámbito profesional y personal. Una revisión de Sambunjak et al.[3] sobre la importancia del *mentoring* en medicina académica examinó la prevalencia del *mentoring* y su relación con el desarrollo profesional, y se halló una asociación significativa entre tener un mentor y ser el investigador principal de estudios de investigación (*odds ratio:* 2.1-3.1). Además, los miembros de la facultad con mentores tuvieron puntajes de satisfacción profesional significativamente más altos que aquellos sin mentores ($p < 0.03$). Sin embargo, a pesar de los beneficios previamente descritos, menos del 50% de los estudiantes de medicina contaban con un mentor reconocido.

Para los estudiantes de cirugía es fundamental poder tener un mentor durante su proceso de formación, ya que esta práctica, única y rigurosa, demanda habilidades y destrezas que requieren acompañamiento por parte de expertos. Así mismo, el entorno de aprendizaje de las ciencias quirúrgicas representa un ambiente desafiante para los estudiantes que apenas empiezan a asimilar la dinámica de este ámbito[2]. Lo anterior se debe a que demanda en su mayoría de componentes netamente prácticos, a las expectativas y personalidades del personal quirúrgico, y al estrés asociado a las salas de cirugía, convirtiendo al *mentoring* en el ámbito quirúrgico en un reto tanto para estudiantes como para docentes. Por ello, el objetivo del presente estudio fue identificar el alcance actual del *mentoring* en cirugía en la Facultad de Medicina de la Pontificia Universidad Javeriana y comparar las percepciones de docentes y estudiantes, con el fin de reconocer el grado de importancia de las características y las competencias de dicha práctica e identificar necesidades a futuro.

Método

Se realizaron dos encuestas en formato electrónico. La primera se aplicó a los estudiantes con el propósito de investigar si consideraban contar con un mentor en el momento y evaluar la importancia de este en el proceso de aprendizaje. Adicionalmente, se evaluó si los estudiantes tenían alguna preferencia en cuanto a características del mentor. Se utilizó una escala de Likert para medir el grado de importancia de cualidades y competencias esperadas en el mentor. Se realizaron preguntas abiertas con el fin de que los estudiantes mencionaran otras posibles variables que no habían sido previamente contempladas. La segunda encuesta se aplicó a los docentes del Departamento de Cirugía de dicha universidad. Se les preguntó cuántos en el momento consideraban ser mentores y la importancia de esta figura desde su perspectiva. Se midió, usando una escala de Likert, el grado de importancia de las cualidades y las competencias evaluadas previamente por los estudiantes y se adicionaron a la encuesta aquellas que fueron referidas por los estudiantes en las preguntas abiertas que no habían sido contempladas en la encuesta inicial. Los encuestados fueron informados del propósito del estudio y su participación fue voluntaria.

Luego de discusiones con grupos focales y revisión de la literatura, el grupo investigador elaboró los cuestionarios después de identificar los ítems y temas a incluir. Para la encuesta a estudiantes se elaboró un cuestionario utilizando la herramienta Google Forms, la cual se dividía en cuatro secciones. La primera de ellas, con tres preguntas, hacía referencia a si creían contar con mentores y la importancia de estos. La segunda sección constaba de dos preguntas e indagaba acerca de las características del mentor. La tercera sección, con tres preguntas, hacía referencia a las cualidades de los mentores. La cuarta sección constaba de tres preguntas sobre las competencias. En total, el instrumento tenía 11 preguntas, ocho de ellas cerradas y tres abiertas.

Para la encuesta a docentes se utilizó un cuestionario similar, creado con la herramienta Google Forms, dividido en tres secciones. La primera sección, con tres preguntas, enfatizó en el reconocimiento de sí mismos como mentores y en la importancia de que los estudiantes contaran con mentores en el ámbito quirúrgico. La segunda sección hacía referencia a las cualidades del mentor y constaba de dos preguntas. La tercera sección, con dos preguntas, indagaba acerca de las competencias con las que debían

contar los mentores. En total, el instrumento presentaba siete preguntas, seis de ellas cerradas y una abierta.

Se realizaron pruebas piloto de las encuestas para evaluar su funcionalidad antes de ser aplicadas. Los instrumentos diseñados fueron difundidos por medio de la red social WhatsApp, haciendo uso de muestreo por conveniencia y por bola de nieve. El instrumento difundido para estudiantes (https://docs.google.com/forms/d/1Fm_kZhGs1N7GVzMABBvju16-QZfxdR-zyHvny6DinDeM/edit) fue habilitado para su diligenciamiento desde el 9 de octubre de 2019 a las 12:00 h hasta el 12 de octubre de 2019 a las 20:00 h. El instrumento difundido para docentes (https://docs.google.com/forms/d/1kVap28lWxemWgeyegqQu5_z92FgZGOvairPfyns6doU/edit) fue habilitado para su diligenciamiento desde el 12 de octubre de 2019 a las 12:00 h hasta el 15 de octubre de 2019 a las 20:00 h.

Para el análisis de los datos se utilizaron las herramientas de Google Forms y Excel®.

En la tabla 1 se exponen las características, las cualidades y las competencias evaluadas en la encuesta a estudiantes.

Para los propósitos de este estudio, el *mentoring* fue definido en las encuestas como «el proceso mediante el cual un mentor o tutor, que se caracteriza por ser una persona con mayor conocimiento, experticia, altamente respetada y empática, guía a otro individuo, "el aprendiz", en el desarrollo de sus propias ideas, aprendizaje y a maximizar su potencial para alcanzar sus objetivos personales y profesionales; además, es responsable de instruir a los alumnos en los aspectos vitales de la compasión, la comunicación, el profesionalismo y la ética de la atención al paciente».

Resultados

Las tasas de respuesta fueron del 72% para estudiantes y del 80% para profesores. Haciendo énfasis en la definición establecida en la encuesta, se encontró que el 84.2% de los docentes consideraron ser mentores, mientras que solo el 38.6% de los estudiantes estimaron contar con uno en dicho momento. El 100% de los estudiantes y el 95% de los docentes expresaron la importancia de contar con un mentor en el ámbito quirúrgico para la identificación de gustos, y como herramienta para guiar y potenciar el proceso de aprendizaje, porque consideran que «lo más importante es aprender desde el ejemplo, ya que

Tabla 1. Características, cualidades y competencias que se evaluaron en la encuesta a estudiantes

Características
– Edad
– Sexo
Cualidades
– Experticia
– Integridad profesional
– Empatía
– Motivación (da apoyo o aliento)
– Paciencia
– Amabilidad/compasión
– Respeto
– Carisma
– Disposición y habilidad para enseñar
Competencias
– Disponibilidad de tiempo
– Enseña al estudiante medidas técnicas y quirúrgicas
– Permite la participación activa del estudiante en la cirugía
– Explica y enseña al estudiante sobre el procedimiento a realizar
– Brinda confianza y seguridad al estudiante en la sala de cirugía
– Proporciona recursos y fuentes para lectura individual
– Ofrece orientación respecto a problemas profesionales
– Orienta y aconseja frente a elección de especialidades en el futuro
– Fomenta las ideas y el trabajo del aprendiz
– Proporciona críticas constructivas y útiles del trabajo del aprendiz
– Desafía al aprendiz a expandir sus habilidades
– Proporciona retroalimentación oportuna, clara y comprensible de las preguntas que realiza al aprendiz
– Respeta la singularidad del aprendiz y de sus contribuciones
– Agradece las contribuciones asistenciales del aprendiz
– Comparte el éxito y los beneficios de los productos y actividades del aprendiz

Escala de Likert: muy importante, medianamente importante, poco importante, no importante.

la cirugía no se aprende en los libros». Así mismo, es «fundamental para obtener un desarrollo integral» y como «forma de inspiración para el desarrollo profesional y personal».

Características

Al indagar acerca de la edad, se encontró que el 70% de los estudiantes no tenía preferencia en cuanto a la edad, pero un 16% prefería docentes de 30-40 años, un 7% prefería docentes menores de 30 años, un 5% prefería mentores de 40-50 años y un 2% preferían mentores mayores de 50 años. En relación al sexo, se encontró que el 89.5% de estudiantes no tenía preferencia y el 10.5% prefería un hombre como mentor.

Cualidades

Con respecto a las cualidades que los estudiantes consideraron más relevantes encontrar en sus mentores, las que fueron calificadas como muy importantes por la mayoría fueron la disposición y la habilidad para
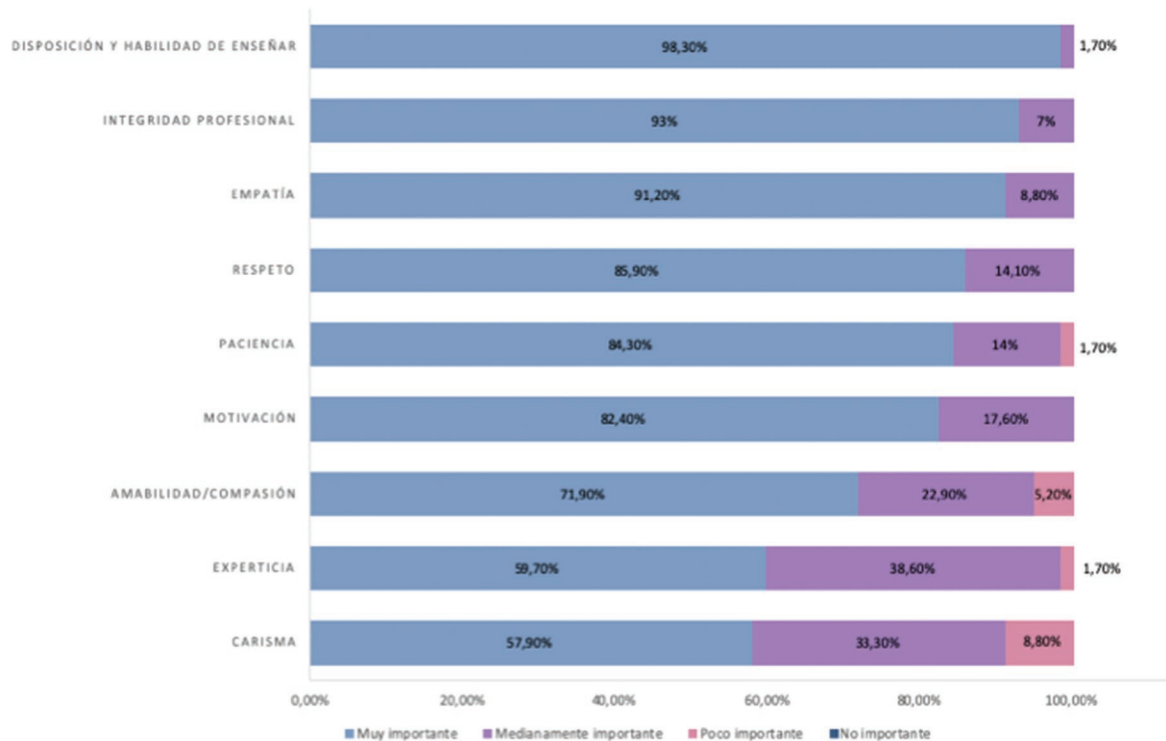
Figura 1. *Resultados de la importancia de las cualidades que los estudiantes esperan encontrar en sus mentores.*

enseñar, la integridad profesional y la empatía (Fig. 1). Por otra parte, la mayoría de los docentes señalaron como muy importante el respeto, la disposición y la habilidad para enseñar, y la integridad profesional (Fig. 2).

Para los estudiantes, en la escala subjetiva, no hubo cualidades dentro de la categoría «no importante»; sin embargo, el 8.8% calificaron como «poco importante» el carisma y el 5.2% la amabilidad/compasión. Con respecto a los docentes, no hubo variables dentro de la categoría «no importante»; sin embargo, el 10% consideró «poco importante» el carisma, el 5% la sencillez y el 5% la puntualidad.

Al interrogar a los estudiantes respecto a la cualidad más importante de las descritas, el 42% consideraron la disposición y la habilidad para enseñar, el 25% la integridad profesional y el 16% la empatía. En contraste, para el 60% de los docentes la más importante de las cualidades fue la integridad profesional, el 15% consideró que la más importante era la vocación y el 10% la disposición y la habilidad para enseñar.

Competencias

Con respecto a las competencias que se espera encontrar en el mentor, las que fueron consideradas como muy importantes por la mayoría de estudiantes fueron la capacidad de explicar y enseñar sobre los procedimientos a realizar, brindar confianza y seguridad en la sala de cirugía, y realizar retroalimentación oportuna y comprensible a las preguntas del aprendiz (Fig. 3). Por otra parte, las que fueron calificadas como muy importantes por la mayoría de los docentes fueron brindar confianza y seguridad al estudiante en la sala de cirugía, fomentar las ideas y el trabajo del aprendiz, y proporcionar críticas constructivas y útiles sobre el trabajo del aprendiz (Fig. 4).

El 30% de los docentes calificaron la enseñanza al estudiante de medidas técnicas y quirúrgicas dentro de la categoría «poco importante», mientras que el 20% incluyeron dentro de la misma la participación activa del estudiante en cirugía. Únicamente el 5% de los docentes calificaron como «no importante» proporcionar fuentes para lectura individual.

Al indagar acerca de la competencia que los estudiantes consideraban más importante encontrar en sus mentores, para el 25% fue explicar y enseñar sobre el procedimiento a realizar, para el 16% fue brindar confianza y seguridad en la sala de cirugía, y para el 16% fue permitir la participación activa del estudiante en la cirugía. En contraste, para los docentes, las competencias más importantes, con un 15% cada una, fueron brindar confianza y seguridad en la sala de
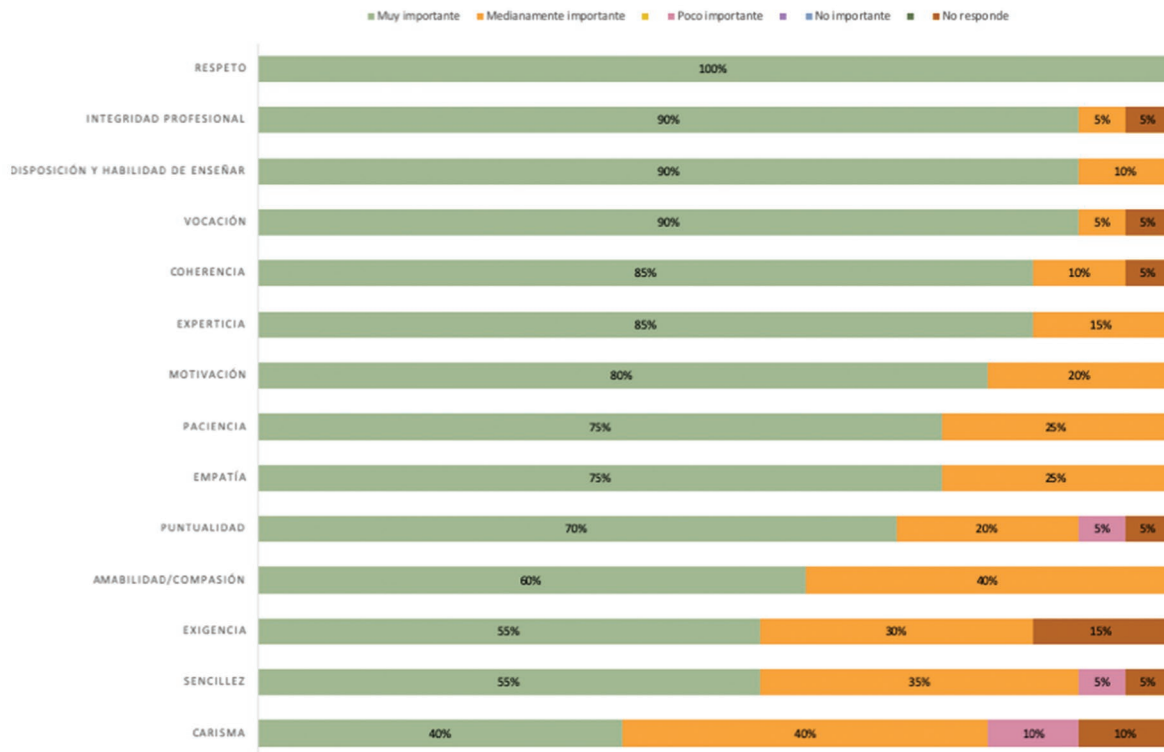
Figura 2. *Resultados de las cualidades que los mentores consideran importantes.*
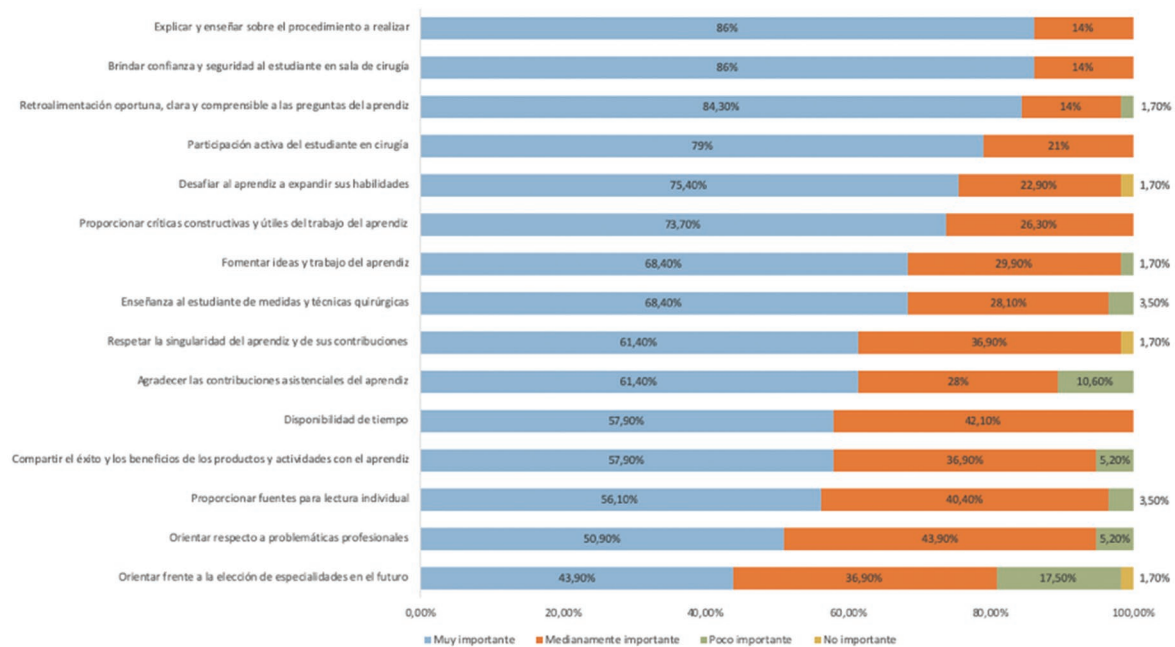
Figura 3. *Resultados de la importancia de las competencias que los estudiantes esperan encontrar en sus mentores.*

cirugía, fomentar ideas y el trabajo del aprendiz, y proporcionar críticas constructivas y útiles sobre el trabajo del aprendiz.

Por otra parte, por medio de grupos focales de discusión se indagó acerca de las barreras existentes que limitan el alcance y el desarrollo de dicho proceso
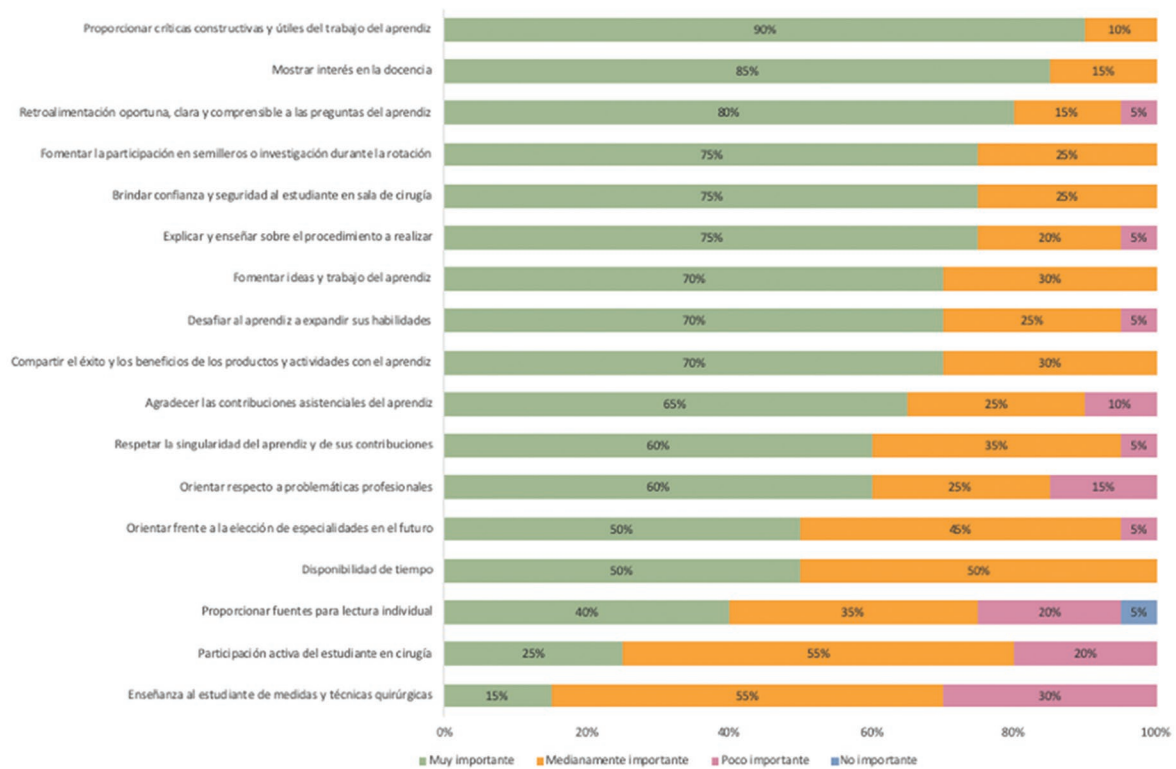
Figura 4. *Resultados de las competencias que los mentores consideran importantes.*

en nuestro medio. Se logró identificar una barrera importante que estaba directamente relacionada con la dinámica de las rotaciones en la actualidad. Se determinó que el método de acompañamiento de un solo mentor durante todo el desarrollo de la carrera profesional y personal está limitado por los currículos actuales, que implican cambios rápidos de rotación y así mismo de docentes, generando tiempos cortos de interacción de ambas partes e interrupciones en las relaciones tanto académicas como personales entre mentor y aprendiz. Se identificó también que muchos estudiantes y docentes consideran que existe la necesidad de un método distinto que se adapte a las dinámicas actuales y que garantice el proceso de acompañamiento para aprovechar todos los beneficios que el *mentoring* brinda.

Discusión

El término «mentor» proviene de la mitología griega, en el siglo viii a.C., cuando a Méntor, hijo de Álcimo, se le encomendó la tarea de velar por los intereses de Odiseo en Ítaca y la educación de su hijo Telémaco cuando partió a Troya. Desde entonces y hasta hoy

en día el nombre de este personaje ha pasado a la lengua como «consejero sabio y experimentado»[4,5].

Fue así como nació el término *mentoring,* una estrategia validada por evidencia empírica que proporciona beneficios tanto objetivos como subjetivos para mentores y aprendices en la educación médica. Así mismo, según el Royal College of Surgeons, la tutoría quirúrgica mejora colectivamente la atención del paciente y la atención quirúrgica a largo plazo, lo que hace que dicha práctica sea aún más valiosa[5,6].

En la población objetivo, es evidente la importancia que tiene el *mentoring* en el área quirúrgica. No obstante, se pudo identificar un comportamiento paradójico, ya que la mayoría de estudiantes no consideran contar con un mentor, mientras que la mayoría de sus profesores sí consideran serlo. Además, se encontró que el modelo de *mentoring* actual, por la dinámica de las rotaciones, tiene barreras en su implementación. Por lo anterior, se propone la creación de un nuevo modelo de *multi-mentor mentoring,* que incluya el apoyo de distintos mentores y que sumando los aportes de todos se logre alcanzar los objetivos planteados. Igualmente pretende incentivar en los docentes dicha práctica, para que todos los mentores que

interactúen por cortos periodos de tiempo en el proceso del aprendiz puedan aportar lo necesario para que el desarrollo personal y profesional de los aprendices sea garantizado y su acompañamiento permanezca, aunque se interrumpa la interacción diaria.

Por otra parte, se encontraron diferencias en la literatura revisada. Según la revisión sistemática realizada por Entezami et al.[2], en 14 de los 38 artículos incluidos se expresa el tema de las diferencias de género como barrera para la implementación del *mentoring,* específicamente por falta de mentoras de sexo femenino. Sin embargo, para la mayoría de estudiantes de nuestra población, el sexo y la edad no parecen ser barreras, ya que no se encuentran preferencias con respecto a dichas características.

Adicionalmente, hay cierto grado de similitud en las cualidades y las competencias que ambos grupos consideran más importantes. Sin embargo, una pequeña proporción de la población varía en sus percepciones. La expertícia y el carisma no parecen ser las cualidades más importantes según los estudiantes; por el contrario, que el mentor explique y enseñe sobre el procedimiento a realizar, la disposición y la habilidad para enseñar, así como que el docente sea considerado un ejemplo a seguir, fueron estimadas como las más importantes cualidades.

Conclusiones

Aunque se cuenta con literatura internacional relativamente amplia sobre el tema, cabe señalar que la revisión realizada puso de manifiesto la falta de estudios y de información respecto al *mentoring* en Latinoamérica y en Colombia, específicamente en el ámbito quirúrgico. Así mismo, existe la necesidad de ampliar los conocimientos en nuestra población, ya que cuenta con una cultura distinta y con currículos diversos de los encontrados en muchos de los estudios internacionales.

Debido a que no existen estudios en Latinoamérica ni en Colombia respecto al tema en mención, no fue posible hacer comparaciones entre poblaciones con currículos y programas parecidos para identificar barreras en la implementación del *mentoring*. Además, existe sesgo al considerar que el presente estudio se limitó a evaluar a estudiantes y docentes de una institución educativa en Colombia.

Agradecimientos

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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Using the health belief model to analyze nurses' perception toward their behaviors for keeping surgical instruments moist: a cross-sectional study

Uso del modelo de creencias en salud para analizar la percepción de las enfermeras sobre sus comportamientos para mantener húmedos los instrumentos quirúrgicos: un estudio transversal

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Abstract

Background: *Nurses' perception toward their behaviors for keeping surgical instruments moist has been rarely studied.* **Methods:** *The survey which utilized a questionnaire regarding respondent's demographic information and a self-designed nurses' perception-behavior scale for keeping surgical instruments moist was conducted with 360 nurses from a hospital in China.* **Results:** *Total score of nurses' perception-behavior scale for keeping surgical instruments moist was 139.93 ± 15.145. Score of nurses' perception-behavior scale for keeping surgical instruments moist varied with age, length of service, and job title, with a statistically significant difference (p < 0.05). Length of service was the main factor affecting nurses' perception toward their behaviors for keeping surgical instruments moist.* **Conclusions:** *Nurses should be offered intensive training on keeping surgical instruments moist due to their inadequate perception on it. The nurses' change in health beliefs and behaviors must be based on developing the right attitude.*

Keywords: Perception. Surgical instruments. Health belief model.

Resumen

Objetivo: *La percepción de los enfermeros sobre sus comportamientos para mantener húmedo el instrumental quirúrgico ha sido poco estudiada.* **Métodos:** *La encuesta que utilizó un cuestionario sobre la información demográfica del encuestado y una escala de percepción y comportamiento de las enfermeras de diseño propio para mantener húmedos los instrumentos quirúrgicos se realizó con 360 enfermeras de un hospital en China.* **Resultados:** *La puntuación total de la escala de percepción-conducta de las enfermeras para mantener húmedo el instrumental quirúrgico fue de 139.93 ± 15.145. La puntuación de la escala de percepción-conducta de las enfermeras para mantener húmedos los instrumentos quirúrgicos varió con la edad, la duración del servicio y el cargo, con una diferencia estadísticamente significativa (p < 0,05). El tiempo de servicio fue el principal factor que influyó en la percepción de los enfermeros sobre sus comportamientos para mantener húmedo el instrumental quirúrgico.* **Conclusión:** *Se debe ofrecer a las enfermeras un entrenamiento intensivo sobre el mantenimiento de la humedad del instrumental quirúrgico por su inadecuada percepción al respecto. El cambio de creencias y comportamientos de salud de las enfermeras debe basarse en el desarrollo de la actitud correcta.*

Palabras clave: Percepción. Instrumentos quirúrgicos. Modelo de creencias sobre la salud.

Introduction

China's national Health Industrial Standard (version number: WS 310.2-2016) which was released in December 2016 states that the user shall timely remove visible contaminants from medical instruments, implements and articles, and keep them moist as required after use. Guidelines of Association of PeriOprative Registered Nurses of the United States also expressly require keeping instruments moist before cleaning[1]. Failure in timely keeping instruments moist will lead to biofilm formation. Biofilm refers to a collective of bacteria attached to the surface of living or non-living objects and enclosed with bacterial extracellular macromolecules. Biofilm is very difficult to remove after formation[2,3]. According to the previous studies, bacteria may develop on dry contaminants in 4-20 min and biofilm will appear in 2 h. Therefore, contaminants shall be timely removed from surgical instruments after use, and subsequently the instruments shall be sent to the central sterile supply department (CSSD) for cleaning within 30 min. If it is not available, it will be necessary to keep instruments moist[4,5]. However, because of conflicts with work schedule of CSSD, surgical instruments may not be immediately cleaned or sterilized by CSSD staff members after use. If surgical instruments are not kept appropriately moist, tarnish or rusting may occur on the instruments, which will not only affect cleaning quality, but also shorten the normal service life of the instruments[6,7]. According to the initial investigation, only 57.59% of the surgical instruments were kept moist in our hospital, and the nurses did not have adequate perception toward their behaviors for keeping instruments moist. We aimed to use the health belief model to analyze the nurses' perception toward their behaviors for keeping surgical instruments moist. This study will contribute to improve implementation rate of keeping surgical instruments moist.

Materials and methods

Setting and participants

The survey was performed with 360 nurses from a grade a tertiary hospital in China during June 1 to August 31, 2019.

Study design

The health belief model (HBM), first proposed by Hochbaum, and revised by Rosenstock[8], was the theoretical base of this study. HBM's 5 components, that is, perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy, were applied to define nurses' perceived susceptibility to instruments not kept moist, perceived severity of instruments not kept moist, perceived benefits of keeping instruments moist, perceived barriers for keeping instruments moist, and self-efficacy in keeping instrument moist[9,10] in analyzing nurses' perception toward their behaviors for keeping surgical instruments moist.

The survey was performed based on an electronic questionnaire regarding respondent's demographic information and a self-designed nurses' perception-behavior scale for keeping surgical instruments moist. The electronic questionnaire was produced through a smartphone application called "WJX." Quick response code of the questionnaire was only shared to the WeChat group for nurses of the hospital. Because WJX is a specialized online questionnaire survey tool and is commonly used in China, we did not test usability and technical functionality of the electronic questionnaire before sharing the quick response code to the WeChat group. Aims and importance of this study and time limit of the investigation were stated in the WeChat group chat. The nurses who were interested in participating in the research study accessed to the questionnaires by scanning the quick response code, and then they filled out the questionnaires voluntarily and anonymously without inputting username and password. Respondents were not provided with any form of incentives to participate in this study.

The questionnaire consisted of 41 questions, and all questions were shown on one page. There were no response options for "not applicable" or "rather not say." Respondents could review and change their answers before submitting the questionnaires. Respondents could scan the quick response code to view the questionnaire again at any time after submitting the questionnaires, but no changes were allowed to their answers after submitting the questionnaire. If respondent did not answer all questions, the questionnaire would not be submitted successfully. We were able to obtain the information of IP addresses and WeChat nicknames of the respondents who successfully submitted the questionnaires. If questionnaires from the same IP address or same WeChat nicknames were submitted multiple times, the first submission would be considered as valid and information from the first submission was analyzed.

The demographic information section was used to gather information about departments where the nurses were working in, and their age, length of service, educational backgrounds, and job titles. The

nurses' perception-behavior scale for keeping surgical instruments moist was designed based on the HBM, with Cronbach's alpha of 0.911 and the great overall consistency. Validity test was performed through the use of content experts. After two rounds of expert consultation, the content validity index of each item ranged from 0.833 to 1.000, and that of universal agreement was 0.852. The nurses' perception-behavior scale for keeping surgical instruments moist covered 5 components and 36 items, of which six items were for the component "perceived susceptibility to instruments not kept moist," six items were for the component "perceived severity of instruments not kept moist," eight items were for the component "perceived benefits of keeping instruments moist," nine items were for the component "perceived barriers for keeping instruments moist," and seven items were for the component "self-efficacy in keeping instrument moist." The 5-point Likert scale was used for scoring, namely, 5 = strongly agree, 4 = agree, 3 = neither agree or disagree, 2 = disagree, and 1 = strongly disagree.

Data collection

Data were collected through cluster sampling. If respondent did not answer all questions in the questionnaire and did not submit the questionnaire successfully, we would not obtain any information about the unsubmitted questionnaire. A total of 360 questionnaires were distributed, and 360 questionnaires were returned, among which 351 questionnaires were valid. The valid response rate was 97.5%.

Statistical methods

Data were analyzed in SPSS Version 20.0. The enumeration data were described with frequency (relative frequency), and the measurement data were expressed with mean (±) and standard deviation (SD). A statistically significant difference ($p < 0.05$) was found through t-test, variance analysis, and multivariable linear regression analysis.

Results

Demographic information of the nurses

The 351 nurses' average length of service was 7.60 ± 8.204 years, their average age was 30.14 ± 7.327 years. 275 (78.35%) of them had bachelor's degree qualifications, and 169 (48.15%) of them were nurse practitioners (Table 1).

Table 1. Demographic information of nurses (n = 351)

Item	n	Assignment	Percentage
Age (years)			
< 25	68	1	19.37
25-30	160	2	45.58
31-35	54	3	15.39
36-40	36	4	10.26
41-45	12	5	3.42
46-50	12	6	3.42
> 50	9	7	2.56
Length of service (years)			
< 1	15	1	4.27
1-5	185	2	52.71
6-10	57	3	16.24
11-15	39	4	11.11
16-20	25	5	7.12
> 20	30	6	8.55
Educational background			
Junior college diploma or below	60	1	17.09
Bachelor	275	2	78.35
Master or above	16	3	4.56
Job title			
Nurse	94	1	26.78
Nurse practitioner	169	2	48.15
Supervising nurse	86	3	24.50
Associate senior nurse	2	4	0.57

Score of nurses' perception-behavior scale for keeping surgical instruments moist

For the 351 nurses, total score of nurses' perception-behavior scale for keeping surgical instruments moist was 139.93 ± 15.145, and the mean scale score was 4.21 ± 0.423. The HBM-based components placed in ascending order of their mean scores were perceived barriers for keeping instruments moist (3.47 ± 0.945), self-efficacy in keeping instruments moist (4.16 ± 0.666), perceived severity of instruments not kept moist (4.50 ± 0.574), perceived benefits of keeping instruments moist (4.57 ± 0.523), and perceived susceptibility to instruments not kept moist (4.62 ± 0.484).

Impact of age

Single factor analysis showed that age had an impact on nurses' perceived barriers for keeping instruments moist, with a statistically significant difference ($p = 0.001 < 0.05$) (Table 2).

Impact of length of service

Single factor analysis showed that length of service had an impact on nurses' perceived benefits of

Table 2. Impact of age on nurses' perception toward their behaviors for keeping surgical instruments moist

Item	Perceived severity of instruments not kept moist	Perceived susceptibility to instruments not kept moist	Perceived benefit of keeping instruments moist	Perceived barriers for keeping instruments moist	Self-efficacy in keeping instruments moist
Age (years)					
< 25	27.2 ± 3.012	24.38 ± 2.144	36.90 ± 4.023	22.57 ± 7.522	28.96 ± 4.180
25–30	27.04 ± 3.633	24.66 ± 1.958	36.81 ± 4.132	20.97 ± 8.645	29.21 ± 4.893
31–35	27.13 ± 3.108	24.46 ± 1.910	36.09 ± 4.319	25.13 ± 8.239	29.22 ± 4.521
36–40	27.03 ± 3.211	24.61 ± 1.793	36.53 ± 4.074	23.47 ± 8.365	29.47 ± 4.313
41–45	26.08 ± 4.033	24.17 ± 2.250	35.42 ± 4.122	26.50 ± 8.274	27.50 ± 4.719
46–50	25.92 ± 4.231	23.67 ± 2.015	35.33 ± 4.997	25.83 ± 8.032	27.92 ± 5.435
> 50	25.67 ± 4.387	23.89 ± 2.619	34.89 ± 5.183	30.56 ± 7.828	30.44 ± 5.615
t	0.652	0.454	0.834	4.033	0.553
p	0.689	0.842	0.544	0.001	0.767

Table 3. Impact of length of service on nurses' perception toward their behaviors for keeping surgical instruments moist

Item	Perceived severity of instruments not kept moist	Perceived susceptibility to instruments not kept moist	Perceived benefit of keeping instruments moist	Perceived barriers for keeping instruments moist	Self-efficacy in keeping instruments moist
Length of service (years)					
< 1	28.00 ± 3.464	25.33 ± 1.633	39.13 ± 2.134	19.87 ± 5.986	29.60 ± 3.795
1–5	27.30 ± 3.320	24.56 ± 2.018	36.88 ± 4.130	21.74 ± 8.636	29.37 ± 4.614
6–10	26.35 ± 3.533	24.47 ± 1.919	35.95 ± 3.988	22.89 ± 8.010	28.70 ± 4.953
11–15	27.05 ± 3.464	24.62 ± 2.021	36.13 ± 4.714	24.62 ± 8.359	29.13 ± 4.691
16–20	26.72 ± 3.234	24.24 ± 1.877	36.04 ± 3.889	23.00 ± 8.495	28.76 ± 3.919
> 20	26.00 ± 4.009	23.87 ± 2.193	35.23 ± 4.651	27.87 ± 8.080	28.40 ± 5.462
t	1.483	0.833	2.396	3.547	0.397
p	0.195	0.527	0.037	0.004	0.851

keeping instruments moist and perceived barriers for keeping instruments moist, with a statistically significant difference (p < 0.05) (Table 3).

Impact of educational background

Single factor analysis showed that educational background had no impact on nurses' perception toward their behaviors for keeping surgical instruments moist (Table 4).

Impact of job title

Single factor analysis showed that job title had an impact on nurses' perceived susceptibility to instruments not kept moist, perceived benefits of keeping instruments moist, and self-efficacy in keeping instruments moist, with a statistically significant difference (p < 0.05) (Table 5).

Multivariable linear regression analysis

Total score of nurses' perception-behavior scale for keeping surgical instruments moist was considered as the dependent variable. Age, length of service, and job title were considered as the independent variable. Stepwise regression (Alpha-to-Enter = 0.05, Alpha-to-Remove = 0.10) of multivariable linear regression analysis was carried out on the data. The analysis showed that one variable was entered into the regression equation, that is, length of service. A statistically significant difference existed, as shown in table 6.

Discussion

As revealed in the results of this study, the mean score of nurses' perception-behavior scale for

Table 4. Impact of educational background on nurses' perception toward their behaviors for keeping surgical instruments moist

Item	Perceived severity of instruments not kept moist	Perceived susceptibility to instruments not kept moist	Perceived benefit of keeping instruments moist	Perceived barriers for keeping instruments moist	Self-efficacy in keeping instruments moist
Educational background					
Junior college diploma or below	27.13 ± 3.332	24.32 ± 2.103	36.35 ± 4.173	22.67 ± 8.136	29.28 ± 5.256
Bachelor	26.89 ± 3.466	24.49 ± 1.992	36.49 ± 4.211	22.87 ± 8.651	29.04 ± 4.519
Master or above	28.29 ± 3.405	25.47 ± 1.463	38.24 ± 3.597	20.88 ± 8.108	29.41 ± 5.075
t	1.124	2.011	1.232	0.167	0.253
p	0.326	0.135	0.293	0.846	0.777

Table 5. Impact of job title on nurses' perception toward their behaviors for keeping surgical instruments moist

Item	Perceived severity of instruments not kept moist	Perceived susceptibility to instruments not kept moist	Perceived benefits of keeping instruments moist	Perceived barriers for keeping instruments moist	Self-efficacy in keeping instruments moist
Job title					
Nurse	27.90 ± 2.915	24.89 ± 1.769	37.86 ± 3.304	21.61 ± 8.751	30.01 ± 4.287
Nurse practitioner	26.67 ± 3.587	24.31 ± 2.150	36.09 ± 4.440	22.05 ± 8.266	28.72 ± 4.783
Supervising nurse	26.67 ± 3.582	24.45 ± 1.883	36.00 ± 4.279	25.48 ± 8.304	29.02 ± 4.733
Associate senior nurse	25.00 ± 1.414	24.00 ± 2.828	35.50 ± 4.950	23.00 ± 5.657	24.50 ± 2.121
t	3.199	1.992	4.422	3.987	2.245
p	0.083	0.008	0.005	0.115	0.024

keeping surgical instruments moist was 4.21 ± 0.423. According to score assignments in the survey, the score above 4 meant "agree"[8]. This indicated that the nurses had positive health belief in keeping surgical instruments moist, possibly because 78.35% of them had bachelor's degree qualifications. The nurses with high levels of education had greater ability to learn and master many new skills and had higher-level perception. Their score for perceived barriers for keeping instruments moist was low, possibly because the hospital where the participants worked in was for women and children and most surgeries here were obstetric and gynecologic ones. The time for preparing each operation was short, the turnover time of operating rooms was short, the operating room nurses were unable to timely moisten surgical instruments, and CSSD staff members were unable to timely receive the surgical instruments. All of these led to low score for perceived barriers for keeping instruments moist[7].

The single factor analysis showed that age, length of service, and job title affected nurses' perception toward their behaviors for keeping surgical instruments moist. With an increase of experience and knowledge, nurses' perception, and behaviors also changed. The nurses with shorter length of service perceived more benefits of keeping surgical instruments moist than those with longer length of service, but had significantly less perceived barriers for keeping instruments moist than those with longer length of service, possibly because the nurses with shorter length of service had less clinical experience and insufficient basic knowledge on keeping surgical instruments moist, and were not familiar with the relevant procedures. However, the nurses with longer length of service experienced occupational fatigue due to long period of working, and had decreasing perception to benefits of keeping surgical instruments moist, which affected their handling of keeping instruments moist.

Multivariable regression analysis showed that length of service had an impact on nurses' perception toward their behaviors for keeping surgical instruments moist. The shorter the length of service was, the greater

Table 6. Multivariable linear regression analysis on factors influencing nurses' perception toward their behaviors for keeping surgical instruments moist

Variable	B	Standard error	β	t	p	95% CI
Age	1.597	1.326	0.147	1.204	0.229	−1.011-4.206
Length of service	−2.923	1.466	−0.261	−1.993	0.047	−5.807-−0.039
Job title	−2.380	1.711	−0.114	−1.391	0.165	−5.745-0.985

R^2=0.055; adjusted R^2=0.047; F=6.721; p=0.001. CI: Confidential interval

perception of nurses to keeping instruments moist. The nurses with longer length of service had poorer attitude for keeping instruments moist than the newly employed nurses, possibly because such new nurses were full of enthusiasm in work but had less experience, and they handled surgical instrument moistening strictly according to requirements. In contrast, the nurses with longer length of service were insensitive to perception of the severity and benefits of keeping surgical instruments moist due to their long period of working, which led to poor health belief in keeping surgical instruments moist.

Conclusions

In summary, training on basic knowledge for keeping surgical instruments moist should be enhanced for nurses with shorter length of service, including regularly attending seminars, reading brochures, watching relevant videos, and weekly post-training follow-up should be strengthened. For nurses with longer length of service, their awareness to benefits of keeping surgical instruments moist and their confidence in overcoming barriers should be enhanced, and eventually they could fulfill their task for keeping surgical instruments moist.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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The effect of low-dose Cordyceps on ischemia-reperfusion injury of the kidney in rats

El efecto de dosis bajas de Cordyceps en la lesión por isquemia-reperfusión del riñón en ratas

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Abstract

Objective: None of studies have been conducted in terms of demonstrating the same effect with the low dose in cordycepin. In our study, we analyzed the histopathological and biochemical changes of low-dose Cordycepin(c) on a rat model in the kidney. **Materials and methods:** Twenty-four male Wistar Albino rats were randomly allocated to three groups (n = 8): the sham-control group (Group 1), the renal I/R-untreated (Group 2) group, and the I/R-C-treated (Group 3) group. Cordyceps was administered intraperitoneally at 5 mg/kg twice. Renal histological changes were compared and the relevant parameters of oxidative stress and inflammation were detected. **Results:** In blood and tissue biochemistry, it was observed that IL-1 Beta, IL 6, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3. It was determined that TAS values were increased in Group 3, and decreased in Group 2. In the histopathological evaluation, while Group 1 was evaluated as normal, significant kidney damage was detected in Group 2. It was determined that there was a significant decrease in kidney damage in Group 3. **Conclusion:** These results suggest that low dose Cordycepin was as effective as normal dose on renal ischemic reperfusion and reduction of damage.

Keywords: Cordyceps. Ischemia-reperfusion injury. Kidney.

Resumen

Objetivo: Ninguno de los estudios se ha realizado en términos de demostrar el mismo efecto con la dosis baja de cordicepina. En nuestro estudio, analizamos los cambios histopatológicos y bioquímicos de Cordycepin(c) en dosis bajas en un modelo de rata con isquemia-reperfusión (I/R) inducida en el riñón. **Materiales y métodos:** Veinticuatro ratas macho Wistar Albino se asignaron al azar a tres grupos (n = 8): el grupo de control simulado (Grupo 1), el grupo sin tratamiento I/R renal (Grupo 2) y el grupo tratado con I/R-C (Grupo 3). Cordyceps se administró por vía intraperitoneal a 5 mg/kg dos veces. Se compararon los cambios histológicos renales y se detectaron los parámetros relevantes de estrés oxidativo e inflamación. **Resultados:** En bioquímica sanguínea y tisular se observó que IL-1 Beta, IL 6, TNF alfa, MDA, TOS y OSI aumentaron en el Grupo 2 y disminuyeron en el Grupo 3. Se determinó que los valores de TAS aumentaron en el Grupo 3, y disminuyó en el Grupo 2. En la evaluación histopatológica, mientras que el Grupo 1 fue evaluado como normal, se detectó daño renal significativo en el Grupo 2. Se determinó que hubo una disminución significativa del daño renal en el grupo 3. **Conclusión:** Estos resultados sugieren que la cordicepina en dosis bajas fue tan efectiva como la dosis normal en la reperfusión isquémica renal y la reducción del daño.

Palabras clave: Cordyceps. Lesión por isquemia-reperfusión. Riñón.

Introduction

One of the most important causes of acute kidney injury (AKI) is the exposure of the kidney to Ischemia-reperfusion (I/R). In clinical practice, AKI may occur in conditions such as systemic hypotension, hypovolemia, cardiac arrest, renovascular surgery, cross-clamping of the aorta, partial nephrectomy, and kidney transplantation[1,2]. Renal ischemia in AKI causes damage and death of kidney cells, but damage may remain in the renal tissue despite reperfusion. The loss of nephrons in the kidney after this damage is significant for the kidney[3,4]. Since short-term ischemia arising after the transplant of a kidney from a living body or a cadaver is correlated with renal transplant rejection and chronic allograft nephropathy, it also gains critical importance for I/R tissue in clinical follow-up[5,6].

After experimental I/R, cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which are accepted as inflammatory mediators, are secreted, and these are considered as determinants in the I/R process[7]. In addition, TAS, TOS, and OSI parameters were used to evaluate the total antioxidant capacity in I/R[8].

Cordycepin, which has been used as a medicine for 300 years in China, is an adenosine analog derived from the *Cordycepin militaris* culture and has been reported as a nucleoside antibiotic for the first time[9]. Recently, the importance of Cordycepin in the treatment of various diseases has been increasing due to its different pharmacological effects. Cordycepin has been proven by many studies to be a potent antioxidant and anti-inflammatory agent[10,11]. Moreover, immunomodulatory, antitumor, antiprotease, antimicrobial, hypolipidemic, hypoglycemic, analgesic, and protective effects of Cordycepin on various organs have been reported. Cordycepin has been reported to exert its anti-inflammatory and analgesic effects through inhibition of IL-1β, IL-6, TNF-α, NFκB, iNOS, and COX-2[9]. These effects are very significant in preventing organ damage after renal I/R. However, some side effects have been observed when used in high doses[12]. Therefore, in our study, we aimed to analyze the histopathological and biochemical changes of intraperitoneally administered low-dose *Cordycepin* in the kidney I/R model created in rats.

Materials and methods

For our study, the decision was made by Dicle University Prof Dr Sabahattin Payzın Health Science Research and Application Center's experimental animals local ethics committee with the protocol number 2021/12. The study was carried out in Dicle University Experimental Study laboratory. 24 male Wistar Albino rats, each weighing 200-250 g, were used in the study. The animals included in the study were randomly divided into three groups. Rats were fed a standard rodent diet and water under appropriate temperature and light conditions.

Preparation, anesthesia, and surgical procedures

General anesthesia was maintained by intramuscular administration of 5-10 mg/kg of Xylazine (Rompun Vet; Bayer AG, Istanbul, Turkey) and 50-70 mg/kg of ketamine hydrochloride (Ketalar; Eczacıbaşı, Istanbul, Turkey) before surgery. The abdomen was cleaned with 10% Povidone-iodine solution after 100 U/kg heparin (intraperitoneal) administration to prevent renal artery thrombosis. The abdomens of the rats were entered with a midline incision. After right nephrectomy, the left renal artery was found to induce I/R, and operations were performed according to the groups.

– Group I (Sham group) (n = 8): All animals underwent left nephrectomy 6 h after right nephrectomy.
– Group II (n = 8): After right nephrectomy, a non-traumatic vessel clamp was placed on the left renal artery for 60 min. Then, the clamp was opened, and the left kidney underwent reperfusion for 6 h. Physiological saline was administered intraperitoneally twice, 30 min after ischemia and just before reperfusion.
– Group III (n = 8): Following the right nephrectomy, a non-traumatic vessel clamp was placed on the left renal artery for 60 min and then reperfusion was applied for 6 h. A total of 5 mg/kg of Cordyceps was administered intraperitoneally twice, 30 min after ischemia and just before reperfusion.

In each stage of the experiment, the animal was prevented from suffering with general anesthesia. No animal perished whereas the experiment was being executed. After 6 h of reperfusion, all rats were sacrificed with high-dose anesthetic agent. The collected blood and a part of each kidney were prepared for the biochemistry laboratory for the biochemical variables IL1, IL6, TNF alpha, total oxidant activity (TOA), and total antioxidant activity (TAA), and the remaining tissue was prepared for the pathology laboratory for histochemical examination.
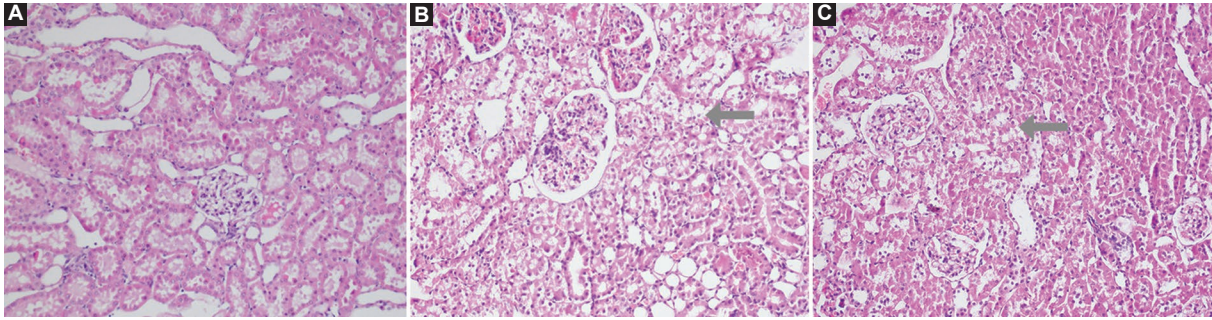
Figure 1. *Representative kidney sections stained with H&E at the end of 6 h' reperfusion.* **A:** *sham-control animals; normal histological characteristic of glomeruli and tubules.* **B:** *rats subjected to renal I/R injury; marked vacuolar changes in tubular epithelium and loss of tubular epithelial cells.* **C:** *rats subjected to renal I/R injury, pretreated with cordycepin: decreased vacuolization of tubule epithelium (H&E, ×200). I/R: Ischemia/reperfusion.*

Biochemical examination

The blood samples obtained were stored in ice and delivered to the Biochemistry Laboratory right after the cardiac puncture. Blood samples were centrifuged at 3000/min for 3 min, serum samples were separated, and IL-6, IL-1β, MDA, TNF-α, TAS, and TOS levels were measured.

The data obtained for tissue biochemistry were processed into a pre-prepared form.

Tissue pieces weighing 0.10-0.22 g were washed with physiological saline several times and dried thoroughly with blotting paper, then placed in Eppendorf tubes and stored at –85 C until the day of examination. The tissues were taken from the freezer and thawed, and then homogenized with an automatic tissue homogenizer when all samplings were completed. IL-6, IL-1β, MDA, TNF-α, TAS, and TOS levels were measured from the collected kidney tissue and blood.

Histopathological examination

Tissue pieces separated for histopathological examination were fixed in 10% formaldehyde solution. Samples that were followed up after fixation were blocked with paraffin. Standard sections with a thickness of 4 μ were prepared for microscopic examination by staining with Hematoxylin-Eosin (HE). All preparations were examined by the same pathologist. Based on the scoring used by Chatterje et al.[13] Scoring was evaluated as Grade 0: no diagnostic change, Grade 1: tubular cell swelling, loss of brush borders, nuclear reduction with up to 1/3 of the tubular profile with nuclear loss, Grade 2: in addition to Grade 1, greater nuclear reduction with up to 2/3 of the tubular profile with nuclear loss, and Grade 3: greater nuclear

reduction with more than 2/3 of the tubular profile with nuclear loss.

Statistical analysis

The data were statistically analyzed with SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was used to compare multiple independent samples. When a significant difference was detected, two independent samples were evaluated by a Mann-Whitney U-test for paired in-group comparison. $p \leq 0.05$ for overall comparisons and $p = 0.017$ for the Bonferroni Corrected Mann-Whitney U test was considered statistically significant.

Results

In blood biochemistry, it was observed that IL-1 Beta, IL 6 TOS, TNF alpha, MDA, and OSI increased in Group 2 and decreased in Group 3. In the comparison between the groups, a statistically significant decrease was observed in IL-1 Beta, IL6, TNF alpha, and OSI values when Group 2 and Group 3 were compared ($p < 0.05$).

In tissue biochemistry, it was observed that IL-1 beta, IL 6, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3. A statistically significant decrease was determined in IL-1 Beta, IL6, TOS, and OSi values when Group 2 and Group 3 were compared ($p < 0.05$) (Table 1).

Blood and tissue

TAS values increased in Group 1 and Group 3, and decreased in Group 2. In the comparison between the groups, a statistically significant increase was observed

Table 1. Tissue parameters

Groups	IL-β	IL-6	TNF-α	MDA	TAS	TOS	OSİ
Group 1 (S)	551.12 ± 50.7	34.47 ± 2.50	67.02 ± 12.82	8.80 ± 2.24	1.07 ± 0.15	49.15 ± 12.3	45.85 ± 12.1
Group 2 (I/R)	643.50 ± 67.4	38.65 ± 2.75	77.24 ± 12.02	13.89 ± 2.52	0.80 ± 0.09	75.72 ± 11.8	94.42 ± 18.6
Group 3 (C)	554.30 ± 18.9	34.74 ± 2.33	69.06 ± 10.3	12.55 ± 1.45	1.07 ± 0.17	55.68 ± 6.48	52.57 ± 10.8
p	0.002	0.018	0.180	0.178	0.009	0.004	0.003

Meaningful comparison (intergroup) 2-3. C: cordycepin, IL-1β (pg/mL): ınterleukin-1 beta, IL-6 (pg/mL): ınterleukin-6, I/R: ıschemia/reperfusion, MDA (µM): malondialdehyde, OSİ (TOS/TAS): oxidative stress index, S: Sham, TAS (µm Toroxequiv./L): total antioxidant status, TNF-α (ng/L): tumor necrosis factor-alpha, TOS (µm H_2O_2 equiv./L): total oxidative stress

Table 2. Blood parameters

Groups	IL-1β	IL-6	TNF	MDA	TAS	TOS	OSİ
Group 1 (S)	659.94 ± 85.1	59.18 ± 11.9	128.75 ± 23.9	20.15 ± 2.65	0.57 ± 0.18	38.78 ± 3.37	71.71 ± 15.9
Group 2 (I/R)	908.32 ± 99.4	76.08 ± 10.6	209.35 ± 86.4	22.52 ± 3.83	0.39 ± 0.07	40.21 ± 2.76	104.14 ± 18.8
Group 3 (C)	752.15 ± 86.8	66.08 ± 3.61	144.39 ± 28.9	20.86 ± 2.65	0.56 ± 0.19	34.15 ± 7.46	64.57 ± 18.4
p	0.013	0.025	0.025	0.33	0.025	0.142	0.003

Meaningful comparison (intergroup) 2-3. C: Cordycepin, IL-1β (pg/mL): ınterleukin-1 beta; IL-6 (pg/mL): ınterleukin-6, I/R: ıschemia/reperfusion, MDA (µM): malondialdehyde, OSİ (TOS/TAS): oxidative stress index, S: Sham, TAS (µm Toroxequiv./L): total antioxidant status, TNF-α (ng/L): tumor necrosis factor-alpha, TOS (µm H_2O_2 equiv./L): total oxidative stress.

between Group 2 and Group 3 (p < 0.05). All biochemical parameters are summarized in table 2.

While no change was detected in Group 1 in the histopathological evaluation, it was observed that six kidneys in Group 2 had Grade 2 and two kidneys had Grade 3 cell and nuclei deterioration (Fig. 1). It was determined that there was a significant decrease in kidney damage in Group 3, which was given Cordycepin, Grade 1 in 6 kidneys, Grade 2 in one kidney and Grade 3 in one kidney. A statistically significant difference was observed when Groups 2 and 3 were compared (p = 0.007). Detailed analysis of the findings is summarized in table 3.

Table 3. Histopathological parameters of the all groups

Groups	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total (%)
Group 1 (S)	8 (100)	0	0	0	8 (100)
Group 2 (I/R)	0	0	6 (75)	2 (25)	8 (100)
Group 3 (C)	0	6 (75)	1 (12.5)	1 (12.5)	8 (100)

Meaningful comparison p = 0.000 (Group 1 vs. 2 and Group 1 vs. 3), p = 0.013 (Group 2 vs. 3). Grade 0: No diagnostic change, Grade 1: tubular cell swelling, loss of brush borders, nuclear reduction with up to 1/3 of the tubular profile with nuclear loss, Grade 2: in addition to Grade 1, greater nuclear reduction with up to 2/3 of the tubular profile with nuclear loss, Grade 3: greater nuclear reduction with more than 2/3 of warm ischemia/reperfusion injury and promotes hepatocyte proliferation. C: Cordycepin, I/R: ıschemia/reperfusion, S: Sham

Discussion

Despite surgical, medical, and pharmacological advances regarding renal vascular injuries, serious problems remain regarding the consequences of short-term I/R after renal vascular surgery, trauma, and transplant[14]. Free oxygen radicals, which are released in large amounts in the ischemic process, occur when they are reperfused, and much more tissue damage occurs[15,16]. Oxidative stress, which plays a role in the pathogenesis of I/R, appears as damage to organs due to an uncontrolled increase in reactive oxygen species (ROS) or a decrease in elimination.

Significant damage occurs in the kidney tubules and glomeruli as a result of increased ROS and pro-inflammatory mediators with reperfusion occurring after the ischemic phase[17,18].

Antioxidant capacity and antioxidant agents are used for the treatment of excessive production of free oxygen radicals due to cellular response after renal I/R[19]. In this study, we investigated the histopathological and biochemical parameters of kidney I/R on a rat model of low dose of Cordycepin[10,11], which has been proven by many studies due to its different pharmacological effects such as antioxidant, anti-inflammatory fibrinolytic, antiapoptotic, antioxidant, antimicrobial,

immunomodulator, nephroprotective, and hepatoprotective and has become increasingly important in the treatment of various diseases.

TNF Alpha, IL1B, and MDA are rapidly released after tissue damage and considered as I/R markers[20]. In addition to these, it has been observed that IL6 is also increased as a pro-inflammatory marker in I/R[21]. TAS value is widely used in the determination of total antioxidant capacity, and OSI is a parameter that shows the affinity of oxidant and antioxidants in the oxidant-antioxidant balance[22,23]. Studies have demonstrated that when an anti-inflammatory substance is used, TAS can increase, and its oxidative values are suppressed by decreasing TOS and OSI values[8]. MDA lipid peroxidation, which is also accepted as a broad marker of oxidative stress, occurs as the final production of the enzyme and has been evaluated from many I/R developments[20]. In our study, it was observed that IL-1 Beta, IL 6 TOS, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3 in biochemistry. In the comparison between the groups, a statistically significant decrease was found in IL-1 Beta, IL6, TNF alpha, TOS, and OSI values when Group 2 and Group 3 were compared (p < 0.05). Again, in the biochemical evaluation, the TAS value was increased in Group 1, Group 3, and decreased in Group 2. In the comparison between groups, rat studies were conducted between Group 2 and Group 3, and in these studies, it was determined that cordycepin given orally in different doses on rat kidneys decreased pro-inflammatory cytokine secretion, inflammatory reaction, decreased oxidative stress and was pathologically beneficial[24].

In another study of rats, 10 mg/kg dose of Cordycepin was found to be beneficial on histological and oxidative stress parameters in the group[25]. With such benefits of Cordycepin, it has been reported that severe stomach and diarrhea symptoms occur in high-dose use[12]. Although there is no dose-dependent study in these patients, no side effects were noted in the studies of drugs given 10 mg. The aim of our study is to demonstrate that lower doses can have the same effect and to reduce the possible side effects of high-dose drug use. When we evaluate all these, we see that administering 5 mg/kg intraperitoneally shows the same protective effect as those at higher doses; however, this will become clear with the sharing of larger studies.

As a result, it is observed that low dose cordycepin is a highly nephroprotective agent against renal I/R when given intraperitoneally in diseases that cause I/R in a short time such as organ transplantation, trauma, and sepsis. In this study, it was demonstrated that the nephroprotective effect of cordycepin could be even at half the dose, and the possible side effects of the drug given overdose were reduced depending on the dose, however, different studies comparing more doses are needed for this result.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Appendiceal neuroendocrine neoplasia: analysis of 50 patients

Neoplasia neuroendocrina apendicular: análisis de 50 pacientes

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Abstract

Objective: The objective of this study was to investigate the clinical, surgical, and pathological findings of appendiceal neuroendocrine neoplasms (ANNs). **Materials and methods:** The demographic, clinical, surgical, and pathological characteristics of 50 patients with ANN were analyzed. The patients were also classified as Group 1 (< 40 years, n = 37) and Group 2 (≥ 40 years, n = 13), and compared each other in terms of all parameters. **Results:** Acute appendicitis was the pre-operative clinical presentation in 48 (96%) patients. Appendectomy (94%) was the most common surgical procedure. Mean tumor size was 8.6 mm (1-70 mm). Approximately half of the tumors (46%) were T1. There was no lymphatic and distant metastasis. The patients in Group 2 (15.4 mm) had a higher mean tumor size than patients in Group 1 (6.3 mm) (p < 0.001). The two groups were similar in other characteristics (p > 0.05). **Conclusions:** ANNs are usually diagnosed after histopathological evaluation due to the lack of specific clinicoradiological signs. Therefore, carefull intraoperative examination of appendectomy specimens may increase the possibility of suspecting these tumors. The results also showed that ANNs were bigger in patients above 40-years-old. Although not statistically significant, ANNs tended to have higher grade and to be more located at the base of the appendix in this group of patients.

Keywords: Appendix. Carcinoid tumor. Neuroendocrine neoplasia.

Resumen

Objetivo: Investigar los hallazgos clínicos, quirúrgicos y patológicos de las neoplasias neuroendocrinas (RNA) apendiculares. **Método:** Se analizaron las características demográficas, clínicas, quirúrgicas y patológicas de 50 pacientes con RNA. Los pacientes también fueron clasificados como Grupo 1 (< 40 años, n = 37) y Grupo 2 (≥ 40 años, n = 13), y se compararon entre sí en términos de todos los parámetros. **Resultados:** La apendicitis aguda fue la presentación clínica preoperatoria en 48 (96%) pacientes. La apendicectomía (94%) fue el procedimiento quirúrgico más común. El tamaño medio del tumor fue de 8,6 mm (1-70 mm). Aproximadamente la mitad de los tumores (46%) eran T1. No hubo metástasis linfáticas ya distancia. Los pacientes del Grupo 2 (15.4 mm) tenían un tamaño tumoral medio mayor que los pacientes del Grupo 1 (6.3 mm) (p < 0.001). Los dos grupos fueron similares en otras características (p > 0.05). **Conclusiones:** Las RNA suelen diagnosticarse tras evaluación histopatológica debido a la falta de signos clínico-radiológicos específicos. Por lo tanto, el examen intraoperatorio cuidadoso de las muestras de apendicectomía puede aumentar la posibilidad de sospechar estos tumores. Los resultados también mostraron que las ANN eran más grandes en pacientes mayores de 40 años. Aunque no estadísticamente significativas, las ANN tendieron a tener mayor grado y estar más ubicadas en la base del apéndice en este grupo de pacientes.

Palabras clave: Apéndice. Tumor carcinoide. Neoplasia neuroendocrina.

Introduction

Primary appendiceal neoplasms are rare tumors and found in up to 1% of all appendectomy specimens[1]. Among those, appendiceal neuroendocrine neoplasms (ANNs), formerly known as carcinoids, are the most common type of tumor[2]. Due to the lack of specific clinical and radiological findings, ANNs are almost always diagnosed as a result of the final pathological evaluation of the appendectomy specimen performed for acute appendicitis.

ANNs are most often observed in the second or third decade of life, although it can be seen in pediatric and geriatric polpulations[3]. In general, ANN is quite slow and rarely develops widespread disease, which makes it one of the cancers with the best prognosis.

In the surgical management, a simple appendectomy is generally considered sufficient for ANNs smaller than 1 cm while a broader surgical approach such as right-sided hemicolectomy may be required for tumors larger than 2 cm. However, there is a gray zone for tumors between 1 and 2 cm[3]. In this group, treatment and prognosis are also related to several factors such as depth of invasion, mitotic and Ki67 index, presence of perineural, and lymphovascular invasion, in addition to tumor size[4].

Due to the low incidence and low probability of preoperative diagnosis, the treatment and follow-up protocols of ANNs are mostly based on retrospective and relatively small-scale clinical studies[5-7]. Therefore, having sufficient information about this rare tumor is of great importance for its proper management. In this study, the clinical, surgical, and pathological findings of these tumors were aimed to present in patients with ANN.

Materials and methods

Study design

The Ethics Committee approval (no: E1-22-2399, date: 23.02.2022) was obtained from Ankara City Hospital. All study procedures were performed in accordance with local ethical standards and with the 1964 Helsinki Declaration and its amendments.

The patients who were diagnosed with ANN between January 2010 and December 2021 were included in this retrospective study. The demographic characteristics, clinical findings, operative data, and histopathological records were collected from the hospital information system. Grading and tumor-node-metastasis staging were evaluated according to the European Neuroendocrine Tumor Society (ENETS)[8]. The patients under 18-years-old and other types of appendiceal tumors were excluded from the study.

All data obtained from the patients included in the study were evaluated by comparing them with clinical studies in the literature. In addition, based on the knowledge that ANNs are most common in the 2nd and 3rd decades, the patients were divided into two groups as under and above 40 years old and compared in terms of all operative and histopathological findings.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows 22.0 (IBM, Armonk, NY). A descriptive analysis was expressed as mean plus standard deviation (SD) for parameters with homogenous distributions or median plus range for parameters with heterogeneous distributions. Categorical variables were expressed as their frequency with respective proportion in percentage. χ^2 (Fisher's exact test) was used to compare two groups. $p = 0.05$ was considered significant.

Results

All clinical parameters, surgical data, and histopathological findings of the study population are presented in Table 1. A total of 50 patients were included in the study, of whom 27 (54%) were male and 23 (46%) were female. The mean age of the patients was 32.2, ranging between 18 and 72 years old. Acute appendicitis was the pre-operative clinical presentation in 48 (96%) patients, whereas two patients (4%) were operated for mesenteric ischemia and gynecological tumor. None of the patients had a suspicion of ANN during the pre-operative work-up period. Appendectomy (94%) was the most common surgical procedure, while right-sided hemicolectomy was performed in three (6%) cases.

According to the final histopathological evaluation, the majority of the tumors (92%) were localized at the tip of the appendix. Mean tumor size was 8.6 mm. Forty-seven (94%) patients had classical type of ANN, while 3 (6%) patients had tubular type. Approximately half of the tumors (46%) were T1 according to the ENETS staging system. There was no lymphatic or distant metastasis.

Table 1. Clinical, surgical, and pathological characteristics of the patients (n = 50)

Patient characteristics	n (%)
Age (mean ± SD, y)	32.2 ± 13.1 (18-72)
Gender (Female/Male)	23 (46%)/27 (54%)
Pre-operative clinical presentation	
Acute appendicitis	43 (93.5%)
Mesentary ischemia	2 (4.3%)
Gynecological procedure	1 (2.2%)
Procedure	
Appendectomy	47 (94%)
Right-sided hemicolectomy	3 (6%)
Tumor localization	
Tip of appendix	45 (90%)
Body of appendix	3 (6%)
Base of appendix	2 (4%)
Histological pattern	
Classical (insular) type	47 (94%)
Tubular type	3 (6%)
Tumor size (mean ± SD, mm)	8.6 ± 3.1 (1-70)
Tumor infiltration (T)	
T1	23 (46%)
T2	10 (20%)
T3	12 (24%)
T4	5 (10%)
Presence of LVI	5 (10%)
Grading	
Grade 1	43 (86%)
Grade 2	5 (10%)
Grade 3	2 (4%)

Age and tumor size were presented as mean ± SD, other variables were presented as n (%).

LVI: lymphovascular invasion; SD: standard deviation; y: year, mm: milimeter.

Two patients died during the follow-up period. The first patient who was operated due to extensive mesentary ischemia died within the 30 days of surgery. The second patient who underwent right hemicolectomy due to big T4 tumor died 1 year after the initial operation, due to the dissemination of cancer.

Given that ANN usually occurs in 2nd and 3rd decads, the patients were divided into two groups as Group 1 (< 40-years-old, n = 37) and Group 2 (≥ 40-years-old, n = 13). The two groups were, then, compared each other in terms of all clinicopathological characteristics (Table 2). The patients in Group 2 had a higher mean tumor size comparison to patients in Group 1. Although there was not a statistically difference, all tumors were found at the tip/body of the appendix in Group 1, while two of 13 tumors (15.5%) were localized at the base of the organ in Group 2 (p = 0.064). Similarly, all tumors were reported as grade 1/2 in Group 1, whereas two patients in Group 2 had grade 3 tumors (p = 0.064).

Discussion

ANNs are quite difficult to diagnosed during the pre-operative workup, due to the rarity and non-specific symptomatology. Therefore, these tumors are generally detected after pathological examination of a resected appendix specimen[1,9,10]. Similarly, none of the patients in our study had a suspicion of ANN pre-operatively. Except for two patients who were diagnosed after surgery for mesenteric ischemia and gynecological tumor, all patients were operated for acute appendicitis. Carcinoid syndrome, characterized by episodic flushing and diarrhea due to systemic effects of serotonin produced by the hepatic lesions, is an extremely rare consequence of ANN and is usually associated with the presence of metastatic disease[3]. There was no patient developed carcinoid syndrome in our series.

ANNs usually occur in young patients of second and third decads of their lives and have been reported slightly more common in women[3,4,11]. In similar, the mean age of the patients was 32.2 years in our cohort. However, males were slightly more numerous than females, probably due to the small number of the study population.

The majority of ANNs are subcentimetric tumors and located at the distal part of the appendix, which can explain the non-specific clinical presentation and the difficult radiological diagnosis[12-14]. In our work, 68% of the tumors were smaller than one centimeter and %90 were localized at the tip of the organ, consistent with the literature. In parallel, ANNs are often limited to the appendix and rarely develop lymphatic or distant metastatic disease. Although various risk factors such as higher tumor size, higher grade, and presence of lymphovascular infiltration have been found to be associated with nodal spread, no patient had metastasis in the present study[15].

Although tumor size is the most important factor for the surgical decision in these tumors, several histological features, including location of lesion within the appendix, Ki-67 proliferation index, and tumor grade based on number of mitoses, are also taken into consideration in the decision process. In this context, the staging system proposed by ENETS differs from the American Joint Commission on Cancer (AJCC) grading system which only considers tumor size. Generally,

Table 2. The comparison of clinical, surgical, and pathological characteristics between the two groups

Parameters	Group 1 (n = 37)	Group 2 (n = 13)	p-value
Female/Male	17/20	6/7	1.000
Pre-operative clinical presentation			0.064
Acute appendicitis	37 (100%)	11 (84.5%)	
Other reasons*	0 (0%)	2 (16.5%)	
Procedure			1.000
Appendectomy	35 (94.6%)	12 (91.7%)	
Right-sided hemicolectomy	2 (5.4%)	1 (8.3%)	
Tumor localization			0.064
Tip/body of appendix	37 (100%)	11 (84.5%)	
Base of appendix	0 (0%)	2 (15.5%)	
Histological pattern			1.000
Classical type	35 (94.6%)	12 (91.7%)	
Tubular type	2 (5.4%)	1 (8.3%)	
Tumor size (mean ± SD, mm)	6.3	15.4	**< 0.001**
Tumor infiltration (T)			0.278
T1	18 (48.7%)	5 (38.5%)	
T2	7 (18.9%)	3 (23%)	
T3	10 (27%)	2 (15.5%)	
T4	2 (5.4%)	3 (23%)	
Presence of LVI	4 (10.8%)	1 (8.3%)	1.000
Grading			0.064
Grade 1-2	37 (100%)	11 (84.5%)	
Grade 3	0 (0%)	2 (15.5%)	

Tumor size was presented as mean ± SD, other variables were presented as n (%).
LVI: lymphovascular invasion; SD: standard deviation; y: year, mm: milimeter.
*Mesentary ischemia and gynecological operation. CI 95%: confidence interval at 95%.

most of the cases with ANNs are well-differentiated and low-grade tumors[16]. In our study, only two patients had high grade tumors according to the higher Ki-67 proliferation index and higher number of mitoses.

The surgical treatment of ANNs mainly depends on the stage of the disease and consists of two main surgical approaches including simple appendectomy and right-sided hemicolectomy[3,8]. Given that these tumors are often small and diagnosed after the appendectomy, no further treatment is required in the majority of cases. In the case of a tumor smaller than one centimeter, appendicectomy is sufficient if the resection margin is clear. The patients with ANNs > 2 cm, however, should be treated with a right-sided hemicolectomy and lymph node dissection[17]. There is a gray zone for the tumors between 1 and 2 cm. In these tumors, the possibility of lymphatic or distant metastasis is not high. However, a right-sided hemicolectomy can be considered for the tumors with negative risk factors including mesoappendiceal infiltration > 3 mm, high grade, and presence of lymphovascular invasion[18,19]. In

case of positive resection margin, after appendectomy should also be required an oncological right-sided hemicolectomy. In our series, a right-sided hemicolectomy was performed for two patients of whom one had a big tumor > 2 cm and one had suncentrimetric tumor with negative risk factors.

Based on the knowledge that appendiceal neuroendocrine tumors are most common in the 20s and 30s, we divided the patients into two groups as under and above 40 years old and examined whether there was a difference between the two age groups in terms of clinicopathological features. To the best of our knowledge, there is no study comparing different age groups in the current literature, which may be due to the low incidence of ANN and the small number of patients in the published case series. In our study, the patients above 40 years had a higher mean tumor size comparison to younger patients. In addition, although there was not a statistically difference, all tumors were found at the tip/body of the appendix in younger group, while two of 13 tumors (15.5%) were localized

at the base of the organ in the older group. Smilarly, all tumors were reported as grade 1 or 2 in younger patients, whereas two patients in other group had grade 3 tumors. It should be noted here that the small number of patients in the subgroups makes it difficult to interpret these results. However, it is a fact that many tumors exhibit different clinicopathological behaviors in different age groups. In this regard, these results obtained from the present study may inspire further larger-scale studies.

Routine post-operative follow-up is not not necessary for the ANNs smaller than 2 cm. However, a complete colonoscopic examination is recommended to rule out synchronous colorectal cancer[9,20,21]. In addition, ANNs may be multifocal or associated with gastrointestinal stromal tumors. Therefore, it should be kept in mind that intraoperative inspection in patients with suspected neuroendocrine neoplasia and detailed radiological evaluation in cases diagnosed incidentally after pathological evaluation should be performed[22]. The patients in our cohort were routinely directed to the medical oncology unit. No synchronous intestinal or colorectal tumor was detected during the post-operative follow-up period.

In general, the prognosis for small ANNs is excellent. However, tumors bigger than 2 cm, which are associated with up to 30% nodal or distant metastasis, have 5-year survival rate of 31%[4]. In addition, goblet cell carcinoid tumor, an aggressive type of ANN, follows a worse course than classical ANN. In the present study, no goblet cell carcinoid tumor was detected histopathologically. Two out of 50 patients died during the follow-up period, of whom one had a big tumor invaded serosa and the other one was operated for extensive mesentary ischemia.

There are a few limitations to this study. First, it was conducted in a single center, which may limit the generalizability of the results. A relatively small sample size is another limitation, which make it difficult to interpret subgroup findings. However, the results may be useful to fill the gap in the literature.

Conclusions

ANNs are usually diagnosed after histopathological evaluation due to the lack of specific clinical and radiological findings. Therefore, carefull examination of appendectomy specimens intraoperatively may increase the possibility of suspecting these tumors. The results showed that ANNs are bigger in patients above 40 years old than in youngers. Alhtough not

statistically significant, these tumors tended to have higher grade and to be more located at the base of the appendix in patients over 40 years. Further larger-scale studies will be useful in demonstrating behavioral trends of ANNs in different age groups.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Simplified acute physiology score II and Mannheim peritonitis index are associated with in-hospital mortality in patients with abdominal sepsis admitted to ICU

Simplified acute physiology score II y Mannheim peritonitis index se asocian a mortalidad intrahospitalaria en pacientes con sepsis abdominal ingresados a la UCI

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Abstract

Objective: The objective of this study was to assess the association and interaction of laboratory parameters, Simplified Acute Physiology Score II (SAPSII), Modified Shock Index (MSI), and Mannheim Peritonitis Index (MPI) with in-hospital mortality. **Material and methods:** We conducted a single-center case–control study. Adult patients with abdominal sepsis were included from May 2015 to May 2020. Baseline characteristics, laboratory parameters, SAPSII, MSI, and MPI scores at admission were collected. A principal component (PC) analysis was applied to evaluate variable interactions. In-hospital mortality risk was determined through logistic regression models. **Results:** One hundred and twenty-seven patients were identified, 60 of which were included for analyses. Non-survivors (48.4%) had a higher frequency of hypertension, lactate and MPI, and lower BE and alactic BE levels. Eight PCs were obtained, PC1 being a linear combination of pH, AG, cAG, alactic BE, bicarbonate, and BE. MPI (OR = 9.87, 95% CI: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, 95%CI: 1.01-1.14, p = 0.01), and PC1 (OR = 2.13, 95%CI: 1.12-4.76, p = 0.04) were significantly associated with mortality in univariate analysis, while MPI (OR = 10.1, 95%CI: 3.03-40.06, p = 0.0003) and SAPSII (OR = 1.07, CI95%: 1.01–1.14, p = 0.02) remained significant after adjusting for age and sex. **Conclusion:** MPI and SAPSII were associated with mortality, although the interaction of laboratory parameters was not.

Keywords: Septic shock. Abdominal sepsis. Mortality.

Resumen

Objetivo: *Evaluar la asociación e interacción de los parámetros de laboratorio, SAPSII, MSI y MPI con la mortalidad intrahospitalaria.* **Materiales y métodos:** *Nosotros realizamos un estudio de casos y controles de pacientes adultos con sepsis abdominal desde mayo 2015 a mayo 2020. Recolectamos las características basales, parámetros de laboratorio, SAPSII, MSI y MPI al ingreso. Se aplicó un Análisis de Componentes Principales. El riesgo de mortalidad intrahospitalaria se determinó mediante modelos de regresión logística.* **Resultados:** *Identificamos 127 pacientes, 60 de los cuales se incluyeron. Los no supervivientes (48,4%) tuvieron mayor frecuencia de HAS, lactato y MPI, y menores niveles de EB y EB aláctico. Se obtuvieron ocho Componentes Principales (PC), siendo PC1 una combinación lineal de pH, AG, cAG, EB aláctico, bicarbonato y EB. MPI (OR = 9.87, IC95%: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, IC95%: 1.01-1.14, p = 0.01) y PC1 (OR = 2.13, IC95%: 1.12-4.76, p = 0.04) se asociaron significativamente con la mortalidad en el análisis univariado, mientras que MPI (OR = 10.1, IC95%: 3.03-40.06, p = 0.0003) y SAPSII (OR = 1.07, IC 95%: 1.01-1.14, p = 0.02) permanecieron significativos después del ajuste por edad y sexo.* **Conclusiones:** *MPI y SAPSII se asociaron con mortalidad, aunque la interacción de los parámetros de laboratorio no lo hizo.*

Palabras clave: *Choque séptico. Sepsis abdominal. Mortalidad.*

Introduction

Intra-abdominal infections are the second most frequent cause of sepsis worldwide, only surpassed by pneumonia. These infections can be classified as uncomplicated or complicated depending on their severity. Uncomplicated intra-abdominal infections seldom cause critical illness. On the contrary, complicated intra-abdominal infections, also referred to as "abdominal sepsis," lead to localized or diffuse peritonitis and subsequent sepsis[1]. Determinants of complicated infections include patient susceptibility, age, and comorbidities, among others[2].

Abdominal sepsis is distinguished by a systemic response to infection which initially develops within the organs of the abdominal cavity[3]. Up to ~5% of patients admitted to an intensive care unit (ICU) due to infectious diseases ultimately have abdominal sepsis[4,5]. Worldwide, it is a major cause of non-trauma deaths in emergency departments[6] with mortality rates being as high as 40%[7]. Therefore, prompt recognition of the infection site and early antimicrobial therapy are essential to reduce mortality[8]. A control on the source of infection should occur within 6-12 h after diagnosis since each hour of delay is associated with higher mortality rates[9].

Various scoring systems have been developed and validated to predict mortality in patients with abdominal sepsis, such as the Simplified Acute Physiology Score II (SAPSII), Modified Shock Index (MSI), and Mannheim Peritonitis Index (MPI), all of which allow for identification of patients at high mortality risk (e.g. MPI > 25 points)[10]. MPI is a mortality prediction index that assesses eight risk factors, with scores ranging from 0 to 47 points. Its sensitivity and specificity are deemed at 95.9% and 80%, respectively[11,12].

In addition, numerous biomarkers such as procalcitonin, neutrophil-to-lymphocyte ratio, and C-reactive protein have also been assessed as potential mortality predictors. Most studies have addressed them separately, and few studies have addressed them concurrently[13-17]. On the other hand, the role of acid-base disturbances, though considered important predictors of adverse outcomes in sepsis[18-20] since they reflect impairment at different levels of organ systems, has seldom been explored in the specific context of intra-abdominal infections, with the exception of serum lactate[21,22].

For the above reasons, the interaction between different scoring systems and laboratory parameters, as well as their weight on mortality in patients with abdominal sepsis, has not been extensively studied. Furthermore, laboratory tests that assess acid-base balance are vast in number, making the identification of those that better explain mortality a priority. Thus, the goal of this study was to assess the association of laboratory parameters, SAPSII, MSI, and MPI scores with in-hospital mortality among ICU patients with abdominal sepsis.

Material and methods

Study design and patients

We conducted a single-center case–control study at the ICU of Hospital No. 14, Unidad Medica de Alta Especialidad (UMAE), Instituto Mexicano del Seguro

Social (IMSS) in Veracruz, México, from May 2015 to May 2020. Inclusion criteria were patients ≥ 18 years with diagnosis of abdominal sepsis, defined as evidence of organ dysfunction characterized but not limited to oliguria, and delayed capillary refill and hypotension with an increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 points compared to baseline at admission, due to intra-abdominal infection regardless of etiology[23] who were admitted to the ICU, on invasive mechanical ventilation, and vasopressor support with norepinephrine. Patients with incomplete medical records, a diagnosis of non-abdominal sepsis, a do-not-resuscitate order, and pregnant patients were all excluded from the study. Consecutive convenience sampling of patients was performed.

All patients were managed according to Surviving Sepsis Campaign guidelines[24] and current Mexican Clinical Practice Guidelines[25]. The study protocol was approved by the Local Institutional Review Board (approval number: R-2019-1001-18) and the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) (approval number: 17_CI_11020_146).

Definitions of outcomes, exposures, cases, and controls

The primary outcome was in-hospital death. Thus, cases were defined as patients who died in-hospital, whereas controls were patients who survived until discharge. Both cases and controls identified amid the entire study period were ascertained through review of patient records. Exposures were defined as presenting with an MPI > 25 points at admission, as well as increasing SAPSII and MSI scores, and the interaction between blood gases and serum laboratory parameters.

Source of data

Data were collected by a Critical Care medicine specialist and a postgraduate year four (PGY-4) General Surgery resident physician. Baseline characteristics (age, sex, and body mass index [BMI]), comorbidities (diabetes mellitus, hypertension [HTN], chronic kidney disease, chronic heart disease), laboratory parameters (arterial pH, arterial partial pressure of oxygen [PaO_2], venous partial pressure of oxygen [PvO_2], arterial partial pressure of carbon dioxide [$PaCO_2$], venous partial pressure of carbon dioxide [$PvCO_2$], arterial oxygen saturation [SaO_2], central venous oxygen saturation [$ScvO_2$], lactate, bicarbonate [HCO_3], base excess [BE], venous-to-arterial carbon dioxide difference [$DvaCO_2$], arterial oxygen content [CaO_2], venous oxygen content [CvO_2], serum anion gap [AG], corrected serum anion gap [cAG], apparent strong ion difference [SIDa], effective strong ion difference [SIDe], strong ion gap [SIG], hemoglobin [Hb], chloride [$Cl-$], sodium [$Na+$], albumin [Alb], alactic base excess [alactic BE], creatinine [Cr], urea [Ur], brain natriuretic peptide [BNP], procalcitonin [PCT]), norepinephrine dose (mcg/kg/min), and PaO_2/FiO_2 (arterial partial pressure of oxygen/fraction of inspired oxygen ratio) were collected at ICU admission. MSI, MPI (Supplementary Table 1), and Simplified Acute Physiology Score II (SAPSII) (Supplementary Table 2) were calculated for all patients. Cutoff value for MPI was deemed at < 25 for statistical purposes[10]. Formulae for calculation of clinical and laboratory parameters (such as BMI, AG, SIDa, SIDe, SIG, alactic BE, PaO_2/FiO_2 ratio, $PvCO_2$, CaO_2, CvO_2 and MSI) are shown in supplementary Table 3. Age and sex were considered as confounding variables.

Statistical analysis

Sample size was calculated according to mortality risk estimates in patients with abdominal sepsis according to the MPI score since a relative risk of 3.62 has been reported for this scoring system[26]. We considered a mortality rate of 29.1% in the population of interest[27], obtaining a final sample size of 41 individuals, allowing for a possible loss of 20%, with an alpha of 0.05 and a statistical power of 80%.

Quantitative continuous variables were presented as median and interquartile range or as mean and standard deviation (SD) where applicable, whereas dichotomous variables were presented as absolute frequency and percentage (%). For comparison between survivors and non-survivors, the Mann–Whitney U test or Student's t-test was applied for quantitative continuous variables, while Chi-square (χ^2) or Fisher's exact test was applied for qualitative (categorical) variables.

A correlation analysis was also applied between laboratory variables by developing a correlation matrix with corresponding Spearman's rank correlation coefficients. Subsequently, an anti-image correlation matrix was applied to determine Kaiser–Meyer–Olkin measure of sampling adequacy (KMO).

A principal component analysis (PCA) was performed to reduce the laboratory dataset dimension and to increase interpretability. In addition, extraction communalities were estimated to acknowledge the proportion of explanation of the variance of each variable in the factor analysis; variables were considered important when they showed communality values > 0.9. Thereafter, principal components (PCs) were analyzed to obtain those that best explained total variance – defined as PC with eigenvalues > 1 and that altogether explained above 70% of the total variance. Similarly, a component score coefficient analysis was performed, defining high correlation components as those with absolute values > 0.5.

To determine the association of SAPSII, MSI, MPI, and PC with mortality, several logistic regression models were developed, considering each score and each PC as independent variables. MPI was introduced in the regression model as a binary variable (< 25 and > 25 points), while SAPSII and MSI were introduced as quantitative variables. Univariate analyses were performed followed by multivariate logistic regression models which were adjusted for age and sex to avoid model overfitting; variables were introduced by the Enter method. Collinearity assumptions were verified to assess that there was no collinearity of variables to create the multivariate models. Results are presented as regression coefficients (β) or Odds Ratios (OR) and 95% confidence intervals (95% CI). Model assumptions were verified by influential values of Cook's distance values (top 3 largest values) and standardized residuals. Goodness of fit of the multivariate logistic regression models was evaluated through Hosmer and Lemeshow test. Model performance was evaluated using the area under the curve (AUC) and Akaike information criterion (AIC). Statistical significance was defined as $p < 0.05$. All analyses and figures were performed using R studio V.1.0.153 and SPSS V.25.

Results

Out of 127 potentially eligible patients identified during the entire study period, 60 patients who met inclusion criteria were included for analyses (Fig. 1). Patient characteristics are shown in Table 1. Thirty-seven patients (61.7%) were female and mean age was 57.7 (SD: 16.7) years. Most patients were located in the > 60 years category (n = 29, 48.3%). HTN was the most frequent comorbidity (n = 27, 45%). Forty-four (73.3%) patients had a pH < 7.35 and 46 (76.7%) had a serum Cr > 1.2 mg/dl. Fifty (83.3%) patients had
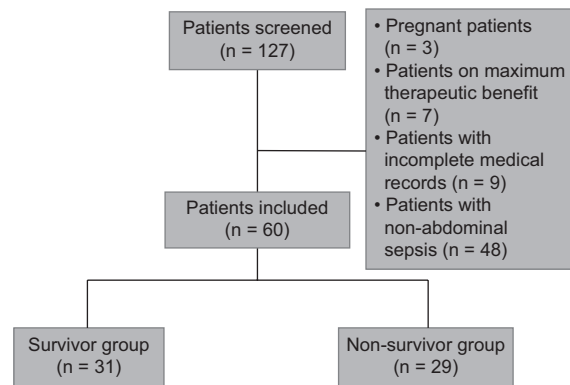

Figure 1. *Patient inclusion flowchart and reasons for exclusion.*

a MSI > 1.3 and 36 (60%) had an MPI score < 25 at admission. The most frequent SAPSII category was 64–77 points (n = 44, 73.3%). The mortality rate in the sample was 48.3% (n = 29). The non-survivor group had a higher frequency of HTN, higher lactate levels, and higher MPI scored, but lower BE and alactic BE levels. Comparison of characteristics of survivors against non-survivors is shown in table 1.

Correlation coefficients among laboratory variables are shown in Figure 2. Highly positive correlation occurred between SIDa and SIG (p = 0.96), AG and cAG (p = 0.97), CaO_2 and Hb (p = 0.98), BE and alactic BE (p = 0.96), and $PaCO_2$ and $PvCO_2$ (p = 0.91), whereas perfect negative correlation was solely noted between SIDe and albumin (–1). The anti-image correlation matrix shows KMO values > 0.5 in all variables, which implies that all of the latter are suitable for PCA (Supplementary Table 4).

PCA retrieved 8 PC with the following eigenvalues: PC1 = 5.4, PC2 = 3.6, PC3 = 2.9, PC4 = 2.8, PC5 = 2.3, PC6 = 2.1, PC7 = 1.9, PC8 = 1.2 (Supplementary Table 5), and explaining: 20%, 13%, 11%, 10%, 9%, 8%, 7%, and 5% of the total variance, respectively. Altogether, the 8 PC explain 83% of the total variance, with a cumulative proportion of 93%. Table S6 shows laboratory variables that display high loading for PC: PC1: pH (–0.59), AG (0.9), cAG (0.92), alactic BE (–0.76), HCO_3 (–0.77), and BE (–0.78); PC2: PaO_2 (–0.46), lactate (–0.45), CaO_2 (0.51), SIDa (0.60), SIG (0.67), Hb (0.58), and Cl– (–0.58); PC3: PvO_2 (0.40), $PaCO_2$ (0.69), CvO_2 (0.68), and PCT (0.51); PC4: SIDe (–0.59), Na+ (0.56), Alb (0.59), Cr (–0.59), and Ur (–0.51); PC5: $ScvO_2$ (0.69) and $DvaCO_2$ (–0.47); PC6: $PvCO_2$ (0.63); and PC7: SaO_2 (0.45) and BNP (0.48). Table S6 also shows that variables PaO_2, PvO_2, PCT, Cr, $ScvO_2$, Ur, $PvCO_2$, SaO_2, and BNP contributed the

Table 1. Baseline characteristics of the study sample and comparison between survivors and non-survivors

Name of Variable	Total sample (n = 60)	Survivors (n = 31)	Non-survivors (n = 29)	p-value
Age, years*	57.7 (16.7)	55.6 (17.3)	60 (16)	0.31
Age categories**				
< 20	3 (5)	2 (6.5)	1 (3.4)	1.0
21–39	3 (5)	2 (6.5)	1 (3.4)	1.0
40–59	25 (41.7)	14 (45.2)	11 (37.9)	0.57
> 60	29 (48.3)	13 (41.9)	16 (55.2)	0.30
Female**	37 (61.7)	17 (54.8)	20 (69)	0.26
Male**	23 (38.3)	14 (45.2)	9 (31)	
Weight (kilograms)*	77.3 (19.7)	81.4 (19.5)	72.5 (19.2)	0.06
Height (meters)*	1.63 (0.9)	1.63 (0.09)	1.63 (0.09)	0.87
Body mass index, kg/m^2**				
< 29.9 (normal)	37 (61.7)	15 (48.4)	22 (75.9)	0.02
30–34.9 (obesity class I)	13 (21.7)	9 (29)	4 (13.8)	0.15
35–39.9 (obesity class II)	5 (8.3)	4 (12.9)	1 (3.4)	0.35
> 40 (obesity class III)	5 (8.3)	3 (9.7)	2 (6.9)	1.0
Comorbidities				
Diabetes mellitus**	21 (35)	8 (25.8)	13 (44.8)	0.12
Hypertension**	27 (45)	10 (32.3)	17 (58.6)	0.04
Chronic kidney disease**	6 (10)	2 (6.5)	4 (13.8)	0.41
Chronic heart disease**	6 (10)	1 (3.2)	5 (17.2)	0.09
Laboratory parameters at admission				
pH *	7.29 (0.08)	7.31 (0.07)	7.27 (0.08)	0.07
< 7.35**	44 (73.3)	20 (64.5)	24 (82.8)	0.11
Arterial partial pressure of oxygen (PaO$_2$), mmHg*	120.7 (54.4)	110.9 (56.4)	131.2 (51)	0.14
Venous partial pressure of oxygen (PvO$_2$), mmHg*	39.7 (9.4)	38.5 (8.1)	40.9 (10.7)	0.35
Arterial partial pressure of carbon dioxide (PaCO$_2$), mmHg*	33.9 (7.2)	35 (5.1)	32.7 (9)	0.24
< 60 mmHg**	4 (6.6)	4 (12.9)	0 (0)	0.11
Venous partial pressure of carbon dioxide (PvCO$_2$), mmHg*	39.6 (7.3)	40.8 (5.3)	38.2 (8.9)	0.19
Arterial oxygen saturation (SaO$_2$), %*	96.8 (3)	96.2 (3.4)	97.4 (2.5)	0.13
Central venous oxygen saturation (ScvO$_2$), %*	66.3 (12.7)	65.8 (11.3)	66.8 (14.3)	0.77
Lactate, mmol/L*	4.1 (2)	3.6 (1.5)	4.7 (2.3)	0.03
Bicarbonate (HCO$_3$), mmol/L*	16.3 (3.5)	17.1 (3.4)	15.4 (3.6)	0.07
Base excess (BE), mmol/L*	−9.5 (5.2)	−8.1 (5.5)	−11.1 (4.3)	0.02
Venous-to-arterial carbon dioxide difference (DvaCO$_2$), mmHg*	5.6 (3.1)	5.8 (2.2)	5.5 (3.9)	0.73
Arterial oxygen content (CaO$_2$), O$_2$ ml per 100 ml of blood*	12.3 (2.4)	12.2 (2.3)	12.3 (2.5)	0.95
Venous oxygen content (CvO$_2$), O$_2$ ml per 100 ml of blood*	8.2 (2.1)	8.1 (1.5)	8.3 (2.6)	0.68
Serum anion gap, mmol/L*	14.8 (6.4)	13.8 (4.4)	15.9 (7.9)	0.21
Corrected serum anion gap, mmol/L*	19.8 (6.6)	18.8 (4.4)	21 (8.3)	0.19
Apparent strong ion difference (SIDa), mmol/L*	−3.8 (5.1)	−4 (3)	−3.5 (6.8)	0.74
Effective strong ion difference (SIDe), mmol/L*	4.2 (1.5)	4.2 (1.4)	4.3 (1.6)	0.68
Strong ion gap (SIG), mmol/L*	−8 (5.4)	−8.2 (3.7)	−7.9 (6.8)	0.84
Hemoglobin (Hb), mg/dl*	9.2 (1.9)	9.2 (1.9)	9.1 (1.9)	0.78
< 7.0**	8 (13.3)	4 (12.9)	4 (13.8)	1.0
Chloride (Cl$^-$), mmol/L*	109.5 (6)	110.1 (5.2)	108.8 (6.7)	0.41
Sodium (Na$^+$), mmol/L*	140.7 (5.7)	141.1 (5.5)	140.2 (6)	0.57
Albumin (Alb), gr/dl*	24.8 (6.1)	25.1 (5.8)	25.5 (6.4)	0.68
Alactic BE, mmol/L*	−13.7 (6.3)	−11.7 (6.4)	−15.8 (5.6)	0.01
Creatinine (Cr), mg/dl*	2.8 (2.5)	2.7 (2.2)	3 (2.8)	0.58
> 1.2**	46 (76.7)	23 (74.2)	23 (79.3)	0.63
Urea (Ur), mg/dl*	97.3 (55.2)	86.7 (50.7)	108.5 (58.4)	0.12
Brain natriuretic peptide (BNP), ng/ml*	679.7 (836.6)	527 (614.4)	842.9 (1008.4)	0.15
Procalcitonin (PCT), ng/ml*	26.3 (23.9)	26.5 (26.7)	26 (21)	0.93
Scores at admission				
Modified shock index (MSI)**				
> 1.3	50 (83.3)	26 (83.9)	24 (82.8)	0.90

(Contd...)

Table 1. Baseline characteristics of the study sample and comparison between survivors and non-survivors *(Continued)*

Name of Variable	Total sample (n = 60)	Survivors (n = 31)	Non-survivors (n = 29)	p-value
Mannheim peritonitis index (MPI)**				0.001
≤ 25	36 (60)	26 (83.9)	10 (34.5)	
> 25	24 (40)	5 (16.1)	19 (65.5)	0.19
Simplified acute physiology score II (SAPSII)**				0.73
41–52	6 (10)	5 (16.1)	1 (3.4)	0.11
53–64	10 (16.7)	6 (19.4)	4 (13.8)	
64–77	44 (73.3)	20 (64.5)	24 (82.8)	
Other characteristics				
Arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2)**				
Mild	36 (60)	15 (48.4)	21 (72.4)	0.05
Moderate	22 (36.7)	15 (48.4)	7 (24.1)	0.05
Severe	2 (3.3)	1 (3.2)	1 (3.4)	0.96
Norepinephrine, mcg/kg/min**	0.39 (0.25)	0.43 (0.25)	0.34 (0.24)	0.16
ICU length of stay, days*	5.8 (4.2)	6.7 (3.7)	4.9 (4.6)	0.10
Duration of mechanical ventilation, days*	4.9 (4)	4.9 (3.4)	4.9 (4.6)	0.99

*Mean, (standard deviation);
**Frequency, (percentage).
FiO_2: fraction of inspired oxygen; ICU: intensive care unit; kg: kilogram; m²: square meter; mmHg: millimeters of mercury; O_2: oxygen; PaO_2: arterial partial pressure of oxygen.

Table 2. Univariate logistic regression analysis

Model	β	OR	95% CI	p-value
MPI	2.290	9.87	3.07-36.61	0.0002
SAPSII	0.071	1.07	1.01-1.14	0.01
MSI	−0.164	0.84	0.23-3.07	0.80
PC1	0.759	2.13	1.12-4.76	0.04
PC2	−0.232	0.79	0.46-1.32	0.38
PC3	0.191	1.21	0.73-2.05	0.46
PC4	−0.061	0.94	0.56-1.57	0.81
PC5	0.067	1.06	0.64-1.80	0.79
PC6	−0.347	0.70	0.40-1.19	0.20
PC7	0.051	1.05	0.63-1.77	0.84
PC8	0.52888	1.69	1.00-3.07	0.06

OR: odds ratio, 95% CI: 95% confidence interval; MPI: Mannheim peritonitis index;
SAPSII: simplified acute physiology score II; MSI; modified shock index; PC: principal component.

least in terms of variation to factor analysis since they showed extraction values of 0.78, 0.85, 0.80, 0.84, 0.88, 0.55, 0.85, 0.82, and 0.77, respectively.

On logistic regression univariate analyses, MPI (OR = 9.87, 95% CI: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, 95% CI: 1.01-1.14, p = 0.01), and PC1 (OR = 2.13, 95% CI: 1.12-4.76, p = 0.04) were significantly associated with patient in-hospital

mortality (Table 2), whereas only MPI (OR = 10.1, 95% CI: 3.03-40.06, p = 0.0003) and SAPSII (OR = 1.07, 95% CI 1.01-1.14, p = 0.02) were significantly associated with mortality after adjusting for age and sex (Table 3). Both models MPI (Hosmer and Lemeshow = 0.40, AUC = 0.79, AIC = 73.37) and SAPSII (Hosmer and Lemeshow = 0.70, AUC = 0.70, AIC = 82.9) showed higher performance in comparison to PC1 (Hosmer and Lemeshow = 0.33, AUC = 0.66, AIC = 84.82). Model assumptions for MPI and SAPSII are shown in figures 3 and 4, respectively.

Discussion

We hypothesized that the scoring systems and laboratory parameters have different associations with in-hospital mortality in patients with abdominal sepsis. In logistic regression models, MPI, SAPSII, and PC1 were significantly associated with in-hospital mortality. Nevertheless, after adjusting for age and sex, only MPI, and SAPSII remained significantly associated with in-hospital mortality. In addition, we found that non-survivors showed a higher frequency of HTN, higher lactate levels, and higher MPI scores but lower BE and alactic BE levels.

To the best of our knowledge, this is the first study to simultaneously evaluate various scoring systems and biomarkers in abdominal sepsis patients. Our findings could suggest that initial and follow-up
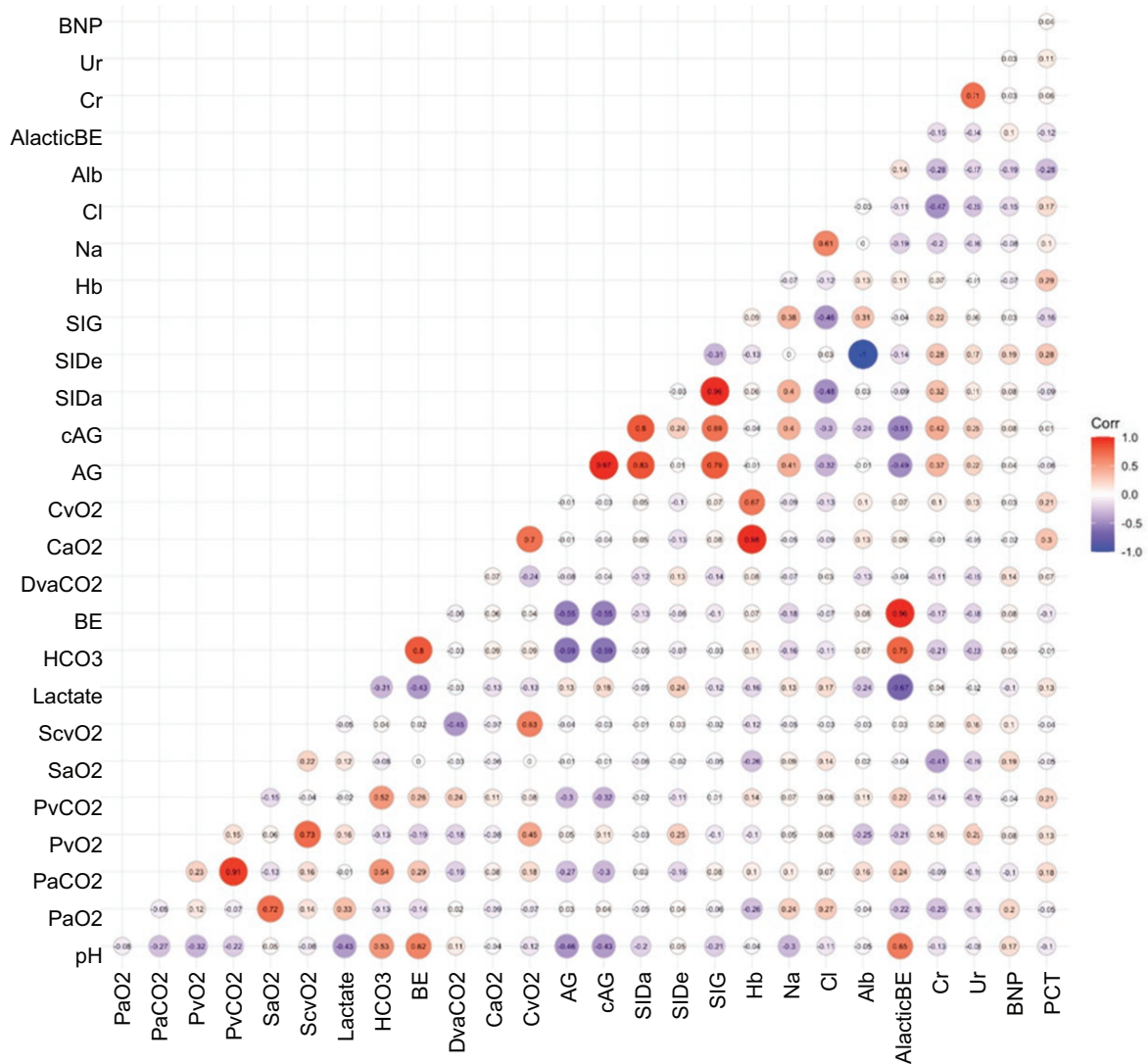
Figure 2. *Heat map. Red color indicates a positive correlation between variables, while blue color indicates a negative correlation.*

assessments of patients be based on the markers that were indeed associated with mortality. In that manner, the choice of a handful of relevant parameters could pave the way for a personalized medical approach in patients with abdominal sepsis. Nonetheless, it is also important to note that our findings are merely observational; hence, they should be viewed as hypotheses generators for future clinical studies, in which relevant markers are assessed as potential therapeutic targets.

Although PC1 – a linear combination of variables pH, AG, cAG, alactic BE, HCO_3^- and BE – was not statistically significantly associated with the outcome after adjusting for confounders, acid-base disturbances still play an important role in abdominal sepsis-associated mortality and their prognostic value should not be underestimated. Acidemia (pH < 7.35) remains a potentially fatal condition, mainly due to its effect on the cardiovascular system. The classification of acidemia on various subtypes such as metabolic (BE < –2 mEq/L and $PaCO_2$ ≤ 42 mmHg), respiratory (BE ≥ –2 mEq/L and $PaCO_2$ > 42 mmHg), and mixed (BE < –2 mEq/L and $PaCO_2$ > 42 mmHg) acidemia is of paramount importance when determining appropriate treatment and prognosis. In fact, mortality in metabolic acidemia is as high as 11% when BE is < 6.7 mEq/L; in respiratory acidemia, it is of 6% when $PaCO_2$ is > 51 mmHg, and in mixed acidemia, it is of 13% when pH is < 7.23[28]. A persistent state of metabolic acidosis harbors negative consequences on patient outcomes and it may also indicate progression of underlying
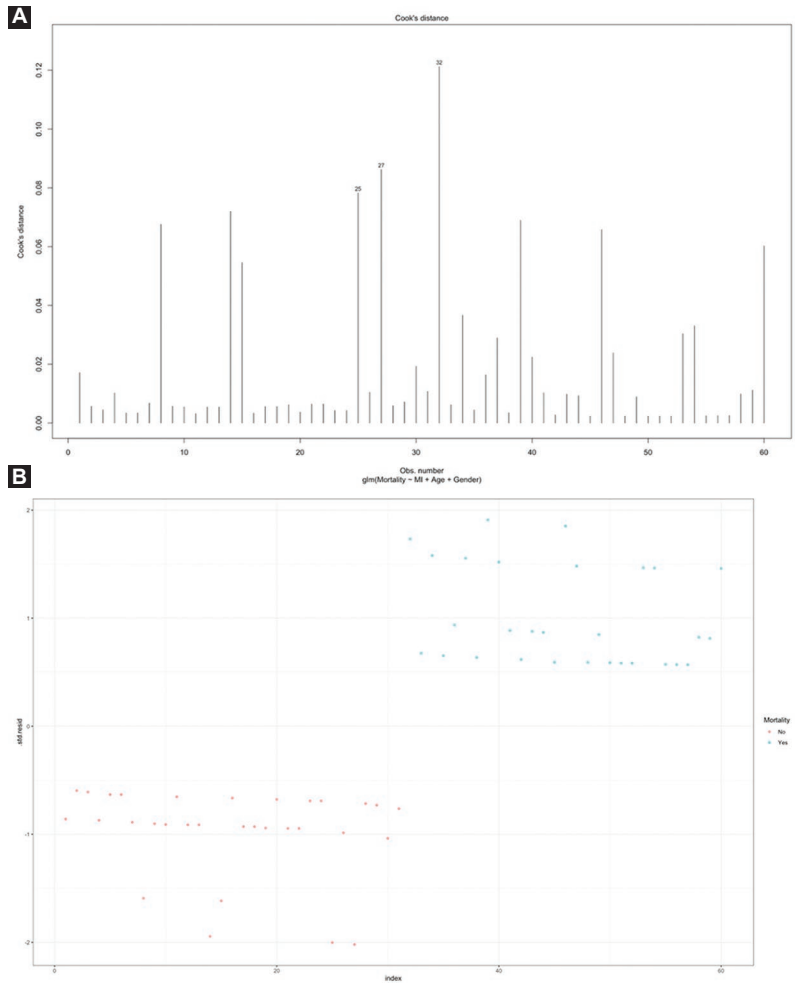
Figure 3. *Model assumptions for logistic regression analysis of MPI:* **(A)** *influential values by Cook's distance values for the top 3 largest values and* **(B)** *standardized residuals values.*

Table 3. Multivariate logistic regression analysis

Model	Variable	β	OR	95% CI	p-value
MPI[a]	MPI	2.318	10.1	3.03-40.06	0.0003
	Sex	−0.78	0.45	0.12-1.04	0.22
	Age	0.007	1	0.94-1.04	0.67
SAPSII[b]	SAPSII	0.069	1.07	1.01-1.14	0.02
	Sex	−0.687	0.5	0.16-1.51	0.22
	Age	0.0104	1.01	0.98-1.04	0.54
PC1[c]	PC1	0.661	1.93	1.01-4.44	0.08
	Sex	−0.319	0.72	0.23-2.25	0.57
	Age	0.011	1.01	0.98-1.04	0.48

All models were adjusted by sex and age.
[a]Hosmer and Lemeshow = 0.40, AUC = 0.79, AIC = 73.37;
[b]Hosmer and Lemeshow = 0.70, AUC = 0.70, AIC = 82.9,
[c]Hosmer and Lemeshow = 0.33, AUC = 0.66, AIC = 84.82.
AIC: Akaike information criterion; AUC: area under the curve; MPI: mannheim peritonitis index; SAPSII: simplified acute physiology score II: MSI; modified shock index;
PC: principal component.

causes. A standard base deficit clearance < 11% (within the first 24 h of ICU admission) increases the risk of mortality in patients with septic shock (< 11% = 65.1% mortality and > 11% = 36% mortality)[29]. A negative value of alactic BE indicates worsening of the renal function and, therefore, an impairment on the clearance of unmeasured anions and lactate. Thus, the more negative the alactic BE is, the greater the renal impairment and, most likely, the worse the prognosis[30]. Increased AG occurs mainly due to accumulation of unmeasured anions. Its highest utility is achieved when used on the differential diagnosis of metabolic acidosis, although it bears prognostic value as well. A recent study found that the greater the AG, the greater the mortality risk: AG ≥ 13 mEq/L (OR 1.02, 95% CI 0.75-1.40, p = 0.891), AG ≥ 15 mEq/L (OR 1.40, 95% CI 1.03-1.91, p = 0.031), and AG ≥ 17 mEq/L (OR 2.78, 95% CI 2.12-3.63, p < 0.001)[31].
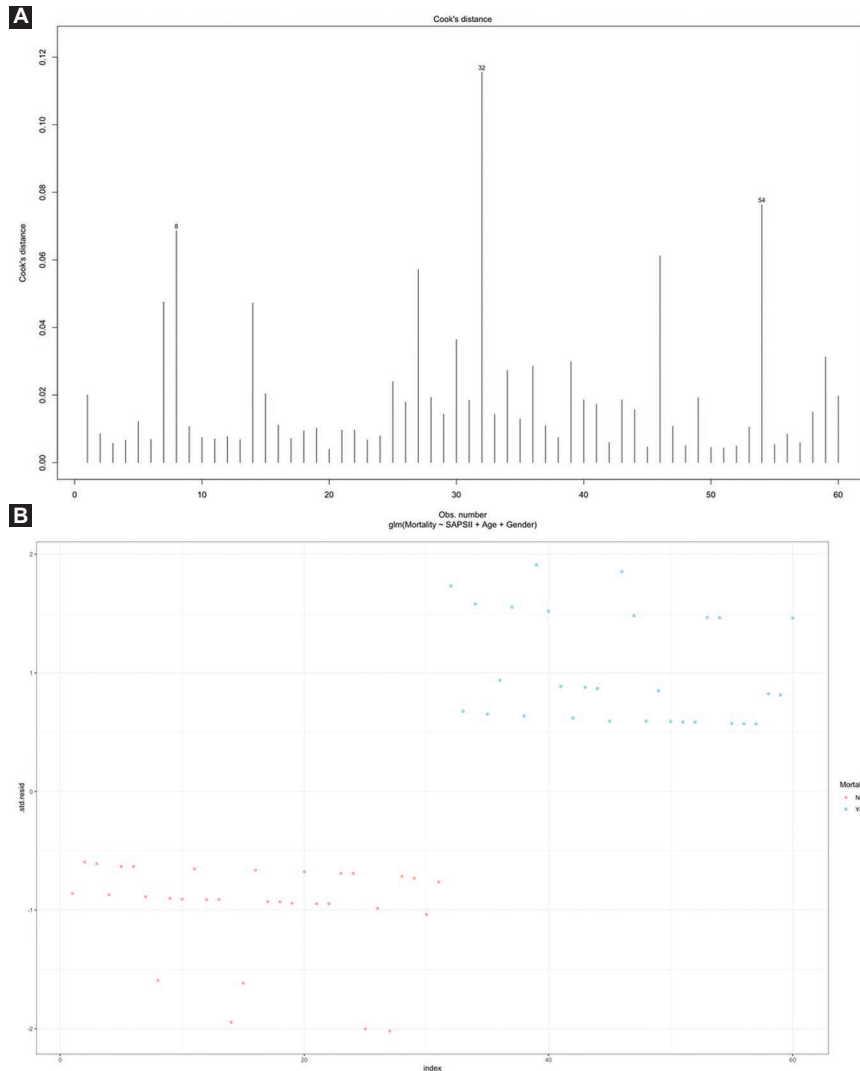
Figure 4. *Model assumptions for logistic regression analysis of SAPSII:* **(A)** *influential values by Cook's distance values for the top 3 largest values and* **(B)** *standardized residuals values.*

Even though PCT helps predict the occurrence of intra-abdominal infections after definitive surgery for intestinal fistulae[32], infected necrotizing pancreatitis[33], and it is also an early biomarker of intra-abdominal infections in post-operative patients with gastrointestinal malignancies[34], this biomarker might not be as useful when used as a predictor of mortality in patients with abdominal sepsis, based on our findings.

We would like to draw attention to the fact that out of all the laboratory parameters included in PC1, HCO_3 is also coincidentally an item in one of the scores associated with mortality (SAPSII). Although the statistical significance of PC1 was lost during multivariate analysis, this finding suggests that there might be room for including new laboratory parameters into

the existing scoring systems that could further improve mortality risk estimates[35,36].

In accordance with their AIC values, we conclude that MPI and SAPSII scoring systems are both equally associated with mortality. Differences observed in OR values are due to the taxonomy of the variables themselves, but the strength of association with mortality is not any different among them (Table 3). In our study, we considered MPI cutoff values as reported on the original paper[37], proving significant association with in-hospital mortality, which is consistent with the literature[38]. Nonetheless, other studies have used cutoff values of > 21, while displaying sensitivity of 97.5% and AUC of 0.976.[39] In addition, SAPSII showed optimal performance, in similar fashion to that reported by Sánchez-Casado et al.[40]

Besides association with mortality, SAPSII has also been associated with overall length of hospital stay[41].

Finally, we want to emphasize that our findings are consistent with the literature regarding the relationship between HTN and adverse outcomes in sepsis patients since non-survivors showed a higher frequency of HTN. A recent study by Garg et al. showed that male gender, HTN, SOFA > 9, and increased creatinine were predictors for mortality in adult patients with diagnosis of sepsis requiring ICU care[42]. Moreover, it appears that HTN, along with other chronic medical conditions, might increase the risk of incident sepsis episodes[43].

Limitations of our study include its retrospective nature, as well as potential sampling bias due to convenience sampling, and having used a selective study cohort, which limits generalizability of results. Since this study was developed in a low-resource hospital in Mexico, we were unable to assess important predictors which were unavailable (i.e., C-reactive protein, interleukin-6), whereas other variables were not presented since they are already included in the scores (i.e., leukocytes and bilirubin). In addition, we did not evaluate specific causes of abdominal sepsis. Another limitation is that even when the sample size was calculated to encounter differences in the main outcome according to MPI scores, it is possible that the study was underpowered to detect differences according to PCA groups. Furthermore, PCA is a technique for reducing the dimensionality of large datasets which can be challenging to interpret; for instance, it is difficult to acknowledge the most important characteristics of the dataset after calculating PC. Although reduction of dimensionality is useful, it does not come without a cost, given that the loss of information is a necessary part of this type of analysis. Balancing dimensionality reduction and loss of information are mandatory when applying PCA.

Conclusion

MPI and SAPSII are both equally associated with in-hospital mortality in abdominal sepsis patients admitted to the ICU. Acid-base disturbances play an important role in abdominal sepsis-related mortality, although they were not significantly associated with in-hospital mortality in our study when adjusting for age and sex. Larger studies are needed to confidently evaluate the association of pH, AG, cAG, alactic BE, HCO_3, and BE with mortality in these patients to better understand pathophysiology of abdominal sepsis.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Supplementary data

Supplementary data are available at 10.24875/CIRU.22000219. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Application of neuronavigation system in intracranial meningioma surgery: a retrospective analysis of 75 cases

Aplicación del sistema de neuronavegación en la cirugía del meningioma intracraneal: un análisis retrospectivo de 75 casos

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Abstract

Objective: *Neuronavigation is an extremely common and useful system in intracranial surgeries. It is used to determine the pre-operative incision, perform the most appropriate craniotomy, and provide intraoperative guidance. However, its use in meningioma surgery is controversial, and there is a dilemma whether it is necessary. This study was performed to determine the effect of neuronavigation in meningioma surgery.* **Materials and methods:** *Information related to pre-operative clinical evaluation and use of neuronavigation, neuroimaging, intraoperative tumor and surgical related information, and post-operative outcomes of 75 consecutive patients with meningiomas between January 2015 and 2020 were retrospectively collected. The values between groups were statistically compared.* **Results:** *There were no significant differences in pre-operative patient and tumor characteristics between the groups. In cases using neuronavigation, the mean operative time, craniotomy size, and blood loss during tumor resection were significantly lower, and post-operative hospital stay was shorter in these patients (p < 0.05). However, there were no differences in post-operative complications and clinical outcomes.* **Conclusion:** *The use of neuronavigation in meningioma surgery reduces blood loss during surgery, reduces the surgical time, and shortens the post-operative hospital stay. Thus, we conclude that the neuronavigation system is useful in meningioma surgery.*

Keywords: *Neuronavigation. Meningioma. Resection.*

Resumen

Objetivo: *La neuronavegación ha tomado su lugar como un sistema muy común y útil para cirugías intracraneales. Este estudio se realizó para revelar su efecto en la cirugía de meningioma.* **Materiales y métodos:** *Se recopiló retrospectivamente información relacionada con la evaluación clínica preoperatoria, neuroimagen, información relacionada con el tumor y la cirugía intraoperatoria y los resultados posoperatorios de 75 casos consecutivos con meningiomas entre enero de 2015 y 2020. Los valores entre grupos se compararon estadísticamente.* **Resultados:** *No hubo diferencias significativas en las características preoperatorias de los pacientes y las características del tumor entre los grupos. En los casos en los que se utilizó neuronavegación, el tiempo operatorio medio, el tamaño de la craneotomía y la pérdida de sangre durante la resección del tumor fueron significativamente menores, y la estancia hospitalaria postoperatoria fue más corta en estos pacientes (p < 0.05). Sin embargo, no hubo diferencia en las complicaciones postoperatorias y los resultados clínicos.* **Conclusión:** *El uso del sistema de neuronavegación en la cirugía del meningioma reduce la pérdida de sangre durante la cirugía, acorta el tiempo*

quirúrgico y reduce la estancia hospitalaria postoperatoria. Creemos que el sistema de neuronavegación es útil en la cirugía del meningioma.

Palabras clave: *Neuronavegación. Meningioma. Resección.*

Introduction

Since the introduction of frame based stereotactic neurosurgery by Spiegel and Wycis four decades ago, the development of frameless stereotactic surgery with computer-assisted three-dimensional digitalization has revolutionized neurosurgery[1]. Frameless stereotaxy or neuronavigation allows pre-operative planning as well as intraoperative guidance, localization, and orientation.

Although the use of the neuronavigation system in intracranial glioma and metastasis surgery has been fully accepted, there is a dilemma whether it is necessary in intracranial meningioma surgery[2]. With the exception of small convexity meningiomas, locating the tumor is usually not a problem in meningioma surgery. The main difficulties are performing the most appropriate craniotomy and dural opening and preventing damage to the arterial and venous structures during surgery and deterioration of intraoperative orientation due to displacement of anatomical landmarks in large tumors[3]. The neuronavigation system stands as a good guide in solving these problems. A search of the English and Turkish literature revealed that the studies presenting the results on the use of the neuronavigation system in meningioma surgery are quite limited. Therefore, this study aimed to examine the effect of neuronavigation on surgical outcomes.

Materials and methods

We retrospectively evaluated 75 patients who underwent surgical resection of meningiomas with or without neuronavigation. This study received approval from the local ethics committee. Information on clinical history, surgical outcome, and pathological and radiological results of patients who underwent surgery for intracranial meningioma between 2015 and 2020 was obtained from their case files and electronic record cards.

The surgeries were performed by different surgeons using the same surgical technique as described in citation[4]; microneurosurgical tumor resection was performed under craniotomy. All procedures were performed by a team headed by a senior surgeon (HHK). Team members had a long-term cranial surgery experience before the initiation of the study.

Neuronavigation was used in meningioma surgery after 2017 (Fig. 1). The senior surgeon had performed hundreds of meningioma surgeries before the start of the study, the first 20 cases in which navigation was used were not included in the study so that the difference in learning curve after the neuronavigation system was introduced did not affect the study results. An infrared-based navigation system (Brainlab Kick; Brainlab AG, Feldkirchen, Germany) was used intraoperatively. The following variables were saved: sex, age, symptoms at presentation, tumor location and size, craniotomy size, operative time, hospital stay, intraoperative blood loss, post-operative complications, and follow-up results. Karnofsky performance status was decided based on the archival records of pre-operative examinations and clinical evaluations.

Tumor size and location were determined based on pre-operative post-contrast magnetic resonance images, and tumor volume was calculated according to the widely used ABC/2 formula[5]. The extent of resection was assessed using the Simpson grading system[6]. Simpson grade I and II resections were considered gross total resection. The extent of resection was decided according to the discretion of the senior neurosurgeon during the surgery and/or the evaluation of the radiological images obtained within the first 48 h postoperatively. The World Health Organization grading system was used to classify the histology of meningiomas[7]. Deaths occurring within the 1st month after surgery and as a result of complications related to surgery were considered surgical mortality. Clinical follow-up results were decided according to the examination 12 months after surgery. The median follow-up duration was 24 months. Magnetic resonance imaging was performed 6 months after initial gross total resection of meningiomas to confirm tumor recurrence.

Statistical analysis

The analysis of this study was conducted using SPSS software, version 22.0 (IBM Corp., Armonk, NY). The distribution of variables was evaluated for normality using the Shapiro–Wilk test. For the evaluation of categorical data, χ^2 test was used if the number of observations was > 5, and Fisher's exact

Figure 1. *Three-dimensional imaging of the tumor with neuronavigation during pre-surgical planning.*

Table 1. A: Patients' demographics. B: pre-operative clinical features and tumor characteristics

A			
Variables	**With navigation**	**Without navigation**	**p-value**
Total cases	43 (57.3%)	32 (42.7%)	0.62
Age	56.4 ± 11	58.5 ± 14	0.48
Gender			
Male	13	8	0.79
Female	30	24	0.40

B			
Variables	**With navigation**	**Without navigation**	**p-value**
Symptoms and signs			
Headache	38	27	0.61
Seizure	17	12	0.85
Vision[+] impairment	7	2	0.28
Gait disturbance	12	11	0.54
Confusion[+]	7	5	0.93
Weakness	18	19	0.81
Tumor location[+]			
Skull base	10	4	0.12
Convexity	23	16	0.32
Parasagittal	8	11	0.42
Other	2	1	0.21
Hounsfield Unit	51.2 ± 10.8	48.81 ± 7	0.52
Tumor size (ml)	37.94 ± 14.6	41.3 ± 13.29	0.31
KPS	83.02 ± 10.8	76.25 ± 16.8	0.52

[+]*Fisher exact test was used*

Chi-squared test was applied if it was < 5. Normally distributed data comprising continuous variables were analyzed using the Student t-test, and non-normally distributed data were compared using the Mann-Whitney U test. $p < 0.05$ was considered statistically significant.

Results

In our study, 43 patients (57.3%) underwent surgical intervention with neuronavigation (2017-2020) and 32 cases (42.7%) underwent surgery without neuronavigation (2015-2017). The mean age of patients in this study was 56 and 58 years in the with- and without-navigation groups, respectively. Before the surgery, there were no differences in terms of patients' demographics and tumor characteristics (Table 1A and B).

The mean operative time, craniotomy size, and blood loss during tumor resection were significantly lower in cases using neuronavigation. Thirty-nine patients (90.7%) underwent Simpson grade I and II resection with neuronavigation and 28 cases (87.3%) underwent grade I and II resection without neuronavigation. Simpson grade I and II resections were considered as gross total resection. There was no significant difference in the extent of tumor resection ($p = 0.62$). Furthermore, 72% of patients in the neuronavigation group and 75% of patients in the non-neuronavigation group had grade I meningioma. There was no significant difference between the groups in terms of histopathological results ($p = 0.92$) (Table 2).

In the post-operative follow-up, there was no difference in hematoma in the surgical cavity, cerebrospinal fluid leakage, surgery-related infections, and systemic complications between the two groups (Fig. 2).

However, the average durations of hospital stay in patients were 13 ± 2 days and 18 ± 3 days in the with- and without-neuronavigation groups, respectively; thus, the hospital stay duration was significantly lower in the neuronavigation group ($p < 0.05$).

The clinical symptoms were significantly improved after tumor resection in both groups. However, with respect to the improvement of symptoms between the groups, there were no significant differences (Table 3).

Discussion

The application of neuronavigation systems in neurosurgical procedures provides the following information: performing minimal and optimal craniotomies, accurately localizing subcortical lesions, and defining lesion boundaries[8]. Pre-operative surgical planning using the guidance of appropriate technological developments will minimize the margin of error during surgery and reduce the risk of complications. The

Table 2. Comparison of intraoperative variables and post-operative pathological results

Parameters	With navigation	Without navigation	p-value
Surgery time (mean, minutes)	206	166	0.02*
Cranitomy size (mean, cm^2)	25.7	34.1	0.02*
Blood loss during surgery (mean, ml)	970	1810	0.01*
Simpson's grading[+] (number of cases, percent)			
Grade I	3 (7%)	2 (6.2%)	0.61
Grade II	36 (83.7%)	26 (81.2%)	0.24
Grade III	3 (7%)	3 (9.3)	0.31
Grade IV	1 (2.3%)	1 (3.1%)	0.42
Histological grade[+] (WHO grade) (number of cases, percent)			
Grade I	31 (72%)	24 (75%)	0.32
Grade II	11 (25.5%)	7 (21.5%)	0.23
Grade III	1 (2.5%)	1 (3.5%)	0.71

*Statistically significant.
[+]Fisher exact test was used.
cm^2: square centimeters; ml: milliliter.

Table 3. Comparison of follow-up results and clinical improvements

Variables	With navigation (n)	Without navigation (n)	p-value
Total cases	43 (57.3%)	32 (42.7%)	0.62
Symptoms and signs[+]			
Headache	19	20	0.61
Seizure	7	5	0.85
Vision impariement	3	1	0.18
Gait disturbance	6	4	0.54
Confusion	2	1	0.93
Weakness	9	7	0.81
30-day mortality	4	3	0.94
KPS (mean)	83.02 ± 10.8	76.25 ± 16.8	0.52

[+]Fisher exact test was used.
The symptoms and signs stated in the table were detected at the post-operative 12th month visit.

neuronavigation system is an important guide in this regard.

The most important goal of neurosurgeons is to perform tumor resection as wide as possible without harming the patient or with the least damage. Barnett reported that neuronavigation contributes to the surgical procedure itself by allowing smaller and better-centered craniotomies[9]. Our study also found that the craniotomy flap was smaller when navigation was used. Bir et al. reported that making the craniotomy

flap the center of the pathology and observing neuro-vascular structure adjacent to the tumor with neuro-navigation during surgery widened the resection margin, and this situation reduced the recurrence rate[1]. However, our study found that the extent of resection was similar in both groups. Meningiomas present as intracranial extra-axial lesions with dural attachment. We believe that meningiomas have a sharp border with the normal parenchyma tissue, and after reaching the meningioma, if there are no features that will prevent tumor resection, gross total resection can be performed. Lemée et al. reported that skull-base location and bone invasion were associated with the poor resection of meningiomas[10].

Paleologos et al. reported that the operative time, amount of intraoperative blood loss, and length of hospital stay after surgery were significantly lower when neuronavigation was used[11]. We also observed that blood loss was lower by approximately 800 mL and the operative time and hospital stay were shorter in the neuronavigation group. Lower intraoperative blood loss is possibly associated with smaller craniotomies and avoidance of major vascular structures. In a meningioma surgery, intraoperative blood loss is mostly caused by the bone flap; therefore, smaller craniotomies reduce blood loss. Planning the most suitable entrance for the lesion and performing small craniotomies reduces the surgical time and blood loss, eliminates the need for brain traction, and prevents brain contusion[12].

The patients' post-operative outcomes were quite satisfactory in many modern series. Mortality rates of convexity and parasagittal meningiomas were almost 0% and exceeded 8% for tumors in the sphenoid wing and 12% for those in the petroclival region[13]. In our study, we found that the post-operative mortality and morbidity rates were consistent with the reported levels, and there was no significant difference in post-operative follow-up results between the two groups.

A biggest problem that can arise, especially in a developing country like ours, where there is scarcity of resources, is the cost of equipment and the cost-benefit ratio. The use of neuronavigation allows safe surgery in which more tumors can be excised intraoperatively, the results of our study and the literature show that it shortens the surgical time and reduces the length of hospital stay. However, the high capital expenditure, absence of intraoperative imaging, and lack of trained dedicated supporting technical staff does make the neuronavigation a strain on the resources. Our study was a retrospective observational study and focused more on surgical outcomes
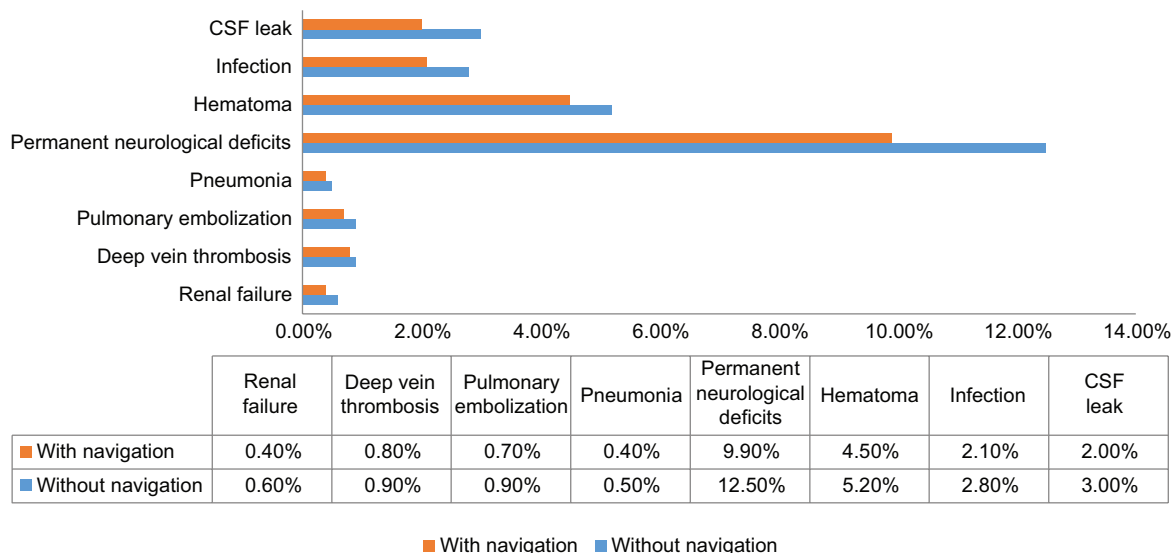
Figure 2. *There was no difference between the two groups in terms of post-operative complications.*

of the navigation system; therefore, a larger randomized trial with more objective criteria would be necessary to provide definitive answers.

Limitation

The patient series was relatively small and the follow-up results were short-term. It would be more appropriate to evaluate the results of long-term follow-up with a larger number of patients.

Conclusion

Neuronavigation technology provides an important advantage for modern surgical approaches. The results of studies with relatively few cases show that operative time and hospital stay are shortened and blood loss during surgery is reduced; however, there were no differences in terms of post-operative complications and follow-up results with the use of this technology in meningioma surgery. Future studies with larger series, especially randomized comparisons conducted with an objective view, are required to compare the true effectiveness and enhance the accuracy of navigation systems in surgical resection of intracranial meningiomas.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study. We obtained local ethic committe approvel from Ataturk University, School of Medicine.

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