Investigation of Inflammatory Effects of Morphine and Fentanyl on Early Wound Healing in Rats: an Experimental Study

Ratlarda Morfin ve Fentanil'in Erken Dönem Yara İyileşmesinde İnflamatuar Etkilerinin İncelenmesi

Ebru Canakci[1], Tuba Catak[2], Ali Ozgul Saltali[2], Abdullah Alper Sahin[3], Muruvvet Akcay Celik[4], Tulin Bayrak[5], Ahmet Bayrak[5]

[1]Ordu University, Faculty of Medicine, Department of Anaesthesiology and Reanimation, Ordu, Turkiye
[2]Ordu University, Training and Research Hospital, Department of Anaesthesiology and Reanimation, Ordu, Turkiye
[3]Ordu University, Faculty of Medicine, Department of Orthopedics and Traumatology, Ordu, Turkiye
[4]Ordu University, Faculty of Medicine, Department of Medical Pathology, Ordu, Turkiye
[5]Ordu University, Faculty of Medicine, Department of Medical Biochemistry, Ordu, Turkiye

ABSTRACT

Objective: It has been shown that increase in proinflammatory cytokines IL-1α, IL1-β, IL-6, and TNF-α strongly increased during the acute inflammatory phase of wound healing. In the present study, we aimed to investigate the effects of local morphine and fentanyl on TNF-α, IL-1β levels, which are important markers of inflammatory response, and wound healing based on histopathological scores in an experimental wound model created on rats.

Methods: 18 male Wistar-Albino rats were included in this study. A 1-cm longitudinal surgical incision containing skin and subcutaneous connective tissue was made in the dorsal region. 3 ml 1500 mcg morphine was injected to the incision line for Group M (n=6). 3 ml diluted fentanyl and 15 mcg fentanyl was injected (n=6) Group F. 3 ml of physiological saline (n=6) was injected for Group C The skin and subcutaneous tissues were sutured with a 4/0 silk thread. A 0.5 ml of blood sample was collected and centrifuged 30 minutes after the procedure. Plasma TNF-α and IL1-β levels were assessed. On the 7th day after the process, a biopsy sample was obtained from the incision line and histopathological wound healing scores were evaluated.

Results: A difference was found in the mean IL1-β levels between the groups (p=0.009). While the mean value was determined as 117.11 in the control group, it was 195.47 in the Morphine group and 154.89 in the Fentanyl group. While the control group had a lower mean value than the Morphine group, no difference was found between the Fentanyl group and the control and morphine groups. TNF-α, active inflammation (AI),chronic inflammation (CI), Granulation (G) , and Fibrosis (F) scores did not differ between the groups (p values: 0.995, 0.365, 0.057, 0.056, and 0.421, respectively). In the morphine group, a strong positive correlation was only found between the CI score and TNF-α (r=0.828; p<0.001).A strong negative correlation was found between the F score and IL1-β in the fentanyl group (r=-0.828; p<0.001).

Conclusions: It has been concluded that morphine and fentanyl play an active role in the acute phase of wound healing and accelerate the migration of polymorphonuclear leukocytes to the wound site. It can be said that opioids contribute to wound healing by exerting immunomodulatory effects, far beyond their role in reducing postoperative pain. We believe that our study will shed light on prospective clinical studies in this regard.

Keywords: Fentanyl, morphine, rat, wound healing, pain
Received: 08.06.2022 **Accepted:** 10.31.2022

ÖZET

Giriş ve Amaç: Yara onarımında proinflamatuar sitokinler olan IL-1α, IL1-β, IL-6 ve TNF-α artışının , iyileşmenin akut inflamatuar süreci boyunca güçlü bir şekilde arttığı gösterilmiştir. Bu çalışmadaki amacımız, ratlarda oluşturulan deneysel yara modelinde,lokal morfin ve fentanil uygulamasının inflamatuar yanıtın önemli belirteçlerinden olan TNF-α, IL-1β, düzeyleri ile yara iyileşmesi histopatolojik skorlar üzerine olan etkilerini araştırmaktır.

Materyal ve Metod: Çalışmaya 18 adet erkek Wistar-Albino rat dahil edildi. Sırt bölgesinde 1 cm'lik cilt ve ciltaltı bağ dokusunu içeren longitüdinal cerrahi kesi yapıldı. İnsizyon dudaklarına 3 ml 1500 mcg morfin Grup M'ye (n=6) yapıldı. Grup F'ye 3 ml sulandırılmış fentanil 15 mcg fentanil (n=6) yapıldı. Grup K'ya ise serum fizyolojik 3 ml (n=6) verildi. 4/0 ipek iplik ile cilt ve cilt altı dokular karşılıklı birleştirildi. İşlem sonrası 30.dakikada 0.5ml kan örneği alınarak santrifüj edildi. Plazma TNF-α, IL1-β düzeylerine bakıldı. İşlem sonrası 7.günde deneklerin insizyon hattından biyopsi alındı ve histopatolojik olarak yara iyileşmesi skorlarına bakıldı.

Bulgular: Gruplara göre IL1-β ortalama değerleri arasında fark vardır (p=0,009). Kontrol grubunda ortalama değer 117,11 iken, Morfin grubunda 195,47 ve Fentanyl grubunda 154,89 olarak elde edilmiştir. Kontrol grubunda elde edilen ortalama değer Morfin grubundan daha düşük iken Fentanyl grubu ile kontrol ve morfin grubu arasında fark yoktur. TNF-α, aktif inflamasyon (AI), kronik inflamasyon (KI), Granülasyon (G) ve Fibrozis (F) skorları gruplara göre farklılık göstermemektedir (p değerleri sırasıyla 0.995, 0.365, 0.057, 0.056 ve 0.421). Morfin grubu içinde de KI skoru ile sadece TNF-α arasında pozitif yönlü güçlü bir ilişki tespit edilmiştir (r=0,828; p<0,001).Fentanyl grubunda F skoru ile IL1-β arasında negatif yönlü güçlü bir ilişki tespit edilmiştir (r=-0,828; p<0,001).

Sonuç: Morfin ve fentanilin yara iyileşmesi akut fazında etkin rol oynadığını , yara yerine polimorf nüveli lokositlerin göçünü hızlandırmaktadır diyebiliriz. Opioidler postoperatif ağrıyı kesmek rollerinin çok ötesinde , immünomodülatör etkiyle yara iyileşmesine katkı sağladıkları söylenebilir.Çalışmamızın ileride yapılacak olan klinik çalışmalara ışık tutacağı inancındayız.

Anahtar Sözcükler: Fentanil, morfin, rat, yara iyileşmesi, ağrı
Geliş Tarihi: 06.08.2022 **Kabul Tarihi:** 31.10.2022

ORCID IDs: E.C.0000-0003-2093-9229, T.C. 0000-0001-8370-0739, A.O.S. 0000-0001-6098-3676, A.A.S. 0000-0002-8973-2050, M.A.C. 0000-0002-0335-4045, T.B. 0000-0002-9552-1751, A.B. 0000-0002-1243-2172

Address for Correspondence / Yazışma Adresi: Ebru Canakci, MD Ordu University, Faculty of Medicine, Department of Anaesthesiology and Reanimation, Bucak Town, Nefs-i Bucak Street Ordu, Turkiye E-mail: canakciebru@gmail.com

doi:http://dx.doi.org/10.12996/gmj.2023.35

INTRODUCTION

The wound is defined as an abnormal anatomical structure and loss of function of the tissue following surgery, incision, penetration, and cuts due to various factors. Wound healing is essential for complete recovery in surgical operations (1).It is one of the major issues in clinical practice among surgical branches and can be affected by many factors related to the patient. Medications used by the patient can also affect this complex process (2). Therefore, some questions arise whether anesthetic drugs that are used during surgery, especially opioids used for intraoperative and/or postoperative pain play a role in wound healing.

Proinflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin 2 (IL-2), interleukin (IL-6), interleukin 12 (IL-12), interferon-alpha (IFN-α), and interferon-gamma (IFN-γ). TNF-α, IL-1β, and IL-6 are mainly produced by macrophages and monocytes. They increase the synthesis of acute-phase proteins such as C-reactive protein, serum amyloid A, fibrinogen, complements, and alpha 1-antitrypsin. Proinflammatory cytokines are induced by microorganisms, microbial products, antigens, inflammatory agents, herbal lectins, lymphokines, and some chemicals (3).It has been shown that proinflammatory cytokines IL-1α, IL1-β, IL-6, and TNF-α increase during the acute inflammatory phase of wound healing (4).

The roles of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α are important in wound healing. These cytokines are at the trauma site; It has various effects such as keratinocyte stimulation and proliferation of fibroblasts, production and degradation of extracellular matrix proteins, fibroblast chemotaxis and regulation of immune response. These cytokines are mainly synthesized by leukocyt with polymorphic nuclei and macrophages, but can also be synthesized by some cells located at the wound site(5). Anti-inflammatory cytokines also have important roles in wound healing. In particular, IL-10 is predicted to play an important role in limiting inflammatory responses. IL-10; It has been shown to inhibit the infiltration of neutrophils and macrophages into the trauma area, reduce matrix deposition and allow scar-free healing, as well as providing expression of several chemokines and proinflammatory cytokines (6).

In the present study, we aimed to investigate the effects of local morphine and fentanyl on TNF-α, IL-1β levels, which are important markers of inflammatory response, and wound healing based on histopathological scores in an experimental wound model created on rats.

MATERIALS and METHODS

Our study was designed as a randomized controlled unblinded experimental study.The rats were numbered and divided into groups by attaching labels to their tails. During the study, all experimental and surgical applications were carried out following the Guide to the Care and Use of Experimental Animals published by the US National Health Institutes and considering ethic principles.

This study was carried out in Ordu University Experimental Research Center after the ethical approval was obtained by the Directorate of Animal Experiments Local Ethics Committee of Ordu University with a decision no 16 dated June 22, 2021 (Date: 22.06.2021; Decision number: 2021/16) . The subjects were obtained from Samsun Ondokuz Mayis University Experimental Animal Breeding and Research Center.

A total of 18 male Wistar-Albino rats, 10-12 weeks old and weighing 250-300 g, were included in the study. The subjects were kept in a standard laboratory environment for a 7 day period, under optimum living conditions, fed with same food, and given water in the same environment with controlled temperature and 12 hours day/night cycle maintained. Experimental animals were monitored in cages, 6 of them in each cage. Wound care was performed once a day with no antibiotics given at any stage of the procedure and after the procedure. No subject died during the seven day period. On day 7, the subjects were sacrificed by taking intracardiac blood under deep anesthesia.

In the present study, 3 (three) study groups were created: the control group (=Group C), the Morphine group (=Group M), and the Fentanyl group (=Group F). Rats were randomly selected (n=6) and tail-tagged with letters and numbers in order to ensure correct match.

Preparation of Medications

Lower concentrations (500µg/ml) were obtained by dissolving 1 ampoule of Morphine (Morphine Hydrochloride 0.01gr /1 ml ampoule, Osel Ilac, Turkey) solution with 19 ml of distilled water. 3 ml of 1500 mcg of diluted morphine was injected into the wound incision line of each rat. 1 ampoule of Fentanyl (Fentaver 100 mcg/2 ml amp, Haver Ilac, Turkey) solution was dissolved in 18 ml of distilled water to obtain lower concentrations (5mcg/ml). 3 ml of 15 mcg of diluted fentanyl was injected into the wound incision line of each rat.

Experimental Research Model

Anesthesia was achieved through the intramuscular injection of 50 mg/kg of ketamine (Ketalarflk., Pfizer Pharma GMBH, Germany) and 10 mg/kg of xylazine hydrochloride (Alfazyne 2%, Alfasan International, Holland). After the disappearance of the corneal reflex and limb withdrawal response, the rats' backs were shaved with an electric shaver. The incision site was wiped with povidone-iodine and dried with sterile gauze after waiting for 2 minutes. Under sterile conditions, a perforated compress was placed, and a 1-cm longitudinal surgical incision containing the skin and subcutaneous connective tissue was made with a scalpel from the midline in the dorsal region. 3 ml 1500 mcg of diluted morphine for Group M, 3 ml of fentanyl 15 mcg diluted for Group F and 3 ml of saline solution for Group C were given to the incision line. The skin and subcutaneous tissues were sutured with a 4/0 silk thread.

Determination of Plasma Cytokine Levels

A 0.5 ml of blood was taken from the tail vein at 30 minutes after the procedure and centrifuged (3000g, 15 minutes, 4°C). The samples were stored at -80°C until measurement. Plasma TNF-α, IL1-β levels were determined using commercial enzyme-linked immunosorbent assay kits (Boster, Boster Biological Technology Co, Ltd, USA) for rats in ELISA device in accordance with the manufacturer's instructions.

All kit standards (TNF-α, IL1-β) were diluted with distilled water in equal amounts as instructed on the label. Each diluted standard was rested for 10-30 minutes. It was mixed carefully so that the mixture and solubility were homogeneous. Dilutions of the standards were made directly in the microwells.

Histopathological Evaluation

On day 7, a 2 x 2 cm strip of biopsy specimen was obtained from the incision line of the subjects. After formalin fixation, paraffin blocks were prepared following the steps of routine tissue processing, from which two 4-5µ thick sections were cut. One of the sections was stained with routine hematoxylin-eosin (HE) while the other was histochemically stained with Masson Trichrome (BESLAB, HistoMed, Ankara). Active inflammation (PMNL infiltration and edema), chronic inflammation (lymphocyte, plasmocyte infiltration), and granulation (vascularization, giant cells, fibroplasia) formation were assessed in HE sections, while fibrosis was assessed (fibroblastic activity increase/collagenization) in Masson trichrome sections. All parameters were scored semi-quantitatively with:0: Absent 1: Mild 2: Moderate 3: Severe (7).

Statistical Analysis

Study data were analyzed using IBM SPSS v23. Conformity to normal distribution was evaluated with the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used to compare the TNF-α and IL1-β values by the groups. Tukey HSD test was used for multiple comparisons as the TNF Alpha variances were homogeneous. The score differences among the groups were evaluated with the Kruskal-Wallis test. The relationship between the scores and TNF-α, IL1-β levels was analyzed using the Spearman's Rho as they did not fit the normal distribution. The results were presented as mean ± s. deviation, median (min-max). The significance level was considered as $p<0.05$.

RESULTS

Distribution of active inflammation (AI) (polymorphonuclear leukocyte infiltration and edema), chronic inflammation (CI) (lymphocyte, plasmocyte infiltration) and granulation (G) (increased vascularization, giant cells, fibroplasia), and fibrosis (F) (increased fibroblastic activity/collagenization) severity of each 3 groups is summarized in Table 1.

Table 1: Distribution level of histopathological scores

Group	Active Inflammation (AI score)	Chronic inflammation (CI Score)	Granulation (G Score)	Fibrosis (F score)
C1	1	2	2	2
C2	1	1	1	2
C3	1	2	1	1
C4	1	1	1	2
C5	1	1	1	2
C6	1	2	1	1
F1	1	2	1	2
F2	1	2	2	2
F3	2	2	1	1
F4	1	2	3	1
F5	2	2	2	1
F6	1	2	2	1
M1	0	1	3	2
M2	1	2	1	2
M3	1	1	2	2
M4	2	1	2	1
M5	1	1	2	1
M6	1	2	3	2

M: Morphine group, F: Fentanyl group C: Control group,
AI: Active Inflammation CI: Chronic Inflammation G: Granulation F: Fibrosis
Histopathological Scoring: 0=Absent, 1= Mild, 2= Moderate, 3= Severe.

Histopathological assessment of inflammation is shown in Figure 1.

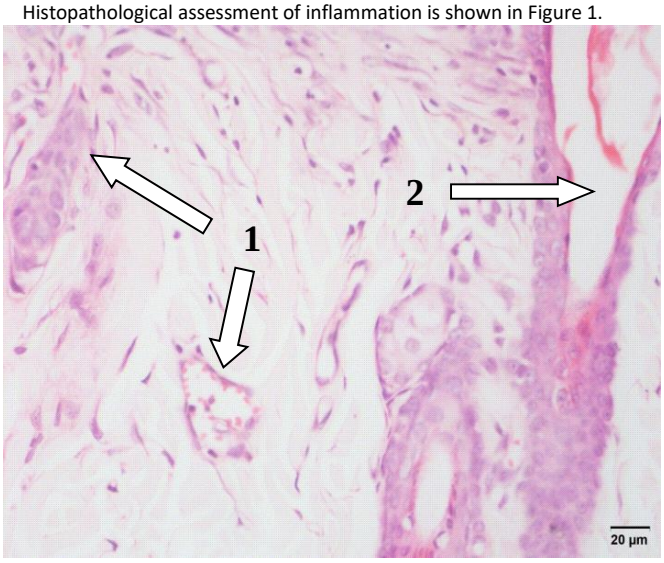

Figure 1: Severe infiltration of polymorphonuclear leukocytes(1) and edema(2) (HEx 400)

TNF-α, IL1-β values and statistical introductory histopathological scores are presented in Table 2 for all 3 groups (control, morphine, and fentanyl).

Table 2. Group comparisons of biochemical parameters and histopathological scores

	Control Mean ± s.deviation	Median (min-max)	Morphine Mean ± s.deviation	Median (min-max)	Fentanyl Mean ± s.deviation	Median (min-max)	p
TNF Alpha ng/L	296.79 ± 47.2	293.2 (227.8 - 373)	295.4 ± 54.81	270.95 (248.1 - 382.6)	294.3 ± 23.27	285.35 (273.3 - 335)	0.995[2]
IL1 Beta pg/ml	117.11 ± 20.56[a]	114.66 (92.98 - 147.01)	195.47 ± 55.03[b]	182.85 (117.62 - 277.48)	154.89 ± 27.21[ab]	151.96 (127.89 - 189.55)	**0.009**[1]
AI Score	1 ± 0	1 (1 - 1)	1 ± 0.63	1 (0-2)	1.33 ± 0.52	1 (1-2)	0.364[2]
CI Score	1.5 ± 0.55	1.5 (1 - 2)	1.33 ± 0.52	1 (1-2)	2 ± 0	2 (2 - 2)	0.057[2]
G Score	1.17 ± 0.41	1 (1-2)	2.17 ± 0.75	2 (1-3)	1.83 ± 0.75	2 (1-3)	0.056[2]
F Score	1.67 ± 0.52	2 (1 - 2)	1.67 ± 0.52	2 (1 - 2)	1.33 ± 0.52	1 (1-2)	0.421[2]

[1]One-way analysis of variance; [2]Kruskal Wallis; [a-b] No difference between groups with the same letter (Tukey HSD)
(AI: Active Inflammation CI: Chronic Inflammation G: Granulation F: Fibrosis)

A difference was found in the mean IL1-β values between the groups (p=0.009). While the mean value was determined as 117.11 in the control group, it was 195.47 in the Morphine group and 154.89 in the Fentanyl group. While the control group had a lower mean value than the Morphine group, no difference was found between the Fentanyl group and the control and morphine groups. TNF-α, AI, CI, G, and F scores did not differ between the groups (p values: 0.995, 0.365, 0.057, 0.056, and 0.421, respectively).

The significant difference between the mean IL1-β values may be associated with the positive contribution of morphine and fentanyl to the active inflammatory phase. Therefore, it can be said that morphine and fentanyl accelerate the migration of polymorphonuclear leukocytes to the wound site and exert positive effects during the acute phase of wound healing. Groups' TNF-α and IL1-β levels are shown in graphs in Figure 2.

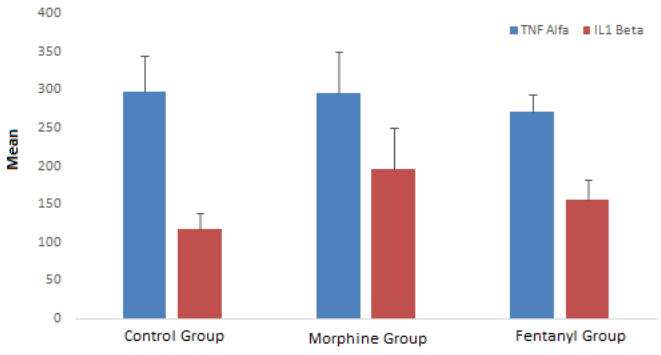

Figure 2: TNF-α and IL1-β values of groups

The results of the correlation analysis between TNF-α, IL1-β and histopathological scores are presented in Figure 3. In the control group, a strong positive correlation was found between the CI score and IL1-β (r=0.878; p<0.001). No significant correlation was found with other scores in the control group. In the morphine group, a strong positive correlation was only found between the CI score and TNF-α (r=0.828; p<0.001).In the fentanyl group, a strong negative correlation was found between the F score and IL1-β (r=-0.828; p<0.001). Other correlation coefficients were not significant.

As shown by the analysis, all correlation coefficients were insignificant regardless of any group distinctions. Hot maps of the correlation coefficients are presented in Figure 3.

Group	Score	TNF-α	IL1-β
Control	AI		
	KI	-0,293	**0,878**
	G	-0,393	0,655
	F	0,000	-0,414
Morphine	AI	0,169	0,338
	KI	**0,828**	0,000
	G	-0,309	-0,802
	F	0,621	0,000
Fentanyl	AI	0,414	0,414
	KI		
	G	-0,154	0,370
	F	-0,414	**-0,828**
Total	AI	0,102	0,347
	KI	0,319	0,231
	G	-0,285	0,386
	F	0,194	-0,323

1,00
0,75
0,50
0,25
0,00
-0,25
-0,50
-0,75
-1,00

Figure 3. Hot maps of correlation coefficients No correlation could be obtained since AI values in the control group and CI values in the Fentanyl group were constant.

The correlation analysis demonstrated a strong correlation between TNF-α levels and CI scores in the morphine group, revealing that morphine exerted positive effects on chronic inflammation.

DISCUSSION

Evaluation of our study results indicates that the significant difference between the mean IL1-β values may be associated with the positive contribution of morphine and fentanyl to the active inflammatory phase. Therefore, it can be said that morphine and fentanyl accelerate the migration of polymorphonuclear leukocytes to the wound site and exert positive effects during the acute phase of wound healing. No significant results were obtained regarding TNF-α levels in the morphine and fentanyl group compared to the control group. The correlation analysis demonstrated a strong correlation between TNF-α levels and CI scores in the morphine group, and that morphine exerted positive effects on chronic inflammation.In terms of histopathological scores, no significant results were obtained in the morphine and fentanyl groups compared to the control group.

In their experimental study, Wu et al. (8) examined the role of morphine in wound healing where they administered a 5 mg/kg of low dose morphine followed by a daily dose of 20-30 mg/kg of morphine in rats, upon which they noted abnormal myofibroblast formation in the experimental wound model triggered by high doses of morphine. The authors concluded that high doses of morphine can trigger chronic inflammation and systemic fibrosis. Similarly, in our study, we found a strong positive correlation between morphine and chronic inflammation scores (CI), while a negative correlation was observed between fentanyl and CI scores, which was consistent with the results of Wu et al.

In their experimental study, Wang et al. (9) showed that opioids offer a unique advantage in wound healing due to their ability to stimulate revascularization and reduce neuroinflammation. Available studies also report that opioids accelerate wound healing by upregulating receptors (10,11).

In their clinical study, Gupta et al. (12) showed that topical application of fentanyl accelerates the healing of ischemic open wounds in diabetic rats, where the authors noted that increased angiogenesis was associated with lymphangiogenesis, peripheral nerve regeneration, fentanyl-induced tissue remodeling, and wound healing. In our study, the IL1-β level was higher among the rats receiving fentanyl compared to the control group.

We found that fentanyl had positive effects during the acute inflammatory phase of wound healing and demonstrated a strong negative correlation between Fibrosis score (F score) and IL1-β levels in the fentanyl group, based on which it can be concluded that fentanyl inhibits fibrosis.Gupta et al. (12) noted that topical opioid treatment of ischemic wounds may be potentially beneficial in the healing of diabetic wounds, augmenting their known analgesic effect. Additionally, authors reported that these data positively regulate the underlying signaling mechanisms lying underneath normal vascular, lymphatic, and nerve architecture in the skin for the regenerative process. Our results are perfectly consistent with the results of Gupta et al.

A review by Ondrovics et al. (13) reported that opioids, which are widely used to manage wound and cancer pain, exert much greater effect that go beyond their classic role of pain relief, stating that increasing evidence show opioids modulate angiogenesis. They stated that opioids (morphine, hydromorphone, and fentanyl) can be an innovative therapeutic avenue for the treatment of chronic wounds and cancer, which was also proposed by Gupta et al. (12).Opioids are innovative therapeutic drugs for the treatment of chronic wounds and cancer (12,13) In fact, while opioids have a proangiogenic effect in chronic wounds, that is, increasing blood supply to the wound site and wound angiogenesis; they inhibit angiogenesis and cell proliferation to reduce tumor growth, as well as showing antiangiogenic effects by reducing vascular endothelial growth factor (VEGF) (12-15).In this context, we can say that opioids are "very smart" drugs and that our results are consistent with the literature.

In a prospective randomized controlled clinical study conducted by Kwon et al. (16), where the cases aged 20-60 years undergoing laparoscopic cholecystectomy were divided into two groups, transdermal fentanyl was administered to one group preoperatively, while no transdermal fentanyl was administered to the control group, and IL-6 and IL-8 levels were assessed at postoperative hours 1, 6, 12, 24, and 48. In the fentanyl patch group, IL-6 and IL-8 were low in the first 24 hours, and there was a statistically significant difference in proinflammatory cytokines (IL-6, IL-8) in the fentanyl patch group compared to the control group. The authors noted that fentanyl exerted immunomodulatory effects, concluding that opioids (fentanyl) go way beyond their classical role of relieving pain, which was also demonstrated by the results of our study. In our study, an experimental open wound was created, whereas Kwon et al. (16) conducted a clinical study in laparoscopic cholecystectomy. We assessed the proinflammatory cytokine levels of TNF-α, IL1-β within 30 minutes following wound creation and found elevated TNF-α, IL1-β levels in the morphine and fentanyl groups compared to the control group. In our study, we found that IL1-β levels were statistically significantly high. Although our results are not in full agreement with the study of Kwon et al., the fact that opioids exert an immunomodulatory effect is certain, in which respect our results are consistent with the literature.

There are some limitations of our study. Firstly, the number of subjects in our study was limited. TNF-α, IL1-β levels were only measured once, rather than multiple measurements, which would have helped to find more supporting evidence for our hypothesis. However, using more subjects and drawing more blood in experimental studies, even for the sake of science, may lead to the death of more animals. The fact that we acted faithfully to the ethics of experimental animals was another limitation of our study.

We can say that morphine and fentanyl play an active role in the acute phase of wound healing and accelerate the migration of polymorphonuclear leukocytes to the wound site, as well as exerting positive effects during the active inflammatory phase of wound healing. Morphine and fentanyl can be safely preferred considering their immunomodulatory effects in intraoperative and/or postoperative analgesia and contribution during the active inflammatory phase. It can be said that opioids contribute to wound healing with their immunomodulatory effects, far beyond their role in reducing postoperative pain. We believe that opioids are "very smart" drugs and our study will shed light on prospective clinical studies.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Robson M C., Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. Current problems in surgery, 2001; 2(38):72-140.
2. Beyene T, Derryberry SL, Barbul A. The effect of comorbidities on wound healing. SurgClinNorth Am 2020;100(4):695-705.
3. Powers JG, Higham C, Broussard K, Phillips TJ. Wound healing and treating wounds: Chronic wound care and management. J Am AcadDermatol 2016; 74:607-625.
4. Honda Y, Higuchi H, Matsuoka Y et al. The Inhibitory Effect of Locally Injected Dexmedetomidine on Carrageenan-induced Nociception in Rats. Eur J Pharmacol. 2015;764:215-9
5. Cañedo-Dorantes L, Cañedo-Ayala M. Skin Acute Wound Healing: A Comprehensive Review Int J Inflam. 2019; 2019: 3706315.
6. Leong M, Phillips LG. (2004) WoundHealing. Townsend MC, SabistonTextbook of Surgery, 17th Edition, Elsevier, USA 2004; 183-208.
7. Drucker M, Cardenas E, Arizti P et al. Experimental studies on the effect of lidocaine on wound healing. World J Surg. 1998; 22(4): 394–398. 52
8. Wu PC, Hsu WL, ChenCL,LamCF,HuangYB,Huang CC et al. Morphine Induces Fibroblast Activation through Up-regulation of Connexin 43 Expression: Implication of Fibrosis in Wound Healing Int J Med Sci. 2018; 15(9): 875–882. Published online 2018 Jun 4. doi: 10.7150/ijms.23074
9. Wang Y, Gupta M , Poonawala T, Farooqui M , Li Y, Peng F et al.Opioids and opioid receptors orchestrate wound repairTransl Res. 2017;185(7): 13–23.
10. Bigliardi PL, Dancik Y, Neumann C, Bigliardi-Qi M. Opioids and skin homeostasis, regeneration and ageing - What's the evidence? Experimental dermatology. 2016; 25(8):586–91
11. Stein C, Kuchler S. Targeting inflammation and wound healing by opioids. Trends in pharmacological sciences. 2013; 34(6):303–12.
12. Gupta M,PoonawalaT,Farooqui M, Ericson ME, Gupta K Topical fentanyl stimulates healing of ischemic wounds in diabetic rats J Diabetes. 2015;7(4): 573–83.
13. OndrovicsM,HoelblKovacicA,FuxDAOpioids: Modulators of angiogenesis in wound healing and cancerOncotarget. 2017;8(15): 25783–25796.
14. Poonawala T, Levay-Young B, Hebbel R, Gupta K. Opioids heal ischemic wounds in the rat. Wound RepairRegen. 2005;13(2): 165-74.
15. Bentov I, Reed MJ. Anesthesia, Microcirculation and Wound Repair in Aging Anesthesiology2014 ; 120(3): 760–772.
16. Kwon Y,HwangSM,JangJS,RyuBY,KangBY,LeeJJ.Effects of a Preoperative Transdermal Fentanyl Patch on Proinflammatory Cytokine and Pain Levels During the Postoperative Period: A Randomized Controlled TrialSurgLaparoscEndoscPercutan Tech. 2019;29(5): 339–34