Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Investigation of inflammatory effects of dexmedetomidine and sugammadex in early wound healing in rats

Mehmet Serif Alp[a], Ebru Canakci[a,*], Muruvvet Akcay Celik[b], Tulin Bayrak[c], Ahmet Bayrak[c]

[a] *Ordu University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Ordu, Türkiye*
[b] *Ordu University, Faculty of Medicine, Department of Medical Pathology, Ordu, Türkiye*
[c] *Ordu University, Faculty of Medicine, Department of Medical Biochemistry, Ordu, Türkiye*

ARTICLE INFO

Keywords:
Wound healing
Rat
Dexmedetomidine
Sugammadex

Received: Apr 17, 2023
Accepted: Aug 02, 2023
Available Online: 25.08.2023

DOI:
10.5455/annalsmedres.2023.04.097

Abstract

Aim: The aim of this study was to determine how local dexmedetomidine and sugammadex application affect TNF- α IL-1β levels, and histopathological scores, which are important markers of inflammatory response, in a rat experimental wound model.

Materials and Methods: In Group D, 2 ml of 10 mcg diluted dexmedetomidine (n=8), 2 ml of 10 mg diluted sugammadex (n=8), and 2 ml of saline (n=8) were infiltrated into the incision lips. Plasma TNF-α, IL1-β levels was measured. The rats were awakened. Their survival was continued for 7 days. On the seventh day following the procedure, a biopsy was taken from the subjects' incision line, and their histopathological wound healing scores were evaluated.

Results: There was a difference between the mean values of TNF-α between the groups (p=0.016). TNF-α was found to have a mean value of 299.59 in the control group, 253.41 in the dexmedetomidine group, and 249.51 in the sugammadex group. IL-1β values, chronic inflammation (CI), granulation (G) and fibrosis (F) scores did not differ between groups (p values 0.752, 0.118, 0.368, and 0.296, respectively). The active inflammation (AI) scores of the all groups differed significantly (p=0.007).

Conclusion: Dexmedetomidine and sugammadex have been shown to accelerate the migration of polymorphous core leukocytes to the wound site. We believe that our research will shed light for future clinical trials.

Introduction

A wound is a loss of function in the tissue caused by an abnormal anatomical structure of the tissue, which can be caused by a variety of factors. Wound healing is essential for complete recovery after surgical operations, is one of the most important issues in clinical practice in the surgical branches and it can be influenced by a variety of patient related factors. The drugs used by the patient may also have an impact on this complex process [1, 2]. Therefore, the question of whether anesthetic drugs administered to patients during surgery, particularly opioids administered for intraoperative and/or postoperative pain, play a role in wound healing arises. Proinflammatory cytokines are tumor necrosis factor–alpha (TNF-α), interleukin-1 beta (IL1β), interleukin-2 (IL-2), interleukin-6 (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 from macrophages and monocytes and increase the synthesis of acute phase proteins such as C-reactive protein (CRP), serum amyloid A, fibrinogen, complement, and alpha 1-antitrypsin. Proinflammatory cytokines are stimulated by microorganisms, microbial products, antigens, inflammatory agents, herbal lectins, lymphokines, and some chemicals [3].

It has been demonstrated that the increase in IL-1α, IL1-β, IL-6 and TNF-α, which are proinflammatory cytokines in wound repair, increases significantly as long as the acute inflammatory healing process continues [4].

Dexmedetomidine has been shown in clinical and experimental studies to inhibit inflammatory cytokines, reduce oxidative stress, regulate reactive oxygen derivatives and antioxidation, and play an important role in preventing reperfusion damage [5]. Simultaneously, there is evidence showing that it reduces mortality by suppressing the inflammatory response in cases of sepsis.Sugammadex, a modified gamma-cyclodextrin, antagonizes the curare-like block induced by steroidal neuromuscular blocking drugs. Human and animal studies have shown that sugammadex can reverse deep neuromuscular blockade caused by

*Corresponding author:
Email address: canakciebru@gmail.com (Ebru Canakci)

rocuronium without muscle weakness [6]. Cyclodextrins have been used to improve the release and bioavailability of drugs approved for different treatments. There have been studies showing that they reduce inflammatory responses such as oxidation and proinflammatory cytokine expression. On the other hand, cyclodextrins have been shown to be effective in cholesterol-mediated inflammation processes [7].

Sugammadex is a reversing agent, so it is used to reverse curare-like block in any case given general anesthesia. It has been proven in clinical and experimental studies that sugammadex has an anti-inflammatory effect as well as a reverse effect [8,9]. We wanted to investigate the role of such a commonly used agent in wound healing because the subject of sugammadex and wound healing is a virgin topic in the literature.

The aim of this study was to examine the effects of local dexmedetomidine and sugammadex application on TNF-α and IL-1β levels, as well as wound healing histopathological scores, which are important markers of inflammatory response, in a rat experimental wound model.

Materials and Methods

Our study was designed as an unblinded experimental study. This study was approved by the Ordu University Rectorate Animal Experiments Local Ethics Committee with decision number 15 made at the meeting dated 22/10/2020 (Decision number:15 Date:22.10.2020) and was conducted at the Ordu University Experimental Research Center. The subjects were relocated from the Samsun Ondokuz Mayıs University Experimental Animals Application and Research Center (DEHAM) to the Ordu University Experimental Animal Breeding Application and Research Center in accordance with the transfer conditions, after adequate and appropriate conditions were obtained and the necessary permits were obtained.

During the study, all experimental and surgical applications were carried out following the Guideto the Care and Use of Experimental Animals published by the US National Health Institutes, and consideringethics principles.

The Ordu University Scientific Research Projects Coordination Unit (ODU-SRPCU) provided funding for this thesis project (ODU-SRPCU Project Number: B-2018).

The study included 24 male Wistar-Albino rats, 10-12 weeks old and weighing 250-300 g. The number of subjects required for this study was planned based on the medical specialty thesis study of Gezer et al.[10]The subjects were kept in standard plastic cages for 7 days, with 12-hour day and 12-hour night cycles at 24-26 ℃ room temperatures and in 50-60% humidity conditions in temperature-controlled shelters until the experiment. The subjects, divided into groups of four per cage, were monitored. Wound care was implemented once a day and no antibiotics were given to the subjects at any point during or after the procedure. During the seven days, no subjects were lost. On the 7th day after the procedure, the subjects were sacrificed by cervical dislocation under deep anesthesia.

The experimental animals were divided into 3 (three) groups of eight rats each. In this study, there are 3 (three) study groups: the control group (=Group C), the Sugammadex group (=Group S), and the Dexmetedomidine group (=Group D). Rats were chosen randomly (n=8) and identified using a letter and number system with tail tagging to ensure a perfect match.

In group D lower concentrations (5µg/ml) of dexmedetomidine were obtained by dissolving one vial of dexmedetomidine solution (Precedex 100 µg/2 ml vial., Abbott Laboratory, Illinois, USA) in 18 ml of distilled water. 10 µg/kg (2 ml) of dexmedetomidine was infiltrated into the wound edges of each rat.

In group S to obtain lower concentrations (5 mg/ml) of sugammadex, 1 ml (100 mg) of sugammadex solution (Bridion 200 mg /2 ml vial., MSD,Hospira, Rocky Mount, NC, USA) was taken from a vial and dissolved with 19 ml of distilled water. For each rat, 10 mg/kg (2 ml) of sugammadex was infiltrated into the wound edges.

2 ml of saline (n=8) was infiltrated into the incision lips of each rat in Group C.

In all experimental animals intramuscular 50 mg/kg ketamine (Pfizer Pharma GMBH, Germany) and 10 mg/kg xylazine hydrochloride (Alfazyne 2%, Alfasan International, Holland) were used to induce anesthesia.

After the loss of extremity-pulling response and corneal reflex, the back hairs were shaved and cleaned. The incision area was wiped with povidone iodine and dried with sterile gauze after 2 minutes. Following the sterile placement of the perforated cover, a longitudinal surgical incision of 1 cm in the midline in the dorsal region was made with a scalpel, including the skin and subcutaneous connective tissue. In Group D, 2 ml of diluted dexmedetomidine (n=8), in group S 2 ml of diluted Sugammadex (n=8) and in control group 2 ml of saline (n=8) were infiltrated into the incision lips. The skin and subcutaneous tissues were joined together with a 4/0 silk thread.

After the procedure, 1.5 ml of blood was drawn from the tail vein 30 minutes after anesthesia, centrifuged (3000 g, 15 minutes, 4'°C), and stored at -80 °C until measurement. TNF-α and IL1β levels in plasma were determined using the enzyme-linked immunosorbent measurement method in an ELISA device using commercial rat kits (Boster, Boster Biological Technology Co., Ltd, USA) in accordance with the package inserts.

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

Rats were kept alive for 7 days. A 2 x 2 cm strip biopsy was taken from the subjects' incision line on the seventh day while they were sedated. All the subjects were sacrificed by cervical dislocation under deep anesthesia.

Following formalin fixation, paraffin blocks from all samples were prepared using the routine tissue follow-up procedure, and two 4-5µ thick sections were cut from these paraffin blocks. One section was stained with hematoxylinand eosin (HE), while the other was histochemically stained with Masson Trichrom stain (BESLAB,

HistoMed, Ankara). Active inflammation (PMNL infiltration and edema), chronic inflammation (lymphocyte, plasmocyte infiltration), and granulation tissue formation (vascularization, giant cells, fibroplasia) were evaluated in HE sections, while fibrosis (fibroblastic activity increase/collagenization) was assessed in Masson trichrome sections. All parameters were scored with the semi-quantitative method as follows: 0: None, 1: Mild 2: Moderate 3: Severe.

Statistical analysis

Data were analyzed with IBM SPSS v23. The Shapiro-Wilk test was used to assess conformity to normal distribution. One-way analysis of variance (ANOVA) was used to compare TNF-α, IL1-β values according to groups. Since the variances in TNF-alpha values were homogeneous for multiple comparisons, the Tukey HSD test was used. The Kruskal-Wallis test was used to determine whether the scores differed by group. Since the scores did not conform to normal distribution, the relationship between the scores and TNF-α, IL1β values was examined using Spearman's rho. Analysis results were presented as mean ± s. deviation, median (min-max). Significance level was taken as $p<0.05$.

Results

Table 1 summarizes the severity of active inflammation (polymorph core leukocyte infiltration and edema),

Table 1. Distribution degree of histopathological scores.

Group	Active Inflammation (AI score)	Chronic ınflammation (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
C7	1	1	1	1
C8	1	1	1	2
S1	1	2	1	1
S2	1	1	1	1
S3	2	2	1	2
S4	2	1	1	2
S5	3	2	1	2
S6	2	1	1	2
S7	1	1	1	2
S8	1	2	1	1
D1	2	2	1	1
D2	1	1	1	2
D3	1	2	1	2
D4	2	2	1	2
D5	2	2	1	2
D6	1	2	1	3
D7	1	2	1	2
D8	2	2	1	2

C: Control group, S: sugammadex experimental group, D: Dexmedetomidine experimental group.

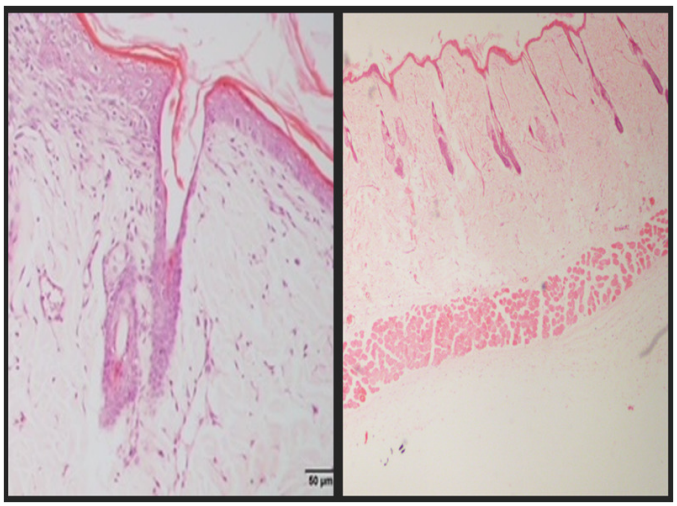

Figure 1. Histopathological examination of inflammation. Severe leukocyte with polymorphic nuclei infiltration and edema on the left (left HEx100), and fibrosis on the right (right HEx40).

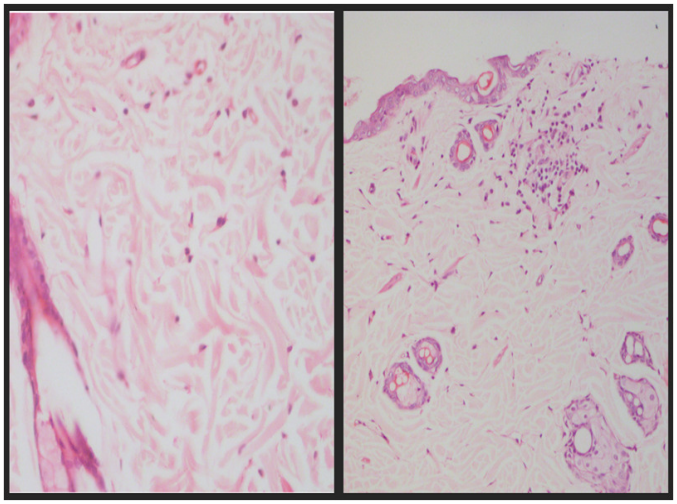

Figure 2. Histopathological examination of inflammation Acute inflammation (HEx400) on the left, angiogenesis (HEx200) on the right.

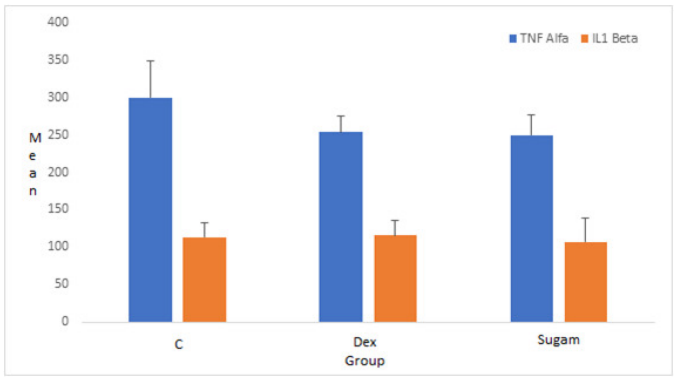

Figure 3. Illustrates the TNF-α and IL1-β levels of the groups graphically.

Table 2. Comparisons by groups.

	Control		Dexmedetomidine		Sugammadex		p
	Mean±S.Deviation	Median (min-max)	Mean±S.Deviation	Median (min-max)	Mean±S.Deviation	Median (min-max)	
TNF Alpha (ng/L)	299.59 ± 49.2[a]	293.2 (227.8- 373)	253.41 ± 22.16b	255.25 (220.6 - 284.1)	249.51 ± 27.2[b]	251.4 (205 - 284.3)	**0.016**[1]
IL1 Beta (pg/ml)	113.63 ± 18.78	106.58 (92.98- 147.01)	116.11 ± 20.47	113.61 (95.18 - 160.39)	107.2 ± 31.37	96.06 (66.46 - 158.79)	0.752[1]
AI score	1 ± 0[a]	1 (1 - 1)	1.38 ± 0.52 [b]	1 (1 - 2)	1.63 ± 0.74 [b]	1.5 (1 - 3)	**0.007**[2]
CI Score	1.38 ± 0.52	1 (1 - 2)	1.88 ± 0.35	2 (1 - 2)	1.5 ± 0.53	1.5 (1 - 2)	0.118[2]
G score	1.13 ± 0.35	1 (1 - 2)	1 ± 0	1 (1 - 1)	1 ± 0	1 (1 - 1)	0.368[2]
F score	1.63 ± 0.52	2 (1 - 2)	2 ± 0.53	2 (1 - 3)	1.63 ± 0.52	2 (1 - 2)	0.296[2]

[1] One-way analysis of variance; [2]Kruskal Wallis; [a-b] No difference between groups with the same letter (Tukey HSD).

Table 3. Results of correlation analysis between the scores and TNF Alpha and IL1 Beta.

Group	Score	TNF Alpha	IL1 Beta
Control	AI	–	–
	CI	-0.169	**0.845***
	G	-0.247	0.577
	F	-0.282	-0.169
Dexmedetomidine	AI	0.282	0.282
	CI	0.082	0.082
	G	–	–
	F	0.327	-0.218
Sugammadex	AI	-0.209	0.352
	CI	0.218	0.436
	G	–	–
	F	-0.169	0.394
Total	AI	-0.250	0.055
	CI	-0.171	**0.549***
	G	0.136	0.256
	F	-0.038	-0.075

*Significant correlation value at 1% significance level (Spearman's rho).

chronic inflammation (lymphocyte, plasmocyte infiltration), granulation tissue (increased vascularization, giant cells, fibroplasia), and fibrosis (fibroblastic activity increase/collagenization) in each of the three groups.

Active Inflammation was indicated as AI,

Chronical Inflammation indicated as CI,

Granulation indicated G and

Fibrosis indicated as F.

Histopathological Scoring was enumerated as 0= None,

1. Mild
2. Moderate
3. Severe

Figures 1 and 2 show histopathological sections of the inflammation.

The descriptive statistical values of TNF-α, IL1-β, and histopathological scores for all three groups (control, dexmedetomidine, and sugammadex) are presented in Table 2.

There is a difference in the mean TNF alpha values between groups (p=0.016). The mean of the control group was 299.59, while it was 253.41 in the Dexmedetomidine group and 249.51 in the Sugammadex group. There is a difference between the AI means according to the groups (p=0.007). The mean was 1 in the control group, 1.38 in the Dexmedetomidine group, and 1.63 in the Sugammadex group. The mean of the control group differed from the other two groups; however, there was no difference between the Dexmedetomidine and Sugammadex groups. IL 1 Beta, CI, G and F scores did not differ according to the groups (p values 0.752; 0.118; 0.368 and 0.296, respectively).

Table 3 shows the results of the correlation analysis between histopathological scores and TNF-α, IL1-β.

When the data was examined separately by group, it was discovered that there was a strong positive correlation between the CI score and IL1-β only in the control group (r=0.845; p<0.001). In the control group, there was no significant correlation between other scores and TNF- α levels. Similarly, there was no significant correlation between the scores and TNF-α and IL1β values in Dexmedetomidine and Sugammadex groups (p>0.05). When the relationship between the scores and TNF- α and IL1β was examined across all groups, it was revealed that there was only a moderate positive correlation between the CI score and IL 1β (r=0.549; p<0.001).

As the G values in the AI, Dexmedetomidine, and Sugammadex groups were constant in the control group, no correlation results could be obtained.

Discussion

The significant difference in the means of TNF-α found in our experimental study suggests that dexmedetomidine and sugammadex both contribute positively to the acute inflammation process. Consequently, dexmedetomidine and sugammadex accelerate the migration of polymorphonuclear leukocytes to the wound site in wound healing and have positive effects in the acute phase of wound healing. These outputs are the primary and secondary endpoints of our results, respectively. Significant results were obtained in the AI score in the dexmedetomidine and sugammadex groups when compared to the control group in terms of histopathological scores. It can be concluded that dexmedetomidine and sugammadex play an active role in the active inflammation phase of wound healing. Kuru et al. revealed in their experimental study that dexmedetomidine has antioxidant and anti-inflammatory effects. Thirty Wistar -Albino rats were di-

vided into 3 groups in the study. They performed a sham operation in one group, cecal abrasion and peritoneal dissection in one group, and 10 mcg/kg/day dexmedetomidine infusion for 10 days in the other group, in addition to cecal abrasion and peritoneal dissection. They found significant differences between the groups in malondialdehyde, myeloperoxidase, total sulfhydryl, and catalase levels. Plasma malondialdehyde and total sulfhydryl levels were also statistically different between these groups. Statistical analyses of mean pathological scores revealed that the cecal abrasion/peritoneal dissection + dexmedetomidine group had significantly less histopathological damage than the control group. Dexmedetomidine, according to the authors, has a significant preventive effect on postoperative intra-abdominal adhesions. The researchers concluded that these effects could be attributed to antioxidant and antiinflammatory properties. Similarly, in our study, TNF- α levels were significantly lower in the dexmedetomidine group compared to the control group, suggesting that they have antiinflammatory properties. In our study, similar to Kuru et al., our CI scores were lower in the dexmedetomidine group in terms of histopathological scores [11]. Deng et al. investigated whether perioperative administration of dexmedetomidine reduces the incidence of post-percutaneous nephrolithotomy lithotripsy (PCNL) systemic inflammatory response syndrome (SIRS) in patients undergoing percutaneous nephrolithotomy in a clinical randomized controlled study on 190 patients (PCNL). Systemic inflammatory response syndrome (SIRS) incidence rates were found to be significantly lower in the dexmedetomidine group compared to the control group (35.8% vs. 50.5%, p=0.04). This study revealed that administering dexmedetomidine during PCNL may help reduce the incidence of SIRS by inhibiting the release of inflammatory mediators. The authors attributed these study results to the inhibition of inflammatory responses and as a result, lower serum levels of IL-6 and TNF-α induced by dexmedetomidine administration. As a result of this study, the authors concluded that future research should look into other effects of dexmedetomidine administration on SIRS [12]. Although our study was an experimental study, our TNF-α levels were found to be lower compared to the control group, similar to the study of Deng et al. Dexmedetomidine decreases TNF-α level by decreasing the inflammatory response. In our study, no decrease in IL-1β levels was detected. Our study results are partially similar to the study results of Deng et al. In an experimental study on rats, the effects of dexmedetomidine on TNF-α, IL-6, IL-10, TAS, TOS, malondialdehyde (MDA), protein carbonyl (PC), superoxide dismutase (SOD), catalase and glutathione peroxide (GPX) levels in the early treatment of mesenteric ischemia reperfusion injury were investigated. The study found that IL-6, TNF-α, and protein carboxylase levels were lower in the group that received dexmedetomidine before the reperfusion injury compared to the group that only obtained ischemia reperfusion. No significant difference was found in the other parameters examined. In the dexmedetomidine receiving group, there were no significant protective changes in intestinal morphology when compared to the group that did not receive dexmedetomidine. The study concluded that dexmedetomidine prevented intestinal ischemia-reperfusion injury in rats receiving dexmedetomidine without reperfusion damage. Dexmedetomidine is reported to prevent significant morphological changes in the intestine, as well as decrease tissue and proinflammatory cytokines and protein oxidation. The results of our experimental study are consistent with those of Kayacan et al. We also observed low levels of proinflammatory cytokines in our study groups [13]. In an experimental study (Li F et al.) , dexmedetomidine has been shown to inhibit inflammatory cytokines, reduce oxidative stress, regulate reactive oxygen derivatives and antioxidation, and play an important role in preventing reperfusion damage [14]. Our study results are compatible with the literatüre. Another rat study revealed that dexmedetomidine administration after acute kidney injury with sepsis suppressed the production of proinflammatory cytokines and reduced kidney tissue damage. Our study results are consistent with the literature findings [15]. Despite the fact that dexmedetomidine is commonly used in clinical and experimental studies today, the number of studies investigating the effects of local application on wound healing is very limited. Perioperative inflammation has been linked to a variety of postoperative complications, including infection and organ failure. Likewise, postoperative surgical pain is primarily caused by inflammation and mediators [16]. As a result, strategies that limit and control the local inflammatory response during the perioperative period will benefit the patient's postoperative wound healing. Sugammadex is a gamma cyclodextrin with a ring structure that contains 8 negatively charged glucose monomers [17]. Cyclodextrins also show anti-inflammatory activity on their own. There have been studies showing that they reduce inflammatory responses such as oxidation and proinflammatory cytokine expression. On the other hand, cyclodextrins have been shown to be effective in cholesterol-mediated inflammation processes [7]. Sugammadex is a cyclodextrin-derived agent which is commonly used in modern medicine to reverse neuromuscular blockages. There have been no clinical or experimental studies on the anti-inflammatory activity of sugammadex on wound healing in the literature. Our study is the first study to examine the effect of sugammadex on wound healing. Gu et al. conducted a retrospective study involving 1615 patients who underwent abdominal surgery for cancer treatment and 795 of the patients were extubated after the surgery by administering 2 mg/kg (maximum 200 mg) sugammadex. As a result of the examination, they reported that sugammadex shortened the extubation time and accelerated the postoperative recovery in cancer patients undergoing abdominal surgery [18].

Conclusion

Consequently, dexmedetomidine and sugammadex accelerate the migration of polymorphonuclear leukocytes and lymphocytes to the wound site. Since dexmedetomidine and sugammadex have positive effects in the active inflammation phase of wound healing due to their immunomodulatory effect, they can be used safely during the perioperative period. We believe that our research will shed light for future clinical trials.

Acknowledgements

Financial support for this article was provided by the ODU –SRCPU unit.Biochemistry kit costs , labarotuary animals and pathological dye costs were covered by the Ordu University Scientific Research Projects Coordination Units(ODU-SRPCU Project Number: B-2018).

Disclosure

The abstract of this article was presented at the 1st International Congress of Eastern Black Sea Family Medicine, which will be held in Ordu, Turkey on May 25-27.

Ethical approval

This study was approved by the Ordu University Rectorate Animal Experiments Local Ethics Committee with decision number 15 made at the meeting dated 22/10/2020 (Decision number: 15 Date: 22.10.2020).

References

1. Robson M.C, Steed DL, Franz MG. Woundhealing: biologicfeaturesandapproachestomaximizehealingtrajectories. Currentproblems in surgery, 2001;38(2):72-140.
2. Beyene RT, Derryberry SL Barbul, A. Theeffect of comorbidities on woundhealing. SurgicalClinics, 2020;100(4): 695-705.
3. Powers JG, Higham C, Broussard K, Phillips, T J. Woundhealingandtreatingwounds: Chronicwoundcareandmanagement. Journal of theAmerican Academy of Dermatology, 2016;74(4):607-625.
4. Honda Y, Higuchi H, Matsuoka Y, Yabuki-Kawase A, Ishii-Maruhama M, Tomoyasu, Y et al. Theinhibitoryeffect of locally-injecteddexmedetomidine on carrageenaninducednociception in rats. EuropeanJournal of Pharmacology,2015; 764:215-219.
5. Li Y, He R.,Chen S, Qu Y. Effect of dexmedetomidine on earlypostoperativecognitivedysfunctionand perioperativeinflammation in elderlypatientsundergoinglaparoscopiccholecystectomy. Experimentalandtherapeutic medicine,2015; 10(5):1635-1642.
6. Naguib M..Sugammadex: anothermilestone in clinicalneuromuscularpharmacology. Anesthesia&Analgesia, 2007;104(3):575-81.
7. Lucia Appleton S, Navarro-Orcajada S, Martínez-Navarro FJ, et al. Cyclodextrins as Anti-inflammatoryAgents: Basis, DrugsandPerspectives. Biomolecules. 2021;11(9):1384 doi:10.3390/biom11091384.
8. Zimmer S, Grebe A, Bakke SS, Bode N, Halvorsen B, Ulas T et al. Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming. Science translational medicine, 2016;8(333), 333ra50-333ra50.
9. Bakke SS, Aune MH, Niyonzima N, Pilely K, Ryan L, Skjelland M et al. Cyclodextrin Reduces Cholesterol Crystal–Induced Inflammation by Modulating Complement Activation. J. Immunol. 2017;199:2910–20.
10. Gezer A.Effect of Dexmedetomidine Infiltration on Early Wound Healing in Rats University of Health Science Dışkapı Yıldırım Beyazıt Education and Research Hospital Ankara /Turkey National Thesis Center 2018 Thesis ID Number:507418.
11. Kuru S, Bozkirli OB, Barlas AM, Duymus ME, Senes M, Yumusak N et al.Thepreventiveeffect of dexmedetomidineagainstpostoperativeintraabdominaladhesions in rats. International surgery, 2015;100(1):87-95.
12. Deng Y, Tan F, Gan X, Li X, Ge M, Gong C et al. Perioperativeapplication of dexmedetomidineforpostoperativesystemicinflammatoryresponsesyndrome in patientsundergoingpercutaneousnephrolithotomylithotripsy: results of a randomisedcontrolledtrial. BMJ open, 2018;8(11): e019008.
13. Kayacan Y, Çetinkaya A, Yazar H, Makaracı Y. Oxidativestressresponsetodifferentexerciseintensitywith an automatedassay: thiol/disulphidehomeostasis. Archives of physiologyandbiochemistry, 2021;127(6):504-508.
14. Li F, Wang X, Deng Z, Zhang X, Gao P, Liu H. Dexmedetomidine reduces oxidative stress and provides neuroprotection in a model of traumatic brain injury via the PGC-1α signaling pathway. Neuropeptides 2018;72, 58-64.
15. Qiu R, Yao W, Ji H, Yuan D, Gao X, Sha W et al. Dexmedetomidine restores septic renal function via promoting inflammation resolution in a rat sepsis model. Life sciences, 2018;204:1-8.
16. Fujita I, Okumura T, Sakakibara A, Kita, Y. Involvement of inflammation in severe post-operativepaindemonstratedbypresurgicaland post- surgicaltreatmentwithpiroxicamandketorolac. Journal of PharmacyandPharmacology 2012;64(5), 747-755.
17. Ren WH, Jahr JS. Reversal of neuromuscularblockwith a selectiverelaxantbindingagent: sugammadex. Americanjournal of therapeutics, 2009;16(4), 295-299.
18. Gu X, Gao R, Li P, Jiao D, Song T, Li T et al. Sugammadex enhances recovery after abdominal surgery in cancer patients: a real-world, observational study. Annals of PalliativeMedicine 2021;10(12), 12566-12574.