EXPERIMENTAL STUDY

Effect of pre-incisional and peritoneal local anesthetics administration on colon anastomosis and wound healing

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ABSTRACT

BACKGROUND: Previous research has shown that levobupivacaine is as effective as bupivacaine but carries a lower risk of cardiac and central nervous system toxicity. This study explores whether levobupivacaine and bupivacaine are preferable for all patients, including those with comorbidities, particularly focusing on their effects on colonic anastomosis. The primary objective is to examine the influence of levobupivacaine and bupivacaine on colonic anastomosis. Additionally, the study will assess their impact on wound healing and their anti-adhesive properties.

METHODS: Conducted between July 28, 2022, to August 4, 2022, at the Hamidiye Animal Experiments Laboratory, this study was approved by the University Science Health, Hamidiye Animal Experiments Local Ethics Committee. This study was conducted using 21 male Sprague rats aged 16-20 weeks. The rats were allocated into three equal groups of seven each: Group C: pre-incisional isotonic; Group B: pre-incisional bupivacaine; and Group L: pre-incisional levobupivacaine. Macroscopic adhesion scores (MAS) were recorded during laparotomy and tissue samples were taken for histopathological examination and hydroxyproline levels measurement. Wound tensile strength along the middle incision line and anastomotic burst pressure were also assessed.

RESULTS: MAS was statistically significantly lower in Groups B and L compared to Group C ($p<0.001$). The wound histopathology score (WHS) was significantly higher in Group L than in Group B ($p=0.021$). Colon histopathology scores (CHSs) were also significantly higher in Group L compared to Group C ($p=0.011$).

CONCLUSION: TThe study found that bupivacaine and levobupivacaine did not significantly enhance wound healing, although levobupivacaine significantly improved WHS relative to bupivacaine. According to the findings of this study, levobupivacaine can enhance clinical practice by being used in patients undergoing colon anastomosis. It contributes significantly to the durability of colon anastomosis, has a more positive effect on wound healing compared to bupivacaine, and exhibits anti-adhesive properties. Additional clinical trials are necessary to validate these results further.

Keywords: Anastomosis; anti-adhesive; bupivacaine; colon; levobupivacaine; wound healing.

Cite this article as: Kesici U, Karatepe YK, Mazlum AF, Bozali K, Genç MS, Ercan LD, Duman MG, Sade AG, Guler EM, Kesıcı S. Effect of pre-incisional and peritoneal local anesthetics administration on colon anastomosis and wound healing. Ulus Travma Acil Cerrahi Derg 2024;30:316-322.

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Ulus Travma Acil Cerrahi Derg 2024;30(5):316-322 DOI: 10.14744/tjtes.2024.39551
Submitted: 05.11.2023 Revised: 07.04.2024 Accepted: 21.04.2024 Published: 13.05.2024

INTRODUCTION

Normal wound healing involves four phases: hemostasis, inflammation, proliferation, and remodeling. During the proliferation phase of normal wound healing, the fibrotic index increases due to a rise in fibroblast activity. Collagen, released from these fibroblasts and its subsequent cross-linking, determines the tensile strength of the wound. Although the amount of collagen and the increase in the fibrotic index are critical determinants of wound healing, issues with collagen structure and defects in collagen fiber binding can negatively impact wound healing.[1] While wound healing shares common features across all tissues, it exhibits fundamental differences in the gastrointestinal system. These differences include the synthesis of collagen by smooth muscle cells in addition to fibroblasts, and alterations in collagen synthesis. Consequently, it is believed that the same active substance may have different effects on skin wound healing and colonic anastomosis healing.[2]

Pre-incisional local anesthesia (LA) infiltration is widely used for postoperative analgesia in most surgical procedures. Bupivacaine and levobupivacaine are local anesthetic agents employed for this purpose, although their effects on wound healing are subject to debate.[1,3] Anastomotic leakage poses significant risks of morbidity and mortality in colonic anastomosis, a common procedure in surgical practice. Despite advancements in perioperative care and surgical techniques, the incidence of this complication remains stubbornly high.[4] Current research efforts focus on preventing or reducing anastomotic leakage. LA's anti-inflammatory and antimicrobial effects have been demonstrated in previous studies. However, there is a scarcity of studies regarding the effects of colonic anastomosis.[4-6] Camargo et al.[4] illustrated the positive impact of peritoneal lavage with bupivacaine on colonic anastomosis in cases of peritonitis. The only study that investigated the effect of local anesthetics as a lavage on colonic anastomosis was conducted by Camargo et al.[4] using bupivacaine. In our literature review, we found no studies examining the effects of levobupivacaine on colonic anastomosis. Investigations have indicated that levobupivacaine is equally effective as bupivacaine but carries a lower risk of cardiac and central nervous system toxicity.[7] Therefore, this study aims to determine whether levobupivacaine and bupivacaine could be preferable for all patients or specifically for those with comorbidities, following an assessment of their effects on colonic anastomosis.

The primary aim of the study is to investigate the effects of levobupivacaine and bupivacaine on colonic anastomosis, while the secondary objective is to demonstrate their impact on wound healing and anti-adhesive activity.

MATERIALS AND METHODS

This study was conducted between July 28, 2022, and August 4, 2022, at the Hamidiye Animal Experiments laboratory, with the approval of the University Science Health, Hamidiye Animal Experiments Local Ethics Committee (Approval date/no: 17.02.2022/02-01). It involved 21 male Sprague rats aged 16-20 weeks. Throughout the study, all rats received humane treatment in accordance with the Guide for the Care and Use of Laboratory Animals. All surgical procedures performed on the rats were conducted under anesthesia. Ketamin Hidroklorür (Ketalar® vial, 50 mg/ml, Eczacıbasi. Istanbul, Türkiye) at a dose of 80 mg/kg intraperitoneally (ip) and Ksilazin Hidroklorür (Rompun® vial, 23.32 mg/ml, Bayer. Istanbul, Türkiye) at a dose of 10 mg/kg intraperitoneally (ip) were used for anesthesia induction.

The rats were divided into three equal groups, each consisting of seven rats, as follows:

Group C (Control): Pre-incisional isotonic solution (3 mL) + laparotomy + colon anastomosis + peritoneal isotonic solution (3 mL).

Group B (Bupivacaine): Pre-incisional bupivacaine (2 mg/kg−1/3mL) + laparotomy + colon anastomosis + peritoneal bupivacaine (2 mg/kg−1/3mL).

Group L (Levobupivacaine): Pre-incisional levobupivacaine (2.5 mg/kg−1/3mL) + laparotomy + colon anastomosis + peritoneal levobupivacaine (2.5 mg/kg−1/3mL).

After an 8-hour fasting period, all rats were weighed under anesthesia and their weights were recorded. Prophylactic cefazolin sodium at a dosage of 30 mg/kg/mL and metronidazole at a dosage of 7.5 mg/kg/mL were administered 30 minutes prior to laparotomy. Following the shaving of abdominal hair and surgical disinfection with povidone iodide in an operating room setting, each rat in Group C received subcutaneously injection of 3 ml of isotonic solution, while rats in Group B received 2 mg/kg−1/3mL of bupivacaine, and those in Group L received 2.5 mg/kg−1/3mL of levobupivacaine before incision. A 3 cm full-thickness abdominal midline incision was then made. After a full-thickness transection at the level of the transverse colon, a single-layer anastomosis was performed using round 5/0 vicryl suture. Subsequently, rats in Group C received 3 mL of isotonic solution, those in Group B received 2 mg/kg−1/3mL of bupivacaine, and those in Group L received 2.5 mg/kg−1/3mL of levobupivacaine intraperitoneally. The midline incision was closed with 4/0 silk sutures. Rats were provided standard rat food on the 8th hour postoperatively. On the 7th postoperative day, all rats were weighed under general anesthesia, and a laparotomy was performed with excision of the anterior abdominal wall 2 cm from the right and left sides of the midline incision. Macroscopic adhesion scores (MAS) were recorded during the laparotomy. Tissue samples were obtained for histopathological examination and assessment of hydroxyproline levels. The middle third of the incision line was preserved at -80°C for evaluation of wound tensile strength. These samples were stored in formaldehyde until histopathological examination and in Eppendorf tubes at -80°C for measurement of hydroxyproline levels. The colonic segment, encompassing 2-3 cm proximal and distal regions

with the anastomosis itself, was excised. The burst pressure of the fresh anastomosis was measured. Subsequently, tissue samples were obtained, including 0.5 cm proximal and distal portions of the anastomosis. Half of these samples were preserved in formaldehyde for histopathological examination until preparation, while the other half was stored in Eppendorf tubes at 80°C until hydroxyproline levels were assessed. Following tissue sample collection, all rats were euthanized via intracardiac puncture.

Measurement of Wound Tension Strength (WTS): The tests were conducted using a uniaxial tensile testing system (Instron 3382 test frame). Results were reported at Newtons (N).[3]

Measurement of Anastomosis Burst Pressure (ABP): Following the method described by Li et al.,[8] a 5 cm intestinal segment, including 2 cm proximal and distal regions of the anastomosis, was resected. An 18G intraluminal catheter was inserted into the intestinal lumen, with one end sutured and the other secured. Methylene blue, diluted with saline, was administered via an infusion pump at a rate of 6 mL/min. A sudden decrease in pressure or detection of blue-colored liquid was considered the burst pressure and recorded in mmHg.[9]

Histopathological Examination: Tissue samples collected from the anastomosis line and the skin incision were routinely embedded in paraffin blocks. After slicing 4-5-micron sections, they were stained with hematoxylin and eosin dye and examined under a light microscope.

Microscopic Examination

I. Inflammatory cell types at the sites of anastomosis and skin incision (polymorphonuclear leukocytes – PMNL), neovascularization, and collagen fiber density were evaluated semi-quantitatively as +, ++, +++.

II. The degree of wound healing at the anastomosis and skin incision sites was scored from 1 to 5 as follows:

Score 1: Presence of only purulent fibrin exudate. Score 2: Granulation formation in less than 25% of anastomosis and skin incision site. Score 3: Granulation formation in 25% to 75% of anastomosis and skin incision site. Score 4: Granulation formation in more than 50% and collagen fibers in less than 25% of anastomosis and skin incision site. Score 5: Presence of collagen fibers in more than 25% of anastomosis and skin incision sites.[10] PMNLs constitute more than half of the cells in the wound area within the first 24 hours and are eliminated from the wound area within 3-4 days.[11] Animal studies report that overactive and prolonged PMNL infiltration may negatively affect wound healing.[12] Since wound healing was evaluated on the 7th day in this study, PMNL scores were subtracted from the sum of neovascularization, collagen fiber scores and granulation scores when calculating total histopathology scores (Colon and wound).

Biochemical Method: Wound and colon tissues were homogenized with a 1/9 (v/v) solution of 1x phosphate-buffered saline (1x PBS, 0.1 mol/L, pH 7.4) in a homogenizer containing ceramic balls (QIAGEN TissueLyser LT, Hilden, Germany). Supernatants were centrifuged at 10,000 x g at +4°C for 10 minutes (Beckman Coulter Allegra® X-30, IN, ABD) for measurements of wound hydroxyproline (WOHP) and colon hydroxyproline (COHP) levels. Protein concentrations in the supernatant were measured at 595 nm using a commercial kit (Coomassie Plus, Protein Assay, ThermoFisher Scientific, Massachusetts, USA) based on the Bradford method. Samples were evaluated by spectrophotometry (BioTek, Synergy™ HTX Flash Multimode reader) at a wavelength of 540 nm. Hydroxyproline levels of samples were determined by comparing them with a predetermined hydroxyproline standard curve.[13]

Macroscopic Adhesion Score (MAS) Evaluation:

- No adhesion: 0 points
- Single band: 1 point
- Double bands: 2 points
- Multiple bands: 3 points
- Direct visceral adhesion, cohesion: 4 points.[14]

Statistical Analysis

Descriptive statistics were employed to characterize the continuous variables. Mean ± standard deviation values were reported for parameters demonstrating a normal distribution, while median (minimum–maximum) values were provided for parameters not exhibiting a normal distribution. The Shapiro-Wilk test was used to determine the adherence of continuous variables to a normal distribution. The Wilcoxon signed-rank test explored the relationship between two dependent, non-normally distributed continuous variables. Variations among more than two groups, not adhering to a normal distribution, were assessed using the Kruskal-Wallis test. Post hoc pairwise comparisons were conducted using the Mann-Whitney U test with Bonferroni correction. The chi-square test (or Fisher's exact test/Yates's continuity correction, as appropriate) examined relationships between categorical variables. Statistical significance was set at 0.05. Analyses were performed using MedCalc statistical software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

RESULTS

During the measurement of WTS, the skin tissue of rat C5 detached from the incision line upon insertion into the device, rendering tensile strength measurement impossible. Additionally, the tissue sample of rat C1 was lost during the study, precluding measurement of the hydroxyproline level.

No statistically significant differences were observed in the initial and postoperative 7th day weights of the groups (p=0.934 and p=0.553, respectively). MAS was statistically significantly lower in Groups B and L than in Group C (p<0.001). No statistically significant difference was noted between Groups L and B. The WTS values were 2.9±0.6, 2.7±0.6, and 2.8±0.4 N in Groups B, C, and L, respectively. There was no statistically significant difference between the groups regard-

ing WTS (p=0.649). The ABP was measured as 155.7±33.6, 128.6±27.5, and 170±25.2 mmHg in Groups B, C, and L, respectively. No statistically significant difference was observed between the groups in terms of ABP (p=0.058).

Upon post hoc dual analysis, no statistically significant difference in wound histopathology scores (WHSs) was observed between Groups B and L compared to Group C (Bonferroni correction Mann-Whitney U test, p=0.828 and p=0.321, respectively). However, the WHS was found to be significantly higher in Group L than in Group B (p=0.021).

Similarly, post hoc dual analysis revealed no statistically significant difference in colon histopathology scores (CHSs) between Groups B and C or between Groups B and L (Bonferroni correction Mann-Whitney U test, p=0.630 and p=0.297, respectively). However, CHSs were significantly higher in Group L compared to Group C (p=0.011). The study results are presented in Table 1. No significant correlation was found between wound WTS and WOHP in all three groups or between ABP and COHP levels within each group. Table 2 displays the results of the intragroup correlation analysis.

DISCUSSION

Local anesthetic infiltration is commonly utilized for postoperative analgesia and surgical procedures.[1,3] While numerous studies have investigated the effects of local anesthetics in the literature, their impact on wound healing has yet to be demonstrated.[1,15-17] Although the primary aim of this study was to assess the effects of local anesthetics on colon anastomosis, it also aimed to evaluate the impact of simultaneous

Table 1. Study results overview

	Group B	Group C	Group L	P
IW				0.934[1]
Mean±SD	298.6±25.4	301.6±28.7	298.6±32.5	
Med (min-max)	292 (271-340)	299 (259-338)	288 (258-340)	
LW				0.553[1]
Mean±SD	287.6±19.1	301.3±31.7	288.7±29.5	
Med (min-max)	288 (262-320)	297 (254-348)	279 (253-327)	
ABP				0.058[1]
Mean±SD	155.7±33.6	128.6±27.5	170±25.2	
Med (min-max)	150 (120-200)	130 (100-180)	180 (120-200)	
MAS				**<0.001**[2]
0	6 (85.7)	-	6 (85.7)	
1	1 (14.3)[a]	7 (100)[b]	1 (14.3)[a]	
WTS				0.649[1]
Mean±SD	2.9±0.6	2.7±0.6	2.8±0.4	
Med (min-max)	3.1 (2.1-3.8)	2.6 (2.1-3.6)	2.9 (2.2-3.5)	
WHS				**0.025**[1]
Mean±SD	1.9±2.3	3.4±2.4	5.4±1.9	
Med (min-max)	2 (-1-6)	3 (1-8)	5 (3-8)	
WOHP				0.283[1]
Mean±SD	2±0.9	1.8±0.4	1.5±0.6	
Med (min-max)	1.8 (1.3-4)	1.8 (1.1-2.4)	1.3 (1-2.2)	
CHS				**0.014**[1]
Mean±SD	4.7±1	3.6±1.6	6.6±1.9	
Med (min-max)	4 (4-6)	3 (1-6)	6 (4-9)	
COHP				0.115[1]
Mean±SD	1.7±0.9	0.9±0.4	1.3±0.6	
Med (min-max)	1.2 (0.7-3)	0.8 (0.6-1.7)	1.2 (0.6-2.5)	

[1]Kruskal-Wallis H Test, 2Pearson Chi-Square. SD: Standard Deviation; Med: Median; Min: Minimum; Max: Maximum. ABP: Anastomosis Burst Pressure; CHS: Colon Histopathology Score; COHP: Colon Hydroxyproline; IW: Initial Weight; LW: Last Weight; MAS: Macroscopic Adhesion Score; WHS: Wound Histopathology Score; WOHP: Wound Hydroxyproline; WTS: Wound Tension Strength.

Table 2. Correlation analysis results

WTS and WOHP	r	p
Group B	-0.714	0.071
Group C	0.100	0.873
Group L	-0.463	0.294
ABP and COHP	**r**	**p**
Group B	0.055	0.908
Group C	0.464	0.294
Group L	-0.259	0.574

infiltration analgesia on wound healing in clinical practice. In a study by Kesici et al.,[3] it was suggested that both bupivacaine and levobupivacaine adversely affect the late phase of wound healing. However, in the early phase, no difference was observed in terms of WTS and maturation scores compared to the control group for either local anesthetic. Although no disparity was noted in the early phase between bupivacaine and levobupivacaine regarding WTS and histopathology, the histopathology score for levobupivacaine was better than that of bupivacaine. In a study by Zeren et al.,[1] despite levobupivacaine showing a significant increase in the fibrotic index, they reported a significant decrease in WTS values. In our study, we found that although not statistically significant, levobupivacaine led to an increase in WHS but had no effect on WTS. The findings from previous studies and our study indicate that larger-scale molecular studies are required to fully understand the effects of local anesthetics on wound healing.

Anastomotic leaks are frequently encountered problems in daily surgical practice, resulting in significant morbidity and mortality. Hence, preventing anastomotic leaks is clinically crucial, necessitating further studies for this purpose. The anti-inflammatory and antimicrobial effects of LAs have been demonstrated in studies in the literature.[4-6,18-20] However, there is limited research on the impact of LAs on colon anastomosis.[4] The only study on the effect of peritoneal administration of local anesthetics on colon anastomosis was conducted using bupivacaine.[4] Levobupivacaine, an S-enantiomer of bupivacaine, possesses longer action and exhibits analgesic and anesthetic activities similar to those of bupivacaine.[21] Moreover, it is known to have lower cardiac and neurotoxic potential.[7] In the review of the English literature, no studies were found concerning the effects of levobupivacaine on colon anastomosis. Therefore, determining the impact of peritoneal levobupivacaine on colon anastomosis is crucial for its clinical application.

Studies on the epidural and spinal administration of bupivacaine have shown no significant effect on ABP.[22,23] In an experimental study by Adanır et al.,[24] despite no significant change in hydroxyproline levels with epidural lidocaine, increased ABP and durability of colon anastomosis were reported. Similarly, in the experimental study by Camargo et al.,[4] peritoneal application of bupivacaine showed a non-significant decrease in Total Energy Rupture test levels in the absence of peritonitis. However, in cases of peritonitis, peritoneal bupivacaine resulted in increased Total Energy Rupture test levels and decreased mortality. This positive effect may be attributed to bupivacaine's anti-inflammatory and antimicrobial potential. In our study, although the peritoneal bupivacaine-administered group exhibited increased CHSs, COHP levels, and ABP values compared to the control groups, it was not statistically significantly, consistent with the findings of Camargo et al.,[4] Thus, our study concluded that intraperitoneal application of bupivacaine did not have an additive effect on colonic anastomotic durability.

A comparison with our study results could not be made as there are no studies in the literature on the effects of peritoneal levobupivacaine application on colon anastomosis. However, our study found that levobupivacaine increased mean COHP and ABP, although not statistically significantly compared to the control group, and the increase in CHSs was statistically significant. These results indicate that intraperitoneal levobupivacaine administration may help increase the durability of colon anastomosis.

Intra-abdominal adhesions, which are common after abdominal surgeries, present significant healthcare challenges. Postoperative adhesions can result in infertility, abdominal pain, and intestinal obstruction, necessitating further surgeries or interventions. In severe cases, they may even require surgical interventions with risks of serious morbidity and mortality. In addition to increasing complication risks, intra-abdominal adhesions also prolong operation times. While anti-adhesive agents have been utilized to prevent adhesions, a definitive solution has yet to be found.[14,25] Although the primary aim of our study was to evaluate the effects of bupivacaine and levobupivacaine on colon anastomosis, we also assessed MAS to determine if they possessed anti-adhesive properties, considering the anti-inflammatory effects of local anesthetics. Both bupivacaine and levobupivacaine exhibited statistically significant anti-adhesive effects compared to the control group.

CONCLUSION

There are limited studies in the literature on the effect of peritoneal administration of local anesthetics on colonic anastomosis. Our study revealed that while bupivacaine did not offer additional benefits to colon anastomosis durability, levobupivacaine had a positive impact. Additionally, our findings showed that both bupivacaine and levobupivacaine did not significantly contribute to wound healing, but levobupivacaine resulted in a significant increase in WHS compared to bupivacaine. Moreover, it was discovered that both local anesthetics exhibited significant anti-adhesive effects. Based on the results of our study, levobupivacaine could be beneficial in clinical practice for patients undergoing colon anastomosis

due to its notable contribution to colon anastomosis durability, its more positive effect on wound healing compared to bupivacaine, and its anti-adhesive activity. Further clinical trials should validate the results of this study.

Ethics Committee Approval: This study was approved by the Saglik Bilimleri University, Hamidiye Animal Experiments laboratory Ethics Committee (Date: 17.02.2022, Decision No: 02-01).

Acknowledgment: For technical support, we would like to thank Prof. Dr. Murat Baydoğan, a faculty member of the Istanbul Technical University Metallurgical and Materials Engineering Department.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: U.K.; Design: U.K.; Supervision: U.K.; Resource: U.K., S.K., Y.K.K.; Materials: U.K., K.B., E.M.G., A.G.S.; Data collection and/or processing: U.K., L.D.E., S.K., M.G.D.; Analysis and/or interpretation: U.K., Y.K.K., L.D.E., S.K.; Literature search: U.K., M.S.G., F.M., L.D.E., M.G.D., A.G.S., K.B.; Writing: U.K.; Critical review: U.K., L.D.E., S.K., M.S.G., F.M., E.M.G., M.G.D.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The author declared that this study has received no financial support.

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DENEYSEL ÇALIŞMA - *ÖZ*

Presizyonel ve peritoneal lokal anestezik uygulamasının kolon anastomozuna ve yara iyileşmesine etkisi

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AMAÇ: Araştırmalar levobupivakainin bupivakain kadar etkili olduğunu, kalp ve merkezi sinir sistemi toksisitesi riskinin daha düşük olduğunu ortaya koymuştur. Bu nedenle bu çalışma, levobupivakain ve bupivakainin kolon anastomozu üzerindeki etkilerini ortaya koyarak tüm hastalarda veya komorbiditesi olan hastalarda tercih edilip edilemeyeceğini belirlemeyi amaçlamaktadır. Çalışmanın öncelikli amacı levobupivakain ve bupivakainin kolon anastomozu üzerine etkilerini araştırmaktır. İkincil amaç ise yara iyileşmesi ve yapışma önleyici aktivite üzerindeki etkilerini göstermektir.

GEREÇ VE YÖNTEM: Bu çalışma, Hamidiye Hayvan Deneyleri Yerel Etik Kurulu onayı alınarak Hamidiye Hayvan Deneyleri laboratuvarında 28/07/2022 ile 04.08.2022 tarihleri arasında gerçekleştirilmiştir. Bu çalışma, 16-20 haftalık 21 Spraque erkek sıçan üzerinde gerçekleştirildi. Sıçanlar her birinde yedi sıçan olacak şekilde üç eşit gruba ayrıldı: Grup C: insizyonel izotonik; Grup B: ön insizyonel bupivakain; ve Grup L: insizyonel levobupivakain. Laparotomi sırasında makroskobik adezyon skorları (MAS) kaydedildi. Histopatolojik inceleme ve hidroksiprolin düzeyleri için doku örnekleri alındı. Orta kesi hattı yarasının gerilme mukavemeti ve anastomoz patlama basıncı ölçüldü.

BULGULAR: MAS Grup B ve L'de Grup C'ye göre istatistiksel olarak anlamlı derecede düşüktü ($p<0.001$). Yara histopatoloji skoru (WHS) Grup L'de Grup B'ye göre istatistiksel olarak anlamlı derecede yüksek bulundu ($p=0.021$). Kolon histopatoloji skorları (KHS) Grup L'de Grup C'ye göre istatistiksel olarak anlamlı derecede yüksek bulundu ($p=0.011$).

SONUÇ: Bu çalışma, bupivakain ve levobupivakainin yara iyileşmesine anlamlı katkı sağlamadığını ancak levobupivakainin bupivakaine göre WHS'de anlamlı artışa neden olduğunu ortaya koydu. Bu çalışmanın bulgularına göre levobupivakain, kolon anastomozu dayanıklılığına önemli katkısı, yara iyileşmesine bupivakaine göre daha olumlu etkisi ve anti-adezif etkisi nedeniyle kolon anastomozu yapılan hastalarda kullanılarak klinik pratiğe katkı sağlayabilir. Klinik çalışmalar bu çalışmanın sonuçlarını desteklemelidir.

Anahtar sözcükler: Anastomoz; anti-adheziv; bupivakain; kolon; levobupivakain; yara iyileşmesi.

Ulus Travma Acil Cerrahi Derg 2024;30(5):316-322 DOI: 10.14744/tjtes.2024.39551