# Comparison of the Effects of Bupivacaine, Lidocaine, and Tramadol Infiltration on Wound Healing in Rats

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**Summary:** Hancı V, Hakimoğlu S, Özaçmak H, Bektaş S, Özaçmak HS, Özdamar ŞO, Yurtlu S, Turan IÖ – Comparison of the Effects of Bupivacaine, Lidocaine, and Tramadol Infiltration on Wound Healing in Rats.

**Background and objectives:** The aim of this study was to investigate the effects of saline solution, bupivacaine, lidocaine and tramadol infiltration on wound healing in rats.

**Method:** Thirty-two male Wistar Albino rats were randomly separated into four groups, receiving 3 mL saline solution in control group (Group C, n = 8), 3 mL of 2% lidocaine in lidocaine group (Group L, n = 8), 3 mL of 0.5% bupivacaine in bupivacaine group (Group B, n = 8), and 3 mL of 5% tramadol in tramadol group (Group T, n = 8). Breaking-strength measurements, collagen bundle counting, and histopathologic evaluation were evaluated in the tissue samples taken from the rats.

**Results:** Comparing the control group with the groups where bupivacaine and lidocaine were used for wound infiltration, collagen production was lower, breaking-strength measurements showed reduced resistance while significantly high edema, vascularity, inflammation scores were found ($p < 0.0125$). Between the control and the tramadol group there were no significant differences in collagen production, breaking-strength measurements, and edema, vascularity, inflammation scores ($p > 0.0125$).

**Conclusion:** In our study, we found bupivacaine and lidocaine reduced the collagen production, wound breaking strength, and caused significantly high scores for edema, vascularity, and inflammation when compared to the control group. There was no significant difference between the control and the tramadol group. Results of this experimental preliminary study on rats support the idea that tramadol can be used for wound infiltration anesthesia without adverse effect on the surgical healing process. These results need to be verified in humans.

**Keywords:** Anesthesia, Local; Tramadol; Bupivacaine; Lidocaine; Wound Healing.



## INTRODUCTION

Infiltrating the wound with local anesthetics is increasingly used as a post-operative analgesia method due to its ease of application, simplicity and few side effects [1-4]. Surgical wound infiltration, especially after minor to intermediate surgeries, reduces post-operative opioid consumption and related complications, hospital stay time and costs [4].

Surgical wound infiltration has been proven to be an effective analgesic and is widely used for post-operative pain relief after abdominal hysterectomy, cesarean section, inguinal hernia repair, lumbar disc hernia, prostatectomy and similar surgeries [5-8].

When infiltration analgesia is installed before the surgical incision, it preemptively increases analgesic efficiency during and after the operation; additionally, it protects against chronic pain [3,5].

Local anesthetic agents commonly used for surgical wound infiltration include lidocaine, prilocaine, bupivacaine, ropivacaine and levobupivacaine [1,3-12]. Tramadol is a synthetic analogue of codeine, which acts through both opioid and non-opioid mechanisms of action [1,13]. Tramadol has shown similar effects to local anesthetics on peripheral nerves [14-20]. Tramadol may be used as a local anesthetic agent for minor surgeries; similarly, it may be used as an adjuvant to local anesthetics[21]. When added as an adjuvant to local anesthetic agents, it has a similar effect to clonidine and can modify the effects of local anesthetics directly or indirectly by affecting sodium channels and, thus, contributing to more effective analgesia [22-27].

To be an effective post-operative analgesic, local anesthetics and other medicines used in wound infiltration should ensure quick and uncomplicated healing to prevent post-oper-

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ative morbidity. For this reason, it is important to know not just the effects of the wound infiltration agents on postoperative pain but their effect in detail on wound healing and whether they are a cause of morbidity in clinical use [3,28-31]. Previous research using experimental models and fibroblast tissue cultures from surgical wounds had looked at the effect of local anesthetic agents such as bupivacaine, prilocaine and lidocaine on wound healing [3,28-31]. There are no known studies on the effects of tramadol, which may be used for wound infiltration and healing [14-21].

Our hypothesis was to investigate whether tramadol applied subcutaneously on rats as a surgical wound infiltration anesthetic had any effects on wound healing. To test this hypothesis, the subcutaneous tissue of rats was injected with saline, tramadol, lidocaine and bupivacaine. The effects of these medications on wound healing were investigated by comparing wound stress test results and histopathologic collagen counts.

## MATERIAL AND METHODS

The study was approved by the Animal Ethics Committee of Zonguldak Bülent Ecevit University Medical School. All animals were treated in compliance with the recommendations of the university's animal care committee and the principles of laboratory animal care (NIH publication No. 85-23, revised 1985). The rats were housed in a temperature-controlled room (24 ± 1°C) on a 12-hour-light – 12-hour-dark cycle and were fed with standard rat chow and water for 12 hours prior to the experimental protocol.

Thirty-two male Wistar Albino rats weighing between 250-300 grams were randomly separated into four groups of eight animals each. Surgical procedures were done under general anesthesia, induced by intraperitoneal injection of 75 $mg.kg^{-1}$ ketamine. The hair on the back of the animal was shaved after the loss of cornea reflex and extremity drawing response were diminished. The area of the incision was cleaned with povidione iodine and was wiped dry with sterile gauges after two minutes.

The areas of the incisions were subcutaneously infiltrated with 3 mL doses of the study drug. The rats in the groups were infiltrated with normal saline in control group (Group C) (n = 8), 2% lidocaine in lidocaine group (Group L) (n = 8), 0.5% bupivacaine in bupivacaine group (Group B) (n = 8), and 5% tramadol in tramadol group (Group T) (n = 8).

After two minutes from study drug infiltration, a 3-cm surgical incision including cutaneous and subcutaneous connective tissue was done with a scalpel under sterile conditions and the tissues were joined with a 4.0 prolene suture. No antibiotics were applied during or after the procedure. The wound was cared for once a day and the animals were euthanized at the end of the 8th day. A band of 6x2 cm tissue samples were taken from the incision line.

### Breaking-Strength Measurements

For the mechanical tension tests, tissue samples strip shaped 5x5 mm were taken just from the middle of incision line. In these tests of scar breaking forces, power transducer (FDT 10-A, May IOBS 99; Commat Co., Ankara, Turkey) and data recording system (MP 30 B-CE; BIopac System, Inc., Santa Barbara, CA, USA) were used. Tissues were stretched at the two edges of the tensiometer. Forces leading to rupture of obtained scar are divided into sample size on each sample and standardized as $gram.cm^{-2}$ [3,28].

### Histopathological evaluation

All samples were fixed in 10% formalin, embedded in paraffin, cut into 5 µm sections, and stained with hematoxylin-eosin (H&E). These sections were then examined under a light microscope for histological changes by a blinded pathologist. Slides were scored for the presence of collagenization, vascularity, edema, and degree of acute and chronic inflammatory cells (0= none, 1= mild, 2= moderate and 3= severe). Masson's trichrome was also applied for histochemical identification of collagenization. H&E and Masson's trichrome stained slides were reviewed by the same pathologist [3,28].

### Morphometric analysis

Morphometric analysis was performed on Masson's trichrome stained histological sections. The number of collagen bundles was measured with Leica, QWINPlus v.3.1.0 software using a Leica (DMLB-100S) microscope. Each slide was measured on one high-power field at x400 magnification including wound healing area; the mean number of collagen bundles of each group was then calculated[3,29].

### Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows (SPSS, Chicago, IL). For the scores and non-normally distributed variables, comparison between groups was done by the Mann-Whitney U and the Kruskal Wallis test. The results were expressed as median (minimum-maximum). A p value $< 0.05$ after Bonferroni correction ($p < 0.0125$) was considered significant.

## RESULTS

Three different methods were used to determine wound healing.

### Breaking-strength findings

The first method is the measurement of breaking-strength via tensiometer. When all of the study groups were evaluated according to the breaking-strength measurements, we observed

a significant difference between the control and Group L (p = 0.001), and Group B (p = 0.004). There was no significant difference between the control and the Group T (p = 0.029). The breaking-strength measurements between Group B and Group L (p = 0.336), Group B and Group T (p = 0.152), Group L and Group T (p = 0.021) were all similar (Table I).

**Table I** – The Breaking-Strength Measurements.

| Group | Force (gram.cm$^{-2}$) |
|---|---|
| Group C | 201.02 (145.12-230.53) |
| Group L | 88.35 (37.46-165.51) * |
| Group B | 124.88 (48.01-159.26) * |
| Group T | 141.75 (105.35-209.52) |

Median (min – max).
*: p < 0.0125 Compared with Group C, Mann Whitney U.

### Morphometric findings

The second method was a morphometric analysis and collagen bundle counting. When all of the study groups were evaluated according to the number of collagen bundles, we observed a significant difference between the control and Group L (p < 0.001), and Group B (p = 0.001). There was no significant difference between the control and Group T (p = 0.014). Collagen bundle counts were significantly higher in Group T than in Group L (p = 0.001) and Group B (p = 0.004). There was no significant difference in the amount of collagen fibers between Group B and Group L (p = 0.338) (Table II).

**Table II** – Collagen Bundle Counts.

| Group | Collagen bundle counts |
|---|---|
| Group C | 624 (494-710) |
| Group L | 265 (221-492) * † |
| Group B | 285 (261-510) * † |
| Group T | 518,50 (420-591) |

Median (min – max).
*: p < 0.0125 Compared with Group C, Mann Whitney U; †: p < 0.0125 Compared with Grup T, Mann Whitney U.

### Histopathological findings

The third indicator of wound healing was determined by histopathologic evaluation. When the working groups were compared in relation to edema, vascularity, inflammatory reaction and collagenization, there were significant differences between the control group and Groups L and B. There was no significant difference between the control group and Group T. No significant differences were found between Groups B and L, Groups B and T and Groups L and T in terms of the histopathologic indicators of edema, vascularity, inflammatory reaction and collagenization (Table III).

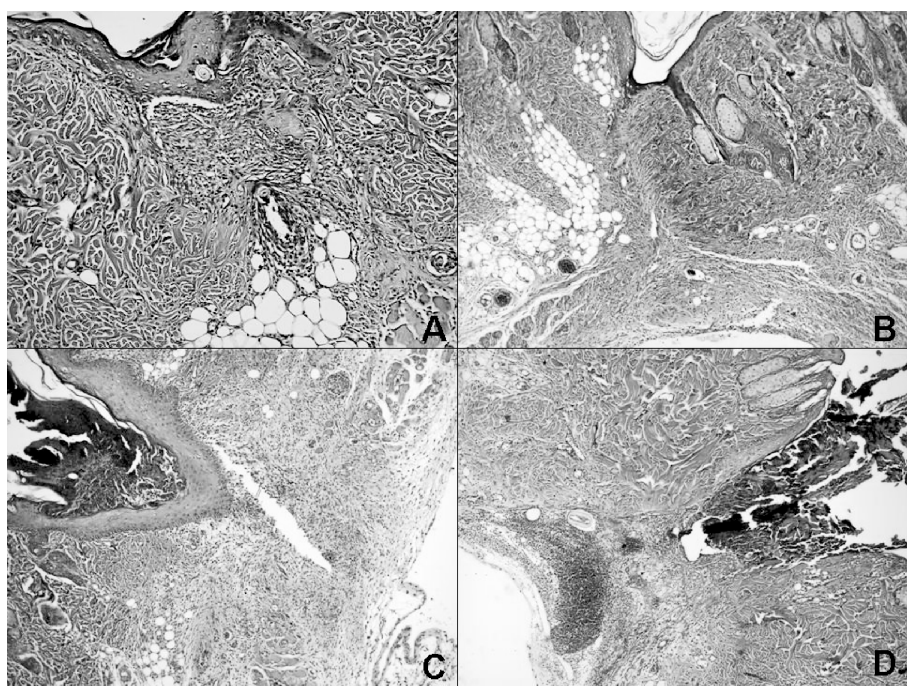


**Figure 1** Mild Edema, Inflammation and Vascularity in control (A) and tramadol (B) Groups (H&E, x400, x100) (B). Moderate edema and severe inflammation in Groups bupivacaine (C) and lidocaine (D) groups (H&E, x200, x200).

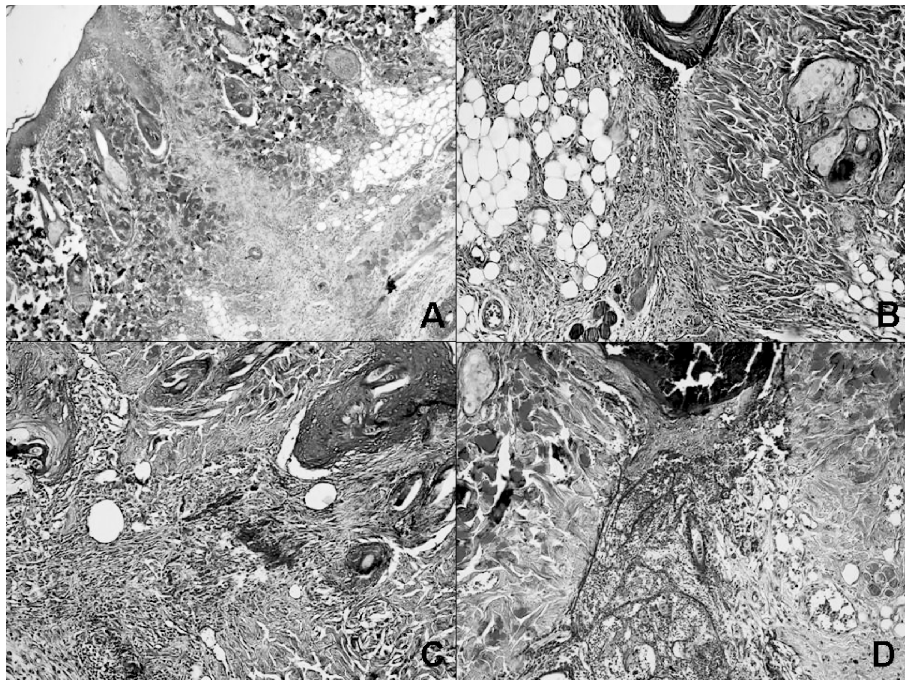


**Figure 2** Masson's Trichrome Stain Showing Collagen Fibers (blue) in Wound Healing. Increased collagenization in control (A) and tramadol (B) groups compared to bupivacaine (C) and lidocaine (D) groups (x100, x100, x200, x200).

Table III – Histopathologic Evaluation Scores.

| Group | Edema | Vascularity | Inflammatory reaction | Collagenization |
|---|---|---|---|---|
| Group C | 1 (0-1) | 0 (0-1) | 1 (0-2) | 3 (2-3) |
| Group L | 2 (2-2)* | 1 (1-3)* | 2,5 (1-3)* | 1 (1-2)* |
| Group B | 2 (1-2)* | 2 (1-3)* | 3 (2-3)* | 1 (1-2)* |
| Group T | 1 (1-2) | 1 (0-2) | 2 (1-2) | 2 (1-2) |

Median (min – max).
*: $p < 0.0125$ Compared with Group C, Mann Whitney U.

## DISCUSSION

Comparing the control group with the groups where bupivacaine and lidocaine were used for wound infiltration, collagen production was lower, breaking-strength measurements showed reduced resistance and significantly high edema, vascularity and inflammation scores were found. Between the control group and the tramadol group, there were no significant differences in collagen production, breaking-strength measurements, as well as edema, vascularity and inflammation scores.

Surgical wound infiltration has been proven to be an effective analgesic and is widely used for postoperative pain relief after abdominal hysterectomy, cesarean section, inguinal hernia repair, lumbar disc hernia, prostatectomy and similar surgeries [1,5-8]. Frequently used local anesthetic agents are lidocaine, bupivacaine, ropivacaine and levobupivacaine [1,3-12]. Research on the effect of these and other local anesthetic agents used for wound infiltration on wound healing is limited and results are controversial [3,28-31].

In a histopathologic study that included wound strength tests, rabbits were given 0.5% lidocaine, 2% lidocaine and 0.5% bupivacaine along a midline ventral abdominal wound. Comparing the control group and the test groups, there were no significant differences found in terms of wound tensile scores on any test. The same study emphasized that a comparison of saline and local anesthetic infiltrated tissues found no significant difference in histopathologic results. They concluded that wound infiltration with lidocaine and bupivacaine had no effect on wound healing in midline abdominal incisions in rabbits [28]. Waite et al. [29] evaluated the effect of lidocaine and bupivacaine on wound healing in mice and found that, although these anesthetics influenced local inflammation and proteolytic factors, they had no effect on wound healing [29].

Other research found that lidocaine and bupivacaine inhibited collagen synthesis in fibroblast tissue cultures, and had cytotoxic effects on different cell lines [30-35].

A study on guinea pig wound healing when given 1% lidocaine evaluated breaking strength, number of collagen fibers by morphometry, and histologic examination of collagenization, edema, vascularity, and presence of acute and chronic inflammatory cells. Comparisons with the control group showed that, though there was no significant difference in breaking strength measurements, the lidocaine group had significant vascularity and morphometric differences, as well as a lower amount of collagen [30]. While the application of lidocaine by local infiltration resulted in significant histopathologic changes, the study emphasized that the breaking strength results

remained the same [30]. Another study on the effects of local anesthetic on human fibroblast found that lidocaine, bupivacaine and ropivacaine produced dose-dependent cytotoxic effects on human fibroblast [31]. Research on lidocaine in wound infiltration of rats found collagenization and effects on mast cell numbers in the wound [36]. Aside from local anesthesia affecting collagen fiber numbers and capillary veins, it may cause varying degrees of inflammation and edema along the wound edges which can affect wound healing [3,37,38].

Past studies have found that the concentration of local anesthetic affects wound healing while high concentrations of local anesthetic delay healing [30,39,40]. While doses inferior to 100 mcg.mL$^{-1}$ of lidocaine had no effect on healing, in a study of corneal epithelial cells, doses above 250 mcg.mL$^{-1}$ delayed epithelial healing in a dose-dependent fashion [41].

Tramadol may be used for peripheral nerve block and in wound infiltration due to its anesthetic effects [14-20]. No study has been found evaluating the effects of tramadol on wound healing, which it is the aim of this study. In our search through the literature, we were not able to find any study that reports the histopathological and physical effects of tramadol on wound healing. We believe our study is the first to concentrate on this subject. Our aim is to evaluate the histopathological and band physical effects of tramadol on the healing of surgical wounds when used for infiltration anesthesia.

While our study found results similar to previous studies on the effects of bupivacaine and lidocaine on wound healing [30-41], no significant difference was found between tramadol and the control group. The antibacterial properties of local anesthetics and other agents used in wound infiltration are important. Previous research emphasized the antibacterial properties of bupivacaine [42-44]. Controversy surrounds lidocaine antibacterial properties though there are studies in the literature emphasizing its antibacterial properties [45]. However, bacterial strains are not inhibited up to 2 hours after 1% lidocaine administration and when biopsy cultures are required within two hours, lidocaine should be used [46]. Previous research has evaluated the antibacterial properties of tramadol [47]. Tramadol exhibits dose and time dependent bactericidal activity for *E. coli* and *S. epidermidis*, and antibacterial against *S. aureus* and *P. aeruginosa* strains. Researchers have emphasized that tramadol may be helpful in reducing bacterial infection risk after local and regional anesthesia due to its antibacterial properties [47]. Our study found no trace of macroscopic infection at the wound site in any subject. This is in accordance with previous studies which emphasized the interaction of local anesthetic and tramadol's antibacterial properties.

Local anesthetics are known for myotoxic effects and when used in infiltration may cause myotoxicity [3,48]. Bupivacaine carries that risk when used as a continuous peripheral nerve block related to the duration of exposure [48,49]. Lidocaine also has myotoxic properties [50]. However, tramadol, without such effects, has been administered intramuscularly for many years [51].

In conclusion, our study of wound infiltration in rats found bupivacaine and lidocaine reduced collagen production, reduced wound breaking strength, and caused significantly high scores for edema, vascularity and inflammation, when compared to the control group. There was no significant difference between the control group and the tramadol wound infiltration group in terms of collagen production, breaking-strength measurements, and edema, vascularity and inflammation scores. Results of this experimental preliminary study on rats support the idea that tramadol can be used for wound infiltration anesthesia without adverse effect on the surgical healing process. These results need to be verified in humans.

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