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Effect of prilocaine and its combination with tramadol on anxiety and pain during nasal packing removal

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Abstract

Purpose To investigate the effect of local usage of prilocaine and ıts combination with tramadol on the pain and anxiety levels of patients during nasal packing removal.

Methods A total of 117 patients who were treated with the Merocel nasal packing after septoplasty were included in the study. Patients whose Merocel nasal packings infiltrated with prilocaine (P group), prilocaine combined with tramadol 1 mg/kg (P + T1 group), prilocaine combined with tramadol 2 mg/kg (P + T2 group), or normal saline solution (Control group) before nasal packing removal were compared for their pain, sedation, and anxiety related to this removal procedure. The visual analog scale (VAS), Ramsay sedation scale (RSS), and State–Trait Anxiety Inventory (STAI) scale were assessed to evaluate the pain, sedation, and anxiety levels of the patients.

Results Groups were found similar according to sex, age, and preoperative STAI scores. The VAS score was significantly lower in P, P + T1, and P + T2 than control group during nasal packing removal ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). However, state anxiety inventory (STAI-S) and RSS were found significantly improved only in P + T1 and P + T2 (STAI-S: $p = 0.032$, RSS: $p = 0.002$, STAI-S: $p = 0.000$, RSS: $p < 0.001$, respectively). In the comparison of P + T1 and P + T2, no significant difference was found in VAS, RSS, and STAI-S ($p = 0.604$, $p = 0.154$, and $p = 0.264$, respectively).

Conclusion The combined infiltration of prilocaine and tramadol 1 mg/kg into the nasal packing is effective in reducing the pain and anxiety of patients during nasal packing removal

Keywords Nasal packing removal · Tramadol · Anxiety · Postoperative pain · Septoplasty

Introduction

Nasal packing is a procedure frequently performed after nasal surgery to control bleeding, prevent the development of septal hematoma, and stabilize mucosal flaps [1]. However, pain during nasal packing removal has been considered extremely disturbing by patients. Patients have even stated that the pain during removal is the worst experience in the perioperative and postoperative process [2]. This situation prompted surgeons to perform nasal packing causing less pain and to develop new practices to make the procedure less painful and to increase patient comfort.

Various methods have been used to decrease pain and anxiety during nasal packing removal and to increase patient comfort [3]. Among these methods, the application of local anesthetics to nasal packing during its removal is most commonly assessed [4]. Although the use of local anesthetics has been effective in decreasing pain, its effect on the anxiety level of patients is controversial.

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Prilocaine is an amid-type local anesthetic that rapidly penetrates into tissues and has low toxicity level. Moreover, this analgesic is found to be effective in decreasing pain during nasal packing removal and thus is widely used as infiltration analgesia. Tramadol is a safe centrally acting opioid that has a sedative effect, nasal absorption capacity, and low risk of addiction and respiratory distress, and it can be used in all types of pain ranging from moderate to severe [5–12]. Based on our literature review, tramadol has never been used as an analgesic during nasal packing removal.

Therefore, the present study aimed to investigate the effect of applying prilocaine alone and the combination of tramadol and prilocaine in nasal packings on the pain and anxiety level of patients during nasal packing removal.

Materials and methods

This study has been performed according to the Declaration of Helsinki. Local ethics committee approval was obtained (approval number: 2019/71). All the patients aged 18–65 to whom Merocel nasal packing was applied after closed technique primary septoplasty, and whose nasal packings were injected with prilocaine, prilocaine combined with tramadol, or normal saline solution (0.9% NaCI) (NSS) before removal between June 2018 and May 2019, were included in this study.

The patients who received treatment with sedatives or tranquilizers or analgesic drugs, except acetaminophen, those diagnosed with neurological or psychiatric (anxiety, depression) or cardiovascular disorders, diabetes mellitus, peripheral neuropathy, chronic pain and renal failure, and those with a previous history of nasal surgery, nasal polyposis, allergic rhinitis, chronic sinusitis, hepatic disease, and recent systemic infection, and those who are smokers were excluded from the study.

Our study was conducted retrospectively in a territory reference center. Patients' demographic data, visual analog scale (VAS) results, Ramsay sedation scale (RSS) scores, preoperative and postoperative anxiety scores, and all the other medical information were extracted from the clinical charts of them. All patients gave written informed consent for their medical records to be reviewed.

Patients whose Merocel nasal packings infiltrated with prilocaine, prilocaine combined with tramadol 1 mg/kg, prilocaine combined with tramadol 2 mg/kg, or NSS (as control group) before nasal packing removal were compared for their pain, sedation, and anxiety related to this removal procedure.

All operations were performed under general anesthesia. The operations were performed by the same surgeon using the same technique. All patients underwent the septoplasty procedure. Lidocaine 2% with epinephrine 1.25:100.000 was infiltrated locally, and hemitransfixion incision was performed. Bilateral mucoperichondrial flaps were elevated. Deviated parts of the septum were fixed preserving tip support. Then the incision was closed.

At the end of the operation, a standard 8-cm Merocel nasal packing (Merocel; MedtronicXomed, Inc., Jacksonville, FL) was placed in both nasal cavities of the patients. Acetaminophen was routinely used for postoperative analgesia and no other medications for pain control were performed to patients. The nasal packs were removed on the second postoperative day.

In the prilocaine group (P group), 5 mL of diluted solution consisting of 2.5 mL of 2% prilocaine (Citanest 2%; AstraZeneca, London, the UK) was injected into the Merocel nasal pack 15 min before its removal. In the prilocaine + tramadol 1 mg/kg group (P + T1 group), 5 mL of diluted solution consisting of 2.5 mL of 2% prilocaine + 1 mg/kg of tramadol (Contramal®; Abdi İbrahim Ltd., İstanbul, Turkey) was injected into the Merocel nasal packing 15 min before its removal. In the prilocaine + tramadol 2 mg/kg (P + T2 group), 5 mL of diluted solution consisting of 2.5 mL of 2% prilocaine + 2 mg/kg of tramadol was injected into the Merocel nasal packing 15 min before its removal [13]. In the control group (C group), 5 mL of NSS was injected into the Merocel nasal packing 15 min before its removal. All solutions were applied directly to the Merocel nasal packing with a 22-gauge needle without contacting the nasal mucosa or septum [14].

The evaluation of the severity of pain after nasal packing removal was conducted using the visual analog scale (VAS), and the results were recorded. All patients were instructed to evaluate the severity of pain during nasal packing removal using the VAS (range: 0–10; 0 = no pain, and 10 = intolerable pain). The VAS scores were evaluated using a ruler with two anchor points, with a score of 0 indicating the absence of pain and 10 indicating the worst pain. After the medications were performed, the patients were evaluated with the Ramsay sedation scale (RSS) during nasal packing removal, and the results were recorded (Table 1).

Table 1 Ramsay sedation scale

Sedation score	Response
1	Patient is anxious and agitated or restless or both
2	Patient is cooperative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

Anxiety levels of patients were measured according to State–Trait Anxiety Inventory (STAI) scale, developed by Spielberger, Gorsuch, and Lushene in 1970, which is the most common test used to measure anxiety and is reported to be gold standard for this in the literature [15, 16]. Trait anxiety inventory (STAI-T) is used to evaluate the participant's general and continual self-feeling mood status, independent from the instant status, whereas State Anxiety Inventory (STAI-S) is used to evaluate the feeling of the individual at a certain time and under certain conditions. In STAI scale, scoring was performed using the range 20–80; high scores indicate high level of anxiety, whereas low scores indicate low level of anxiety [17, 18].

In this study, for the evaluation of preoperative anxiety, STAI-S and STAI-T were used, whereas postoperative evaluation of anxiety was done according to STAI-S. Patient anxiety levels were first measured 24 h before the operation, and then on the second postoperative day 15 min before and after infiltration of nasal packings with prilocaine or prilocaine combined with 1 mg/kg tramadol or prilocaine combined with 2 mg/kg tramadol or NSS.

Statistical analysis

The data of the present study were evaluated with the Statistical Package for the Social Sciences software for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation, frequency distribution, and percentage. Variables with normal distribution were evaluated with the Shapiro–Wilk test. For continuous variables, the Mann–Whitney *U* test and Kruskal–Wallis test were used for data analysis. The categorical variables were evaluated with the Chi-square test. A p value < 0.05 was considered statistically significant.

Results

A total of 117 patients aged between 18 and 65 years were enrolled in the present study. Among the patients, 34 (29.05%) were men and 83 (70.94%) were women. The four groups were similar and comparable in terms of demographic data, as shown in Table 2.

The VAS score was significantly lower in the P group than in the control group. However, no significant difference was observed in terms of the RSS scores ($p < 0.001$ and 0.595, respectively). Therefore, prilocaine was effective in decreasing pain (Table 3).

A significant improvement was observed in terms of both VAS and RSS scores in the P + T1 and P + T2 groups (VAS: $p < 0.001$, RSS: $p = 0.002$, VAS: $p < 0.001$, RSS: $p < 0.001$, respectively) (Table 3).

In the comparison of P and P + T1 groups, the addition of tramadol resulted in a significant improvement in both VAS and RSS scores ($p = 0.016$ and 0.010, respectively) (Table 3).

The VAS and RSS scores between the P + T1 and P + T2 groups were compared to determine the efficient dose of tramadol. However, no significant difference was found (VAS: $p = 0.604$, RSS: $p = 0.154$) (Table 3). Thus, tramadol was considered effective as an analgesic and sedative at lower doses.

In the comparison of preoperative STAI-T and STAI-S scores for the evaluation of the basal anxiety levels of the four groups, no significant difference was found among groups ($p = 0.940$ and $p = 0.078$, respectively) (Table 4). In the evaluation of postoperative STAI-S scores, those

Table 3 Visual analog scale and Ramsay sedation scale scores of each group

	VAS score	p^a value	RSS score	p^a value
P group ($n = 28$)	3.63 ± 1.44	< 0.001	1.66 ± 0.47	0.595
C group ($n = 27$)	5.53 ± 2.01		1.60 ± 0.49	
P + T1 group ($n = 32$)	2.76 ± 1.27	< 0.001	1.93 ± 0.25	0.002
C group ($n = 27$)	5.53 ± 2.01		1.60 ± 0.49	
P + T2 group ($n = 30$)	2.56 ± 1.13	< 0.001	2.00 ± 0.00	< 0.001
C group ($n = 27$)	5.53 ± 2.01		1.60 ± 0.49	
P group($n = 28$)	3.63 ± 1.44	0.016	1.66 ± 0.47	0.010
P + T1 group ($n = 32$)	2.76 ± 1.27		1.93 ± 0.25	
P + T1 group ($n = 32$)	2.76 ± 1.27	0.604	1.93 ± 0.25	0.154
P + T2 group ($n = 30$)	2.56 ± 1.13		2.00 ± 0.00	

P group prilocaine group, *P + T1 group* prilocaine + tramadol 1 mg/kg group, *P + T2 group* prilocaine + tramadol 2 mg/kg group, *C group* control group, *n* number of patients, *a* Mann–Whitney *U* test, *VAS* visual analog scale, *RSS* Ramsay sedation scale

Table 2 Demographic characteristics of the patients

	P group ($n = 28$)	P + T1 group ($n = 32$)	P + T2 group ($n = 30$)	C group ($n = 27$)	p value
Age, years median (min–max)	29.00 (19–56)	32.50 (18–60)	28.50 (18–65)	27.00 (18–51)	0.523a
Gender (M/F)	10/18	5/27	7/23	12/15	0.073b
Weight (kg) median (min–max)	75.00 (60–90)	76.50 (60–92)	75.00 (51–90)	75.00 (50–90)	0.289a

n number of patients, *min* minimum, *max* maximum, *a* Kruskal–Wallis test, *b* Chi-square test, *P* prilocaine group, *P + T1* prilocaine + tramadol 1 mg/kg group, *P + T2* prilocaine + tramadol 2 mg/kg group, *C group* control group, *M* male, *F* female

Table 4 Preoperative State–Trait Anxiety Inventory (STAI) evaluation results

	STAI-T preoperative Median (min–max)	STAI-S preoperative Median (min–max)
P group ($n=28$)	41.00 (25–62)	37.00 (22–54)
P + T1 group ($n=32$)	41.00 (26–60)	35.00 (28–55)
P + T2 group ($n=30$)	42.00 (24–62)	36.00 (22–56)
C group ($n=27$)	41.00 (27–62)	35.00 (31–54)
p^a	0.940	0.078

P group prilocaine group, *P + T1 group* prilocaine + tramadol 1 mg/kg group, *P + T2 group* prilocaine + tramadol 2 mg/kg group, *C group* control group, *n* number of patients, *STAI-T* trait anxiety inventory, *STAI-S* State Anxiety Inventory, *a* Kruskal–Wallis test, *min* minimum, *max* maximum

are measured on the second postoperative day before and after medication of nasal packings, a significant improvement was found in the group P + T1 and P + T2 in terms of STAI-S. ($p=0.032$ and $p=0.000$, respectively). However, this improvement was not found in P and Control groups. ($p=0.158$ and $p=0.373$, respectively) (Table 5).

In the comparison of P + T1 group and P + T2 group according to STAI-S on the second postoperative day before and after medication of nasal packings, no significantly difference was found ($p=0.264$).

All applications were well tolerated by the patients. The patients were re-evaluated on the second day and then at the first and second months after the removal of the nasal pack, and none of the patients presented with septal perforation and nasal crusting.

Discussion

Nasal septal surgery is one of the most common surgical procedures carried out in otolaryngology clinics. In septoplasty, the fear of the nasal packing removal process and its associated anxiety are major problems. These fears are among the factors causing refusal to undergo operation [19].

To decrease the pain during the removal of nasal packing and the anxiety associated with this procedure, various drugs and methods have been used [4]. Some methods include performing sphenopalatine ganglion blockage, placing the nasal packing for a shorter time in the nose, and wetting of nasal packing with topical local anesthetics (tetracaine, prilocaine, and bupivacaine) before removal [19–24].

To reduce pain and anxiety, the ideal drug that should be applied on nasal packing prior to removal must be safe and has the ability to be absorbed locally. Moreover, it should be easy to use and has a few systemic side effects [19]. In our literature review, prilocaine is one of the most suitable local anesthetics that can be used for this purpose. Although prilocaine decreases pain, its effect on anxiety is controversial [4, 19, 20]. Therefore, in our study, to decrease anxiety and pain, the effect of the combined use of tramadol and prilocaine was investigated. The sedative effect of tramadol has been observed in previous studies, and its clinical analgesic efficacy was proven. Furthermore, its local anesthetic effect on the peripheral nerves was observed in clinical and laboratory studies, and can be used via the nasal mucosal route [4, 9–12]. It has good safety profile and can be used safely as it has low-risk potential for respiratory depression, cardiovascular diseases, and drug abuse and dependence. In relation to this reason, the present study aimed to investigate the effect of the combination of prilocaine and tramadol on pain, sedation, and anxiety, and to compare the efficacy of this combination with that of prilocaine and intranasal NSS.

To the best of our knowledge, the effect of intranasal tramadol on pain and anxiety during nasal packing removal was not reported in the literature. In the study of Apuhan et al. the analgesic effect of levobupivacaine and prilocaine before nasal packing removal was evaluated using the VAS and its sedative effects were assessed with the RSS. Moreover, the study has reported that the analgesic and sedative effects were significantly higher in the prilocaine and levobupivacaine groups than in the control group [20]. In the study of Sahin C and Aras H, the analgesic and anxiolytic effect of lidocaine infiltration into nasal packing before nasal packing removal was investigated [14].They revealed that the infiltration of lidocaine into the packing significantly reduced patient's pain and

Table 5 Pre- and post-medication State Anxiety Inventory (STAI-S) evaluation results

	Stai-S pre medication Median (min–max)	Stai-S post-medication Median (min–max)	p^a
P group ($n=28$)	37.50 (32–50)	36.50 (29–49)	0.158
P + T1 group ($n=32$)	37.50 (25–56)	35.50 (25–46)	0.032
P + T2 group ($n=30$)	36.50 (25–49)	35.50 (25–48)	0.000
C group ($n=27$)	36.00 (31–54)	35.00 (30–42)	0.373

P group prilocaine group, *P + T1 group* prilocaine + tramadol 1 mg/kg group, *P + T2 group* prilocaine + tramadol 2 mg/kg group, *C group* control group, *n* number of patients, *STAI-T* trait anxiety inventory, *STAI-S* state anxiety inventory, *a* Kruskal–Wallis test, *min* minimum, *max* maximum

anxiety levels. However, in the aforementioned two studies, the mechanism of local anesthesia that is associated with sedation and anxiety was not addressed.

Our study revealed that the combination of tramadol with prilocaine has improved analgesic and anxiolytic effect during nasal packing removal and it is thought that this effect depends on the opiate analgesic tramadol's mild sedative effect shown by RSS**.**

The superiority of our study over previous studies is that STAI-S and STAI-T anxiety scores were used. These scales allows to measure the preoperative basal anxiety of the patients, and current situational changes of patients' anxiety levels during nasal packing removal that reveals the effect of medications on patients' anxiety alterations.

In a randomized study by Karaaslan et al., the analgesic and sedative effects of meperidine, an opioid analgesic, during nasal packing removal were investigated. They revealed that the use of prilocaine alone did not significantly decrease pain and anxiety; however, the combination of meperidine and prilocaine significantly reduced the pain and anxiety levels [4]. Although the investigators mentioned lower anxiety levels in their study, they did not used any specific scale for measuring anxiety. RSS scale used in their study measures sedation state primarily and does not give any information about anxiety. In our study, the anxiety levels of the patients were evaluated by STAI scale which is the primary scale for measuring the basal and situational anxiety levels. Furthermore, in our study, in terms of safety and lower risk of respiratory depression, we preferred tramadol rather than meperidine [25].

In terms of cost-effectiveness and drug overdose, we investigated the most appropriate dose for tramadol, and no difference was found between 1 and 2 mg/kg of tramadol with regard to their effects on pain and anxiety. Therefore, the usage of 1 mg/kg dose is effective in relieving pain and anxiety, decreasing the cost of treatment, and preventing overdose.

The retrospective design and the lack of systemic levels of the drugs which might have importance for showing the local absorption rate of the drugs to systemic circulation might be encountered as a limitation for this study.

Conclusion

To the best of our knowledge, this study is the first that revealed the effect of tramadol combined with prilocaine application on pain and anxiety related to nasal packing removal. Furthermore, this study revealed that 1 mg/kg tramadol usage is sufficient for decreasing the pain and anxiety of patients.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by KGT, EA, RGT, and HY. The first draft of the manuscript was written by KGT and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Balikesir University Faculty of Medicine Ethics Committee (Ethical committee approval number: 2019/71) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study**.**

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