The relations between the level of Mu-opioid receptor (μORs) and postoperative analgesic use in patients undergoing septoplasty: A prospective randomized controlled trial.

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Abstract

Background

In this study, the μ-Opioid receptor activity was examined before the septoplasty. We assessed preoperative μ-Opioid receptor activity association with postoperative pain level and second analgesic requirement in patients undergoing septoplasty.

Methods

In our prospective study, 120 adult patients underwent septoplasty from June 2015 to January 2019 were randomly divided into preop 2 groups. The first group (n=60) was patients given tramadol (1-2 mgr/kg) for postop analgesia, and the second group (control group) (n=60) was initially performed only fentanyl (1 µg/ kg-i.v.) in the induction. The μ-Opioid receptors activities were investigated in preoperative blood samples and compared post-op pain level and requiring time for second analgesic agent. The visual analogue score(VAS) was used to evaluate the postoperative pain degree (0 no pain,10 worst pain). Patients' post op VAS scores were evaluated upon arrival to recovery room, and at 1st, 3rd, 7th, 10th, and 24 th hours in postoperative period.

Results

Demographic data and perioperative variables was similar in both study group (p<0.05). There was no significant difference between the receptor levels in both two groups and the mean receptor level was 200.94 pg/ml. While the highest receptor level was 489.92 pg/ ml, the lowest receptor level was 94.56 pg/ml. In patients who used tradomal, as the levels of μ-Opioid receptors increased, VAS scores of patients and second analgesic use decreased in post-operative period. Vas scores were lower in the tramadol group compared to the control group. Patients in Tramadol group needed second pain killer later than patients in the Control group.

Conclusions

In this study, we revealed that postoperative pain level and second analgesic requirement decreased as μ-Opioid receptor levels increased in tramadol group.

Background

Nasal septal surgery is one of the most common operations in otorhinolaryngology, alone or in
combination with other procedures, such as inferior turbinoplasty, endoscopic sinus surgery and rhinoplasty. Nasal septal surgery performed by otolaryngologists may cause severe pain postoperatively. In post-surgery term, patients usually suffer from severe pain during several days and the pain decreases step by step in following 4 days [1]. Non-steroidal anti-inflammatory (NSAI) drugs, acetaminophen and opioid analgesics can be used as medications in post-surgical pain control. Different methods and techniques have been used to reduce pain, including improved intraoperative anesthetic pain regimens, adjustment of surgical technique, intra-operative local anesthesia infiltration and korticosteroids. At present, the drugs used in the field of postoperative analgesia are mainly opioids. Opioid analgesics provide significant benefits for relief of moderate to severe pain. A number of opioids are available for clinical use, including fentanyl, remifentanl and tramadol. Tramadol commonly used as an opioid analgesic for postoperative analgesia. Tramadol and the metabolite O-desmethyl-tramadol (M1) are agonists of the mu opioid receptors [2]. Tramadol, a centrally acting analgesic and also stimulates presinaptic release of serotonin and inhibits serotonin reuptake. Therefore tramadol increases inhibitory effects on pain transmission both by opioid and monoaminergic mechanisms [3,4]. Due to its pharmacological properties, tramadol is a safe drug as drug abuse and dependence, respiratory depression, cardiovascular side effects unlike other opioids [5].

Opioid receptor types are the mu-opioid receptors (MOP-R), kappa-opioid receptors (KOP-R) and delta-opioid receptors (DOP-R); additional heterodimerization may cause diversity [6].

The pharmacological effects of opioid analgesics are derived from their complex interactions with three opioid receptor types (mu, delta, and kappa). The mu opioid receptor gene (OPRM1) (opiod receptor, mu 1) produces a receptor (the MOP-r) that is a site of action for commonly used opioid analgesics [7]. μ-Opioid receptors (μORs) are the major receptors that mediate the analgesic effects of opioids. Mu (μ)-Opioid receptor agonists such as fentanyl, remifentanl and morphine are the gold standard treatment for severe pain. But opioid analgesic agents have abuse potential due to a high addictive effect and their use may cause undesirable side-effects including respiratory distress, sedation, locomotor activity, constipation, narcotic addiction and tolerance. The use of these agents in
postoperative analgesia is limited due to mechanisms such as respiratory depression, sedation, tolerance and dependence. Figure 1 shows the shape of the mu-opioid receptor in human and rhesus monkey. μ-Opioid receptors (μORs) are binded to G proteins, and receptor activity in periaqueductal gray matter and brainstem is associated with analgesic effects [8]. Figure 1

In our study, we aimed to investigate the relationship between the μ-Opioid receptors activities with postoperative pain level and second analgesic requirement in nasal septal surgery patients.

**Methods**

This is a randomized, double-blind, prospective trial. Between June 2015 and January 2019, 120 adult patients underwent septoplasty at Otorhinolaryngology Clinic of Bozok University Research Hospital were included to the study. There were 52 female and 68 male patients (ranged from 18 to 45 years of age). The approval of the Ethics Committee was obtained (date: May 25, 2015, number: 25/12). This trial was registered retrospectively (The ACTRN: ACTRN12619001652167, registration date: 26/11/2019).

The informed consents were obtained from all patients and followed the guidelines of Helsinki. All patients in the study were randomly selected to have into two groups. For postoperative analgesia, the first group (n = 60) is patients using tramadol and the second group (n = 60) is control group in which patients are initially given fentanyl in the induction. Fentanyl (1 μg/ kg-i.v.), propofol (2–3 mgr/kg), and muscle relaxant (rocuronium bromide 0,6 mgr/ kg) were administered to all patients for induction. At the end of the surgery to first group patients was given tramadol (1–2 mgr/ kg) for postoperative analgesia. The medications that should be given intravenously to each group before awakened were performed by the Anesthesia Care Team.

The inclusion criteria for the study additionally consisted of patients aged between 18–45 years, who were categorized as I and II according to the American Society of Anesthesiology physical status classification and scheduled for elective surgery for septoplasty operation under general anesthesia. The exclusion criteria consisted of the patients who had ECG changes, receiving opioids for chronic pain, additional nasal pathologies and thus receiving additional surgical intervention, and history of allergies to local anesthetics, pregnancy, renal insufficiency, cognitive dysfunction and refusal of
participation to the study.

All patients were operated by using the classic septoplasty operation technique under general anesthesia. Venous blood samples were obtained from the patients for research the μ-Opioid receptors activities in preoperative term. The sera were transferred into unused cover tubes. The tubes were stored at -20_C in the deep-freezer and studied as groups μ-Opioid receptors levels were studied in the Olympus AU 600 autoanalyzer (Olympus Optical Co., Japan) using Randox kits. All the patients’ vital signs were monitored during the operation. In patients both group, the changes of mean arterial pressure, heart rate and Ramsay Sedation Scales (RASS) were measured at predetermined time points as arrival to the recovery room, and at the 1st, 3rd, 7th, 10th, 24 th hours in postoperative period.

To determine the level of postoperative pain, a continuous 10 cm visual analog scale (VAS), was used. On the scale, 0 indicated ‘no pain’, and 10 indicated ‘severe pain’. The patients were asked to mark their pain at different times on the scale, and the results were calculated and recorded in millimeters. First measurements were made on arrival to the recovery room in postoperative period, and they were repeated at the 1st, 3rd, 7th, 10th, and 24 th hours. At the times when the pain was the most severe, the patients were given upon arrival to the recovery room: Acetaminophen 1 gr (i.v.), at other time points: Acetaminophen with codeine analgesic 325/ 30 mg (p.o) as needed second analgesic agent and both timing and amount of analgesics used were recorded. The relations between μ-Opioid receptors level and VAS pain scale and second analgesic need was investigated in patients.

**Statistical Analysis**

The data were analyzed using the SPSS 21.0 software package. The number, mean and standard deviations of the demographic variables were tabulated, and student t test was used to compare the groups. ANOVA test (two ways classification with repeated measures) was used for statistical analysis of VAS values. P < 0.05 was accepted as statistically significant. The effect of time (each post-operative day) on VAS values was significant.

**Results**

120 adult patients underwent septoplasty were randomly selected to have into two groups. Simple
randomization was performed by another anesthesiologist who was blinded to intervention. The participants were also blind to the intervention. The first group (n = 60) is patients using tramadol, and the second group (n = 60) is the control group in which patients are initially given fentanyl in the induction for analgesia. One hundred twenty-six patients enrolled randomization and 120 were included in the analysis. Six patients were excluded the study because they did not agree to participate. Consort flow diagram of the study is shown in Figure 2. Figure 2

The two groups were comparable with respect to age, gender, American Society of Anesthesiologists Scale (ASA), body mass index (BMI), surgical time, and anesthesia time. There was no statistically significant difference between the two groups in terms of demographic data and perioperative variables. Table 1

Mean arterial pressure was significantly lower in the 1st and 3rd hours in postoperative period in the tramadol group compared to the control group. Similarly, heart rate of patients was higher in the control group than in the tramadol group at the arrival in the recovery room and postoperative 1st and 3rd hours. Table 2

There was no statistical difference between the measured receptor levels of the groups. Table 3 shows the measured receptor levels of all patients. Table 3

In tramadol group, compared to patients with a μORs level of 200.94–489.92 pg / ml and patients with a μORs level of 94.56–200.94 pg / ml, patients with a higher receptor level were less painful and the VAS scores were lower at the recovery room, 1st, 3rd, 7th, 10th in postoperative period. In the control group, while the VAS scores in patients with higher receptor levels (range, 200.94–489.92 pg / ml) were lower in the recovery room, 1st and 3rd hours, there was no significant difference in other time points. Additionally, compared to the control group, the VAS scores were significantly lower in tramadol group patients with both receptor level 200.94–489.92 pg / ml and receptor level 94.56–200.94 pg / ml. There was a statistical significance between mean VAS values of study groups (Tramadol group and Control group) and requiring time for second analgesic. We commented these data as follow: the severity pain of post septoplasty in study group patients was less seen in the tramadol group than the control group patients on postoperative arrival, 1st, 3rd, 7th, and 10th hours.
Moreover, the effect of time (postoperative hours) on VAS values was significant in both the tramadol group and the control group (Table 4). The mean amount of Tramadol used in all of study patients were 100 mgr (1-2mgr/ kg). In the control group, the average dose of fentanyl was 75 mcg and performed only during induction. The second analgesic agent requirement was significantly different between tramadol group and control group. Patients in the tradomol group required a second painkillers later than patients in the control group in which initially only received fentanyl. Compared to patients with μORs level: 200.94–489.92 pg / ml and patients with μORs level: 94.56–200.94 pg / ml in the tramadol group, secondary analgesic requirement was significantly lower in patients with higher receptor levels. In the control group, when the patients whose μORs level were above the average (200.94 pg /ml) and those below the mean were compared, secondary analgesic use was higher in patients with μORs level: 94.56–200.94 pg/ml (Table 4). These results are commented as more affecting opioids in patients with high receptor levels and therefore, patients felt lower pain in the postoperative period. Visual analogue scale (VAS) and second analgesic use in both tramadol group and the control group were showed in Table 4.

Ramsay Sedation Scale (RASS) were similar in both groups. However, patients in the control group were observed to be more agitated at the postoperative 3rd and 7th hour time points. RASS of the patients in both study groups were in Table 5.

Comparison of the incidence of vomiting between the groups did not show any significant difference during postoperative period. All of patients 8 patients had postoperative nausea and vomiting, 5 patients developed respiratory distress and 2 patients were entubated again. Only 3 patients had bleeding as postoperative complications.

Discussion
This is the first prospective study investigating the relationship between μ-opioid receptor level and postoperative pain and analgesic use. As the level of the μ-Opioid receptors (μORs) increased, the effect of opioid analgesics such as the tramadol increases in study group patients.

After elective rhinologic surgery, pain is prominent in the first 3 days, but rapidly decreases in the ongoing days[9]. Patients who undergo septoplasty operations will experience the most pain within the
first 24 hours, and patients often need additional analgesics during this period. This pain that occurs in the postoperative period is mostly associated with surgical trauma and the release of pain mediators into the circulation[1]. Controlling pain during postoperative period reduces pain-related anxiety in the patient and thus prevents the development of a cascade that may have negative consequences for the patient [10]. Low pain level of the patient will speed up recovery, provide a comfortable process and minimize the cost [11]. It is beneficial for the patient to apply a local anesthetic agent to the surgical area during the surgery, as it causes decreased postoperative pain scores and additional analgesic requirements [12]. In a recent study, the addition of a local anesthetic agent to the nasal packs after septal surgery has been shown to have positive effects in reducing postoperative pain within the first 12 hours [13].

Steroids such as methylprednisolone are used due to anti-inflammatory and immunosuppressive effects14]. Their effects take place by altering the gene expression with specific intracellular receptors action; this leads to the blockage of the formation of certain substances, and the acceleration of the production of others. As a result, There is reduced edema and fibrosis during healing [15]. Dexamethasone may reduce inflammation at the surgery site by reducing release of inflammatory mediators into the circulation [16]. Dexamethasone significantly reduced the μ-opioid receptor binding in the adrenal cortex and affects differently opioid receptor binding in the hypothalamus and pituitary gland17].

It is important to consider the effect of dexamethasone on receptors and pain.Knezevic NN and colleagues [18] revealed that addition of dexamethasone to local anesthetic solutions in the brachial plexus block significantly improved postoperative pain without increasing complications. Kim JH et al. [19] revealed that oral administration of 150 mg of pregabalin twice in the early postoperative period is an effective and safe option in early postoperative pain relief in patients undergoing septoplasty. Non-opioid analgesics and NSAI s are commonly used drugs to reduce pain and inflammation after surgery. However, the use of these drugs by clinicians is limited, as excessive use of these agents can lead to gastrointestinal damage, which can be serious enough to cause bleeding. Tramadol, an opioid analgesic for pain control in the postoperative period, has been used frequently
in recent decades. Opioid drugs show their analgesic effects by affecting μ-Opioid receptors (μORs).

One of the ways under the analgesic effect of tramadol is the affinity to μ opioid receptors. It binds stronger to μ-Opioid receptors than δ-Opioid receptors and κ-Opioid receptors. However, its affinity to μORs is weaker than codeine and morphine [2]. Another factor contributing to the analgesic effect of tramadol is the inhibition of the reuptake of monoamines such as Norepinephrin and 5-Hidroksitriptamin, which play a role in the transmission of pain in the central nervous system (CNS) [11]. Tramadol’s analgesic effect lasts 2–3 times longer than fentanyl and provides analgesia for about 7–8 hours [2].

Agents such as carbamazepine and cimetidine, which induce hepatic enzyme decreases the effect of tramadol. It has been shown in studies that the dose of tramadol should be increased when used with such drugs. The interaction of tramadol with anticoagulants (warfarin, coumadin) has not been clarified yet [20]. Even so, it should not be forgotten that tramadol can extend INR value (the International Normalized Ratio) especially when used with oral anticoagulants [21]. Granados-Soto and colleagues showed that tramadol combined with gabapentin showed a synergistic effect in both systemic and spinal administration [22]. Tramadol is contraindicated in combination with monoamine oxidase inhibitors (MAOI), and It can be given only after 2 weeks of treatment MAOI. Tramadol can cause serotonin syndrome when with serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressant (TCA). A case of serotonin syndrome has been reported in the literature related to sertraline [23].

Recently μ-opioid receptors have been shown to be in many cancer cell lines including non-small cell lung cancer, breast cancer, adenocarcinoma and gastric carcinoma [24,25]. Recent studies on both non-small cell lung cancer and prostate cancer have revealed that MOR expression correlated with, tumor aggressiveness, progression-free survival, and survival26].

Levins KJ and colleagues [27] revealed that there are the relationship between some tumor cells in the body and the anesthetic technique and μ-Opioid receptors. In their study, they emphasized that tumoral MOR expression is a difference and that this difference has prognostic importance in most types of cancer. It is possible that difference in μ-Opioid receptors may be caused by the interaction
between opioid analgesic use (morphine) and the OPRM1 gene causing an increase in MOR expression. They reported a relationship between MOR expression and anesthetic technique and suggested that the use of regional anesthetic techniques and total intravenous anesthesia could be more appropriate anesthesia methods in oncoanesthesia.

Endogenous opioids acting by binding to μ-Opioid receptors are likely to interact with hormones released from the hypothalamic-pituitary-adrenal axis in physiological and pathophysiological conditions [28].

**Limitations**

We included 120 adult patients in the study. Similar studies can be carried out with more participants.

**Conclusions**

In this study, we found that the efficacy of opioid analgesic agents was higher and the need for additional analgesics was lower in patients with higher μ-Opioid receptor (μORs) levels. As the level of the μ-Opioid receptor (μORs) increased in the study groups, the duration of the second analgesic requirement increased. Patients with a high level of μORs in both study group experienced less analgesic need in the post-op period. Additionally, Tramadol is a safe and effective a opioid analgesic agent that reduces the postoperative pain and it may be effective analgesic agent of choice in septoplasty operations. We recommend the use of opioids such as tramadol in patients with higher opioid receptor levels for more comfortable postoperative periods.

**Abbreviations**

- **μORs**: Mu-opioid receptor
- **KORs**: Kappa-opioid receptors (KOP-R)
- **DOP-R**: Delta-opioid receptors (DOP-R)
- **VAS**: Visual analog scale
- **RASS**: The ramsay sedation scale
- **NE**: Norepinephrine
- **5-HT**: 5-Hidroksitriptofan
- **SSRIs**: Serotonin reuptake inhibitors

**Declarations**
Notes

Muzaffer Gencer and Ayşe Yeşim Göçmen contributed equally to this work.

Ethics approval and consent to participate

This study was approved by the Internal Review Board at Bozok University and patients gave written informed consent for study participation (date: May 25, 2015, number: 25/12).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MG conceived the study. MG and AYG collected the data and drafted the manuscript. MG and AYG revised the manuscript and language. AYG conducted the data analysis. All authors have read and approved the manuscript.

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Tables
Table 1. Demographic data and perioperative variables

|            | Tramadol (n=60) | Control (n=60) | *P value |
|------------|----------------|---------------|----------|
| Age (yr)   | 28.4 ± 10.02   | 32.26 ± 11.78 | 0.352    |
Sex (F/M)  24/36  28/32  0.466
ASA Score I/II  21/39  31/29  0.231
BMI (kg/m²)  23.4 ± 3.0  25.3 ± 5.0  0.285
Duration of surgery (min)  74.44±23.81  80.48±25.14  0.406
Duration of anesthesia (min)  82.91±25.75  85.38±29.31  0.763

*Student t test, p>0.05

Data are expressed as number of patients and mean ± SD. ASA: American society of Anesthesiologists. BMI: Body Mass Index. F: Female, M: Male.* Student t test, p>0.05

Table 2. The changes of mean arterial pressure and heart rate at different time points

| MAP (Mean ± SD) | Tramadol group (n=60) | Control group (n=60) | p-value |
|-----------------|-----------------------|----------------------|---------|
| Arrival         | 116.54±15.92          | 124.91±11.06         | 0.354   |
| 1st h           | 98.54±15.88           | 106.88±11.66         | 0.048** |
| 3rd h           | 91.78±3.36            | 93.62±2.12           | 0.030** |
| 7th h           | 83.34±10.06           | 84.20±10.96          | 0.846   |
| 10th h          | 78.20±7.62            | 77.00±6.82           | 0.636   |
| 24th h          | 71.54±3.34            | 72.76±2.46           | 0.172   |

SD: Standard deviation, MAP: Mean arterial pressure, HR: Heart rate, h: hour. Student t test * p<0.01, **p<0.05

Table 3. The levels of the μ-Opioid receptor (μORs) in both group

| Measured receptor levels | value (pg*/ml) |
|--------------------------|----------------|
| Average                  | 200.94 pg/ml   |
| Highest                  | 489.92 pg/ml   |
| Lowest                   | 94.56 pg/ml    |

Table 4. Visual analogue scale (VAS) and second analgesic use

| μORs level: 200.94-489.92 pg/ml |
|---------------------------------|
| Group T (n=32) VAS score | 1 | 1 | 2 | 1 | 1 | 1 |

15
S. Analgesic*  
(0-2)   (0-2)   (1-3)   (0-2)   (0-1)   (0-1)

Group C (n=31) VAS score
5   4   3   2   2   1
(3-8)   (3-5)   (2-5)   (1-3)   (1-2)   (0-2)

μORs level: 94.56-200.94 pg/ml

Group T (n=28) VAS score
3   3   3   2   2   1
(2-5)   (1-5)   (1-5)   (1-3)   (1-2)   (0-1)

Group C (n=29) VAS score
6   5   4   3   2   1
(4-8)   (3-7)   (3-5)   (1-3)   (1-2)   (0-2)

* Arrival to the recovery room: Perfalgan 1 gr (i.v.), at other time points: Acetaminophen with codeine analgesic 325/30 mg (p.o). + ; single dose analgesic use.

Table 5. Ramsay sedation scores of the patients

|          | Arrival | 1st hour | 3rd hour | 7th hour | 10th hour | 24th hour |
|----------|---------|----------|----------|----------|-----------|-----------|
| Tramadol (n=60) | 3       | 2        | 2        | 2        | 2         | 2         |
|           | (2-3)   | (2-2)    | (2-2)    | (2-2)    | (2-2)     | (2-2)     |
| Control (n=60)  | 3       | 2        | 1        | 1        | 2         | 2         |
|           | (1-3)   | (1-2)    | (1-2)    | (1-1)    | (1-1)     | (1-1)     |

Data are expressed as median

Figures
Figure 1
Shape of the mu-opioid receptor in human and rhesus monkey. Mu-opioid receptors (MOR) have the seven transmembrane structure which shown with open circles representing amino acids. (Miller Gregory M., Madras Bertha K, in The Laboratory Primate, 2005)
Figure 2
Flow chart of the study