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A STUDY OF THE EFFECTIVENESS OF FENTANYL NASAL PACKS IN POSTOPERATIVE PAIN ASSESSMENT FOLLOWING FUNCTIONAL ENDOSCOPIC SINUS SURGERY

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Abstract

Background: Nasal packing is usually performed to control bleeding after endoscopic sinus surgery (ESS). Although new packing materials have been developed, they still cause pain. This study was designed to evaluate the effect of lidocaine-soaked packs on pain after ESS.

Aim and objective: to evaluate the effect of fentanyl-soaked packing as a method of controlling pain after nasal surgeries in a prospective, randomized, double-blind controlled trial.

Methods: 52 patients who have undergone closed nasal bone fracture reduction surgery were included in this study. 26 patients were treated postoperatively with 50 mcg of fentanyl-soaked MerocelV, a biodegradable synthetic polyurethane foam, and the other 26 patients were treated with saline-soaked packings. To analyze the relative nasal pain control effect of fentanyl, the Numeric Rating Scale, patient satisfaction, and Ramsay Sedation Scale were used. Patients were closely monitored to record relevant cardiopulmonary indicators and the degree of adverse symptoms such as headaches or sore throats.

Results: The fentanyl group had a significantly lower Numeric Rating Scale and higher patient satisfaction for most of the time periods after operation ($p < .05$). The symptoms of headaches and sore throats were also significantly reduced. Ramsay Sedation Scale scores improved compared to the control group ($p < .05$). No significant differences in cardiopulmonary relevant indicators between the two experimental groups were observed ($p > .05$).

Conclusion: Fentanyl-soaked packing significantly decreased postoperative pain with no observable adverse effects. Our results demonstrate that topical fentanyl application to nasal packing is an effective method of postoperative pain control after closed nasal bone fracture reduction surgery.

Keywords: fentanyl nasal pack, endoscopic sinus, surgery

Endoscopic sinus surgery (ESS) has become a widely accepted procedure for the treatment of medically refractory chronic rhinosinusitis (CRS). Bleeding after ESS is commonly encountered in the early postoperative period. [1-2] Nonabsorbable nasal packs have been widely used to control bleeding and to prevent the accumulation of blood after ESS. Although modified techniques of nasal packing have been introduced to reduce pain during packing removal, [3] the presence of nasal packing and its subsequent removal is usually uncomfortable and painful and is often rated as the most unpleasant aspect of the ESS surgical experience by patients. [4] Recently, absorbable packing materials are replacing non-absorbable ones and are commonly used to reduce pain by obviating the need for removal. [5] However, headaches and facial pain are still common complaints in the early postoperative period, even when absorbable nasal packing is used.

Postoperative pain control is relevant to all members of a patient's care team and is a particularly active area of research for anesthesiologists, pharmacologists, and physical therapists. Currently, opioids, including fentanyl, morphine, and hydromorphone, and nonsteroidal anti-inflammatory drugs (NSAIDs), are administered via oral, intravenous (IV), and intramuscular (IM) routes and via patient-controlled analgesia (PCA) to manage postoperative pain [6]. However, numerous issues associated with traditional routes of analgesic administration, such as discomfort and safety concerning systemic effects and errors and failures associated with PCA, remain to be addressed [7]. Intranasal administration is a convenient route of analgesic administration that can be used for several opioids. Of note, intranasal fentanyl (INF), a highly lipophilic step 3 opioid on WHO Ladder, has recently been shown to have a very fast analgesic effect in postoperative pain, acute pain in emergency departments [8], procedural wound care pain, child premedication, and cancer-related breakthrough pain [9–10]. Fentanyl can be applied topically and absorbed transmucosally due to its lipophilic profile, leading to enhanced effect duration with a lower dosage and minimal adverse effects compared to IV administration [11]. In fact, the terminal half-life of fentanyl administered subcutaneously is known to last for more than 10 h compared to the 3 h half-life of IV fentanyl [12]. Furthermore, topical nasal pain control with fentanyl results in minimal systemic side effects, low plasma concentration, and few first-pass effects with good patient tolerance [13]. This is because fentanyl's agonistic effects on opioid receptors in the ethmoid nerve and maxillary nerve in tissues of the nasal area are more effective than system-wide analgesia [9, 14]. Accordingly, studies have shown that INF does not affect vital signs such as heart rate or blood pressure and does not cause respiratory depression with a similar analgesic effect, in contrast to IV fentanyl [15]. Therefore, mucosal fentanyl is a promising alternative to traditional routes of analgesic administration for postoperative pain control.

Recent work by Apuhan T et al. has demonstrated that Merocel packing rehydration with levobupivacaine or prilocane solution is an easy, inexpensive, safe, and effective analgesic method for patients undergoing nasal surgery [16]. Nasal packing rehydration can provide effective analgesia during packing removal, which has been reported to cause significant discomfort [17]. While use of levobupivacaine and prilocaine resulted in statistically significant differences in visual analog score (VAS) and Ramsay sedation scores, fentanyl is a short-acting synthetic opioid with a pharmacokinetic profile better suited for fast relief of brief episodic pain, is longer-acting, and is more cost-efficient than lidocaine [7]. Therefore, we performed a prospective, randomized, double-blind controlled trial to evaluate the effectiveness of fentanyl-soaked nasal packing in alleviating postoperative pain following closed nasal bone fracture reduction.

Materials and Methods

A prospective, randomized, double-blinded, placebo-controlled trial was conducted on 52 consecutive patients aged 18–65 years with CRS with or without polyps who underwent bilateral symmetric ESS. All patients were diagnosed with CRS, were refractory to maximal medical therapy, and had evidence of significant disease on computed tomography imaging. Patients meeting inclusion criteria were enrolled consecutively in this randomized, controlled, and blinded study.

Ethics approval was obtained from the Internal Review Board of the (write the name of the working location), and informed consent was obtained from all patients before enrollment. Patients were excluded if they were ~ 18 years old, were ineligible for informed consent, had a history of coronary artery disease, heart disease, or seizure, or had any history of intolerance to lidocaine. Patients who underwent additional septal or turbinate surgery were also excluded. After induction of general anesthesia, the nose was prepared with topical 1:1000 epinephrine to decongest the nasal mucosa. A submucosal injection of 1:100,000 epinephrine was performed to control bleeding at the incision site at the beginning of the operation. ESS was then performed bilaterally using similar techniques by two surgeons (J.M. and Y.C.). No local anesthetic was used preoperatively or intraoperatively.

To measure the extent of postoperative pain in both groups, all patients were asked to rate their pain at 1, 3, 6, 12, 24, and 36 hours after surgery using an 11-point Numeric Rating Scale (NRS). One anesthesiologic resident was blinded to the group assignment, and patient information was assigned to gather the patients' responses. At the same time, patient satisfaction (SAT) and the Ramsay Sedation Scale (RSS) were also measured. The NRS pain score ranged from 0 (no pain) to 10 (the most severe pain that the patient had ever experienced) [18]. Patient satisfaction (SAT) was evaluated using a scale of 0 to 10, with 0 being unsatisfactory and 10 being very satisfactory [19–20]. The RSS score evaluates the sedation effects at six different levels for reliability. The table below shows the RSS score criteria [21].

Score Criteria	Criteria
1	The patient is awake and is anxious, agitated, or restless.
2	The patient is awake and calm, cooperative, and communicative.
3	The patient is asleep but responds quickly to voice commands.
4	The patient is asleep, and the response is slow.
5	The patient is asleep, and the response is slow.
6	No response at all.

The severity of pain was asked by an anesthesiologist who was ignorant of the types of surgery and packing material to maintain blindness. Relevant cardiopulmonary values were monitored to identify any effect of fentanyl on vital signs; the values consisted of systolic arterial pressure (SAP) and diastolic arterial pressure (DAP). andheart rate (HR). The values were checked before surgery, and at 1, 3, 6, 12, 24, and 36 hours after surgery. Furthermore, the presence of any adverse effects, including headache, dizziness, nausea, vomiting, and severe facial pain, was tracked during the 1, 3, 6, 12, 24, and 36-hour postoperative time period. All values were recorded by the same medical staff to minimize observer variations [22]. Supplemental analgesics, 50 mg of IV fentanyl in the post-anesthesia care unit and ketorolac tromethamine 30 mg/1 ml IV or tramadol HCl 50 mg/1 ml IV bolus in the general ward, were administered at the patients' request during the recovery period, and the usage of additional analgesics was also recorded to reflect the impact on the target pain parameter. Both the patients and the surgeon were blinded to which type of packing was used in the surgical process.

Statistical analysis

The assumptions of normality and equal variance of continuous variables in each group were confirmed by the Shapiro-Wilk test. The mean and standard deviation were presented when the assumption was satisfied, and the mean difference between the two groups was evaluated by the independent t-test. When the assumption was not satisfied, the median and range were presented, and the Mann-Whitney U test was used to evaluate the median difference between two groups. Categorical variables were presented as numbers and proportions, and the difference in proportion

between the two groups was evaluated by Fisher's exact test. Linear mixed effects models with restricted maximum likelihood estimates were used to assess the differences in longitudinal change (slopes) and the differences at each time point in NRS, SAT, and RSS scores between the two groups.

Observation and Result

The 60 patients screened—52 patients who completed the trial—came from North India and were predominantly male (34 male, 18 female). The age mean of the total participants was 43.34±5.3. Among the 60 screened patients, the fentanyl group of 26 patients was treated with 50 mcg of fentanyl-soaked synthetic polyurethane foam packing MerocelVR (Medtronic Inc., Minneapolis, MN), and the control group of 26 patients was treated with saline-soaked packings. The two groups did not show any statistically significant differences in the demographic data (Table 1). After the collection of all relevant data, experimental parameters, including NRS pain scores, SAT patient satisfaction scores, and the Ramsay Sedation Scale, were analyzed. The fentanyl group showed a significantly lower NRS value compared to that of the control group, and the comparison results at 3, 6, and 12 h showed the same trend of satisfaction enhancement ($p < .05$) (Table 4 and Figure 1). The SAT score of the fentanyl group was higher than that of the control group at any time period, and the comparison results at 3 and 6 h showed the same trend of satisfaction enhancement ($p < .05$) (Table 4; Figure 2). Furthermore, for closed nasal bone fracture reduction, the fentanyl group rated a higher average RSS score than the control group ($p > .05$) (Table 7).

The use of supplementary analgesic drugs in the control group was higher in frequency and dosage than in the fentanyl group (Table 1). The number of patients requesting additional analgesic treatment differed between the two groups. Patients in the control group also requested the NSAID usage more than the fentanyl group in the postoperative 1–24 h period. The changes in blood pressure after surgery were not significantly different between the two groups ($p > .05$; Table 7; Figures 3 and 4). The results in the heart rate after surgery were not significantly different between the two groups ($p > .05$; Table 5; Figure 5). As for the side effects monitored, the fentanyl group suffered fewer headaches and sore throats in the postoperative hours (Table 6). No patient suffered from nausea and vomiting, and no adverse events related to opioids or tramadol were found in fentanyl-treated patients.

Table 1. Baseline characteristics of the patients in the control group.

Characteristics	**Fentanyl (N-26) Mean±SD**	**Control (N-26) Mean±SD**	**p-value**
Age (years)	42±6.09	43.35±5.3	0.332
BMI(kg/m2)	26.38±3.9	25.46±3.9	0.39
Sex (M:f)	16:10	18:8	

Table 2: ASA PS classification,

classification	**Fentanyl (N-26)**		**Control (N-26)**		**p-value**
	N	%	N	%	
I	19	73.08	20	76.92	
II	7	26.92	6	26.08	

Table 3: Presence of medical history, N (%)

History	**Fentanyl (N-26)**		**Control (N-26)**		**p-value**
	N	%	N	%	
HTN	3	11.54	5	19.23	0.421
DM	5	19.23	1	3.85	0.324

Table 4: Additional drug injection

Drug injection	Fentanyl (N-26)		Control (N-26)		p-value
	N	%	N	%	
Fentanyl	11	42.31	8	30.77	0.52
NSAID	26	100	23	88.46	0.46

Table 5. Scores on NRS at postoperative time points and comparison of the difference in longitudinal changes between two groups.

NRS score,	Fentanyl Mean±SD	Control Mean±SD	P-value
Postop: 1 hour	7.21±0.79	7.64±0.53	0.025
Postop 3 hour	5.21±1.14	6.08±0.89	0.003
Postop: 6 hours	4.44±0.58	5.05±1.00	0.01
Postop 12 hour	3.04±0.75	3.92±0.92	0.000
Postop 24 hours	2.02±0.58	2.67±0.99	0.005
Postop: 36 hours	1.08±0.6	1.55±0.72	0.014

Table 6. SAT at postoperative time points and comparison of the difference in longitudinal changes between two groups.

SAT score,	Fentanyl Mean±SD	Control Mean±SD	P-value
Postop: 1 hour	3.68±0.78	2.86±0.85	0.001
Postop 3 hour	5.25±0.87	3.52±1.02	0.000
Postop: 6 hours	6.38±0.59	4.84±1.15	0.000
Postop 12 hour	7.43±0.57	6.41±0.69	0.000
Postop 24 hours	8.72±0.99	7.83±0.5	0.000
Postop: 36 hours	9.65±0.99	9.07±1.14	0.056

Figure 1. The NRS score of patients who applied nasal packing with fentanyl or saline. NRS: numeric rating scale; the fentanyl group: red bar; the saline group: deep blue bar.

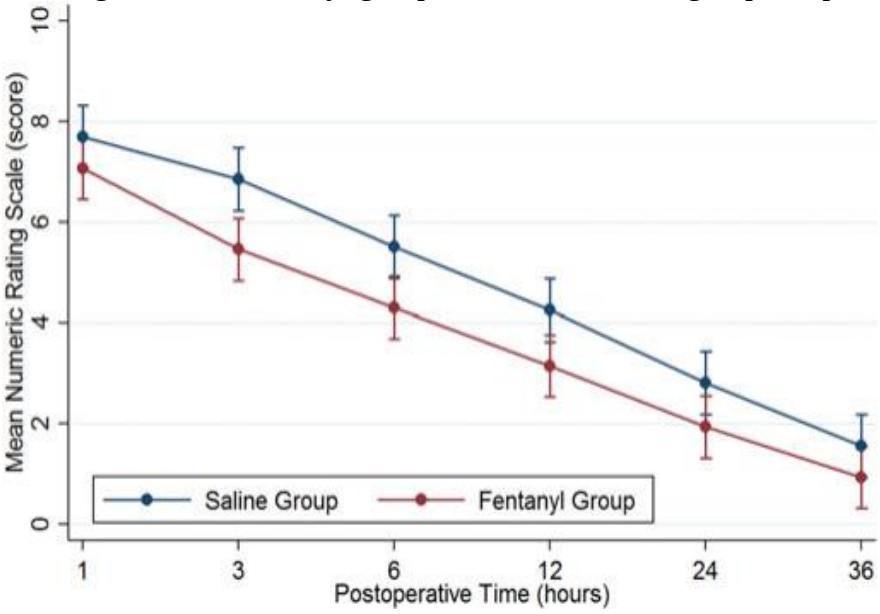

Figure 2. The SAT score of patients who applied nasal packing with fentanyl or saline. SAT patient satisfaction; The fentanyl group: red bar; the saline group: deep blue bar

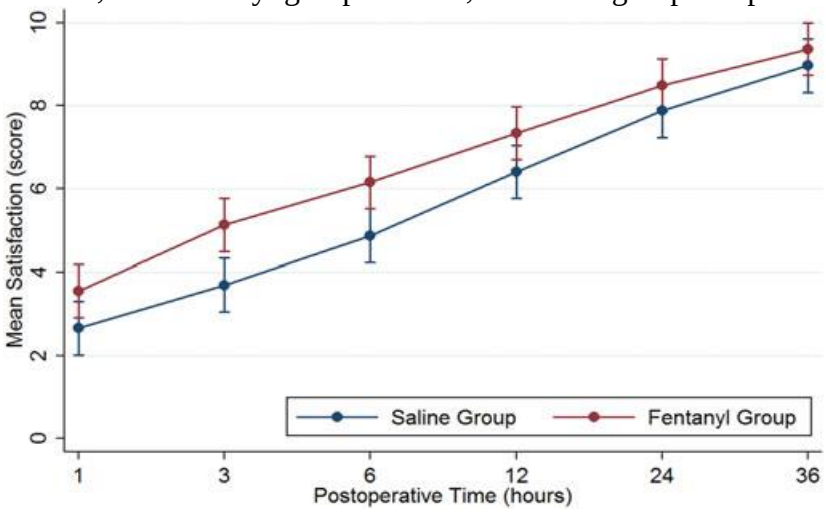

Figure 3. Comparison of sBP with fentanyl or saline soaking. sBP: systolic blood pressure; the fentanyl group: red bar; the saline group: deep blue bar.

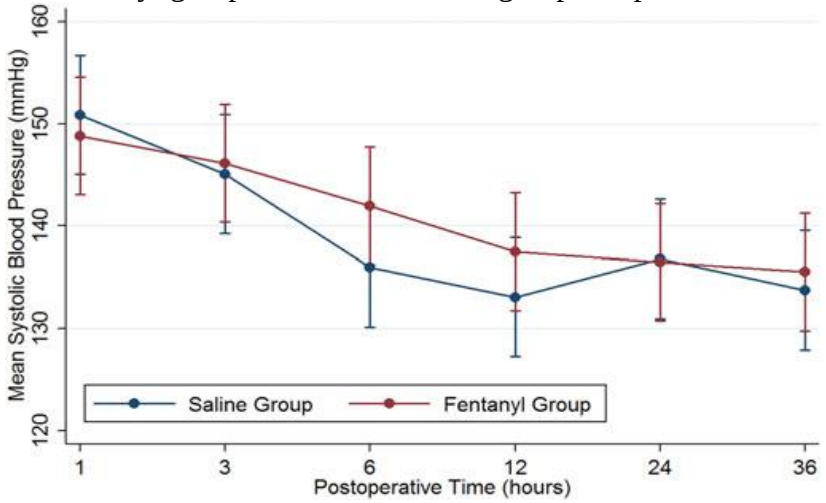

Figure 4. Comparison of dBP with fentanyl or saline soaking. dBP: diastolic blood pressure; the fentanyl group: red bar; the saline group: deep blue bar.

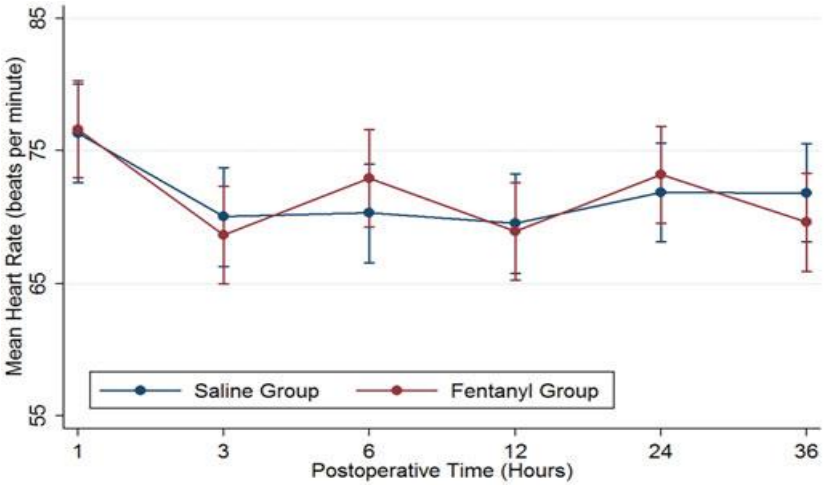

Figure 5. Comparison of HR with fentanyl or saline soaking. HR: heart rate; The fentanyl group: red bar; the saline group: deep blue bar

Table 7. Comparison of the outcomes from packing to removal between two groups.

Outcomes	**Fentanyl (N= 26)**	**Control (N = 26)**	**p-value**
RSS score, N (%)			
Did not change	12(46.15%)	10(38.46%)	**0.492**
Improved	2(7.69%)	2(7.69%)	
Worse	12(%)	14(53.85%)	
Changes in SBP after packing, N (%)			
Did not change	14(53.85%)	1557.69(%)	**0.23**
Decreased more than 20 mmHg	10(38.46%)	11(42.31%)	
Increased more than 20 mmHg	2v	0(%)	
Changes of DBP after packing, N (%)			
Did not change	16(61.54%)	16(%)	**0.91**
Decreased more than 15 mmHg	10(38.46%)	10(38.46%)	
Increased more than 15 mmHg	**0**	**0**	
Changes in HR after packing, N (%)			
Did not change	**23**(88.46%)	**24**(92.31%)	**0.42**
Decreased more than 20 beats/min	3(11.54%)	**2**(7.69%)	
Increased more than 20 beats/min	**0**(%)	**0**(%)	
Complications, N (%)			
Bleeding	**1**(3.85%)	**2**(7.69%)	**0.522**
Headache	**5**(19.23%)	**6**(23.08%)	
Sorethroat	**2**(7.69%)	**2**(7.69%)	
Near-site pain	**2**(7.69%)	**6**(23.08%)	
Insomnia	**0**(%)	**1**(%)	

Discussion

Nasal packing is usually placed to prevent postoperative bleeding after ESS because the risk of delayed postoperative bleeding may be higher without nasal packing. [23] Nonabsorbable nasal packing has been the most common method to control postoperative bleeding and to prevent adhesion formation, middle turbinate lateralization, and restenosis after ESS. However, these materials cause considerable discomfort and pain to patients, both caused by the presence of the packing material and by its subsequent removal.12 Von Schoenberg et al. [24] showed that patients undergoing endonasal surgery often consider packing removal to be the most unpleasant aspect of the perioperative experience. Therefore, various absorbable materials have been developed and marketed to obviate the need for removal and overcome the disadvantages of not packing. However, it was reported that even the absorbable pack causes significant pain and discomfort compared with the traditional nonabsorbable nasal pack in terms of the duration of nasal packing. [25] The application of opioids such as fentanyl to mucous membranes in the context of nasal surgery has not yet been widely studied. This study is the first to evaluate the postoperative pain control effects of topical opioid application in nasal surgeries and Our results demonstrate that patients can benefit from Merocel packing rehydration with fentanyl solution with decreased discomfort and pain and improved tolerance to packing. Both the experimental and control groups showed a strong trend of initial pain eventually declining over time. However, the pain score for the group using fentanyl, although not statistically significant, peaked after 6 hours. Such results indicate that fentanyl's mucosa infiltration and analgesic effects are comparable to those of IV because fentanyl is likely to

be effective in initial pain management but shows a decreased effect after its half-life. Such interpretation is consistent with the fact that the two curves illustrating NRS and SAT are parallel as time passes, since the effect of fentanyl will gradually diminish as the half-life passes, and at the same time, the amount of fentanyl diffused over the effective area and absorbed through the mucosa drops over time. Therefore, the effect of fentanyl can be considered clinically effective for initial pain control.

The fact that patients treated with fentanyl had a lower rate of adverse events at a statistically significant level ($p < .05$) also adds to the merit of using fentanyl nasal packing. Any undesirable symptoms of intramucosal fentanyl had been identified before administration; the most common side effects are reported to be GI disturbances of nausea, vomiting, drowsiness, confusion, and pruritus [7]. Throughout the study, the fentanyl group showed a rare occurrence of GI disturbance. No further side effects from nasal packing rehydration were observed in this study. Both groups did not show any significant gaps in BP and HR, whereas patients in the fentanyl group showed lower cardiopulmonary parameter fluctuations. This suggests that fentanyl can stabilize patients with its natural opioid analgesic effect, with the fentanyl group experiencing less pain and thus suffering less from headaches and sore throats. The relatively small fentanyl dosage used in this experiment lacked the potential to cause a drastic effect on RSS sedation scores, suggesting that the sedative effect was not a major factor in stabilization. Since fentanyl is the most commonly used medication for post-operative pain control and is thus very familiar to anesthetists [26], using it in local anesthesia should be easy to implement and will have the significant benefit of reducing systemic adverse effects.

Safety concerns may be an issue when using fentanyl because it can cause serious complications such as respiratory depression or decreased blood pressure. However, IV fentanyl 1–2 mcg/kg is a commonly used dose without complications in the post-anesthesia care unit as postoperative pain control [27]. Because mucosal fentanyl has a less systemic effect than IV, less systemic side effects are expected to occur [28]. Accordingly, no patient in the fentanyl group showed respiratory depression. However, patients who are at risk of respiratory depression or decreased blood pressure should still be closely monitored to avoid complications. Fentanyl may be considered an excessive treatment for nasal pain since nasal operations are often not considered to be severely painful, and in many cases, fentanyl is overused based on expected preoperative pain by NRS [29–30]. However, the importance of postoperative pain control can never be overemphasized, as it improves patient satisfaction, prevents complications associated with postoperative pain (deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia, etc.), shortens the hospital stay of patients, and eventually increases the quality of patients' lives [31]. While opioids are still the mainstay of postoperative pain therapy, fear of complications associated with opioids can result in failure to provide adequate postoperative analgesia [32]. Therefore, local administration, with its decreased risk of systemic effects, is a promising alternative to IV administration that can still achieve adequate analgesia. There are several limitations to our study.

The first limitation is the deviation in gender distribution that has appeared in this study: 61.54% of the fentanyl group (16 among 26 subjects) and 69.23% of the control group (18 among 26 subjects) were male. It is possible that this difference may have affected the results, but stratification according to gender was not possible due to a lack of suitable female participants. This may be due to the fact that the cause of nasal fracture is mainly trauma, of which the incidence is much higher for men [33]. Future work should utilize stratification according to gender with a sufficient number of female participants. Another limitation was that we used rehydration with saline instead of Naþ channel blockers such as lidocaine, as previously reported, as our control group. While this was done to mirror the methodology of previous work, comparisons of nasalfentanyl's analgesic effects and side effects with Na channel blockers should be performed in further studies. Finally, this study did not analyze the pharmacological mechanism beyond the first-pass effects. Our results suggest that the systemic kinetics of fentanyl appear to be different for the intranasal and IV routes of

administration. Although similar trials were carried out using intranasal local anesthetics, fentanyl was not studied via randomized clinical trials. Therefore, this trial has an important role in developing new guidelines in otolaryngologic surgery for controlling postoperative pain. Future studies should evaluate the pharmacokinetics and pharmacodynamics of fentanyl delivered via nasal packing rehydration with additional fentanyl dosages and weight ranges to develop optimal fentanyl dosing guidelines. This is the first study to apply local opioid anesthesia to a nasal bone fracture. Reduction in additional pain killer dosage, significantly lower NRS pain scores and higher SAT patient satisfaction scores during the immediate postoperative time periods, and the difference in the tendency of overall scores between the control and experimental groups, all leading to the conclusion that using fentanyl-applied Merocel has significant clinical potential. While the results have not demonstrated a statistically significant level of benefits ($p < .05$ over the traditional methods, the potential. The nasal packing rehydration with fentanyl to improve postoperative pain control demonstrated throughout this report suggests that this method should be investigated further.

Conclusion

This study suggests the potential of topical fentanyl administration as an acute nasal pain management method, especially in controlling postoperative nasal pain. Although IV fentanyl is routinely used in many cases, our randomized double-blind controlled trial and relevant statistical analysis propose that the topical intranasal administration of fentanyl can also be a localized and effective way of alleviating postoperative nasal pain.

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