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Analgesic effects of nefopam in patients undergoing bimaxillary osteotomy: A double-blind, randomized, placebo-controlled study

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ABSTRACT

Purpose: Many studies have examined the postoperative analgesic effects of nefopam in various settings. However, although nefopam is expected to be useful in bimaxillary osteotomy, no published data are available.

Material and methods: We divided 42 patients into nefopam [n = 21, nefopam 20 mg intravenous (i.v.) 30 min before surgery, followed by an i.v. infusion (5 mg/h) beginning immediately postoperatively for 24 h] and control [n = 21, normal saline] groups. Then we compared the analgesic efficacy, side effects, and degree of patient satisfaction with postoperative analgesia.

Results: Pain was lower in the nefopam group than in the controls in the recovery room [4.6 (3.0–6.0) vs. 6.0 (5.5–7.0), median (interquartile range), $P = 0.002$] and on the ward. Fewer patients in the nefopam group required rescue analgesics, and the degree of patient satisfaction was significantly higher in the nefopam group ($P < 0.001$). There were no significant differences in other side effects between the groups. However, the control group showed more sedation 1 h postoperatively ($P = 0.009$).

Conclusion: Nefopam is an effective analgesic in bimaxillary osteotomy in that it can reduce the use of opioids and nonsteroidal anti-inflammatory drugs, thereby reducing the side effects of conventional analgesics.

(Trial Registration: ClinicalTrials.gov (NCT 01461031))

1. Introduction

A bimaxillary osteotomy involves a bilateral sagittal split osteotomy and Le Fort I osteotomy. It is one of the most common oral and maxillofacial surgeries. The postoperative pain caused by a bimaxillary osteotomy is the most severe in oral and maxillofacial surgery (Niederhagen et al., 1997). This severe pain can lower the degree of patient satisfaction in the immediate postoperative period (Chen et al., 2002). In addition, since acute postoperative pain can also progress to chronic pain (Perkins and Kehlet, 2000), a meticulous strategy of postoperative pain control is necessary.

Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to control postoperative pain. Opioids are appropriate for controlling severe pain due to a lack of ceiling effects, whereas NSAIDs inhibit the synthesis of various inflammatory substances involved in the sensitization of nociceptors, leading to analgesic effects. Therefore, both agents might be ideal for controlling severe postoperative pain. However, opioids have the disadvantage of causing postoperative sedation and respiratory depression, whereas NSAIDs use can be limited in patients with platelet, hepatic, or renal dysfunction, or severe intraoperative bleeding. These disadvantages can be fatal in bimaxillary osteotomy.

Nefopam is a centrally acting nonopioid analgesic that inhibits the reuptake of serotonin, norepinephrine, and dopamine (Piercey and Schroeder, 1981). Unlike NSAIDs, it does not inhibit platelet function, and it lacks the sedative properties of opioids. These virtues might be valuable in bimaxillary osteotomy. However, although studies have examined the analgesic effects of nefopam in various other surgical settings (Aveline et al., 2009; Beloeil et al., 2004; Du Manoir et al., 2003; Richebe et al., 2013; Tirault et al., 2006; Tramoni et al., 2003; Yoo et al., 2015), there are no published data on its analgesic efficacy in bimaxillary osteotomy.

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Therefore, we conducted this double-blind, randomized, placebo-controlled study to examine the analgesic effects and safety of nefopam in patients undergoing bimaxillary osteotomy.

2. Material and methods

This double-blinded, randomized, placebo-controlled study was approved by the institutional review board of Catholic University Seoul Saint Mary's Hospital and registered at clinical trial. Written informed consent was obtained from all study subjects. The study included 42 patients (aged 20–65 years) undergoing elective bimaxillary osteotomy under general anesthesia. Exclusion criteria included an inability to comprehend the visual analogue scale (VAS) for pain; neuropsychiatric problems; cardiovascular, hepatic or renal disease; a history of NSAIDs allergy; any use of monoamine oxidase inhibitors; closed angle glaucoma; urinary retention arising from urethral or prostatic disease; daily use of analgesics or use of any analgesic in the 24 h before surgery; pregnancy; or breastfeeding.

Patients were assigned randomly to either the nefopam (n = 21) or control (n = 21) group, using a computer-generated random number table. In addition, they were blinded to the study treatments, which were packed in opaque vinyl bags labeled with a randomization number. No patients were told details of the study treatments until completion of the study. The nefopam group received nefopam 20 mg intravenously (i.v.) with 50 mL of normal saline 30 min before inducing general anesthesia, followed by a 24-h i.v. infusion (5 mg/10 mL/h) beginning immediately postoperatively. The control group received normal saline as a placebo, following the same schedule.

No premedication was given. During the pre-anesthetic assessment, the patients were instructed on the use of a VAS from 0 to 10 points, where 0 indicates 'no pain' and 10 indicates 'the worst pain imaginable', as a tool for evaluating the severity of postoperative pain. They were also instructed to contact the clinical research nurse immediately if postoperative pain ≥5 points developed or if they required analgesia. In all the patients, we evaluated risk factors for postoperative nausea and vomiting (PONV), such as female sex, a history of PONV, or motion sickness and a smoking history.

In the operating room, we monitored the electrocardiogram, heart rate, noninvasive blood pressure, pulse oximetry, and end-tidal carbon dioxide pressure. Anesthesia was induced with propofol 1.5–2.5 mg/kg, remifentanil 0.1–1 μg/kg, and rocuronium 0.8 mg/kg, and was maintained with 0.05–10 μg/kg/min remifentanil and 2–3% sevoflurane (inspired concentration) in 50% air/oxygen to keep the bispectral index at 30–60 and within ±20% of the baseline systolic blood pressure. Ventilation was controlled mechanically and then adjusted to maintain end-tidal CO_2 values at 30–40 mmHg throughout surgery. Additional rocuronium was administered as required. To prevent PONV, all of the patients were given ramosetron 0.3 mg i.v. 30 min before the end of anesthesia. At the completion of the surgical procedure, the remifentanil infusion was discontinued, and the amount used was recorded. This was followed by the initiation of the study treatment at a dose of 10 mL/h until 24 h postoperatively. After spontaneous ventilation was restored, the residual neuromuscular blockade was overcome with pyridostigmine 10 mg and glycopyrrolate 0.4 mg. After waking, patients were transferred to the recovery room while endotracheal intubation was maintained. Other types of analgesic were prohibited during the operation.

All of the surgical procedures, comprising a bilateral sagittal split osteotomy and a Le Fort I osteotomy, were performed by a single board-certified specialist. After the incision, the upper and lower jaws were moved to their preoperatively planned positions. The maxilla and mandible were fixed rigidly with plates and screws and repositioned using bi-cortical screws, respectively. Light intermaxillary elastic bands were placed to stabilize the new jaw position postoperatively.

In the recovery room, an anesthetist nurse blinded to the study group evaluated the Aldrete score of the patients at 15-min intervals. When they reached an Aldrete score ≥10 points and had no further bleeding, they were extubated. Once they had achieved a stable hemodynamic profile for 30 min after tracheal extubation, they were transferred to the ward.

2.1. Analgesic efficacy assessment

An investigator who was blinded to the study group evaluated pain at the surgical sites (not associated with the nasotracheal tube) using the VAS at 0.5, 1, 6, and 24 h postoperatively. In the recovery room, if the patients complained of a pain VAS >5 or requested analgesia, they were given intravenous fentanyl 50 μg and the dose was recorded. On the ward, if the patients needed analgesia, they were given an intramuscular injection of diclofenac sodium 75 mg; if they needed additional analgesia within the next 8 h, they were given fentanyl 50 μg i.v. and the dose was recorded.

2.2. Safety and patient satisfaction assessment

To assess safety, we also recorded side effects such as nausea, vomiting (or retching), sinus tachycardia (heart rate >100/min for >30 min), sweating, postoperative bleeding, and urticaria at 1 and 24 h postoperatively. The sedation level was evaluated 1 h after the operation: none (awake), mild (response to verbal commands), moderate (response to touch or painful stimuli), and severe (no response). We also evaluated the degree of patient satisfaction with postoperative analgesia using a VAS (0 = not at all satisfactory and 10 = maximum satisfaction) 24 h postoperatively.

2.3. Statistical analysis

The primary outcome was pain severity immediately after surgery. The sample size of 21 was calculated to detect a 20% decrease in the VAS score at the recovery room by nefopam use (two-sided test with a power of 80% and $\alpha = 0.05$, considering 10% dropouts) based on the preliminary data from 9 patients who underwent the same surgical procedures under the same anesthesia.

Data are presented as mean ± SD, median (interquartile range), or numbers (percentile) as appropriate. A Student *t*-test or Mann–Whitney *U*-test was used to compare continuous variables (demographic data, operation time, intraoperative dose of remifentanil, and VAS scores). A Bonferroni-corrected α level of 0.05/4 = 0.0125 was used for multiple comparison of the pain VAS scores. The χ^2 test or Fisher exact test was also used for categorical data such as the incidence of side effects. A *P*-value of <0.05 was considered statistically significant. Statistical analysis was done using the SPSS version18.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline and clinical characteristics of the patients

This study enrolled 42 patients in two groups of 21 patients each. Of these, one patient in the nefopam group was excluded because the study drug infusor broke 5 h postoperatively. The remaining patients all completed the study (Fig. 1). There were no significant differences between groups in regard to demographic data (e.g., sex, age, height, and weight), preoperative risk factors for PONV, operating time, and intraoperative amount of remifentanil

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