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Bilateral mandibular block improves pain relief and morphine consumption in mandibular osteotomies: a prospective, randomized, double-blind, placebo-controlled clinical trial

Marina Bertuit,¹ Francesca Rapido,¹ Habib Ly,¹ Charlotte Vannucci,¹ Jérôme Ridolfo,¹ Nicolas Molinari,² Marie De Boutray,³ Sophie Galmiche,³ Christophe Dadure,⁴ Pierre-François Perrigault,¹ Xavier Capdevila,⁵ Gérald Chanques^{1,6,7}

ABSTRACT

Background The sensory innervation of the lower jaw mainly depends on the third root of the trigeminal nerve, the mandibular nerve (V3). The aim of this single-center, prospective, randomized, double-blind, placebo-controlled study was to evaluate the effectiveness of bilateral V3 block for postoperative analgesia management in mandibular osteotomies.

Methods 107 patients undergoing mandibular surgery (75 scheduled osteotomies and 32 mandible fractures) were randomized in two groups. A bilateral V3 block was performed in each group, either with ropivacaine 0.75% (block group, n=50) or with a placebo (placebo group, n=57). A postoperative multimodal analgesia was equally provided to both groups. The primary outcome was the cumulative morphine consumption at 24 hours. Secondary outcomes were the occurrence of severe pain and the incidence of postoperative nausea and vomiting (PONV) in the first 24 hours. Data were analyzed on an intention-to-treat basis.

Results The cumulative morphine consumption at 24 hours was significantly lower in the block group (median 8.0 mg (IQR 2.0–21.3) vs 12.0 mg (IQR 8.0–22.0), $p=0.03$), as well as the incidence of severe pain during the 24 hours of follow-up (4.0% vs 22.8%, $p<0.01$). The mandibular block had no impact on the incidence of PONV.

Conclusion Bilateral V3 block for mandibular osteotomies is an effective opioid-sparing procedure. It provided better postoperative analgesia in the first 24 hours, and it did not affect PONV incidence.

Trial registration number NCT02618993.

INTRODUCTION

Mandible surgeries are frequently performed in orthognathic surgery to correct dentofacial deformities or in trauma to provide surgical repair of mandible fractures, which account for a significant portion of maxillofacial injuries.¹ These surgical procedures are typically severely painful, especially in the first 24 hours.^{2–8} Consequently, opioids are frequently used, increasing the incidence of postoperative nausea and vomiting (PONV), which has an unusually high prevalence among these patients.⁸

Despite that, pain management after mandibular surgery is a relatively unexplored field, and limited data are available on the use of regional anesthesia, especially concerning emergency surgery.^{9–14}

The sensory innervation of the jaw mainly depends on the mandibular nerve (V3) that is the third root of the fifth cranial nerve (trigeminal nerve), the only sensorimotor nerve of the face. V3 can be anesthetized by a percutaneous puncture.^{12–14–15} This transcutaneous technique is simple and easy to learn, with a high success rate when performed using a nerve stimulator.^{10–11}

The V3 bilateral block has been successfully adopted for providing optimal postoperative analgesia in oropharynx cancer surgery, and in this context, it significantly reduced morphine postoperative consumption at 12 and 24 hours.¹⁶ The use of the inferior alveolar nerve block, a mandibular nerve (V3) branch and the endo-oral V3 block¹⁷ also decreases the intraoperative morphine requirements during orthognathic surgeries and reduces the incidence of PONV.^{16–19} In a recent unstrictly blinded study on elective bimaxillary orthognathic surgery, maxillary and V3 block performed without the use of a nerve stimulator reduced postoperative pain, discomfort and consumption of analgesics.¹³ The use of an ultrasound-guided technique for the trigeminal nerve block has also been described.¹⁴ Despite these encouraging results, the use of locoregional analgesia remains limited, and the available studies focused on elective surgery.

Our study aimed to evaluate the efficacy and safety of nerve stimulator-guided bilateral V3 block for postoperative analgesia after mandibular surgeries. We tested the hypothesis that performing a V3 block before orthognathic surgery could reduce postoperative morphine consumption (primary outcome) and PONV, improving pain control in the first 24 hours after surgery.

METHODS

Trial design

This was a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study. The study was conducted at Gui de Chauliac Hospital, at the neuroscience department

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of the University Hospital of Montpellier (France), between 2 December 2015 and 30 July 2018.

Inclusion and exclusion criteria

All patients between 18 and 70 years old (between 15 and 70 from September 2016) undergoing mandibular surgery were eligible for study participation. The surgeries involved were elective orthognathic surgery (bilateral sagittal split ramus osteotomy (BSSRO), bimaxillary surgery (BIMAX, BSSRO associated with a LeFort I osteotomy) or traumatic mandibular fracture with planned surgery within 48 hours. Genioplasty or dental extractions could be performed in the same surgical procedure. Other inclusion criteria were American Society of Anesthesiologists (ASA) physical status classification between 1 and 3, and affiliation with the national social security system.

Pregnant women, patients with pre-existing infection at the block site or pre-existing neurological deficits, severe coagulopathy, allergy to local anesthetics, psychiatric disorders or patients unable to give their informed consent were excluded from the study.

Conduct of the study

The anesthetists screened the patients for inclusion/exclusion criteria, got their informed/written consent, enrolled and randomly allocated them into two parallel groups to receive either bilateral V3 block with 10 mL (5 mL right side+5 mL left side) of ropivacaine 0.75% (block group), or the V3 block performed with the same volume of isotonic saline (placebo group). The surgeon was informed about the research and provided the information to the anesthetist regarding the type of surgery expected to be performed.

The bilateral mandibular block was performed by a senior anesthetist or a supervised resident, in the operating room, just before the induction of general anesthesia (see online supplemental file). A sterile 25-Gauge needle (B. Braun, Melsungen, Germany) was connected to the nerve stimulator (Stimuplex, B. Braun). The needle was inserted perpendicular to the skin in the sigmoid fossa, a depression located below the zygomatic arch, between the coronoid apophysis and the condyloid process. A stimulation time of 0.1 ms, a frequency of 1 Hz and an adjustable stimulation intensity between 0.5 and 5.0 mA were used. The needle was advanced slowly until the pterygoid apophysis contact (around 20–30 mm), and it was then oriented with a 45°–60° angle. At about 40 mm of depth, masticator muscle contraction at low current intensity (0.5 mA) confirmed the V3 stimulation. After a negative blood aspiration test, 5 mL of the anesthetic solution was injected, slowly and fractionally. The same procedure was performed on the other side, following previous reports.^{12 14 15} In the BIMAXs, a block of the maxillary branch of the trigeminal nerve (V2) was performed bilaterally in both groups, according to the technique described by Stajcič and Todorovič.²⁰

For the patient's comfort, a mild-sedation to deep-sedation analgesia with remifentanyl target controlled infusion (TCI) (Primea Base, Minto model) was administered during the procedure in all patients. Depending on the patient's agitation and pain, the senior anesthetist could decide to realize the V3 block under general anesthesia.

The time required to perform the described block on each side and the total time were recorded for each patient.

Intraoperative management

The anesthesia induction was performed using a total intravenous anesthesia target controlled infusion technique with

propofol (Schnider model, target site effect 4–8 mcg/mL) and remifentanyl (Minto model, target site effect 4–6 ng/mL). No myorelaxant was administered during the surgery.

Maintenance of anesthesia was via sevoflurane (minimal alveolar concentration 0.8–1.2) and remifentanyl in TCI mode. No controlled arterial hypotension strategy was used in our department. The dose of remifentanyl and anesthetic agents were modified according to the anesthetist, based on hemodynamic changes. An antibiotic prophylaxis was administered according to the current guidelines for this type of surgery. All the patients received antiemetic prophylaxis with droperidol 1.25 mg and methylprednisolone 1 mg/kg intravenously (also used as an antioedematous prophylaxis), whatever their Apfel score or PONV history.

Pain management

A ketamine bolus (0.5 mg/kg) was administered at the anesthesia induction. Thirty minutes before the end of the surgery, all patients received a standard intraoperative analgesic therapy consisting of acetaminophen 1 g, nefopam 20 mg and ketoprofen 100 mg.

In the recovery room, intravenous administration of ondansetron 4 mg was used in case of PONV. The evaluation of pain was noted every 30 min after extubation using a Numerical Rating Scale (NRS),²¹ and intravenous morphine titration (intravenous boluses of 1–3 mg at an interval of 5–10 min, according to the age of the patient, the NRS value and the Richmond Agitation–Sedation Scale) was provided if the NRS score was higher than 3.

For the postoperative period, a multimodal analgesia was used with acetaminophen 1 g every 6 hours and ketoprofen 100 mg every 12 hours; nefopam 120 mg/24 hours (continuous intravenous infusion) was used in case of contraindication to anti-inflammatory drugs. An intravenous morphine patient-controlled analgesia (PCA) pump was prescribed in the two groups. PCA dosing regimen was identical for all patients: 1 mg intravenous bolus doses of morphine (with 0.05 mg of droperidol) 'on-demand', with a minimum lockout interval of 7 min and no continuous background morphine infusion.

Data collection

Morphine consumption (in milligram) was collected at the discharge from the recovery room and at 24 hours. The presence of PONV was evaluated and reported by nurses following standard practices.

The NRS score was evaluated every 30 min after extubation in the recovery room and every 4 hours by nurses in the ward. Any NRS score of >6 at any time in the first 24 hours was recorded and defined a severe pain episode.

Unmasking of the allocation group was ensured in the recovery room and ward by the fact that nurses working in these areas were not involved in the anesthesia procedure occurring in the operating room.

Primary and secondary outcomes

The primary outcome of the study was the total morphine consumption in the first 24 hours.

Secondary outcomes were the incidence of severe pain (max NRS score >6) and PONV during the first 24 hours after surgery.

Intraoperative bleeding was also evaluated. The amount of aspirated blood and the weight of the soaked gauzes were recorded. The surgeon was also required to give a subjective evaluation of the bleeding during the surgery using a scale from 0 to 10 (0: no bleeding, 10: major bleeding).

Sample size

Based on the expected variability of morphine consumption in a previous report on mandibular osteotomy¹⁹ (11.9 ± 9.2 mg) and considering a 50% decrease in morphine consumption as clinically significant,¹¹ a type 1 error of 0.05 and a type 2 error of 0.1, the number of patients required to detect this difference with 90% power under a bilateral hypothesis was 104. The number of subjects was increased to 108, to counterbalance a 2% of 24 hours of follow-up missing data and a planned *interim analysis* to adjust the sample size calculation accuracy, and to assess the efficacy or futility of the study, in the absence of published data (the use of the conservative Haybittle-Peto boundary ($p < 0.001$) allows the final analysis to be performed using an unchanged level of significance, $p = 0.05$). The analysis, performed after the enrollment of 54 patients, showed a prevalence of trauma surgery that was higher in one group, leading to adjust the following randomization process for stratification on the type of surgery.

Randomization

The randomization list was generated by the clinical research unit of the department of medical information. The anesthetist was in charge of the enrollment of the patient.

The group allocation was concealed in sealed opaque envelopes that were opened after the enrollment of the patient by an anesthesia nurse not involved in the patient's care. The same nurse was responsible for preparing the 10 mL syringes used for the V3 block. The syringes were unlabeled, indistinguishable in color, shape and smell for both groups. All medical and paramedic personnel in charge of the patient was blinded to the group allocation during the whole study. All blisters were kept for a systematic, independent research monitoring of enrollment/randomization process and data recording, by the direction of clinical research of the hospital, ensuring the research quality.

Statistical analysis

Data were analyzed on an intention-to-treat (ITT) basis. Variables are presented as means and SD, medians and IQR or frequency count as appropriate.

Data were tested for normal distribution using the Shapiro-Wilk test. Student's t-test and Wilcoxon-Mann-Whitney test were used to compare continuous parametric and non-parametric data, respectively. Frequencies and categorical data were compared using the Fisher's exact test or Pearson test as appropriate. Significance was defined at $p < 0.05$ (two-sided). Analyses were conducted using the SAS V.9.1 statistical package by the clinical research unit of the department of medical information (Montpellier University Hospital).

The statisticians were blinded to the allocation group for both interim and final analyses. Comparability between the two groups was verified for all the baseline characteristics that were likely to influence the outcomes. A linear regression model was used to analyze the association between the primary endpoint and several variables of interest. Variables with a p value of ≤ 0.15 were then retained to build a multivariate model. A stepwise regression procedure was used, and the choice of predictive variables was based on a p value of ≤ 0.05 .

RESULTS

During the study period, 272 patients were eligible for the study, 160 undergoing emergency surgery and 112 scheduled surgery. The study's flowchart is shown in figure 1. One hundred and eight patients met the inclusions criteria and were randomized.

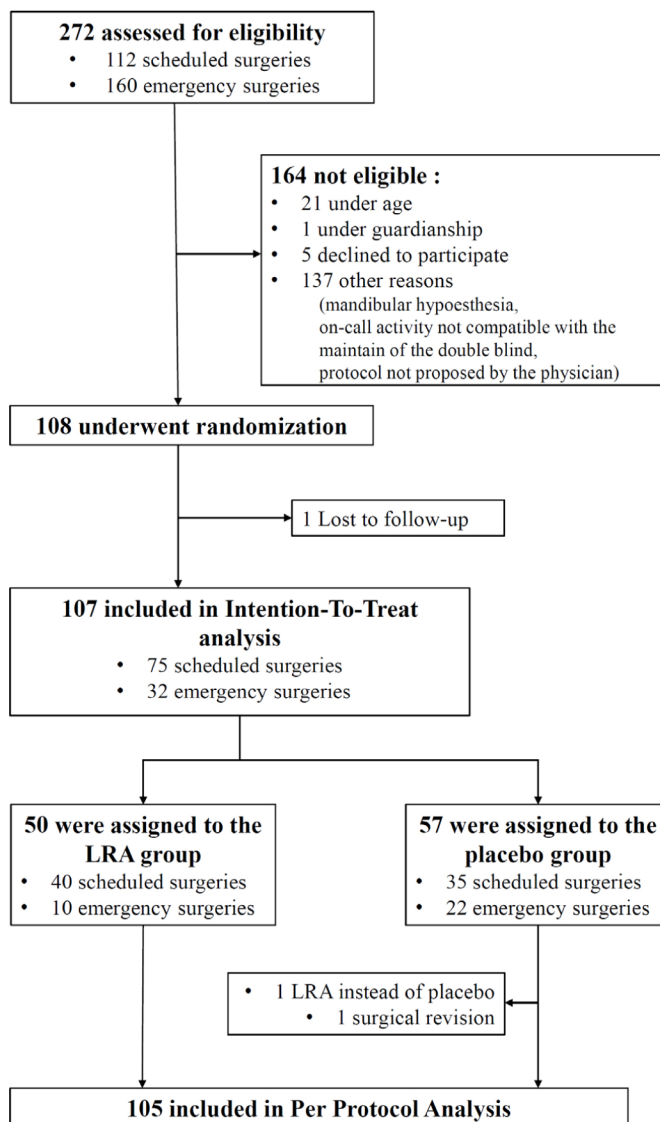


Figure 1 Consolidated Standards of Reporting Trials flow diagram of the study. LRA, locoregional anesthesia.

There was one patient lost to follow-up. In the placebo group, one patient received regional anesthesia instead of placebo treatment, and one patient was enrolled despite the presence of an exclusion criterion (surgical revision). These two errors were found during an independent research monitoring. The randomization error was made after the change of the randomization list after interim analysis (error of envelope). Both participants were included in the ITT analysis and excluded for the per protocol analysis. A total of 107 patients were analyzed on an ITT basis, 50 in the block group and 57 in the placebo group (figure 1).

Demographic and baseline characteristics of patients, including age, gender, Body Mass Index (BMI), ASA physical status, Apfel score,²² types of surgery and anxiolytic premedication used, are summarized in table 1. Scheduled versus emergency surgery was more significantly frequent in the block group ($n = 40$ vs $n = 35$, $p = 0.04$), and the Apfel score was also higher in that group ($2.50 (\pm 1.25)$ vs $1.81 (\pm 1.27)$, $p < 0.01$).

The technical characteristics of the mandibular block were comparable in both groups (table 2). There was no puncture failure. Four vascular punctures were identified by the aspiration test, leading to perform of a new puncture. No complication was identified.

| | Block group | Placebo group | P value |
|--|------------------|------------------|---------|
| Sample size, n | 50 | 57 | |
| Age (years), median (IQR) | 27.0 (19.0–36.0) | 26.0 (19.0–37.0) | 0.70 |
| BMI (kg/m ²), mean (SD) | 22.5 (±4.7) | 22.6 (±4.4) | 0.39 |
| Gender, n (%) | | | |
| Male | 21 (42.0) | 34 (59.7) | 0.07 |
| Female | 29 (58.0) | 23 (40.4) | |
| ASA physical status, n (%) | | | |
| 1 | 46 (92.0) | 47 (82.5) | 0.29 |
| 2 | 4 (8.0) | 8 (14.0) | |
| 3 | 0 (0.0) | 2 (3.5) | |
| Apfel score, mean (SD) | 2.5 (±1.2) | 1.8 (±1.3) | <0.01 |
| Anxiolytic premedication before the beginning of the anesthetic procedure, n (%) | | | |
| Alprazolam | 11 (22.0) | 16 (28.1) | 0.13 |
| Other | 29 (58.0) | 37 (64.9) | |
| No premedication | 10 (20.0) | 4 (7.0) | |
| Type of surgery | | | |
| Emergency surgery | 10 (20.0) | 22 (38.6) | 0.04 |
| Scheduled surgery | 40 (80.0) | 35 (61.4) | |
| Mandibular fracture repair | 10 (20.0) | 22 (38.6) | 0.10 |
| BSSRO, n (%) | 23 (46.0) | 22 (38.6) | |
| BIMAX, n (%) | 17 (34.0) | 13 (22.8) | |

Apfel score, simplified predictive risk score for PONV (includes female gender, history of PONV and/or motion sickness, non-smoking status and postoperative use of opioids)

BIMAX is BSSRO associated with a LeFort I osteotomy.

BIMAX, bimaxillary surgery; BMI, Body Mass Index; BSSRO, bilateral sagittal split ramus osteotomy; PONV, postoperative nausea and vomiting.

Primary outcome: 24-hour morphine consumption

Median morphine consumption at 24 hours was significantly lower in the mandibular block group (8.0 mg (2.0–21.3) vs 12.0 mg (8.0–22.0), $p=0.03$) (table 3).

Linear regression models were performed, as a sensitivity analysis, in order to analyze the association between the primary outcome and several variables of interest (ie, randomization group, type of surgery, gender, age, BMI, ASA physical status, Apfel score, remifentanyl consumption, presence of perioperative hypotension or hypertension, experience of the anesthesiologist who performed the mandibular block (resident vs senior), duration of surgery, blood loss, surgical evaluation of bleeding, needle depth during block and block procedure duration). The

| | Block group | Placebo group | P value |
|---|-------------|---------------|---------|
| Sample size, n | 50 | 57 | |
| Mandibular block performed by | | | |
| Resident, n (%) | 15 (30.0) | 19 (33.3) | 0.71 |
| Senior anesthesiologist, n (%) | 35 (70.0) | 38 (66.7) | |
| Nerve stimulation intensity (mA), mean (SD) | 0.4 (±0.2) | 0.5 (±0.3) | 0.24 |
| Right needle depth (cm), mean (SD) | 3.6 (±0.9) | 3.5 (±0.9) | 0.90 |
| Left needle depth (cm), mean (SD) | 3.6 (±0.8) | 3.6 (±1.0) | 0.88 |
| V3 execution time (min), mean (SD) | 6.7 (±4.4) | 6.0 (±3.8) | 0.38 |

V3, mandibular nerve.

primary outcome was not modified by the multivariate analysis, with the mandibular block being significantly and independently associated with a lower morphine consumption (estimation -6.5 ± 2.3 , $p < 0.01$), even after adjustment on scheduled osteotomies that were associated with a higher morphine consumption (estimation 10.5 ± 2.4 , $p < 0.0001$).

A per-protocol analysis was performed for the primary outcome (105 patients) and confirmed the results obtained with the ITT analysis (morphine consumption at 24 hours: 8.0 mg (2.0–21.3) in the block group vs 13.0 mg (8.0–23.0) in the placebo group, $p=0.02$).

Secondary outcomes: incidence of severe pain and PONV at 24 hours

The incidence of severe pain (NRS score > 6) during postoperative follow-up was significantly lower in the mandibular block group (4.0% vs 22.8%, $p < 0.01$) (table 3). A multivariate analysis showed that the placebo group was the only independent predictor of severe postoperative pain (OR 5.1, 95% CI 1.0 to 25.0, $p < 0.05$).

The incidence of PONV during the 24 hours of postoperative follow-up was significantly higher in the mandibular block group (46.0% vs 21.1%, $p < 0.01$) (table 3). Nevertheless, the univariate and multivariate analyses showed that PONV were mainly dependent on Apfel score (OR 1.8, 95% CI 1.1 to 3.1, $p=0.03$), while the block group had no significant impact on PONV after multivariate adjustment (OR 2.8, 95% CI 0.9 to 8.4, $p=0.07$).

No significant difference in postoperative bleeding or other adverse events was recorded (table 3).

DISCUSSION

In this prospective, randomized, double-blind, placebo-controlled study, a bilateral V3 block allowed opioids sparing and improved postoperative severe pain control in patients undergoing orthognathic surgery or mandibular fracture treatment.

The main finding of our study was a decrease in cumulative morphine consumption in the first postoperative 24 hours. These results correlate with two available randomized controlled studies, in which a maxillary and V3 block reduced postoperative pain, discomfort and consumption of analgesics.^{13 14} In our study however, we proposed a placebo group by the realization of the V3 block with isotonic saline and a real double-blind design in which no caregiver was aware of the patient's group. The use of a nerve stimulator allowed us to increase the accuracy and success rate of the regional block. Furthermore, a multimodal postoperative analgesia protocol was well defined and was used identically for all patients in both groups, including a morphine PCA pump. Finally, we also included emergency surgeries, which usually record higher demand for opioids.

Elective mandibular osteotomies were more frequently represented in the block group. This could be considered as a potential selection bias because this type of surgery was significantly associated with higher opioid requirements. Nevertheless, opioid requirements were significantly lower in the block group, and that group was associated with lower opioid requirements even after multivariate adjustment on the type of surgery. Thus, this potential bias should instead increase the strength of the results in favor of regional anesthesia. The incidence of severe pain, defined as an NRS score of > 6 , in the first 24 hours was also significantly decreased in the block group, confirming a better postoperative pain management with regional anesthesia. A multivariate analysis showed that the absence of regional

Table 3 Analysis of primary and secondary outcomes

| Sample size (n) | Block group | Placebo group | P value |
|---|--------------------------|--------------------------|-----------------|
| | 50 | 57 | |
| Primary outcome | | | |
| Total morphine consumption at 24 hours (mg), median (IQR) | 8.0 (2.0–21.3) | 12.0 (8.0–22.0) | 0.03 |
| Morphine titration in RR (mg), median (IQR) | 3.5 (0.0–7.0) | 5.0 (2.0–7.0) | 0.19 |
| Morphine from PCA, RR-24 hours (mg), median (IQR) | 5.0 (0.0–12.0) | 8.0 (3.00–14.0) | 0.05 |
| Intraoperative variables | | | |
| Remifentanyl consumption (µg), median (IQR) | 1278.5 (836.5–1795.5) | 1453.0 (877.0–2370.0) | 0.30 |
| Blood loss (mL), median (IQR) | 200.0 (100.0–400.0) | 175.00 (100.0–475.0) | 0.80 |
| Surgical evaluation of bleeding (pts), median (IQR) | 3.0 (2.0–5.0) | 3.0 (0.0–5.0) | 0.41 |
| Duration of surgery (min), median (IQR) | 110.5 (90.0–158.0) | 111.0 (73.0–176.0) | 0.86 |
| Postoperative variables—secondary outcomes | | | |
| PONV (RR), n (%) | 12 (24.0) | 15 (26.3) | 0.78 |
| PONV (ward to 24 hours of follow-up), n (%) | 23 (46.0) | 12 (21.1) | <0.01 |
| NRS>6 (RR), n % | 15 (30.0) | 26 (45.6) | 0.10 |
| NRS>6 (ward to 24 hours of follow-up), n % | 2 (4.0) | 13 (22.8) | <0.01 |
| Use of other analgesic drugs, n (%)* | | | |
| Acetaminophen | 49 (98.0) | 56 (100.0) | 0.47 |
| Ketoprofen | 37 (74.0) | 43 (76.8) | 0.74 |
| Nefopam | 9 (18.0) | 10 (17.8) | 0.98 |

Surgical evaluation of bleeding: the surgeon was asked to subjectively evaluate the bleeding at the end of the procedure using a scale of 1 (no bleeding) to 10 (excessive bleeding). *Data were obtained for 56 out of the 57 patients enrolled in the placebo group.

NRS, Numerical Rating Scale; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting; pts, points; RR, recovery room.

anesthesia was the only predictive factor for the occurrence of severe pain in the postoperative period.

As a secondary outcome, we chose to analyze the postoperative incidence of nausea and vomiting. Postoperative nausea and vomiting are particularly frequent in mandibular surgery, with a recorded incidence within the first 24 hours of 27% and 67%, respectively.^{23–24} Chatellier and colleagues¹⁹ showed its significant reduction (from 42.9% to 6.3%) after mandibular osteotomies when lower alveolar nerve block alone is performed. In our study, PONV occurrence was higher during the postoperative 24 hours in the block group. However, the baseline Apfel score was also higher in this group, and PONV were not significantly associated with the block group after multivariate adjustment on the Apfel score.

Intraoperative bleeding was also evaluated in our study, as mentioned before. Espitalier and colleagues¹⁵ described a decrease in intraoperative bleeding after V3 block with ropivacaine in 38 mandibular osteotomies. This result was explained by a reduced response of the autonomic nervous system to the surgical stress and the local vasoconstrictive properties of ropivacaine.^{25–26} In our study, we did not find a significant decrease in blood loss in the block group. However, the non-comparability of the groups on the type of surgery prevents us from being conclusive about surgical bleeding.

V3 block can be performed quickly. In our study, it took a maximum of 6 min to perform it on both sides. The anatomical markers are easy to locate, and the use of a nerve stimulator optimizes the V3 detection, reducing the risk of maxillary artery puncture and increasing the rate of success of this percutaneous technique.²⁷ The use of ultrasound to guide the procedure is seldom described.^{12–28} Only four vascular punctures (3.7%) were observed in the present study without relevant complication. No other complication has been reported.

Study limitations

There are several limitations to our study. First, it is a single-center study, including a limited number of patients. More extensive multicenter studies are needed to measure the feasibility, safety and effectiveness of this procedure technique.

Second, the study was designed based on literature about orthognathic surgery. Given the influence of the type of surgery on the evaluated outcomes, other studies should be performed to assess the clinical interest of V3 block based on each surgery subgroup (scheduled vs emergency surgery). Because no published data about the performing of this procedure in non-cancer orthognathic surgery existed, we performed an interim analysis that revealed a disequilibrium in the randomization of patients regarding the type of surgery. After consultation with the ethics committee by the statistics department, it was decided to modify the randomization process, including a stratification on the type of surgery to limit the disequilibrium. For that reason, the number of subjects in each group is unequal. Moreover, a multivariate analysis adjusted for the type of surgery and other relevant parameters was performed to confirm the results.

Third, a V2 bilateral block was systematically performed in case of BIMAX to highlight a difference in analgesia exclusively related to the V3 territory. However, the effectiveness of this block cannot be guaranteed. The exclusively sensitive nature of this nerve prevents using the nerve stimulator to confirm the correct position of the needle, unless using the lesser known and described technique based on paresthesias evocation through electrical stimulation. The ultrasound-guided V2 block has been well described in children,²⁹ but this approach has not yet been validated in adults.

Fourth, no formal anesthesia protocol was used to adapt anesthetics and remifentanyl. This could explain the absence

of significant between group difference regarding anesthetic agents or remifentanyl consumption. The preoperative use of a processed electroencephalographic monitoring and an analgesia monitoring (eg, videopupillometry and heart rate variation analysis) could have helped in reducing the dose of anesthetics and opioids during the surgery.

Finally, we did not systematically collect data regarding the patient's satisfaction. This point should be considered for a next study, since it is essential to combine analgesic management and patients' experience and satisfaction.

CONCLUSION

The bilateral V3 block is an efficient regional anesthesia technique in mandibular surgery. It significantly decreases the use of opioids and limits the occurrence of severe postoperative pain in the first 24 hours after mandibular surgery, especially in the case of elective osteotomies, the most painful surgeries.

No difference in the incidence of PONV or intraoperative bleeding could be demonstrated.

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Contributors MB, GC and P-FP designed and led the clinical trial. MB, FR, HL, JR, MDB and SG assisted with patient's enrollment and data collection. NM, CV, CD and GC assisted with the design of the experiments. NM analyzed the clinical data. FR, GC, CD and XC drafted the first version of the manuscript. All authors edited the manuscript.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study protocol was approved by the South Mediterranean Ethics Committee I (Comité de Protection des Personnes Sud Méditerranée I, 13 May 2015, 2015-001345-88, Marseille, France), registered with ClinicalTrials.gov (first submitted 3 November 2015) and conducted according to good clinical practice guidelines, the Declaration of Helsinki (2008) and European Directive 2001/20/CE. The ethics committee was consulted for enrolling younger patients up to 15 years old, which was authorized as from September 2016. Written and oral informed consent was obtained from all subjects before their inclusion in the study, as well as at least one legal representative for minors.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Our database can be available after request and approval of the local ethic committee.

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