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Title: Effects of ultrasound-guided maxillary nerve block performed after bimaxillary osteotomy in adult patients

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1. SUMMARY

Bimaxillary osteotomy is a surgery procedure of the orthognathic surgery field for correction of dental and facial abnormalities, for both functional and aesthetic cases. The incidence of this abnormality is 5-10% of the population, and the etiology is unknown, with genetic, environmental and embryonic factors related. The surgery technic is complex, and requires osteotomy of the maxilla and jaw, which allows toward, forward, impact and rotation of these bones to fix the edges of the face. The anesthetic management of these patients is a challenge because of the difficult airway management and the perioperative pain control. Multimodal approach for pain control is a fact, and the use of local and regional anesthesia is mandatory. We propose bilateral ultrasound-guided suprazigomatic maxillary nerve block after bimaxillary osteotomy for a proper control of postoperative pain.

2. INTRODUCTION

Bimaxillary osteotomy is a surgical procedure in the field of orthognathic surgery (from Latin; "orthos" rectum and "gnathos" mandible) for the correction of dentofacial deformities, both for functional and aesthetic reasons. The incidence of this deformity is estimated to be in the order of 5-10% of the population; and its origin is still unknown, and genetic, environmental and embryonic factors are postulated. The surgical technique is complex, with the performance of mandibular and upper jaw osteotomies that allow these bones to be advanced, retracted, impacted and rotated, to align the facial axes. For all these reasons, the anesthetic management of these patients is a challenge. First, the foreseeable difficulty of managing the patient's airway; and second, the control of the patient's pain in the perioperative period.

Therefore, we say that bimaxillary osteotomy is a frequent and potentially painful surgery in adults. Bimaxillary surgery under general anesthesia is common practice. And isolated non-ultrasound-guided peripheral nerve blocks and surgical field infiltration are widely used practices by surgeons. These minor blockages and infiltrations are used to avoid the unwanted effects of anesthetics and analgesics; particularly the adverse respiratory effects of opioids. The practice of loco-regional anesthesia therefore provides perioperative pain control

in a multimodal way, showing effective postoperative analgesia and minimizing respiratory depression due to excessive use of opioids.

The introduction of loco-regional nerve blocks in the last three decades has meant a revolution in the management and control of perioperative pain for the anesthesiologist. The expansion of the practice of loco-regional nerve blocks has been seen in both the upper and lower limbs, as well as the trunk and abdomen. Conversely, facial blocks, superficial and deep, have not experienced the same; relegating its practice to the surgeon, or to the anesthesiologist who works in the field of chronic pain. The subsequent introduction of ultrasonography (USG) in the 1990s in the perioperative period was also an important advance for the anesthesiologist, both in terms of safety and in terms of ease of handling catheterizations of the venous and arterial lines, and the practice of loco-regional blocks.

Consequently, anesthesiologists already experienced at the USG have recently published on the use of ultrasound (US) for facial nerve block in children and adults undergoing maxillofacial surgery. USG devices are becoming more accessible, more portable, cheaper, and more secure; And therefore, its introduction in the field of perioperative pain management of maxillofacial surgery still has a long way to go.

The maxillary nerve, like the ophthalmic nerve, is only sensory. It is detached from the anterolateral border of the trigeminal ganglion, laterally to the ophthalmic. From its origin, it heads anteriorly, traverses the foramen round, and penetrates the background of the infratemporal fossa until it enters the pterygopalatine fossa (except for the middle meningeal nerve, all its branches reach the pterygopalatine fossa before reaching the facies). In the pterygopalatine fossa, the maxillary nerve is located at the top of the cavity and passes superiorly to the maxillary artery and superolaterally to the pterygopalatine ganglion. The maxillary nerve receives and conducts through its endings the sensitivity of the skin of the cheek, lower eyelid, wing of the nose and upper lip. Its deep branches conduct the sensitivity of the mucosa of the lower part of the nasal cavities or respiratory area, of the tooth roots and of the gums of the maxilla.

Therefore, in order to produce an effective anesthesia of the maxillary area, we can introduce the needle through the pterygomaxillary fissure to the pterygopalatine fossa, with the risk of vascular and nerve puncture. But with the real-time view of ultrasound-guided block, these risks will be limited, allowing direct localization of the maxillary artery, needle position, and distribution of the LA within the pterygopalatine fossa. The pterygopalatine fossa is anatomically deep and surrounded by bones. The most optimal ultrasound window is the infrazygomatic pathway, allowing visualization of the entire axis of the pterygopalatine fossa up to the foramen round.

To carry out the maxillary nerve block, several approaches have been described. However, placing the ultrasound probe in an infrazygomatic position, and introducing the needle by suprazygomatic route from the frontozygomatic angle is one of the safest and most recommended routes to reach the round foramen. This trajectory limits the insertion of the needle into the anterior portion of the foramen round, thus preventing inadvertent puncture of the intraorbital contents through the infraorbital fissure.

In general, in bimaxillary surgery it is the surgeon who performs the infiltrations with local anesthetic (AL) in a pre-incisional way to block the terminal branches of the maxillary nerve intraorally and intranasally. The choice of LA is influenced by considerations such as onset of action, duration, and toxicity. A wide range of LA have been used in maxillofacial surgery, such as lidocaine and bupivacaine, among others. The two LAs produce a reversible blockade of the sodium channel of the neuronal membrane, and are synthetic derivatives of cocaine. Both have three essential functional units (hydrophilic tertiary amide chain, linked by an intermediate amide chain to another lipophilic aromatic ring-portion). That is, they are both AL of the amide type; but even though they belong to the same group of LA, there are great differences in terms of initiation of action, duration of action and toxicity. Lidocaine has a faster onset of action (short latency) than bupivacaine, and has an antiarrhythmic effect. Bupivacaine is more

potent and has a longer duration of action than lidocaine, although more cardiotoxic than other AL teams such as ropivacaine.

To date, the gold standard anesthetic technique has not been described, nor is the ideal time to perform it in patients who have undergone bimaxillary osteotomy surgery. We now propose the performance of bilateral ultrasound-guided maxillary nerve block by suprazygomatic route with bupivacaine after bimaxillary osteotomy surgery for greater control of postoperative pain. In this way, we aim to maintain the pre-incisional infiltration of LA with lidocaine plus bupivacaine and adrenaline in the surgical field performed by the surgeon with its well-known benefits and to perform the ultrasound-guided block of the maxillary nerve with bupivacaine after surgery, before extubation to prolong its effect even more in the immediate postoperative period.

We use a combination of LA (lidocaine and bupivacaine) for pre-incisional infiltration of the surgical field. The combination of several local anesthetics in the same nerve block is sometimes used in perioperative anesthesia with the intention of compensating for the short duration of action of some agents with a rapid onset of action, such as lidocaine, and the high latency of agents with a longer action, such as bupivacaine. The combination of lidocaine and bupivacaine offers clinical advantages (rapid onset, long duration). This is a widespread practice among professionals in maxillofacial surgery. It is also a way to avoid the use of maximum doses of these LAs.

By performing the bilateral ultrasound-guided maxillary nerve block with bupivacaine after the surgical incision, we were able to extend the effect of the nerve block for greater control of postoperative pain. Postoperative pain control is a key factor in achieving greater patient satisfaction, better rehabilitation and shorter hospital stays. Current clinical guidelines recommend the management of postoperative pain control in a multimodal manner; and this includes the use of LA for infiltration of the surgical field and the performance of peripheral nerve blocks.

To date, studies describing maxillary nerve block prior to surgeries of the middle third of the face (orthognathic surgery, cleft palate, trauma) have been described; However, there are no studies of the practice of maxillary nerve block at the end of surgery, prior to extubation. If we assume that the patient receives general anesthesia (with their respective analgesics in the form of opioids, anti-inflammatories, paracetamol and other adjuvants) together with the infiltration of LA from the surgical field before starting surgery, and that this implies sufficient intraoperative analgesic coverage, we propose with this study that we could postpone the maxillary nerve block at the end of surgery. for a greater long-term benefit of the patient in the immediate postoperative period.

3. HYPOTHESIS

- H0: Patients who receive surgical field infiltration and ultrasound-guided maxillary nerve block prior to surgery have better postoperative pain control.
- H1: Patients who receive surgical field infiltration before surgery and ultrasound-guided maxillary nerve block after surgery have less postoperative pain.

4. OBJECTIVES

The main objective of the study is the evaluation of the effectiveness of bilateral maxillary nerve block guided by ultrasound via the suprazygomatic route with bupivacaine performed at the end of surgery, compared with performing the same block before starting surgery, on the control of postoperative pain in patients undergoing elective bimaxillary osteotomy, evaluated using the visual analog pain scale in the immediate postoperative period

(2 hours postoperative).
Secondary objectives of the study include: the comparison of pain at 4 hours, 8 hours and up to 18 hours after surgery, the comparison of the use of rescue opioids (milligrams of methadone) in the immediate postoperative period in resuscitation ward (milligrams of intravenous methadone at 2 hours postoperative) and in the hospitalization ward (milligrams of subcutaneous methadone from 2 to 18 hours postoperative), the comparison of the incidence of immediate postoperative nausea and vomiting (PONV) in resuscitation ward (2 hours postoperative) and up to 18 hours after surgery and the comparison of the time until oral tolerance begins after completing surgery.

5. MATERIALS and METHODS

Study dessign

The researchers propose a double-blind (patient and nurse) prospective comparative experimental study. After the approval of the ethical committee of our hospital center and the informed consent signed by each of the patients included in the study, the patients will be scheduled for bimaxillary osteotomy and will be assigned consecutively and prospectively to one of the two groups with a plan to register up to 50 patients. A 1:1 randomization table for patient allocation will be generated by a statistician who will not otherwise be involved in the study. Immediately upon the patient's arrival to the operating room, the research anesthesiologist will open a sealed, sequentially numbered opaque envelope containing the patient's assignment (block before surgery or block after surgery). Only anesthesiologists and operating room surgeons will not be blinded to patient assignment. This will be a double-blind study (patient and nurse). Patients will be unaware of the group they have been consecutively assigned to; and both the postoperative resuscitation nurses and the hospitalization ward nurses who will record VAS, analgesic consumption, onset of oral tolerance, PONV and postoperative complications, will also be unaware of the analgesic treatment that the patient has received in the operating room**.**

- Control group: patients undergoing elective bimaxillary osteotomy who receive ultrasound-guided maxillary nerve block before surgery.
- Study group: patients undergoing elective bimaxillary osteotomy who receive ultrasound-guided maxillary nerve block at the end of surgery.

Population

The source and mechanism of subject selection is a convenience sample, with consecutive recruitment in our clinical care setting at the Maxillofacial Institute of Teknon Medical Center.

The criteria for subject selection are as follows. The inclusion criterion is patients undergoing scheduled bimaxillary surgery. The exclusion criteria are: refusal to participate in the study, patients scheduled for bimaxillary surgery together with another complementary surgical procedure (such as rhinoplasty, blepharoplasty), age < 18 years, reinterventions, urgent surgeries, allergies to local anesthetics, allergies to anti-inflammatories, allergies to opioids, ASA ≥3.

Intervention

Patients will be received in the surgical area and a venous access line will be placed through which premedication (Midazolam 2mg/ev) and antibiotic prophylaxis (amoxicillin-clavulanate 2g/ev or Clindamycin 900mg/ev + Gentamicin 240mg/ev) will be administered. ev in patients allergic to beta-lactams). In the operating room they will be

monitored (SpO2, electrocardiogram, non-invasive blood pressure, Bispectral index, Train of four TOF – CUFF neuromuscular monitor) and intravenous general anesthesia will be performed (fentanyl 2mcg/kg/ev, propofol 2mg/kg/ev, rocuronium 0.6mg/kg/ev) and balanced anesthetic maintenance (sevoflurane CAM 1.2 and remifentanil TCI effective concentration 2ng/ml). After nasal intubation of the patient, the following will be carried out:

- Control Group: the anesthesiologist will proceed to bilaterally block the maxillary nerve under ultrasound guidance via the suprazygomatic route with bupivacaine before starting surgery.
- Study Group: the surgery will proceed, and at the end of this, the anesthesiologist will proceed with the bilateral block of the maxillary nerve guided by ultrasound via the suprazygomatic route with bupivacaine.

PHARMACOLOGICAL TREATMENTS

- Control group: Bilateral ultrasound-guided maxillary nerve block via post-intubation and pre-incisional suprazygomatic route with 5ml of bupivacaine performed by the anesthesiologist.
- Study group: Bilateral ultrasound-guided maxillary nerve block via suprazygomatic route post-intervention and pre-extubation performed by the anesthesiologist.

Prior to the surgical incision, all patients will be administered methadone 2mg/ev again and the traget-controlled infusion (TCI) infusion of remifentanil will be initiated in an effective concentration of 2mcg/ml. And as adjuvant therapy it will be administered to all patients, as long as there is no contraindication, intraoperatively corticotherapy (methylprednisolone 15mg/kg/ev), antifibrinolytic (tranexamic acid 15mg/kg/ev), gastric protection (pantoprazole 40mg/ev) , antiemetic (ondansetron 4mg/ev, haloperidol 2mg/ev) and analgesics (paracetamol 1g/ev, dexketoprofen 50mg/ev, diclofenac 75mg/im) and ketamine in subanesthetic doses (ketamine 20mg/ev in induction and ketamine 40mg/ev administration slow intraoperatively).

Volume-controlled mechanical ventilation (6ml/kg) will be adjusted to maintain a CO2 at the end of expiration around 32-38mmHg. Intraoperatively, in cases of changes in baseline BP equal to or greater than 20%, remifentanil will be increased/reduced in TCI 0.2mcg/ml. If the increases in BP last more than 5 minutes, a bolus of remifentanil 2 mcg/ev will be administered. If the decreases in BP exceed decreases of 60mmHg in Mean Blood Pressure (<60MAP), Ephedrine 6mg/ev will be administered.

Patients will be extubated in the operating room after removal of pharyngeal packing, gastric aspiration and reversal of neuromuscular relaxation and recovery of protective airway reflexes.

In the postoperative period, a VAS value greater than 3 will be considered insufficient pain control and rescue analgesia will be administered (opioid methadone 2mg/IV in resuscitation or methadone 5mg/SC in the hospital ward).

Definition of variables

- demographic data: age (years), sex (male/female)
- anthropometric data: weight (kg), height (cm)
- comorbidities: free text
- ASA: 1-3
- Temporal structure of evaluations:
    - Postoperative pain measured with the Visual Analog Scale (VAS 0-10):

at 2, 4, 8 and 18 hours postoperatively.

- Total dose of intravenous opioids-methadone in the immediate postoperative period (mg) in resuscitation (2h postoperative) and in the hospitalization ward (18h postoperative).
- Presence of PONV at 2, 4, 8 and up to 18 hours postoperatively.

- Time from leaving the operating room to the beginning of oral tolerance (hours)
- Complications derived from the administration of AL
  - Complications derived from bilateral maxillary nerve block guided by suprazygomatic ultrasound with bupivacaine.

Data collection:

The collection of data from the patients' medical history in the preanesthetic consultation (Office 60, Teknon Medical Center), visualization of pain records, medical prescriptions and oral tolerance (Casiopea C3), will depend on the main researchers (Molins Ballabriga G ; Valls Ontañon A), as well as the secondary researchers (Hernández Alfaro F; Durán Vallés F). To ensure privacy standards, the medical record number will be used to identify patients.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

The sample selection method provides for the consecutive assignment of patients to two groups:

1. Control group: maxillary nerve block before surgery
2. Test group: maxillary nerve block after surgery

The degree of pain is evaluated using a visual analogue scale (VAS) at different times after surgery: 2, 4, 8 and 18 hours. To estimate the necessary sample size, ***the pain measurement 2 hours later*** will be considered as the primary response.

The sample size will depend directly on the minimum clinically relevant difference between the average 2-h pain level of both groups.
It is assumed that the response variable will follow a normal distribution and the independent samples t test will be used. Otherwise, the alternative non-parametric Mann-Whitney test will be used.

The following table provides sample sizes for different minimum difference values:

Table 1.- Total sample size necessary to differentiate the mean degree of pain and statistical power, assuming a standard deviation ± 0.85* for a 95% confidence level and an independent samples t test.

Minimum difference to detect on Visual Analogue Scale	Effect size (d)	**Power achieved**		
		70%	**80%**	**90%**
0,20	**0,23 (small)**	448	570	762

0,45	**0,53 (medium)**	92	114	152
0,75	**0,82 (large)**	40	50	64

**A standard deviation ± 0.85 has been used, based on information from the reference articles. For example, Göçmen reports a mean VAS value at 2h equal to 6.6 ± 0.84 in a group with mandibular nerve block. Similarly, Cuvillon reports in some groups of local anesthetics at 12h a range (0-4) for the interval between 5th and 95th percentiles, compatible with a standard deviation around ±1, that is, of a similar order to that of the other author.*

Interpretation of the table:

For example, assume an average VAS pain level at 2 hours equal to 5 and in the other group 5.75. This difference, assuming a deviation ± 0.85, is equivalent to an effect size d=0.82, which is considered a large magnitude. If for the researcher a 0.75 point difference in pain is already relevant, a total of 50 patients (25 per group) are necessary to detect the difference as significant with a power of 80%.

Note that the minimum relevant differences considered are not very high, because the authors Göçmen and Cuvillon describe very similar mean VAS values between the different groups with which they work. They did not reach statistical significance, partly also because the sample size per group was not high (n=20).

Regarding the future statistical methodology to be used, it is also planned to use a non-parametric Brunner-Langer model for longitudinal data (equivalent to the classic ANOVA), in order to compare the groups in terms of general pattern of evolution. This model contrasts the hypothesis of homogeneity of the evolution of the degree of pain, and not only the comparison at a specific time-point.

7. LIMITATIONS

The use of LA with a vasoconstrictor (Adrenaline) in pre-incisional infiltrations performed by the surgeon provides the following advantages: prolongs the duration of anesthesia, reduces systemic toxicity by decreasing the proportion of LA that is absorbed into the bloodstream, It increases the intensity of the blockade through direct alpha agonist effects on the antinociceptive neurons of the spinal cord, provides local vasoconstriction and decreases bleeding in the surgical field, and assists us in the detection of accidental intravascular injection. For all these reasons, we propose in both groups (control and test) to continue asking the surgeon to perform infiltrations of lidocaine, bupivacaine and adrenaline in the same places where he performs the peripheral block of the maxillary nerve so that they provide vasoconstriction and dissection of the field. necessary surgical.

In the case of bimaxillary osteotomy surgery, the nerves involved are both the maxillary nerve and the mandibular nerve. It is reasonable to think that it would be necessary to perform both ultrasound-guided blocks of the maxillary and mandibular nerves for optimal pain control. But we do not perform mandibular nerve block because there is a lack of studies on cadavers and more conclusive clinical studies in the medical literature to know the most efficient and safest approach.

8. ETHICS

All information will be provided to the patient before making the decision to participate or not in the study.

The information is based on the elements included in the Declaration of Helsinki guidelines (updated version at the 64th General Assembly, Fortaleza, Brazil, October 2013).and GCP ICH Guidelines.
The researcher will describe to the patient all the measures that will be carried out for the protection of the patient's data and privacy in accordance with European Directive 95/46 EC - European Data Protection Regulation (EU) 2016/679 and the Law Organic 3/2018, of December 5, on Protection of Personal Data and guarantee of digital rights.
The researcher must explain to the patient the limitations and risks of the study and the possibility of interrupting their participation in any of the stages of the study without affecting the relationship with the researcher and/or healthcare personnel.
The information sheet and informed consent will be provided to the patient along with a verbal explanation. The patient must accept and sign before starting any procedure related to the study.

9. FINANCIAL REPORT

This study is not subject to additional costs, since all the necessary data, software and anesthetic-surgical techniques are used in routine daily clinical practice, and no additional procedures are introduced.

Disclosure of financial information

- The researchers state that there is no financial transaction involved in the study.
- The authors declare not to have any interest conflicts.

10. EXPECTED RESULTS

LA infiltration into the terminal branches of the maxillary nerve is common practice for bimaxillary osteotomy surgery, along with the administration of intravenous opioids for perioperative pain control. All of this has been seen to increase nausea and vomiting, resulting in greater patient dissatisfaction and longer hospital stay. Therefore, recently, ultrasound-guided maxillary nerve block has been introduced. It is an efficient and safe technique for perioperative pain control. The studies so far in the medical literature are with maxillary nerve blocks performed before midface surgeries. We now propose maxillary nerve block at the end of surgery, hoping to reduce postoperative pain and consequently also reduce postoperative opioid doses, increasing patient safety and satisfaction, along with decreasing PONV; as well as accelerating oral tolerance in the postoperative period and hospital discharge, with reduced costs and greater effectiveness for the hospital entity as a whole.
The choice of LA (bupivacaine) reflects the balance between the rapidity of onset of action and the desire for a prolonged duration of postoperative analgesia. Since maxillofacial procedures produce significant postoperative pain, the use of long-acting LAs will be a recommendation.

11. CRONOGRAMA

- January-June 2024: Study design, writing of the study protocol and presentation of the protocol to the Ethics Committee at the Teknon Medical Center in Barcelona.
- June-July 2024: Patient recruitment and review of patient medical records to obtain relevant clinical data (study variables).
- July 2024: Review of data obtained. Statistic analysis.
- July-August 2024: Final evaluation and conclusions of the study. Drafting of the

manuscript. Publication in a high-impact scientific journal.

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