

COVER PAGE STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN:

OFFICIAL TITLE:

Does it worth to reinforce with additional anesthesia to improve postoperative course after orthognathic surgery?

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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 anesthesia is mandatory. The investigators propose the infiltration of local anesthesia in two different times, first pre-incision and second before awaking the patient, for a proper control of postoperative pain.

INTRODUCTION

Bimaxillary osteotomy is a surgical procedure in the field of orthognathic surgery (from Latin, "orthos" straight and "gnathos" jaw) for the correction of dentofacial deformities, both for functional and aesthetic reasons. The incidence of this deformity is estimated to be around the 5-10% of the population. Genetic, environmental and embryonic factors are postulated to be the origin of such deformity, though its origin is still unknown. The surgical technique is complex, with the performance of mandibular and upper jaw osteotomies that allow to advance, retrude, impact and rotate these bones, 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, bimaxillary osteotomy is a frequent surgery and potentially painful in adults. Bimaxillary surgery under general anesthesia is the common practice. And peripheral non-ultrasound-guided peripheral nerve blocks are widely used by surgeons. These minor blockades are used to avoid the undesired effects of anesthetics and analgesics; mainly the adverse respiratory effects of opioids. The practice of loco-regional anesthesia provides a control of perioperative pain in a multimodal way showing effective postoperative analgesia and minimizing the respiratory depression caused by the excess use of opioids.

In general, during bimaxillary surgery the surgeon performs the infiltrations with local anesthetic (LA) in a pre-incisional manner for the blockade of the terminal branches of the maxillary and mandibular nerve intranasally and intraorally. The choice of LA is influenced by considerations such as the start of action, duration and toxicity. A wide range of LA has been used in maxillofacial surgery, such as lidocaine and ropivacaine among others. Both LA produce a reversible blockade of the sodium channel of the neuronal membrane, and are synthetic derivatives of cocaine. Both possess three essential functional units (hydrophilic tertiary amide chain, linked by an intermediate amide chain, to another lipophilic aromatic ring-portion). This means, both LA are amide type; but even if they belong to the same group of LA there is still great differences in the beginning of action, duration of action and toxicity. Lidocaine has a faster start of action (short latency) than ropivacaine, and has an antiarrhythmic effect. Ropivacaine is more potent, the action last longer than lidocaine, has vasoconstrictor effect by itself and is less cardiotoxic than other equipotent LA such as bupivacaine and levobupivacaine.

The investigators avoid the use of a combination of LA for maxillary and mandibular nerve block. The combination of several local anesthetics in the same nerve block is sometimes used in perioperative anesthesia with the intention of compensating the short duration of action of some agents whose start of action is fast, such as lidocaine, and the high latency of the agents that present a more lasting action, such as ropivacaine. The combination of lidocaine and ropivacaine offers clinical advantages (rapid onset, long duration). However, to date, indications for combining LA are scarce because of the use of catheters in many forms of regional anesthesia that allow to prolong

the duration of the block. This is nevertheless not an extended practice among anesthesiologists in maxillofacial surgery. On the other hand, it is important to also remember avoiding the use of maximum doses of two LA combined, which is based on the erroneous belief that their toxicities are independent; on the contrary, the toxicities have an additive character.

Multiple drugs have been used to increase the time of action of LA, such as adrenaline, clonidine, dexamethasone, ketamine and dexmedetomidine, among others. In our patients, adrenaline is always administered along with physiological serum pre-incision by the surgeon at the local level to improve the surgical field. The use of clonidine is ruled out because it is not supplied in the hospital center where the researchers will carry out the study. The use of dexamethasone and ketamine is ruled out, because they will be administered intravenously in the patient's perioperative period as anti-inflammatory agents and anesthetic adjuvant, respectively. And the use of dexmedetomidine is also ruled out in order to prolong the effect of the nerve blockade as this indication is not in the technical file.

Thus, the investigators propose to use firstly lidocaine and adrenaline pre-incision (antiarrhythmic effect and short duration of action). And secondly, they propose to use ropivacaine without adjuvant before extubation (vasoconstrictor effect and longer duration of action).

The control of postoperative pain is a primary factor to achieve greater patient satisfaction, better rehabilitation and shorter hospital stay. The current clinical guidelines recommend the management of postoperative pain control in a multimodal manner; and this includes the use of local anesthetics.

HYPOTHESIS

Hypothesis tests:

- H0: Patients who receive LA infiltration in two stages (pre-incision with lidocaine+adrenaline and pre-extubation with ropivacaine) do not have less postoperative pain.
- H1: Patients who receive AL infiltration in two stages (preincisional with lidocaine+adrenaline and pre-extubation with ropivacaine) have less postoperative pain.

OBJECTIVES

The main objective of the study is the evaluation of the effect of a peripheral preincisional minor nerve block with the use of a single local anesthetic (lidocaine), compared with the same nerve block in two times with different local anesthetics (lidocaine-preincisional and ropivacaine-pre-extubation), on the postoperative pain of patients undergoing elective bimaxillary osteotomy, evaluated by means of the visual analogue scale (VAS) of pain in the immediate postoperative period (2 hours postoperatively). The secondary objectives of the study are: the comparison of pain at 4, 8 and up to 18 hours after surgery, the comparison of the opioid use of rescue (intravenous methadone milligrams) in the postoperative period of bimaxillary osteotomy in the two groups of patients in the immediate postoperative period in resuscitation (2 hours postoperatively) and in the hospitalization floor (18 hours postoperatively), comparing the incidence of postoperative nausea and vomiting (PONV) in the immediate postoperative period in resuscitation (2 hours postoperatively) and up to 18 hours after the surgery in the two groups of patients, and the registry of complications derived from the two infiltrations.

MATERIAL AND METHODS

Study design

The investigators propose a double-blinded prospective comparative experimental study (patient and nurse). After the approval of the ethics committee of our hospital and the signed consent from each of the patients in the study, patients will be scheduled for bimaxillary osteotomy and will be randomly and prospectively assigned to one of the two groups with a plan to register up to 52 patients. Patients will not know the group that they have been assigned consecutively; and both the postoperative resuscitation nurses and the hospitalization nurses who will perform VAS records, opioid consumption, PONV and postoperative complications, will also be unaware of the analgesic treatment that the patient has received in the operating room. Patients will be assigned randomly to one group or another:

- Control group: patients undergoing elective bimaxillary osteotomy who receive a preincisional infiltration of lidocaine and adrenaline.
- Study group: patients undergoing elective bimaxillary osteotomy who receive two infiltrations (firstly pre-incision with lidocaine and adrenaline, secondly pre-extubation with ropivacaine).

Population

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

The criteria for the selection of subjects is the following. The inclusion criteria are patients who undergo scheduled bimaxillary surgery. The exclusion criteria are: the refusal to participate in the study, patients who are scheduled for bimaxillary surgery together with another complementary surgical procedure (such as mentoplasty, rhinoplasty, blepharoplasty), age <18 years, reinterventions, urgent surgeries, allergies to local anesthetics, allergies to anti-inflammatories agents, allergies to opioids, American Society of Anesthesiology Physical Status Examination System (ASA) >3.

Procedure/Intervention

Patients will be received in the surgical area and a venous access line will be placed where premedication (Midazolam 2mg/intravenous) and antibiotic prophylaxis (amoxicillin-clavulanic 2g/intravenous or Clindamycin 600mg/intravenous in case of patients allergic to beta-lactams) will be administered. They will be monitored in the operating room (plasma oxygen saturation, electrocardiogram, non-invasive blood pressure -NIBP-, Bispectral index, Train of four TOF - CUFF neuromuscular monitor) and general intravenous anesthesia will be carried out (anesthetic induction: fentanyl 2mcg/kg/intravenous, propofol 2mg/kg/intravenous, rocuronium 0.6mg/kg/intravenous; and anesthetic maintenance: sevoflurane Minimum Alveolar Concentration (MAC) 1.2 and remifentanil (RMF) Target Controlled Infusion (TCI) - Effective Concentration 2ng/ml). After the nasal intubation of the patient, the administration of the LA will proceed by the following routes:

- Control Group: the surgeon will proceed with pre-incisional infiltration with lidocaine and adrenaline at the intraoral and intranasal submucosal level in the maxilla and jaw to block the terminal branches of the maxillary and mandibular nerve.
- Study Group: the surgeon will proceed firstly with pre-incisional infiltration with lidocaine and adrenaline and secondly with pre-extubation infiltration with ropivacaine at the intraoral and intranasal submucosal level in the maxilla and jaw to block the terminal branches of the maxillary and mandibular nerve.

PHARMACOLOGICAL TREATMENTS

- Control group: Infiltration performed by the surgeon at the intraoral and intranasal submucosal level in the maxilla and jaw (blockage of terminal branches of the maxillary and mandibular nerve) after intubation and previous to surgical incision.
A total of 50ml of the following preincisional mixture is infiltrated: $\frac{1}{2}$ blister 1mg/ml Adrenaline + 1blister 10ml Lidocaine 2% in physiological saline 100ml.
- Study group: Two infiltrations. Firstly, infiltration performed by the surgeon at the intraoral and intranasal submucosal level in the maxilla and jaw (blockage of terminal branches of the maxillary and mandibular nerve) after intubation and previous to surgical incision. A total of 50 ml of the following preincisional mixture is infiltrated: $\frac{1}{2}$ blister 1 mg/ml Adrenaline + 1blister 10ml Lidocaine 2% in physiological saline 100ml.
Secondly, infiltration performed by the surgeon at the intraoral and intranasal submucosal level in the maxilla and jaw (blockade of terminal branches of the maxillary and mandibular nerve) before extubation. A total of 20 ml of ropivacaine 0,37%.

Previous to the surgical incision, fentanyl 0.5mcg/kg/ev will be administered again to all patients and infusion of TCI of RMF at 2 ng/ml effect concentration will be initiated. It will be administered intraoperative to all patients as adjuvant therapy, as long as there is no contraindication, corticotherapy (methylprednisolone 15mg/kg/intravenous), antifibrinolytic

agent (tranexamic acid 15mg/kg/intravenous), gastric protection (ranitidine 50mg/intravenous) , antiemetic agent (ondansetron 4mg/intravenous) and analgesics (paracetamol 1g/intravenous, dexketoprofen 50mg/intravenous, diclofenac 75mg/intramuscular) and ketamine in subanesthetic doses (ketamine 20mg/intravenous in the induction and ketamine 40mg/intravenous slow intraoperative administration). The mechanical ventilation by controlled volume (6ml/kg) will be adjusted to maintain a CO₂ at the end of expiration around 32-38mmHg. In the intraoperative period, in cases of changes in basal NIBP equal to or greater than 20%, remifentanil will be increased/reduced in TCI 0.2ng/ml. If NIBP increases last longer than 5 minutes, administration of remifentanil bolus 2mcg/intravenous will proceed. If abrupt drops of the NIBP will proceed to stop the TCI RMF. Patients will be extubated in the operating room after removal of pharyngeal tamponade, 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 as insufficient pain control and rescue analgesia will be administered (first anti-inflammatory metamizole 2g/intravenous, and second opioid methadone 2mg/15minutes/intravenous in resuscitation, up to a total of 10mg/intravenous in the 2hours stay in resuscitation, and methadone 5mg/6hours/subcutaneous in hospital ward 2-18hours post-operative).

Definition of the variables

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- demographic data: age (years), sex (man/woman)
- anthropometric data: weight (kg), height (cm)
- comorbidities: free text
- ASA (American Society of Anesthesiologists) physical status classification system: 1-3
- Temporary structure of evaluations:
 - Post-operative pain measured with the Visual Analogue Scale (VAS 0-10): at 2, 4, 8 and 18hours postoperatively.
 - Total intraoperative opioid dose (TCI-RMF effect concentration).
 - Total intravenous dose of opioids-methadone in the postoperative period (mg) in resuscitation (2hours postoperative) and subcutaneous methadone in hospitalization (2-18hours postoperative).
 - Presence of PONV at 2, 4, 8 and up to 18hours postoperatively.
 - Complications derived from infiltration with lidocaine and adrenaline
 - Complications derived from infiltration with ropivacaine

CALCULATION OF THE SAMPLE AND STATISTICAL ANALYSIS

The sample selection method foresees the consecutive allocation of patients to two groups:

1. Control Group: a single pre-incision infiltration of LA lidocaine+adrenaline
2. Study Group: two infiltrations with pre-incision lidocaine+adrenaline and pre-extubation with ropivacaine.

The degree of pain is assessed using a visual analog scale (VAS) at different times after surgery: 2, 4, 8 and 18hours. For the necessary sample size estimations, the pain measurement in 2hours postoperative will be considered as the primary response. The sample size will directly depend on the clinically relevant minimum difference between the 2hours average pain level of both groups. 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 \pm 1.25 for a confidence level of 95% and a t test for independent samples.

Minimum difference to be detected in VAS	Effect size (d)	Power reached		
		70%	80%	90%
0,5	0,4 (medium)	158	200	266
1	0,8 (large)	42	52	68
1,5	1,2 (very large)	20	24	32

For example, assume a mean VAS pain level at 2hours equal to 5 and in the other group 6. That difference, assuming a deviation ± 1.25 , equals a size of effect $d = 0.8$, which is considered a large magnitude. If for the researchers 1 point of difference in pain is already relevant, a total of 52 patients (26 per group) are needed to detect the difference as significant with a power of 80%.

In some articles (Annand, Göçmen) standard deviations between 0.84 and 1.6 are reported in different groups of local anesthetics and in the measurement times closer to 2hours. For this reason, this level of variability has been assumed (± 1.25). For a minimum difference of the largest clinically relevant pain score, for example, 1.5 points (5 vs. 6.5 in the groups), a total size of only 24 cases (12 per group) would be sufficient under the same conditions above. However, such low sizes should be avoided due to possible problems in ensuring the normal distribution of the data and being able to apply parametric tests, such as the t-test.

LIMITATIONS

The choice of LA reflects the balance between the rapidity of the 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 LA will be a recommendation. The combined solutions of LA have the disadvantage of a short duration of action compared to the isolated use of a long-acting LA. In our study, the researchers propose the infiltration of prolonged LA after the surgical procedure is completed before extubation of the patient. In this way, the investigators benefit both from the effects of the first pre-incisional infiltration with lidocaine and from the effects of the second pre-extubation infiltration with Ropivacaine. Pre-incisional lidocaine will allow us to control intraoperative pain quickly and maintain up to 2hours, which is longer than what the bimaxillary osteotomy lasts with the team of surgeons the investigators work with, a good surgical field with the addition of adrenaline, and the antiarrhythmic effects in a surgery with high incidence of intraoperative arrhythmias. With the pre-extubation infiltration with ropivacaine the researchers will obtain a dense sensory block of up to 6-12 hours in the postoperative period that will benefit the patient in global terms, with less postoperative pain and greater patient comfort, with a decrease in postoperative nausea and vomiting, initiation of tolerance orally progressively faster and discharge earlier in hospital, with lower costs and greater effectiveness for the hospital entity as a whole.

On the other hand, the use of catheters for continuous infusion of LA to prolong the analgesic effect in postoperative patients with bimaxillary osteotomy is ruled out. In bimaxillary surgery more than one catheter should be used with the risk of infection and loss that this implies. It has also been considered that for the control of mild-moderate pain beyond 12hours after surgery it is satisfactory with the administration of oral analgesic drugs.

ETHICS

All information is 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 guidelines of the Declaration of Helsinki and Good Clinical Practices International - Conference Harmonisation Guidelines (GCP ICH Guides). The investigator will describe to the patient all the measures that will be carried out for data protection and patient privacy according with the Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. "It is the adaptation to the Spanish legal system of Regulation (European Union) 2016/679 of the European Parliament and the Council of April 27 of 2016.

The investigator 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 health 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 initiating any procedure related to the study.

EXPECTED RESULTS

The choice of LA reflects the balance between the rapidity of the 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. The combined solutions of LA have the disadvantage of a short duration of action compared to the isolated use of a long-acting LA. In this study the investigators propose the infiltration of prolonged LA after the surgical procedure is completed before extubation of the patient. In this way the patient benefit both from the effects of the first pre-incisional infiltration with lidocaine and from the effects of the second pre-extubation infiltration with Ropivacaine. Pre-incidental lidocaine will allow the investigators to control intraoperative pain quickly and maintain up to 2hours, which is longer than what the bimaxillary osteotomy lasts with the team of surgeons the researchers work with, a good field of surgical work with the addition of adrenaline, and the antiarrhythmic effects in a surgery with high incidence of intraoperative arrhythmias. With the pre-extubation ropivacaine we will obtain a dense sensory block of up to 6-12hours in the postoperative period that will benefit the patient in global terms, with less postoperative pain and greater patient comfort, with a decrease in postoperative nausea and vomiting, initiation of tolerance orally progressively faster and discharge earlier in hospital, with lower costs and greater effectiveness for the hospital entity as a whole.

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