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Ropivacaine versus placebo on postoperative analgesia and chronic pain following third molar extraction: a prospective randomized controlled study

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ClinicalTrial registration: NCT0154105

Key words : ropivacaine, local anesthetic, molar extraction , outcome

Abstract

Purpose

The present study aimed at assessing the efficiency of ropivacaine on post-operative pain for extraction of third molars.

Methods

In a single centre, prospective, parallel, double blind randomised trial, patients scheduled for removal of all four third molars, ASA I-III patients < 65 year-old patients were included. After intubation under general anesthesia (using intravenous remifentanyl and propofol), for each of the third molars, 2mL of ropivacaine (7.5mg/ml) or placebo (0.9% saline solution) was injected into the vestibular capsule (total: 8 mL) before extraction. At the end of surgery, similar analgesia was injected for both groups (intravenous paracetamol 1g and ketoprofene 100 mg). The primary outcome was postoperative pain assessed by Visual Analog Scale (VAS). Postoperative consumption of analgesics (morphine titration in post-operative care unit when VAS > 3/10, followed by oral tramadol 50 mg after discharge), patient satisfaction, chronic pain (1-3 month), time in PACU and total hospitalization time were also recorded.

Results

50 patients were analysed in each group with similar characteristics (ropivacaine vs control, for age (years) 18 [17 - 21] vs 18 [17 - 21], for sex (female) 33 (66%) vs 25 (50%), and BMI (Kg/m²): 20 [19-23] vs 21 [19 -23]). Area Under the Curve for VAS pain (0 to 4h) was lower for Ropivacaine group: 0.43 [0.19-0.66] vs 0.63 [0.43-0.87], p=0.005. Use of morphine in PACU (8 vs 18, p =0.02) and median length of stay in ambulatory setting (5 vs 6 h, p=0.03) were reduced in Ropivacaine vs Placebo group. At days 1 and 4, VAS of pain was higher in Ropivacaine group (respectively 4 vs 2, p=0.006 and 3 vs 2, p=0.05). At month 1 and 3, pain and

DN4 score were similar between groups, with a median VAS pain score at 0 for both groups (p=0.42). No difference was observed for patient satisfaction and adverse events.

Conclusions: Ropivacaine provides an immediate efficient pain relief after extraction of third molars without benefit after discharge.

Introduction

Removal of the third molars is a frequent performed surgery with significant short-term pain; yet as it is performed as day surgery, patients have limited recourse to analgesics post-operatively.

There are also reports of chronic pain affecting 2.2% patients following surgery.¹ Anaesthesia can take the form of local, regional (truncal infiltration of the dental nerve, with or without sedation) or combined with general anaesthetic. The prolonged action of local anaesthetic into the post-operative period confers an additional advantage, with the various treatments possessing differing durations and quality of pain relief. There is currently no “gold standard” of anaesthetic for such procedures, although lidocaine appears to be most commonly used in the USA and UK.^{2,3}

However, this is a short-acting product, thus alternatives with better properties would be welcome.

Ropivacaine, a long-acting local anaesthetic has been recently considered as a potential replacement (vs lidocaine). Previous studies on ropivacaine have compared it against other nerve blocks (lidocaine, mepivacaine, and articaine), although no studies have yet compared ropivacaine against a placebo control.⁴⁻⁶ Previous studies have identified a dose of 0.75% as the best adapted.^{7,8} However, no study evaluated benefit after hospital discharge for ambulatory day case surgery and incidence on chronic pain.

The purpose of this study was to compare ropivacaine against placebo as local analgesia on post-operative short- and long-term pain following extraction of all four third molars. Our hypothesis was that ropivacaine will be superior to placebo for reducing post-operative pain.

Methods

Study design

We designed a one single centre, 1:1 two-parallel arms, prospective, placebo-controlled double-blind trial comparing ropivacaine (7.5mg/mL) versus placebo (0.9% saline solution) regional anaesthesia. Patients were followed for 3 months.

According to the French law, the official Institutional Review Board approved the study (Comité Protection Personne, Sud Méditerranée III, 2012, Hôpital Universitaire de Nîmes, France, Chairman: Pr Thierry Lavabre Bertrand and registered at EudraCT: 2011-004972-13). Prior to first patient enrollment, the study was registered at ClinicalTrials.gov (NCT01541059; 29 feb. 2012, principal investigator: Pr Jacques Ripart, see author).⁹ A written informed consent was obtained for every participant before inclusion, this study followed the guidelines of Helsinki declaration for human investigation.

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Participants

Subjects requiring bilateral surgery of inferior and superior third molars only under general anaesthesia were recruited from the University Hospital of Nîmes. Were included 16 to <65 yo patients with an ASA physical status grade I-III and after having given an informed consent (guardians also signed for patient < 18 year old). Were not included: refusal, pregnant and parturient patients, patients using ineffective contraception, or suffered from addiction or chronic pain treated with opioid, patients with a contra-indication for regional anaesthesia or the local or general anaesthetics and analgesics used in the protocol, or if a hypersensitivity to ropivacaine or

other local anaesthetics with amide links was reported. Patients with predicted difficulties in cooperation or psychiatric disorders that could interfere with assessments were also excluded.

Management of general anaesthesia

All patients underwent oral premedication with hydroxyzine (1mg/kg) one hour before the operation. Intravenous antibiotic prophylaxis was used prior to induction. Standard general anaesthesia was used: briefly, anaesthesia was induced using propofol (2.5-3 mg/kg) and remifentanyl via target-controlled infusion (TCI). Depth of anaesthesia was monitored, with objective between 40-60 according to bispectral index (BIS). The use of intubation was left at the discretion of the anaesthetist. Arterial pressure and heart rate were maintained at $\pm 20\%$ of baseline just before induction using ephedrine. For postoperative analgesia, paracetamol (1g four times daily/five days) and ketoprofene (100mg/12 hours for three days) were systematically given to patients prior to awakening. In post-anaesthesia care unit (PACU), after approximately 30 minutes post-awakening, patients declaring pain to be $>3/10$ were offered iv morphine administered in line with standard procedures (3mg plus 2-3mg/5 minutes until VAS pain score was $< 3/10$). Patients were discharged from the PACU according to normal criteria; modified Aldrete score >12 . Additional 'rescue' analgesia was available for patients during hospitalization and upon return home: tramadol (50mg / 4 hours orally as needed). Then, patients were given mouthwash to be used three times daily for 10 days.

Intervention

The same operator (experience: >15 yrs) performed extraction in all patients. For each of the third molars, 2 mL of ropivacaine (7.5mg/mL) or placebo (0.9% saline solution) was injected into the vestibular capsule (total of 8 mL). The surgeon and operating room nurse who prepared the

product were aware of the nature of the injection. The anaesthetist, anaesthetic nurse and the outcomes assessors were blinded to patient group. The syringe was prepared in a separate room to ensure blindness of other staff. Surgical notes and anaesthetic notes were completed independently for respecting the double blinded design.

Primary outcome

The primary outcome of this study was patient-reported pain by visual analogue scale (VAS) (0-10) at 0 (time of awakening), 1.5, 3, 4, 6, 8 and 24 hours after awakening, evaluated by the anaesthetic team (blinded to patient allocation). For the evaluation 24 hours after awakening, a call was made to the patient's home by a clinical study technician.

Secondary outcomes

Secondary outcomes measures were: the consumption of propofol and remifentanyl peri-operatively; post-operative pain at day 1 (D1), D4, Month 1 (M1) and M3; consumption of morphine and tramadol post-operatively; time until first request for tramadol; consumption of analgesics in hospital; time spent in PACU; hospitalization duration; consumption of analgesics at home until D3; total analgesic consumption; patient satisfaction at D4; chronic post-operative pain as assessed by the DN4 questionnaire (10 pain measures: Yes/No; cut-off for positive pain = 4)(10) and the secondary effects of medications and regional anaesthetic (pruritus, nausea, vomiting, bleeding of the mouth, loss of feeling, respiratory difficulties, drowsiness, headache, sweating, palpitations, cutaneous rash, swallowing difficulties and dysarthria).

Data collection

Before surgery, patient information was collected (age, weight, height, sex), physical status was scored according to the ASA score, and ease of intubation was scored in consultation by Mallampati score. Patient's VAS was recorded at anaesthesia consultation and the morning of intervention. In addition, each patient had to complete the DNA survey composed of four questions and 10 items which generates a score between 0 and 10. The surgeon was asked to anticipate the difficulty of the operation according to the Pederson Difficulty Index (0-10 scale) pre-operatively and then to rate the difficulty encountered on the same scale post-operatively. During surgery, modified Cormack-Lehane score, times of induction, infiltration, incision- end of surgery, end of anaesthesia, consumption of propofol and remifentanyl and use of anti-emetics were collected. Bleeding in per- and post-operation was ranked as minimal, average or high (subjective evaluation performed by surgeon), and complications encountered during surgery were recorded. After surgery, patient's VAS was collected at awakening (0), 1.5, 4 and 24 hours after awakening and then at day 4 (D4), month 1 (M1) and month 3 (M3) post-surgery. The consumption of morphine in PACU and tramadol after PACU, the first time of tramadol request, the use of anti-emetics and the secondary effects of medications and regional anaesthetic were collected during hospitalization. At day 1 and day 4, patients were contacted to request pain evaluation by VAS, use of analgesic and secondary effects and satisfaction. Finally, at M1 and M3 patients were called to collect information on pain by VAS and DNA score.

Sample size and randomization

Sample size was determined based on the results of a prospective pilot study from our team. Pain was evaluated by VAS until 5.5 hours post-surgery, we found that patients treated with ropivacaine (n=18) had an average area under the curve (AUC) of 0.28 ± 0.31 compared to 0.52 ± 0.35 in placebo patients (n=11). In order to detect a superiority of ropivacaine with an alpha risk of

0.05 and a power of 0.9, we required 33 patients in each group. To account for potential 20% missing data for the primary outcome and approximation of estimations, a total of 50 patients per group were required. The randomization list was computer generated using SAS Software version 9.4 (SAS Institute Inc. Cary, USA) by the methodologist of the Biostatistics Department of Nimes University Hospital appointed to the study and not involved in-group allocation. The allocation was made using an online randomization application designed for clinical research projects. Randomization was performed in random blocks of 4 or 6 without stratification with a 1:1 allocation ratio. Randomization was performed following recruitment of eligible participants by the surgeon who was the only person aware of which group to assign the patient.

Data analysis

All analyses were conducted following the intent-to-treat (ITT) principle. Studied parameters were expressed as means \pm standard deviations (SD), or medians with interquartile, or in frequencies and percentages when appropriate. Analysis of unbalanced percentages when appropriate. The group differences were not subjected to statistical tests due to the randomization principle (CONSORT guidelines).¹⁰ Comparisons for pain (for primary or secondary endpoints) were one-sided and a p-value of <0.05 was required to exclude the null hypothesis. Other comparisons were two-sided with the same p-value threshold. For the primary endpoint, area under curve (AUC) was estimated using the trapezoidal method. AUC were estimated using VAS evaluation at 0, 1.5, 3 and 4 hours after awakening. Evaluation of pain at 24 hours was compared by a Wilcoxon test. For both these elements of the primary endpoint, potential covariates (identified when comparing groups) were tested in univariate analysis and a multivariate general linear regression model with appropriate distribution was realized. For secondary endpoints,

comparisons between groups were performed using unpaired Student's *t*-tests, Wilcoxon tests and chi-square tests \pm Fischer exact tests when appropriate. To estimate the time until tramadol request, a survival analysis was performed and the comparison was made with a log-rank test. Statistical analysis was conducted using SAS (release 9.4; SAS institute, Cary, USA).

Results

From June 2012 to May 2015, 103 patients were recruited to the study, with a follow-up of three months (Fig1). 100 patients were finally included in the study and allocated to the two groups (Figure 1). Baseline patient characteristics and surgical duration are shown in table 1. There were more women in ropivacaine group.

Primary end point

The median AUC values of the VAS from H0 to H+4 were 0.63 [0.43 - 0.87] and 0.43 [0.19 - 0.66] ($p < 0.01$) in the Placebo and Ropivacaine groups, respectively. As there were more women in Ropivacaine group, sex was studied as a variable in univariate analysis with a lower AUC in men (median 0.45 [0.22 - 0.57]) than in women (median 0.660 [0.37 - 0.96]) ($p = 0.0078$). After having performed a general linear regression model with gamma distribution using sex and randomization arm as covariables, sex (men) ($p < 0.01$) and randomisation arm (Ropivacaine) ($p = 0.03$) were associated with a lower AUC of VAS. At H24 and D4, VAS pain score was higher in the Ropivacaine group than Placebo group (Table2).

By month 1 and month 3, few patients in either group reported pain (median 0), and the inter-group differences were not significant ($p = 0.42$ and $p = 0.29$ respectively).

Secondary end points

More patients in the Placebo group used morphine between H0-H1.5 than the Ropivacaine group (36.7% vs. 16.3%, $p = 0.002$) or tramadol between H0-H4 (6.7 % vs 15.2 %, $p < 0.01$) and tramadol until H24 (Table 2). Multivariate analysis was performed using tramadol usage and

treatment arm as variables. Tramadol ($p=0.03$) and ropivacaine ($p<0.01$) were associated with a lower AUC of VAS.

Satisfaction, length of time in PACU and in hospital, the number of patients with complication did not differ between groups (Table 2).

Discussion

The results of this study demonstrate that infiltration of ropivacaine for the four third molar removal improved early postoperative pain and time discharge from hospital, but we did not find a significant difference after day 1.

Third molar removal is the most common surgical procedure and many patients need time off work and their quality of life is significantly affected for several days due to severe pain, swelling and trismus.¹¹⁻¹⁴ Various types of medication and local anaesthetics have been used to control postoperative pain following surgical third molar removal. Previous studies have suggested that maximal pain is felt during the first 3 to 5 hours postoperatively, which is in line with our results (Table 2)(11). This time (3-5h) exceeded duration of short acting LA (lidocaine, mepivacaine), reducing the interest for these agents. In contrast, we demonstrated an efficient potent of long acting local anaesthetic on pain relief compared to placebo. Because early discharge and pain relief are considered as quality makers in ambulatory unit, the use of ropivacaine (or similar long acting LA) in this surgery should be considered.

Few studies have shown the effectiveness of ropivacaine in dental anaesthesia. El-Sharrawy et al. found that 0.5% and 0.75% concentrations were effective for intra oral nerve blockade, with a rapid onset and prolonged duration of pain control.⁸ Similar findings were reported by Brkovic et al with high dose of ropivacaine (1%), by Budharapu et al, by Krzeminski et al, and by Ernberg et al with various concentrations (0.375 to 0.75%).^{4, 6-7, 14-15} However, all of these studies were limited to onset and duration of LA without any data for early (D1, D4) or delayed (1-3 months) evaluations. The present study is the first one to demonstrate that ropivacaine is, as expected, effective on pain relief in the first 4 postoperative hours (on VAS pain score, on opioid rescue, on time discharge); but also highlighted that secondary outcomes recorded in the study after day

case surgery, were similar vs placebo. Also, no benefit of 0.75% ropivacaine on pain relief at D1 and D4 or on chronic pain at D30 and D90 was reported.

Analgesics including paracetamol or acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used to control pain after this surgery.¹¹ Therefore, the present study used paracetamol and NSAIDs to reduce postoperative pain. But, our results demonstrated that many patients needed additional tramadol after PACU and that ropivacaine group had higher pain score at 24h. Similar results were observed when single nerve blocks were performed in orthopaedic surgery: rebound effect. If ropivacaine becomes adopted as the local anaesthetic of choice, the anesthetist would need to ensure that the patient was adequately informed prior to discharge (block duration) that they should keep to the pain medication schedule regardless of whether they had yet experienced pain or not. High doses of oral opioid are not commonly used for analgesia in dentistry probably as they are not suitable for ambulatory surgery because of high incidence of drug-related adverse effects, especially nausea and vomiting.^{12,13} In the present study, ropivacaine led to lower dose of opioid in PACU allowing a more rapid hospital discharge (one hour less). We did not assess the impact of this shorter hospital duration on cost.

In this study, we performed infiltration before surgery, but we did not reported intra operative opioid or hypnotic sparing. Remifentanyl and propofol consumption were similar in both groups (Table 2).

The rate of adverse events did not differ between ropivacaine and placebo, although we believe that this LA is an optimal choice for analgesia because it has extended duration of analgesia and negligible toxicity. Effect of sex, surgical experience and level of anxiety were reported for this surgery in previous study.¹⁶⁻²⁰ Similarly, our results found sex effect on postoperative pain and tramadol rescue.

Limitations of this study were the lack of data collection beyond four hours after surgery, preventing us from more precisely evaluating the time line of benefit from ropivacaine.

Moreover, we choose high dose of ropivacaine, lower concentrations may produce similar results.

Bias arising from surgeon experience was avoided by using the same surgeon for all extractions.¹⁸

In conclusion, our results support the theory that ropivacaine represents an effective LA for third molar extraction without major adverse events, with the quicker discharge affording a potential economical benefit to the institute.

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Figure legend

Fig 1: Flow chart

Table 1: Patient and surgical considerations

	Ropivacaine n=50	Placebo n=50
Age (year)	18 [17 - 21]	18 [17 - 21]
BMI (Kg/m ²)	20.7 [19.1 - 23.6]	21.5 [19.3 - 23.8]
Sex (female), n	33 (66%)	25 (50%)
ASA score (1/2), n	47 / 3	50 / 0
Preoperative pain (VAS, 0-10)	0 [0 - 1]	0
Preoperative surgical difficulties (0-10)	3 [2 - 3]	3 [2 - 3]
Mallampati score, n (%)		
1	43 (87.8)	45 (91.8)
2	6 (12.2)	4 (8.2)
Modified Cormack-Lehane score, n (%)		
Grade 1	49 (98)	50 (100)
Grade 2	1 (2)	-

Anaesthetic duration (min)	38 [34 - 43]	39 [33 - 45]
Surgical duration (min)	21 [17 - 24]	19 [17 - 24]
Intraoperative bleeding, n (%)		
Minimal	34 (69)	30 (64)
Average	13 (26)	9 (19)
Serious	8 (15)	8 (17)
Post-operative bleeding (D1), n (%)		
Minimal	28 (57)	30 (63)
Average	13 (26)	9 (20)
Serious	8 (17)	8 (17)

Data are expressed in median (interquartile) and number (percentage), D (Day)

Table 2: Anaesthetic agent, rescue analgesia, time and patient satisfaction at day 4

	Ropivacaine n=50	Placebo n=50	p
Remifentanil dose ($\mu\text{g}/\text{kg}$)	6.71 [4.83-7.8]	7.19 [5.79-9.62]	0.1
Propofol dose (mg/kg)	10.17 [8.81-12.6]	10.67 [9.24-12.5]	0.69
Use of morphine in PACU, n	8 (16.3)	18 (36.7)	0.02
Use of tramadol (PACU-H4), n	3 (6.7)	7 (15.2)	0.31
Use of tramadol (H4-H24), n	6 (3)	2 (1.5)	0.31
Delay until 1st Tramadol (min)	48 [19- 96]	141 [53-171]	0.22
Time spent in PACU (min)	78 [67-102]	86 [67-107]	0.35
Time spent in hospital (h)	5 [4-6]	6 [5-6]	0.03
Patient satisfaction at Day 4 (0-10)	8 [7- 9]	8 [7- 9]	0.24
Occurrence of at least one complication at home (Day 1-3)	43 (89)	42 (85)	0.56

Values are expressed in median (interquartile) or number (percentages)

