Preoperative Local Administration of Morphine as an Add-on Therapy in Patients Undergoing Surgical Removal of an Odontogenic Maxillary Cyst. A Randomized, Double-Blind Pilot Study

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Preliminary findings were presented at the 17th International Congress of the Polish Society of Anaesthesiology and Intensive Therapy, Gdansk, Poland, September 21–24, 2011.

Aims: To evaluate whether a combination of locally administered morphine (1 mg) and lidocaine as part of a multimodal analgesic approach is safe, and whether it improves pain control during the first 24 hours after odontogenic maxillary cyst removal under general anesthesia compared to local lidocaine alone. **Methods:** In a double-blind, sham-controlled, single-center trial, patients scheduled for surgical removal of an odontogenic maxillary cyst under general anesthesia were randomly assigned to receive a local injection of lidocaine solution with either 1 mg of morphine (MLA group) or with no morphine (LA group). Pain management included intravenous acetaminophen (1 g every 6 hours) in all patients. Upon request, the patients could additionally receive ketoprofen (first-line additional analgesia) or tramadol (second-line additional analgesia). Pain intensity was assessed using a numeric rating scale. Primary outcome measures were *(1)* no need for any additional analgesic therapy and *(2)* time to the first rescue analgesic therapy during the first 24 hours after the surgery. **Results:** Of 48 eligible patients, 24 were allocated to the MLA group and 24 to the LA group. The necessity of additional ketoprofen therapy did not differ significantly between the groups (25.0% vs 50.0%, $P = .074$). According to the Kaplan-Meier analysis, the probability of remaining without additional analgesic intervention was significantly higher in the MLA group (log-rank test, $P = .040$), but there were no significant ($P > .05$) differences in overall and maximum pain severity between the two groups. No adverse effects of morphine were recorded. **Conclusion:** Within the limitations of this study, local administration of 1 mg of morphine prior to the surgical removal of an odontogenic maxillary cyst was safe, but it did not prove to be very effective as an add-on therapy for postoperative pain control. *J Oral Facial Pain Headache 2015;29:378–383. doi: 10.11607/ofph.1307*

Keywords: *inflammatory pain, odontogenic cysts, opioid receptors, oral surgery, peripheral opioid analgesia*

Analgesic therapy utilizing the synergistic action of a local anesthetic (LA) and an opioid is often used for many surgical procedures.[1] However, the discussion about analgesic efficacy of locally administered opioids is still ongoing,[2] and the effectiveness of locally administered morphine (1 mg) for dental and maxillofacial surgery has been reported only in a few studies.[3,4]

Opioid receptors are synthesized in spinal dorsal root ganglia neurons and transported to a peripheral site of inflammation via intraaxonal transport.[5] Inflammation is associated with an upregulation of opioid receptors, mainly in the small-sized primary afferent neurons, and it also enhances the efficiency of "second messengers," which may contribute to the peripheral antinociceptive effects of morphine in painful inflammation.[6] Similar processes have been described in the trigeminal system.[7]

Previous studies on the peripheral analgesic efficacy of intraarticular and locally administered opioids in patients undergoing dental and maxillofacial surgery have demonstrated pain reduction only if inflammatory pain was present before the surgery.[2,3,8,9] Odontogenic jaw cysts are

accompanied by pain in about 42% of cases,[10] but their formation and development involve proinflammatory cytokines[11,12] that activate peripheral antinociceptive opioid mechanisms in inflamed tissues.[13] This theoretically justifies the use of locally administered morphine for odontogenic jaw cyst surgery, even in patients not experiencing pain before the procedure.

The aim of this study was to evaluate whether a combination of locally administered morphine (1 mg) and lidocaine as part of a multimodal analgesic approach is safe and whether it improves pain control during the first 24 hours after odontogenic maxillary cyst removal under general anesthesia compared to local lidocaine alone.

Materials and Methods

Study Design and Patients

This was a randomized, double-blind, sham-controlled study that enrolled patients scheduled for a surgical removal of an odontogenic maxillary cyst under total intravenous anesthesia at the Department of Cranio-Maxillofacial Surgery, Oral Surgery and Implantology, Medical University of Warsaw, from December 2009 to March 2011. The diagnosis was based on clinical and radiological examination. Patients with a physical status score > 2 on the American Society of Anesthesiologists (ASA) scale,[14] body weight < 50 kg, and those receiving pain medication within 24 hours prior to the surgery were excluded from the study. The study was approved by the Bioethics Committee of the Medical University of Warsaw (KB/66/2009).

Study Procedures and Randomization

Eligible patients, after signing an informed consent form, were randomly allocated using an urn adaptive biased-coin method[15,16] in a 1:1 ratio to one of two groups: *(1)* the morphine and local anesthetic group (MLA) that received regional anesthesia with 5 mL of a 2% solution of lidocaine with norepinephrine (Lignocainum 2% c Noradrenalino 0.00125% WZF, Polfa Warszawa SA) and 1 mg of morphine (Morphini Sulfas WZF, 10 mg/mL, Polfa Warszawa SA), and the local anesthetic group (LA) that received an identical solution but without morphine.

Local anesthesia involved a slow injection of the analgesic solution into the operated area, which was done by the surgeon after induction of general anesthesia. To exclude the impact of the systemic action of locally administrated morphine in the MLA group, patients from the LA group received subcutaneously 1 mg of morphine in 1 mL of 0.9% NaCl. The solution was simultaneously injected in the patient's left arm by the anesthesiologist. To keep the study double-blinded, patients from the MLA group were given 1 mL of 0.9% NaCl subcutaneously. The solutions were provided in identical unlabeled syringes by the randomizing researcher who did not participate in the subsequent stages of the study.

Total intravenous anesthesia included propofol (Propofol 1% MCT/LCT Fresenius, Fresenius Kabi) and remifentanil (Ultiva, Glaxo SmithKline). At the end of the procedure and after scoring at least 9 points on the Aldrete scale,[17] the patients were transferred to the postoperative unit.

Pain control during the first 24 hours after the surgery was achieved by intravenous administration of 1 g acetaminophen (Perfalgan, Bristol-Myers Squibb) every 6 hours in each patient. The first dose was administered prior to general anesthesia. As a preplanned additional therapy, upon request, the patient could receive an intravenous infusion of 50 mg ketoprofen (Ketonal 50 mg/mL, Sandoz), up to 200 mg/d. Second-line additional analgesia was also available with intravenous tramadol 50 mg (Poltram 50, 50 mg/mL, Pharmaceutical Works Polpharma), up to 400 mg/d. If the above-mentioned measures were not sufficient, strong opioids were to be administered beyond the study protocol.

Pain intensity was assessed according to a numeric rating scale (NRS; 0 representing no pain at all and 10 representing the worst pain imaginable). The NRS scores were recorded directly before the surgery and then 3, 6, 9, 12, 18, and 24 hours after the administration of local anesthesia.

Outcome Measures

The primary endpoints were: *(1)* no need for any additional analgesic therapy during the first 24 hours after the surgery; *(2)* time to the first rescue analgesic therapy. The secondary endpoints included: *(1)* maximal pain intensity; *(2)* proportion of patients reporting suboptimal pain control (NRS score $\geq$ 3) at 3, 6, 9, 12, 18, or 24 hours after surgery; and *(3)* pain intensity (NRS score) at 3, 6, 9, 12, 18, or 24 hours after the surgery. Patients were also carefully observed for side effects of the opioid therapy, including respiratory depression assessed by arterial blood oxygen saturation (SpO_2), occurrence of postoperative nausea and vomiting (PONV), and pruritus.

Statistical Analyses

Categorical variables are presented as percentages and compared with the chi-square test (two-tailed Fisher's exact test was used if the expected values in a 2 $\times$ 2 contingency table were < 5). Continuous variables are presented as mean and standard deviation (SD), but due to their non-normal distribution (according to the Shapiro-Wilk normality test), the Mann-Whitney *U* test was used for comparisons. Changes in pain intensity during the first 24 hours

Table 1 Patient Demographics and Perioperative Data

	MLA group (n = 24)	LA group (n = 24)	*P*
Age (y), mean ± SD	36.5 ± 13.0	44.9 ± 15.3	.033
Male sex, no. (%)	11 (45.8)	11 (45.8)	.999
BMI, mean ± SD	25.8 ± 4.6	24.6 ± 2.6	.483
Pain before surgery (NRS), mean ± SD	0.3 ± 0.8	0.2 ± 0.5	.727
Duration of anesthesia (min), mean ± SD	56.3 ± 20.4	59.0 ± 17.7	.619
Operation time (min), mean ± SD	41.7 ± 17.5	44.4 ± 17.3	.527
Total propofol used (mg), mean ± SD	646 ± 231	575 ± 182	.338
Total remifentanyl used (µg), mean ±S D	633 ± 334	667 ± 422	.910
Extubation time (min), mean ± SD	6.6 ± 2.6	7.0 ± 2.3	.421

BMI = body mass index (kg/m2^2); NRS = numeric rating scale; extubation time = time from cessation of drug infusion until extubation.

Table 2 Additional Analgesic Interventions and Pain Intensity During the First 24 Hours After Surgery

	MLA group (n = 24)	LA group (n = 24)	*P*
Use of additional analgesia*, no. (%)			
Not necessary	12 (50.0)	6 (25.0)	.074
Once	10 (41.7)	12 (50.0)	.562
Twice	2 (8.3)	6 (25.0)	.245†
Maximal pain intensity (NRS), mean ± SD	3.3 ± 3.0	3.7 ± 3.0	.560
Postsurgical pain ≥ 3 points on NRS, no. (%)			
At any time point	11 (45.8)	13 (54.2)	.564
3 h postsurgery	8 (33.3)	9 (37.5)	.763
6 h postsurgery	3 (12.5)	5 (20.8)	.439
9 h postsurgery	4 (16.7)	7 (29.2)	.303
12 h postsurgery	3 (12.5)	2 (8.3)	.999†
18 h postsurgery	1 (4.2)	3 (12.5)	.609†
24 h postsurgery	5 (20.8)	2 (8.3)	.416†

*50 mg ketoprofen.
†Two tailed Fisher's exact test was used.
NRS = numeric rating scale.

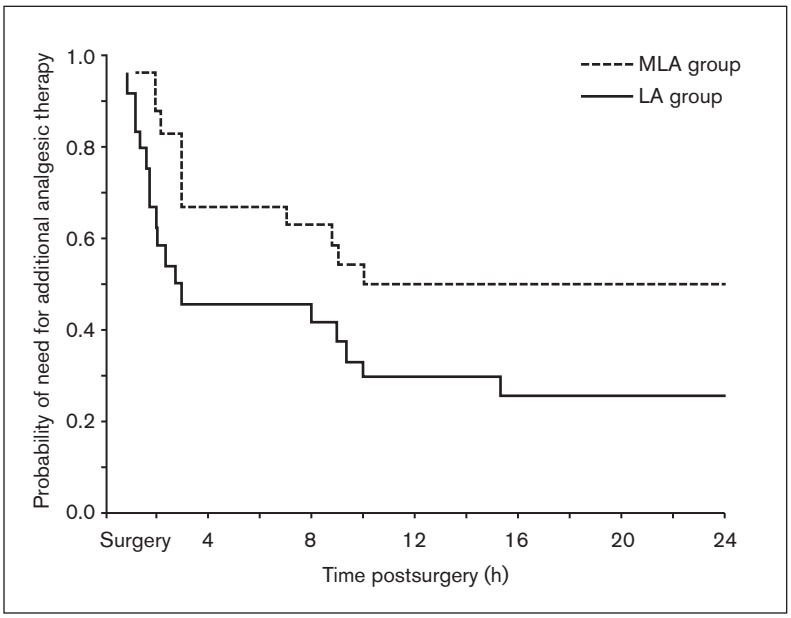

Fig 1 Probability of not needing any additional analgesic therapy during the first 24 hours after surgery. Kaplan-Meier analysis (log-rank test: 2.056, *P* = .040).

after surgery were graphically presented as median with quartile 1 and quartile 3. Probability of not needing any additional analgesic therapy throughout the first 24 hours after the surgery was evaluated using the Kaplan-Meier analysis with the log-rank test. All calculations were carried out in STATISTICA 9.0 (2010; StatSoft). A *P* value of < .05 was considered significant.

Results

Baseline Characteristics

A total of 60 patients were screened and 48 patients met the inclusion criteria. They were randomly assigned into the MLA group (n = 24) and LA group (n = 24). All patients completed the study according to the protocol and none of them were lost from the follow-up. Baseline characteristics of both groups were mostly well-matched and there were no significant differences between the groups in these characteristics (Table 1).

Primary Outcome Measures

The MLA group showed a tendency for a higher proportion of patients who required no additional ketoprofen as first-line additional therapy, but the difference between groups was not significant (50.0% vs 25.0%, *P* = .074) (Table 2). According to the Kaplan-Meier analysis, the probability of not needing any additional analgesic therapy was significantly higher in the MLA group (log-rank test 2.056, *P* = .040) (Fig 1). The second-line additional therapy was not used in either group.

Secondary Outcome Measures

There were no differences in maximum pain intensity and in the proportion of patients reporting suboptimal pain control (NRS scores ≥ 3) at any given time after the surgery (Table 2). Changes in the average pain intensity measured with the NRS at the predefined time points are shown in Fig 2. Significant differences in median

pain intensity between the MLA group and the LA group were observed only 12 hours after the surgery (1.0 vs 0.0, $P = .047$) and 18 hours after the surgery (0.0 vs 1.0, $P = .012$).

Side Effects

No side effects of morphine were observed, including respiratory depression, PONV, or pruritus.

Discussion

The present study has demonstrated that local administration of 1 mg morphine as add-on therapy before the removal of an odontogenic maxillary cyst is safe but is not very effective in reducing the need for additional analgesics during the first 24 hours after the surgery. The results suggest that locally administered morphine may potentially have a small analgesic effect as an add-on therapy. However, in terms of clinical benefit, it is probably marginal. It should be noted that the results refer exclusively to peripheral morphine analgesic mechanisms.

Regardless of the route of opiate administration,[3,4,18,19] peripheral opioid analgesic mechanisms may be effective only in painful inflammatory states[20] that are normally not found in maxillofacial surgical patients without ongoing inflammation.[2,4] Odontogenic jaw cyst formation and growth potentially activate peripheral antinociceptive opioid mechanisms, but in the current study it was not accompanied by inflammatory pain before the operation (see Fig 2).

Locally administered morphine may also potentially affect central analgesic mechanisms. A dose-dependent analgesic action of regionally administered morphine after knee surgery[21] can be caused in part by systemic mechanisms.[22] However, the concentration of morphine in the knee after intra-articular injection may by over 1,000 times higher than after the systemic application of morphine.[23] Therefore, its central analgesic effect seems to be of minor importance when locally administered.

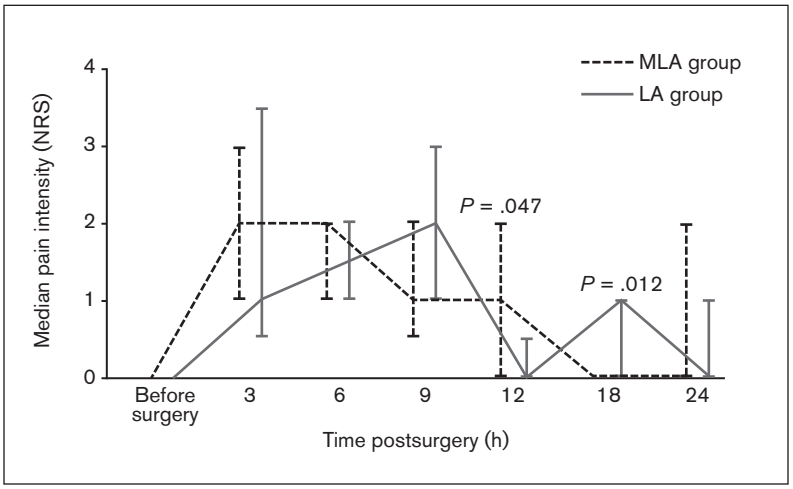

Fig 2 Changes in pain intensity during the first 24 hours after surgery; bars represent quartile 1 and quartile 3. NRS = numeric rating scale.

Animal studies have shown local analgesic properties of morphine in an inflammatory pain model of temporomandibular joint pain and therefore support the presence of peripheral opioid receptors that may play a role in modulating craniofacial nociceptive responses.[24] Inflammatory muscle pain in rats triggers significant upregulation of opioid receptor expression in the trigeminal nerve, and their activation results in antinociception.[7] However, this phenomenon appears to be more specific for the trigeminal nerve–innervated areas.[25]

To control for a potential central opioid analgesic action, morphine was injected in the LA group with an identical dose to that of the MLA group, but in the left arm, well away from the operating area. Despite the possibility of marginal clinical, peripheral, and central effects of systematically administered low morphine doses, this approach allowed for the measurement of the peripheral effect of locally administered morphine. The dose of 1 mg followed the choice made in other human studies on orofacial inflammatory pain.[3,4,26] Therefore, it may not be excluded that local administration of higher doses would produce a stronger analgesic effect.

Morphine gel applied directly to the wound after wisdom tooth extraction has been reported not to be superior to placebo in a single study.[27] However, locally injected morphine has already been shown to reduce the need for nonsteroidal anti-inflammatory drugs (NSAIDs) in patients undergoing dental surgery in inflamed tissues.[3,4] In the present study, the proportion of patients requiring additional analgesic interventions tended to be higher in the LA group. The daily dose of ketoprofen was much less than reported by Kaczmarzyk and Stypulkowska and did not exceed 100 mg (see Table 2), which is only half of the recommended maximum daily dose.[3)] However, multimodal preemptive analgesia and regular doses of acetaminophen, irrespective of the pain experienced, were not used in previous studies.[3,4,8] It is possible that the overall use of additional analgesics may be reduced by preemptive and postoperative acetaminophen.[28] However, such a regimen is recommended by Polish guidelines for management of postoperative pain.[29]

The Kaplan-Meier analysis revealed that patients from the MLA group had a significantly higher probability of not needing any additional analgesic therapy. The discrepancy between different times to rescue analgesia despite similar pain control is probably due to the fact that pain intensity was measured in fixed time points, whilst additional analgesic therapy could be requested at any time that it was considered necessary by the patient. Therefore, the measured pain intensity was at least partially a function of the medication taken. For this reason, the time to rescue analgesia was chosen as a more reliable endpoint. It is also important to note that the Kaplan-Meier curves diverged within the first 3 hours after the surgery.

Pain assessment with the NRS indicates trends and the magnitude of change in pain intensity, but this approach is less reliable in measuring the absolute pain itself and patients' suffering.[30] Immediately prior to surgery and at 3, 6, 9, 12, 18, and 24 hours after administration of local anesthesia, median postoperative pain intensity was less than 3 points on the NRS. However, incomplete pain control (NRS score $\geq$ 3) at least once after the surgery was reported by 50% of patients from both groups, which is in line with previous observations.[31] Pain control thresholds used in the current study may seem rigorous, as additional analgesic therapy is usually recommended for NRS scores of 4 points or more.[32–34] However, elective surgery in patients with maxillofacial conditions is not associated with high levels of postoperative pain. Patients in the present study usually did not experience significant pain before admission and none of them required analgesia within 24 hours prior to the surgery.

It is important to note potential gender differences in response to opioid therapy. Peripherally applied morphine showed better suppression of jaw muscle electromyographic activity reflexively evoked by glutamate application to craniofacial tissues in male rats compared to female rats; this corresponded with inflammatory induced upregulation of opioid receptor expression in the trigeminal nerve and testosterone levels.[35–37] Although postoperative pain, including extraction of impacted third molars, is more severe in women,[38] intravenous opioid consumption in patients undergoing orthognathic surgery was not gender-dependent,[39] which may be partly explained by the lack of preoperative inflammatory pain.

The present study is the first randomized investigation suggesting that locally administered morphine may modify the nociceptive processes after oral surgery in humans and has the potential for weak additional analgesic effects in patients without preexisting inflammatory pain. One may speculate that inflammatory mediators associated with the growth of bone cysts[11,12] may also be associated with peripheral mechanisms related to opioid analgesia,[13] but further studies are needed. No significant side effects of morphine were observed in the current study, which is fully consistent with the previous reports.[2,21,40]

The study had some limitations. It addressed a population of patients who were very homogeneous in terms of the pathologic condition. It is possible that a larger sample size would have resulted in a significant difference in the proportion of patients requiring additional analgesia. Given the results, 59 patients in each group would be sufficient to obtain 80% statistical power and a 5% significance level; the study was thus underpowered (43%). In addition, the study investigated only one arbitrarily chosen dose of morphine and was not powered enough to account for factors that may modify the response to treatment, such as gender.

In conclusion, the present study has shown that the combination of locally administered morphine (1 mg) and lidocaine as part of a multimodal analgesic approach in patients undergoing surgical removal of a maxillary odontogenic cyst under general anesthesia is safe. However, the approach did not prove to be much more effective for pain control compared to local injection of lidocaine. Further randomized studies are needed to verify this effect in other groups of patients with no clear underlying inflammatory process.

Acknowledgments

The authors gratefully acknowledge Prof Ewa Mayzner-Zawadzka, Assoc Prof Danuta Samolczyk-Wanyura, and Assoc Prof Tomasz Lazowski for their support of this study. The authors report no conflicts of interest related to this study.

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