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Peripheral morphine reduces acute pain in inflamed tissue after third molar extraction: A double-blind, randomized, active-controlled clinical trial

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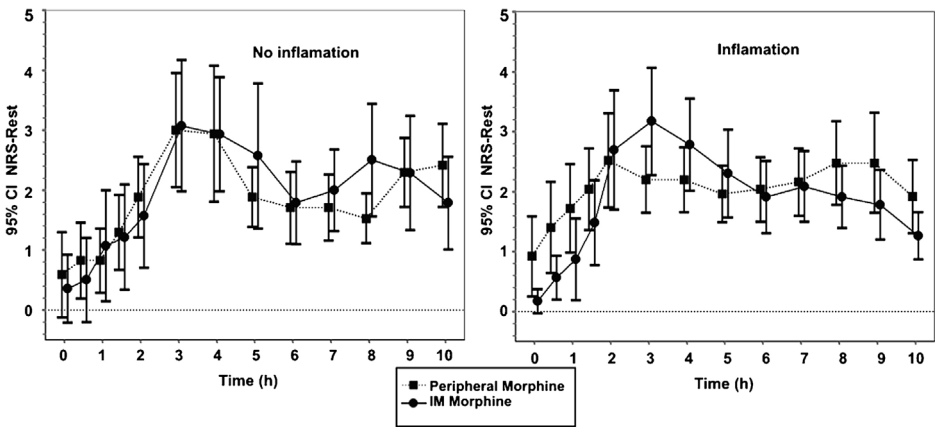
HIGHLIGHTS

- Pain on swallowing after oral surgery with inflamed peridental tissue was reduced by 2 mg local morphine.
- Sedation scores were significantly higher in the peripheral morphine group only 1 h after surgery.
- Patients receiving 2 mg morphine into non-inflamed tissue did not show any reduction in pain scores.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The clinical use of peripheral analgesic effects of opioids has been investigated in numerous controlled clinical trials. The majorities of these have tested the local, intra-articular administration of morphine in knee surgery and have demonstrated marginal postoperative analgesia.
Objective: We examined direct morphine infiltration of the surgical site in a clinical model of tooth pain under two different conditions. Eighty-eight patients undergoing surgical tooth removal entered into the two prospective, parallel, randomized, double-blind studies.
Methods: Patients undergoing surgical tooth removal received a standard local anaesthetic solution (articaine plus epinephrine) before surgery.

Patients were assigned to an injection of peripheral 2 mg morphine either into non-inflamed (Trial I) or inflamed (Trial II) submucous tissue before the surgery. Patients who received an intramuscular

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morphine in the upper arm were concomitantly given 1 ml isotonic saline (NaCl) as a submucous injection. Patients who received a submucous injection of morphine peripherally were concomitantly given an intramuscular injection (IM) of 1 ml of NaCl in the upper arm. Postoperative pain intensity was assessed by the numeric rating scale every 30 min for the first 2 h and then every hour for the next 8 h after surgery. In addition, patients recorded the occurrence of side effects and the supplemental consumption of ibuprophen and codeine + paracetamol combination tablets.

Results: Of the eighty-eight original participants, nine patients (4 patients in Trial I and 5 patients in Trial II) were withdrawn for protocol noncompliance and loss at follow-up. Thirty-one patients in trial I and forty-eight patients in trial II were analyzed. Patients receiving 2 mg morphine into non-inflamed tissue did not show any further reduction in pain scores and pain medication consumption compared to IM morphine group (Trial I).

In patients receiving 2 mg morphine into inflamed tissue, pain scores at rest were reduced to a similar extent in both groups at all measurement times up to 10 h in the follow-up (Trial II). At the same time, in the area under the curves pain scores on swallowing between 2 and 6 h in the peripheral morphine group (5.2 ± 5.6) were significantly lower than in the IM morphine group (9.3 ± 7.3, $p = 0.03$), demonstrating the marginal analgesic efficacy of additional morphine. Sedation scores were significantly higher in the peripheral morphine group only 1 h after surgery in Trial I ($p = 0.008$). The time to first analgesic intake was similar between groups. No serious side effects were reported.

Conclusions: Our results showed in patients undergoing surgical tooth removal that injection of 2 mg of morphine into inflamed tissue results in significantly lower pain scores on swallowing in the early postoperative state while administration into non-inflamed tissue is not effective.

Implications: Our studies indicate that the peripheral administration of opioids, at the doses and conditions set out for these two studies, produces significant analgesia by a pharmacologically specific mechanism that is active in chronically, but not acutely, inflamed tissue. Thus, consistent with preclinical experimental studies, the requirement of an inflammatory process for the occurrence of the peripheral opioid effects is also found in the clinical setting.

1. Introduction

Opioids are usually administered systemically to control pain. However, opioid receptors are known to be present on cutaneous sensory nerves in rats and humans. The peripheral administration of opioids has been found to produce analgesia without systemic side effects in humans [1]. However, subsequent, properly designed studies clearly document that there is in fact no analgesic effect of intra-articular morphine [2,3]. The recent meta-analyses indicated a statistically significant reduction in VAS scores for peripherally applied opioid at 6–8 and 12 h postoperatively; however, the effect sizes were small and may not be of clinical relevance. Meanwhile, meta-analysis indicated a significant increase in time to taking first analgesic of 2.5 h for peripheral opioid vs. placebo which may be of clinical relevance [4].

Peripherally administered opioids produce negligible analgesia in uninflamed tissue but potent analgesia in inflamed tissue [5]. It has been shown that the administration of 1 mg morphine together with the local anaesthetic at the site of inflammatory tooth pain results in significant and long-lasting improvement of post-operative analgesia following dental surgery [6,7]. These trials tested morphine in a similar dental surgery model, but with limited sensory assessments and without intramuscular morphine as control [6,7].

Important prerequisites for the occurrence of peripheral analgesic effects of the opioids are accessibility to the painful site, presence of clinically relevant pain, signs of local inflammation, exclusion of a fast systemic absorption, and adequately potent analgesic substances [8]. The oral cavity can fulfil all these requirements. Local inflammation, in particular, has been shown to be crucial for the peripheral action of opioids. It has been shown that the opioid receptors at the peripheral nerve endings directly relate to local inflammation and can be reversed by opioid antagonists [8].

The purpose of this study was to examine the clinical utility of peripheral opioid action in a site other than an intraarticular space using a clinical model of dental surgery that allowed for direct infiltration of morphine in and about the surgical wound. We hypothesized that the peripheral administration of morphine is superior to the same doses of intramuscular administration of morphine after inflammatory tooth pain model. The study was designed to compare at the site of inflammatory and non-inflammatory tooth pain, under randomized double-blind conditions, the effects of morphine versus saline solution, with intramuscular administration of morphine as control for dental surgery.

2. Patients and methods

2.1. Patients

A single-dose active-controlled, parallel-group randomized double-blinded study was carried out in two trials on patients who had undergone surgery to remove one impacted mandibular third molar at the Outpatient Clinic Department of Oral Surgery at Oulu University Hospital. The analgesic efficacy of peripheral morphine treatment was examined under the following conditions in a clinical model of dental pain: administration of morphine into non-inflamed submucous (Trial I) and inflamed (Trial II) submucous tissue. Patients in Trial I presented without any signs of inflammation and pain in their mandibular third molars. Patients in Trial II presented with severe localized inflammation (pericoronitis) and pain in their mandibular third molars.

Pericoronitis refers to inflammation of gingiva in relation the crown of an incompletely erupted tooth. Pericoronitis may be acute, subacute, or chronic. There is constant inflammation in the area, so it is always considered subacute or chronically infected, even acute symptoms are not present. Subacute pericoronitis symptoms are pain, dysphagia, intraoral swelling, halitosis pus discharge, sore

throat. The individual does not have limited mouth opening. This is a distinguishing feature from acute pericoronitis.

Permission for this study was obtained from the local Ethics Committee and the patients signed an informed and appropriate written consent before taking part in each trial. Both trials were conducted in the same hospital in a double-blind, randomized, parallel group and active-controlled manner.

2.2. Inclusion and exclusion criteria

Healthy patients aged 18–40 years and scheduled to undergo surgical removal of one impacted mandibular third molar were recruited for the study. Patients with acute pericoronitis or other regional infections, a known sensitivity to any of the trial drugs, or any acute or chronic diseases were excluded from these two trials.

2.3. Study design

Patients came to the outpatient clinic of the Department of Oral and Maxillofacial Surgery for elective surgery for extraction one impacted mandibular third molar. Trial I patients presented without any signs of inflammation and pain, and Trial II patients had signs of localized inflammation and pain in a mandibular third molar.

In both trials patients received a perineural local anaesthetic (articaine plus epinephrine, 4% Ultracaine with 1:100.000 epinephrine; Sanofi, Vienna, Austria) injection of the mandibular nerve. Patients were randomly assigned, according to a computerized random-number generator, to receive either an intramuscular or submucousal injection of 2 mg morphine (morphin hydrochlorid, Leiras Takeda Pharmaceuticals Ab, Helsinki, Finland) before surgery. We used one random list for both trials. The treatment group was chosen randomly using sealed instructions given to a surgical nurse before the patient was given local anaesthesia. This nurse was not involved in the operation or patient care.

Patients who received 2 mg morphine hydrochloride (2 mg/ml) intramuscularly in the upper arm were given concomitantly a submucousal injection of 1 ml isotonic saline. Patients who received morphine peripherally as a submucousal injection of 2 mg morphine hydrochloride were given concomitantly an intramuscular injection of 1 ml of isotonic saline in the upper arm. Neither the patient nor the surgeon knew the site on which peripheral morphine had been injected.

Third molars were removed under local anaesthesia by the same oral surgeon (K. A.) according to a standardized procedure. Using a buccal approach, minimal bone was removed with a burr.

2.3.1. Primary outcomes

A numerical rating scale (NRS: 0 no pain, 10 worst pain imaginable) was used to evaluate postoperative pain [9]. Baseline assessments of pain intensity (NRS) were made just after the operation. Response to treatment was evaluated by the patients' self-rating of pain intensity (NRS) first at rest and then on swallowing. The study coordinator instructed patients in the use of pain medication and keeping a pain diary with assessment scales. Patients assessed pain intensity every 30 min for the first 2 h and then every hour for the next 10 h after surgery.

2.3.2. Secondary outcomes

The presence and intensity of side effects and pain medication consumption were evaluated simultaneously with pain intensity assessments. The effect of the local anaesthesia was scored as either effective or not. Postoperative sedation was evaluated at 1 and 2 h on a four-point categorical verbal rating scale: 3 = strong, 2 = moderate, 1 = weak, 0 = no effect. Patients were reviewed in the outpatient department on the 14th postoperative day, and pain diaries were collected. Pain medication was available to any patient, as needed, throughout the study. All patients were discharged with a free-of-charge pain medication of twenty ibuprofen 800 mg (Burana® Orion, Finland) tablets and paracetamol (500 mg) codeine (30 mg) combination (Panacod®, Sanofi), to use if sufficient pain relief was not reached with the study treatment.

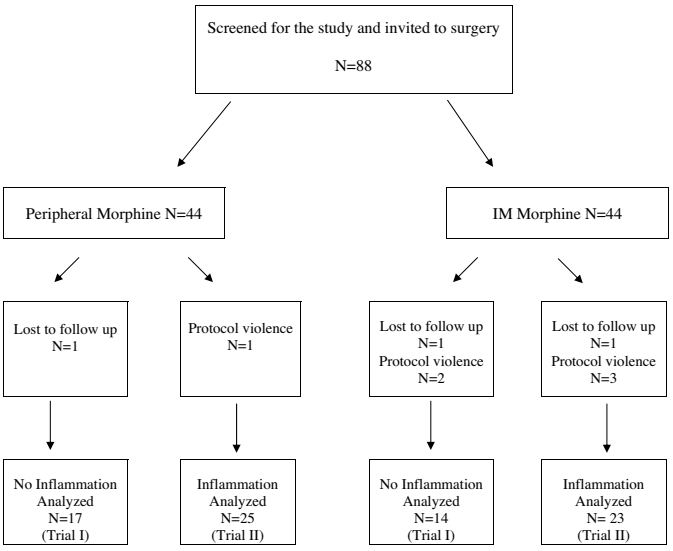

Fig. 1. Flow chart of screened, treated, and evaluated patients.

2.4. Statistical analysis

Sample size calculations were performed by approximation to the normal distribution. According to data from a previous study [10], the standard deviation of the change in NRS scores over time could be assumed to be approximately 2. With a two-sided significance level of 5% and a power of 90%, it was estimated that 16 patients should be included in each group. To compensate for unbalance in group sample sizes due to congruent randomization list and a drop outs, a total of 88 subjects were included in the study. The statistical software package SPSS for Windows version 22 was used for data analyses. NRS pain scores were plotted against time and the area under the resultant curves was calculated. The AUC was calculated for the postoperative NRS measurements from 0 to 2 h, 2 to 6 h and 6 to 10 h.

Statistical analysis was performed using Mann–Whitney *U*-test for skewed data and Student's *t*-test for normally distributed data. Data are presented as means with standard derivation (SD) or median with 95% CI and range as appropriate; two-tailed *p*-values are presented. The times to use of rescue medication were compared using Kaplan–Meier survival curves and differences between treatment groups were tested using the log-rank test.

3. Results

A total of 88 patients were recruited to be assigned to either the intramuscular group or the peripheral morphine group. Nine patients were withdrawn for protocol non-compliance and loss of follow-up (Fig. 1). After these exclusions we analyzed the remaining 79 participants. We randomly assigned patients to Trial I or Trial II based on the presence and absence of inflammation. There were 31 patients in the group with no inflammation (Trail I) and 48 in the group with inflammation (Trial II). There were no significant differences between the groups with respect to demographics and patient baseline characteristics (Table 1).

Table 1
Patient demographics and patient baseline characteristics (mean; Std. Deviation) were comparable between the groups. Duration of local anaesthesia time was significantly longer at peripheral morphine group in Trial I ($p = 0.046$), other clinical characteristics of the study patients remain similar.

Variable	Trial I (no inflammation) n = 31		Trial II (inflammation) $n = 48$	
	Peripheral morphine	IM morphine	Peripheral morphine	IM morphine
Number of patients	17	14	25	23
Age	23 (2.7)	25 (6.1)	24.6 (4.1)	23.5 (4.3)
Gender ratio male/female	3/14	5/9	7/18	9/14
Weight kg	66.5 (9.3)	63.4 (14.5)	64.1 (11)	67.7 (14.6)
Height cm	166.6 (5.8)	168.7 (8.9)	168.8 (7.2)	172.1 (9.2)
Pericoronitis[a] subacute/chronic	0/0	0/0	20/5	19/4
Fear of the blockade/operation	3.1 (2.2)	4.5 (2.3)	4.5 (2.8)	3.5 (2.6)
Pain of the blockade	3.7 (1.8)	3 (1.7)	2.8 (2.4)	2.4 (1.7)
Operation time (min)	19 (16)	16 (9)	19 (10)	15 (6)
Sensation of local anaesthesia after operation (min)	51 (48)*	90 (55)*	66 (60)	73 (46)
Time to use of rescue medication (hours)	2.7 (2.7)	2.9 (2.9)	2.1 (2.3)	2.4 (2.4)

[a] Pericoronitis (acute, subacute, or chronic) refer to inflammation of gingiva in relation the crown of an incompletely erupted tooth.
* Significant different between groups ($p < 0.05$).

Table 2
The numerical rating scale pain score expressed as area under the curve (AUC) at rest and on swallowing during the first 10 h and pain medicine consumption after removal of a single impacted mandibular third molar. AUC pain scores on swallowing between 2 and 6 h after surgery were significantly lower in peripheral morphine group than active control IM group in Trail II. Sedation assessment after surgery by rating the intensity on a 4-point verbal scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe), Sedation scores were significantly higher in peripheral group at 1 h in Trial I, and 1 and 2 h after surgery if Trial I and II data were analyzed together. Requirement for analgesia during the operation and first postoperative day (1. Postop.) was similar. The mean analgesic consumption (mg), Nonsteroidal anti-inflammatory (NSAID) drug consumption is described as Ibuprofen consumption, by converting other analgesics into a comparable dosage of ibuprofen (Panacod® (paracetamol 500 mg + codeine 30 mg) converted as 400 mg iburofen). Data are mean (SD) (Student's *t*-test and Pearson Chi-Square test).

	Total (Trail I and II) $n = 79$			Trial I (no inflammation) $n = 31$			Trial II (inflammation) $n = 48$		
	Peripheral morphine	IM morphine	*P*	Peripheral morphine	IM morphine	*P*	Peripheral morphine	IM morphine	*P*
Pain at rest AUC									
0–2 h	3 (2.8)	2.1 (2.3)	0.11	2.1 (6.4)	1.9 (2.5)	0.72	3.2 (3.2)	2.2 (2.3)	0.09
2–6 h	9.1 (4.2)	10.4 (1.5)	0.24	9.7 (4.6)	10. (5.9)	0.78	8.6 (3.9)	10.6 (6.4)	0.21
6–10 h	8.5 (5)	8.4 (5.5)	0.92	7.6 (3.4)	8.6 (4.5)	0.49	9.1 (5.9)	8.2 (6.1)	0.62
Pain on swallowing AUC									
0–2 h	1.3 (1.9)	1.5 (1.9)	0.51	0.9 (1.4)	1.5 (2.1)	0.38	1.4 (2.3)	1.6 (1.9)	0.85
2–6 h	5.3 (5.1)	8.9 (7.4)	0.01	5.6 (4.5)	8.4 (7.8)	0.21	5.2 (5.6)	9.3 (7.3)	0.03
6–10 h	5.9 (5.9)	6.9 (5.8)	0.45	5.6 (5.3)	7.0 (6.7)	0.53	6.1 (6.4)	6.8 (5.2)	0.66
Sedation									
1 h	17/21/3/1	27/9/1/0	0.03	4/11/2/0	11/2/1/0	0.008	13/10/1/1	16/7/0/0	0.43
2 h	15/14/12/1	23/11/2/1	0.03	5/8/4/0	9/4/1/0	0.1	10/6/8/1	14/7/1/1	0.1
Operation day consumptions (mg)									
NSAID	1188 (776)	1114 (722)	0.79	952 (819)	1174 (1052)	0.34	1047 (800)	1151 (930)	0.60
Codeine	33 (48)	19 (27)	0.42	25 (44)	31 (59)	0.68	28 (45)	26 (49)	0.87
1 Postop day consumptions (mg)									
NSAID	1858 (747)	1723 (574)	0.59	1840 (903)	1817 (1080)	0.93	1848 (834)	1783 (921)	0.75
Codeine	42 (52)	23 (37)	0.27	31 (49)	36 (61)	0.71	36 (50)	32 (53)	0.72

The duration of effective local anaesthesia time was significantly shorter in the peripheral morphine group in Trial I, 51 (48) min vs. 90 (55) min (mean (SD)) (Table 1). Other clinical characteristics of the patients were similar (Table 1).

Patients receiving 2 mg morphine into non-inflamed tissue (Trial I) did not show any further reduction in pain scores compared to IM morphine group (Table 2).

In patients receiving 2 mg morphine into inflamed tissue (Trial II), pain scores at rest similar compared to the control group at all measurement times up to 10 h flow up (Fig. 2, Table 2). At the same time, AUC pain scores on swallowing between 2 and 6 h after surgery were significantly lower in the peripheral morphine (5.2 ± 5.6) than in the active control IM (9.3 ± 7.3) groups ($p = 0.03$), demonstrating the marginal analgesic efficacy of additional morphine (Fig. 3, Table 2).

The time to first analgesic intake and the total amount of and supplemental NSAID and codeine were similar between groups (Table 1). Sedation scores were significantly higher in the peripheral group at 1 h after surgery in Trial I. Moreover sedation scores were significantly higher in peripheral morphine groups compared to the IM groups if Trial I and II data are analyzed altogether 1 and 2 h after surgery. No serious side effects were reported.

4. Discussion

Once the local anaesthetic effect wore off, this effect became significant only after 2 h but lasted up to 6 h. Meanwhile Trial I results suggest that under the non-inflamed conditions of the study protocol, there is no value in utilizing a morphine submucous injection at the surgical site for third molar extraction analgesia.

Several studies in humans and animals have shown that peripheral applications of low doses of opioids induce significant analgesia under inflammatory conditions [5–7]. Our results are in line with these previous studies demonstrating the effect of local administration of morphine in inflamed oral tissues [5–7].

Likar et al. showed in patients undergoing dental surgery that injection of 1 mg of morphine into inflamed tissue results in significant and prolonged postoperative analgesia, whereas administration into non-inflamed tissue or perineurally is not effective [6]. Thus, consistent with our own and other studies, the

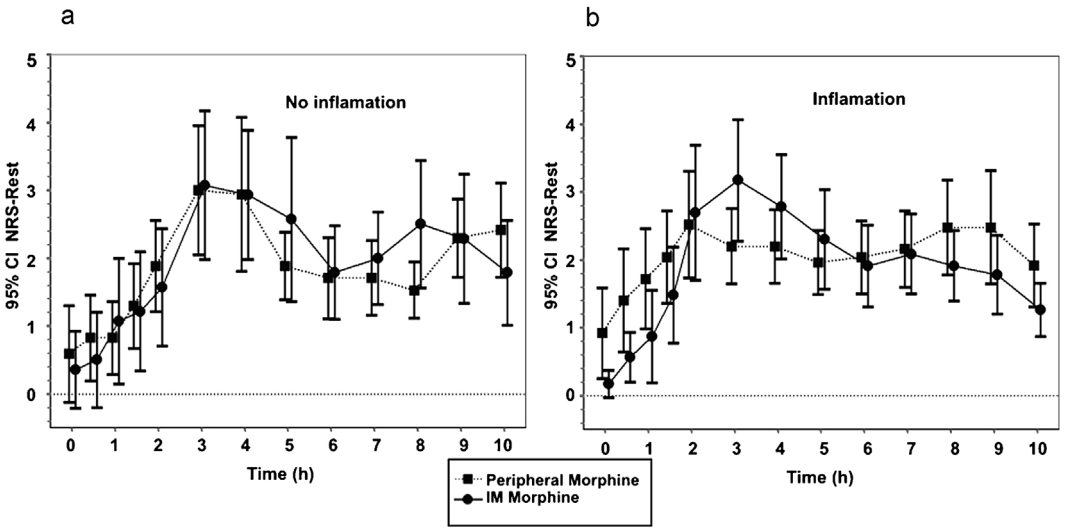

Fig. 2. Postoperative NRS pain scores (median, 95% confidence interval (CI)) at rest after third molar extraction on the IM morphine and peripheral morphine injection into non-inflamed (a, Trial I) and inflamed (b, Trial II) submucous tissue. No significant difference between groups.

requirement of an inflammatory process for the occurrence of peripheral opioid effects is found in the clinical setting. Dionne et al. demonstrated that a low dose of morphine administered into the intraligamentory space of a chronically inflamed hyperalgesic tooth produced dose-related naloxone-reversible analgesia. These data support the hypothesis that peripheral opioid analgesia can be evoked in a clinical model of endodontic pain characterized by chronic inflammation but not in a surgical model of acute pain and inflammation [5].

Kaczmarzyk et al. found that peripheral administration of morphine with local articaine anaesthesia in inflamed oral and maxillofacial tissues results in significant improvement of intra- and post-operative analgesia. The analgesic effect appears soon after the administration of morphine and lasts for about 12 h [11].

According to the meta-analysis by Nielsen et al. [4] in the subgroup for dental surgery, there are statistically and clinically significant decreases in VAS scores for peripherally applied opioid vs. placebo at 6–8 and 12 h postoperatively, with two studies [7,11] of inflammation of peripheral tissue reporting larger and significant effect sizes.

These findings agree with previous suggestions based on experiments in laboratory animals that pointed towards an important role for inflammation-induced upregulation of peripheral opioid receptors in peripheral opioid analgesia [8]. Peripheral opioid receptors have been suggested to be involved in analgesic effects of injected opioids [12] and endogenous opioid peptides secreted from immune cells at the site of inflammation [8].

This study has some potential limitations. Because we randomized both trials together, the number of subjects in each trial is different, making Trial II more powerful to detect pain differences than Trial I.

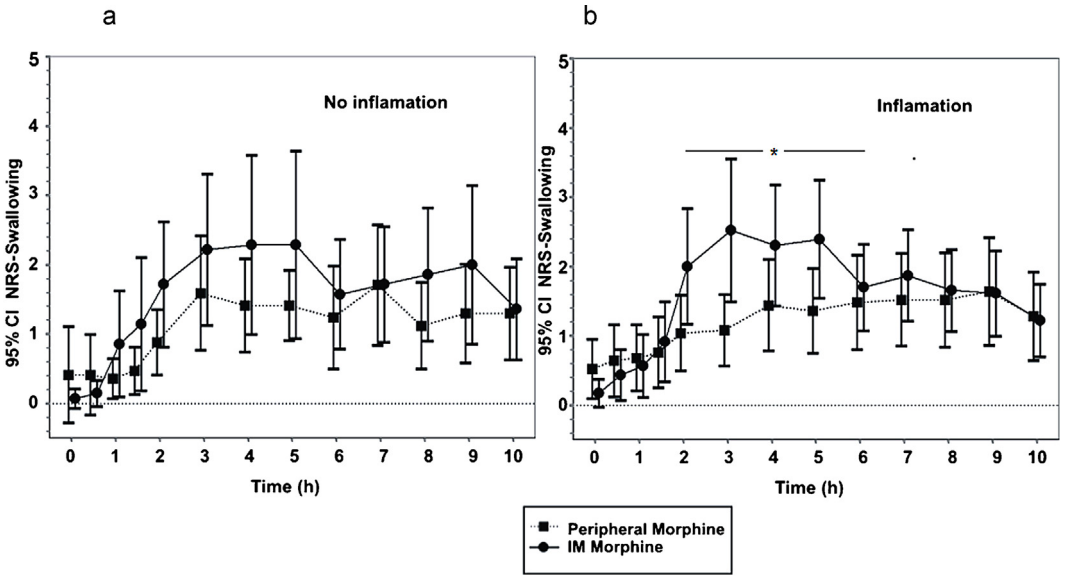

Fig. 3. Postoperative NRS pain scores (median, 95% CI) on swallowing after third molar extraction on the IM morphine and peripheral morphine injection into non-inflamed, (a, Trial I) and inflamed (b, Trial II) submucous tissue. AUC pain scores on swallowing were significant lower between the groups at 2–6 h after dental operation in the inflammation. * Significant different between groups ($p < 0.05$).

5. Conclusions

Our results showed in patients undergoing dental surgery that injection of 2 mg of morphine into inflamed tissue results in significant lower pain scores on swallowing and prolonged postoperative analgesia whereas administration into non-inflamed tissue was not effective. Thus, consistent with experimental studies, the requirement of an inflammatory process for the occurrence of peripheral opioid effects is also found in the clinical setting.

6. Implications

Under the conditions of non-inflamed tooth pain in our protocol design in Trial I, submucous injection of 2 mg morphine did not result in significant analgesia. We found that in Trial II morphine produced a definite reduction in postoperative pain intensity only on swallowing compared with active control, and this was seen during early postoperative phases.

The effect of peripherally applied morphine in chronically inflamed tissue in our study was statistically significant, but clinically of moderate effect-size and of only a few hours duration. Therefore, the clinical implication for daily dental or oral surgical practice is not a major one.

Conflict of interest

The authors declare no conflicts of interest.

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