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Editorial comment

Why do we have opioid-receptors in peripheral tissues? Not for relief of pain by opioids

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In this issue of the *Scandinavian Journal of Pain*, Ethem Akural and coworkers [1] report pain relieving effect of peripheral morphine after surgical removal of third molars from inflamed tissue. The authors compared morphine 2 mg injected locally with intra-muscular injection. Their analyses indicated that morphine produced better pain relief when injected locally into inflamed tissue around the molar-bed, compared with morphine injected systemically into a muscle. The effect appeared to depend on local inflammation because they did not observe this analgesic effect of morphine injected into non-inflamed tissue. The classification of tissue with an inflammatory or a non-inflammatory reaction was made prior to randomization. The most prominent difference in pain relief appeared between 2 and 6 h after the surgical intervention.

1. Peripheral analgesic effects of morphine

The concept of injecting morphine into *loco dolenti* was presented by the Finnish professor Knut Felix von Willebrand as early as 1876 [2]. He focused on the undesirable opioid side effects of systemically administered morphine, and he presented four case reports that indicated that morphine should be administered into the painful tissue. About 100 years later peripheral antinociceptive effect of morphine was demonstrated after subcutaneous injection of prostaglandin E_2 in rats [3], and the degree of a local inflammatory process and effects of peripheral opioids seemed to be related [4]. However, the degree of acute local inflammation and how this relates to human pain perception has not been fully explored.

2. Third molar removal causes moderate-severe pain and can test analgesic effects

Single dose analgesic drug trials on acute pain-relief are often performed on patients after removal of 3rd molars. Pain, swelling, and redness are easy to register and most patients experience moderate to severe pain and need analgesic treatment [5].

This pain model is well suited for studies of acute inflammatory pain. However, there are few randomized controlled trials (RCTs) of the effect of locally injected morphine using this pain model. A recent meta-analysis by Nielsen et al. included only one placebo-controlled RCT [6]. In that quantitative systematic review they found a statistically significant effect of locally injected morphine between 6 and 8 h, and the studies with inflammation of peripheral tissue reported larger effect sizes. Although the studies found statistically significant effects, the effects are of limited clinical relevance with a mean difference of only12 mm on a visual analogue scale (VAS) of 0–100 mm.

3. Arthroscopic knee interventions cause only mild-to-moderate pain and are poor analgesic test models of intra-articular morphine

The analgesic effect of peripheral morphine has been studied in several other acute pain models but mostly by studies of knee arthroscopic procedures. The more than 50 RCTs designed to test the analgesic effect of intra-articular (IA) morphine compared with placebo resulted in conflicting results. Most of these RCTs of peripheral morphine included patients receiving test-drugs at the end of surgery, before baseline pain could be assessed [7].

4. In order to measure pain relief, obviously the patient must have pain

This design, giving test drug without knowing if the patient has pain, violates well-established principles of pain- study methodology requiring a baseline pain intensity that is large enough for effects of a test drug to be measurable [8–10]. Results from trials where the patients are included while anesthetized, a "pre-emptive" design, are difficult to interpret. The researchers seemed to assume that pain after knee arthroscopic procedures always is of significant intensity. The pain experienced by untreated patients was not documented. Moreover, published trials indicated that the variance was large, e.g. mean visual-analogue-scale (VAS) pain-intensity in the placebo group was 36.5 mm (on a VAS of 0–100 mm)

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and the standard deviation (SD) was 28 mm in one study [11] and mean 37 mm and SD = 32 mm in another [12].

5. Therefore, we designed a new trial-model giving test drug after documenting baseline pain

The intra-articular catheter technique enables the researcher to observe the natural course of pain after IA-procedures and to include patients with moderate or severe pain [13,14]. Observations of the natural course of pain after knee arthroscopic interventions and analyses of possible risk factors for significant postoperative pain revealed a statistically significant gender difference: women have more pain than men [15]. Two RCTs with this IA catheter design comparing IA morphine with IA placebo, including only patients with moderate-to-severe pain are published. Both studies documented that IA morphine has no analgesic effect [16,17].

6. Pain-relief can be documented only if there is proven significant pain before test-treatment

For a pain-intensity study to have predictive power, it must be able to detect differences between a new drug and placebo or a new drug and a known active pain relieving drug. A patient's ability to discriminate between two pain-relieving treatments is limited if pre-treatment pain intensity is low [18]. Clinical trials comparing two differently effective analgesics, e.g. morphine and paracetamol, may fail to show a difference if pre-treatment pain intensity is low, and erroneous evaluation, e.g. that paracetamol is as effective as morphine, may be the result [9].

Postoperative pain trials on surgical patients will often include patients without pain or with only mild pain if the intervention starts before surgery or before the anaesthetic has worn off, i.e. before the patient can experience pain. In such studies in which drugs are given pre-emptively, baseline pain cannot be measured. This type of study-design can only be used when the pain model has a documented high incidence of significant pain after surgery, and the variance has to be low.

Valid acute pain trials are performed on patient populations experiencing moderate or severe pain on inclusion. Performing RCTs on patients with unknown or little pain is scientifically unsound. They may even be unethical, because they offer a minimal chance of finding effects even of potent analgesic drugs [19]. Third molar removal is a standardized surgical intervention and most patients will experience pain [20].

However, pain intensity varies greatly after most kinds of surgery [21], and therefore inclusion of only patients with moderate to severe pain is necessary [22]. Morphine can be injected locally to patients with significant postoperative (baseline) pain. This was done after temporomandibular joint surgery [14] and after arthroscopic knee surgery [16,17], and local morphine injection did not have any analgesic effect in these correctly designed studies.

7. The Akural et al. study [1] had no documentation of baseline pain

In the study by Akural et al. morphine was injected locally before local anaesthesia had dissipated and before the acute postoperative pain was known, i.e. a pre-emptive study design. Pain intensity was generally low, markedly decreasing the assay sensitivity [22]. However, the confidence intervals were surprisingly narrow, indicating a modest variance. Interestingly, patients with per-operative inflammation reported lower pain intensity when randomized to local compared to systemic morphine, and between 2 and 6 h the difference was statistically significant. The authors concluded that there may be some pain relieving effect of peripheral morphine injected into inflamed tissue after 3rd molar removal, but they also question the clinical significance [1].

8. Explanatory and pragmatic clinical trials

In order to fully interpret their study, it may be necessary to know if the purpose of the Akural et al. trial was explanatory or pragmatic.

An *explanatory trial* seeks to establish a biological principle of a treatment and its results may have validity outside the particular clinical condition studied in the trial.

A *pragmatic trial* seeks to find the best way to treat patients in a specific clinical situation [9,23]. An explanatory study generates a hypothesis; a pragmatic study tests the hypothesis. In a pragmatic clinical trial the null hypothesis stating no difference between the treatments compared will be rejected or accepted.

Inspecting the figures displaying pain intensity in the observation period may be helpful [1].

The treatment groups in the two parts of their study (patients with or without inflammatory changes) have almost equal acute pain course, except during the time period between 2 h and 6 h in the inflammation study arm. The authors report a statistically significant difference and reject the null hypothesis.

They discuss limitations, but we should add some more: The study seems to aim at answering if peripheral morphine should be included in the treatment of 3rd molar removal patients, i.e. a pragmatic study.

However, the analyses did not address the multiple testing problems properly. Table 2 in their paper presents the main results [1] and displays all together 36 repeated statistical tests (Student's *t*-test or Pearson Chi square). Statistical significance was reported when *p*-values were less than 0.05, without any correction for multiple tests.

If correction by the Bonferroni procedure was applied, all significance would have disappeared as $p < 0.05$ divided with the number of statistical tests – 36 – is 0.0014. So, for these differences to have been statistically significant a *p*-value less than 0.0014 would have been necessary. However, the Bonferroni procedure is not an appropriate procedure for these results. There are more reasonable methods for dealing with multiple comparison [24], but we should read the crude, uncorrected, *p*-values with caution.

9. Peripheral analgesia caused by opioids and by NSAIDs – do they exist?

Why should we do more studies of peripheral analgesia? The early enthusiasm from the "discovery" of pain relief after peripheral morphine is now over [25]. Still, infiltration of local anaesthetics in combination with opioids, non-steroidal anti-inflammatory drugs (NSAIDs), or adrenaline is common practice [26]. Whether the effects of NSAIDs are related to the classical inhibition of cyclo-oxygenases or by cyclo-oxygenase-independent effects [27] are not fully explored. Reports of nephrotoxic effects after local infiltrated ketorolac indicate that the observed effects and side effects in fact may be systemic [28].

10. Conclusion

The acute pain trial model using 3rd molar extraction/surgical removal used in the study by Akural et al. can be well suited for studies of acute pain and possible effects of peripherally acting analgesics. However, documentations of pain relief by peripheral mechanisms (as opposed to CNS-mechanisms) of morphine (in

inflamed tissues), NSAIDs, or other analgesics, are weak and must be proven in patient populations with significant baseline pain.

Conflict of interest

The author declares no conflicts of interest.

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