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Editorial comment

Warming and alkalinisation of lidocaine with epinephrine mixture: Some useful aspects at first glance, but not so simple?

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In this issue of the *Scandinavian Journal of Pain*, Kuivalainen and coworkers report a study on important details when lidocaine with epinephrine (adrenaline) is used for local infiltration analgesia [1]. It is well known that adding epinephrine to lidocaine causes faster onset, more solid and longer duration of analgesia, and it reduces systemic toxicity and improves perioperative haemostasis [2]. Kuivalainen and coworkers studied if adjusting pH and temperature of the local anaesthetic solution could further improve pain on infiltration, onset and duration of anaesthesia [1].

1. What happens to the effects of lidocaine with epinephrine when pH and temperature are increased?

A solution of lidocaine with epinephrine is acidic (low pH compared to tissue fluids), it diffuses slowly through tissue barriers, it has room temperature or colder, and it causes pain during and immediately after injection. The clinical results of modifying such a pre-made solution of lidocaine and epinephrine to make it less acidic and closer in temperature to that of body fluids are not obvious: Will the modified mixture cause less pain during infiltration, as the authors intended? Will the modified mixture result in more rapid onset of analgesia and readiness for surgery? Will these modifications result in a more potent local anaesthetic mixture? Will the duration and quality of analgesia improve?

The mechanisms for these different clinical effects are not identical, thus effect on one aspect does not imply benefits on others. In the choice between a modified mixture and the original, decision should be taken on a total evaluation of all qualities that may change.

2. Pain on infiltration of the local anaesthetic

The mechanism for pain during infiltration is due to direct pain stimuli and trauma to the tissues by the needle, from increased pressure (and possibly ischaemia) in the tissue and from physical–chemical irritation of the pain sensitive nerve endings. The local anaesthetic molecules have an analgesic effect via blockade of sodium channels, but this takes time, it does not happen at the exactly same second they are infiltrated. Therefore, the injection pain may be reduced if direct stimulations of thermo-receptors and acid-receptors are reduced. In the study of Kuivalainen et al. [1], they adjusted the temperature up to cause less stimulation of cold pain receptors, and they reduced the number of H^+ ions, thus stimulating less the H^+ sensitive pain receptors. The results are as expected: less infiltration pain [1,3].

3. Onset of local analgesia

While the pH adjustment also should allow local anaesthetic molecules to diffuse more readily into nerve fibres and act more rapidly on transmission of pain-impulses from pain receptors in nerve-endings, this is more difficult to study because observing time course of onset will be important and this is not easily done accurately in a clinical situation.

In the study, they used a composite statement of pain-report from the patients during the bone-marrow puncture at 2 min after infiltration of local anaesthetic. While such a 2 min delay is somewhat short to allow full effect of the local anaesthetic, one may expect the less acid and therefore faster acting solution to be superior.

On the other hand, the local anaesthetic was not infiltrated into but close to periost, so that 2 min may be too short for the local anaesthetic to have any effect here. Thus, it may be argued that waiting longer before starting the procedure could have resulted in a clear difference between the groups. This potential difference in onset time would not have been present only 2 min after starting the local anaesthetic infiltration.

Although practically difficult to observe, there may also be a difference in the pain from skin puncture, the pain from movement of harvest needle through subcutaneous tissue and the pain from penetration of periost and bone. Actually, the authors do some differentiation, they ask for pain during puncture, pain during aspiration, pain during biopsy and pain immediately after the procedure. Interestingly, the pain immediately after the procedure

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is significantly stronger ($p = 0.017$) with the modified mixture and there is a tendency (ns, $p = 0.17$) for more pain during aspiration.

4. Is warming the local anaesthetic solution counterproductive?

We can only speculate why this is so: Maybe warming will counteract vasoconstriction by the epinephrine, and maybe the more soluble form at neutral pH is more susceptible to diffusion into vessels and removal from the area?

As the authors also point out, there are limitations in the methodology and design of this study.

The study was not double-blinded and the use of midazolam or alfentanil was not well controlled. Although impact of anxiety on pain is well supported by the study data, we do not know the influence of the analgo-sedative drugs as these have been given in a non-standardized way to patients, probably to those with a special need of anxiolyses or disposition for pain and anxiety.

We do not know from this study whether it is warming or alkalinisation that reduces pain during infiltration, but other studies support both measures [3,4]. Whereas warming is simple and safe to perform, alkalinisation implies a minor risk of contamination and errors in dosing and mixing of two solutions.

Epinephrine containing solutions need to be in a refrigerator when stored for prolonged times, and they are sometimes used at lower than room temperature. This may increase irritation of cold-pain receptors further, but also have other effects on vasomotor tone and analgesia per se [5].

While leaving some questions uncovered and others with controversies, the study of Kuivalainen and coworkers [1] shed light on some very basic and interesting mechanisms of local anaesthetic infiltration. Still, while reducing pain during injection, the conclusion on the overall benefit of warming and neutralising epinephrine containing lidocaine for bone-marrow puncture and harvest is not completely settled.

Conflict of interest statement

No conflicts of interest are declared.

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