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Editorial comment

# Local infiltration analgesia (LIA) and repeated bolus or continuous infusion peripheral nerve blocks for acute postoperative pain: Be ware of local anaesthetic toxicity, especially in elderly patients with cardiac co-morbidities!

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Peripheral nerve blocks for postoperative pain, repeated bolus injections or continuous infusion through catheters placed near a plexus or peripheral nerves is an effective way of relieving localized acute pain after surgery, e.g. femoral nerve block after total knee replacement [1]. Electrical nerve stimulation and ultrasound guided localization of peripheral nerves make this technique more effective [2]. Local infiltration of a large dose of a local anaesthetic drug during major joint surgery and subsequent bolus injection through a catheter left in situ is a recently popularized technique. Total knee replacement is the operation in which such local infiltration analgesia (LIA) is documented to be effective [3,4]. LIA is less effective for pain after hip arthroplasty [4]. In addition to the local anaesthetic, adrenaline and an NSAID are added in the LIA technique. Adrenaline is usually not added for intermittent or continuous femoral nerve block [1,3,4].

## 1. Local infiltration analgesia is simple, but is it safe?

The LIA-technique has become popular because of its simplicity and apparent safety [3,4]. However, both the LIA and the femoral nerve block techniques require relatively large amounts of local anaesthetic drugs in order to be effective. The single dose of ropivacaine for the traditional LIA-techniques is 300 mg, which is above the "officially" recommended maximum dose of 225 mg [5]. Local anaesthetic cardiotoxic and central nervous system toxicity are serious, potentially life-threatening complications.

## 2. Near toxic to toxic plasma concentrations of ropivacaine during LIA and femoral nerve block for pain-relief after knee joint replacement: risk of cardiotoxic events in elderly patients

In this issue of the *Scandinavian Journal of Pain*, Affas and co-workers in Carl-Olav Stiller's research group at the Karolinska Institute publish an investigator-initiated quality study of plasma concentrations of ropivacaine during femoral nerve block compared with plasma concentrations after LIA for total knee replacement [6]. They also measured plasma concentrations of ketorolac, a potential nephrotoxic NSAID, especially in elderly patients with already reduced kidney functions.

In their LIA-patients 300 mg of ropivacaine was co-administered with adrenaline 0.5 mg and ketorolac 30 mg. In the femoral block patients ropivacaine 240 mg *without* adrenaline was administered during the first 24 h, and ketorolac 10 mg was given i.v. every 8 h. The maximal ropivacaine plasma concentration occurred 4–6 h after release of the femoral tourniquet of the LIA. It was significantly higher than the plasma concentrations measured after the last femoral nerve bolus injection of 30 mg ropivacaine (total 24-h dose = 240 mg). They measured up to 1.74 μg/ml plasma in the LIA patients and up to 1.2 μg/ml plasma in the femoral block patients. These are in the concentration-range where signs of toxicity have been observed [7]. Considering that major joint replacement surgery is done mostly in elderly patients, often with cardiac co-morbidity, these plasma concentrations of ropivacaine are worrisome. I agree with Affas and co-workers [6] that this mandates a robust cardiovascular monitoring regime during ongoing femoral block analgesia. LIA patients must have cardiac monitoring during the first few hours after surgery. If a bolus top-up doses of ropivacaine through an indwelling catheter is given 18–24 h after surgery, cardiac monitoring must continue at least for another 6–10 h.

## 3. Acute-phase proteins reduce risk of cardiotoxic reactions

After surgery, acute phase proteins are secreted into extracellular fluids. Acid α-glucoprotein increases in plasma and binds ropivacaine so that the free ropivacaine molecule, which is the cardiotoxic moiety, does not increase as much as the total plasma concentration. This adds a measure of safety in patients receiving continuous infusions of low doses of local anaesthetics. However, we cannot know when secretions of α-glucoprotein are high enough in a specific patient to give this protection against local anaesthetic toxicity.

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## 4. Adrenaline reduces the risk of cardiotoxic reactions because it delays absorption of ropivacaine

Definitely, we know that a more rapid increase in plasma concentrations of a local anaesthetic is more cardiotoxic and CNS toxic, than a slowly increasing plasma concentration [5]. Therefore it is extremely important that the adrenaline is included in the LIA-technique [6].

## 5. Ketorolac is a potent nephrotoxic drug, especially for elderly patients having major joint replacement surgery

The maximal ketorolac plasma concentrations with 30 mg administered during the LIA-technique occurred 1–2 h after release of the tourniquet and was similar to those measured 2–3 h after the last of 8 bolus i.v. injections of ketorolac 10 mg. Ketorolac is a potent NSAID, popular for i.v. administration after surgery because of its significant pain relieving properties. This also means that ketorolac is a potentially dangerous drug for elderly patients with already age-related reduced kidney functions. Although this is a transient nephrotoxic effect, it may mean fluid retention and aggravation of any subclinical or overt cardiac insufficiency. This can precipitating acute heart failure, pulmonary oedema and a critical cardiac event in a patient who is also on the brink of cardiotoxic adverse effects of a rising local anaesthetic concentration.

## 6. Apparent safety of LIA is not documented: unpleasant surprises are lurking in the early postoperative hours

The now large experience of LIA for elderly patients having knee or hip replacement surgery appears to indicate that this is a safe technique for obtaining good to excellent pain relief in the first few hours after surgery [3,4]. However, Affas and co-workers have documented that LIA may expose patients to risks of cardiotoxic concentrations of ropivacaine [6]. The amount of ketorolac administered with LIA results in concentrations similar to plasma concentrations after maximally recommended i.v. doses of this potent nephrotoxic NSAID [6]. These drugs have different adverse effects profiles that may be additive or even synergistic. The age of elderly patients having major joint replacement increases. The amount of age-related co-morbidities will also increase, and sooner rather than later the *apparent* safety of LIA will be unmasked to show a significant risk for our elderly orthopaedic patients.

## 7. There are excellent alternative methods for postoperative pain relief after joint replacement

Alternative, effective and less risky methods for relieving postoperative pain are readily available: A glucocorticoid [8,9], paracetamol plus a low-risk coxib, a gabapentinoid, and a small dose of opioid as needed [4]. Such multimodal pharmacological methods will be better than LIA after the first few immediate postoperative hours, and they can be continued as needed [4]. These patients suffer considerable pain during the postoperative rehabilitation period, for days and even weeks after surgery. At this time LIA and femoral nerve blocks are already old history for these patients, without any documented long term effect on subacute or chronic postoperative pain [4].

## 8. Wound infiltration, transverse abdominis plane (TAP) bock, and paravertebral blocks with large amounts of local anaesthetic drugs may have similar safety risks

Similar “hidden” rare, but potentially serious complications from local anaesthetic toxicity are associated with other techniques that depend on relatively large amounts of local anaesthetic drugs: This is true for wound infusion with catheter techniques, a technique that in fact is not documented to be very effective [10], transverses abdominis plane (TAP) block [11], and thoracic paravertebral block [12]. The latter is not more effective than thoracic epidural analgesia where only small doses of a local anaesthetic drug is needed in combination with minute doses of an opioid (e.g. fentanyl) and adrenaline [13].

## References

[1] Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tønnesen EK, Søballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. Acta Orthop 2007;78:172–9.
[2] Sauter AR, Dodgson MS, Stubhaug A, Halstensen AM, Klaastad Ø. Electrical nerve stimulation or ultrasound guidance for lateral sagital infraclavicular blocks: a randomized, controlled, observer-blinded, comparative study. Anesth Analg 2008;106:1910–5.
[3] Raeder J, Spreng UJ. Local infiltration anaeshthesia (LIA): post-operative pain management revisited and appraised by the surgeons? Acta Anaesth Scand 2011;55:772–4.
[4] Kehlet H, Andersen LØ. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. Acta Anaesth Scand 2011;55:778–84.
[5] Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004;29:564–75.
[6] Affas F, Stiller C-O, Nygårds E-B, Stephanson N, Wretenberg P, Olofsson C. A randomized study comparing plasma concentration of ropivacaine after local infiltration analgesia and femoral block in primary total knee arthroplasty. Scand J Pain 2012;3:46–51.
[7] Scott D, Lee A, Fagan D, Bowler G, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563–9.
[8] Romundstad L, Stubhaug A, Roald H, Skolleborg K, Haugen T, Breivik H. Methylprednisolone reduces pain, emesis, and fatigue after breast augmentation surgery: a single-dose, randomized, parallel-group study with methylprednisolone 125 mg, parecoxib 40 mg, and placebo. Anesth Analg 2006;102:418–25.
[9] Lunn TH, Kristensen BB, Andersen LØ, Husted H, Otte KS, Gaarn-Larsen L, Kehlet H. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth 2011;106:230–8.
[10] Møiniche S, Dahl JB. Wound catheters for post-operative pain management: overture or finale? Acta Anaesth Scand 2011;55:775–7.
[11] De Oliveira Jr GS, Fitzgerald PC, Marcus RJ, Ahmad S, McCarthy RJ. A dose-ranging study of the effect of transverses abdominis block on postoperative quality of recovery and analgesia after outpatient laparoscopy. Anesth Analg 2011;113:1218–25.
[12] Kairaluoma PM, Bachmann MS, Korpinen AK, Rosenberg PH, Pere PJ. Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy. Anesth Analg 2004 Dec;99(6):1837–43.
[13] Norum H, Breivik H. A systematic review of comparative studies indicates that paravertebral block is neither superior nor safer than epidural analgesia for pain after thoracotomy. Scand J Pain 2010;1:12–23.