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Editorial comment

Terminal cancer pain intractable by conventional pain management can be effectively relieved by intrathecal administration of a local anaesthetic plus an opioid and an alfa$_2$-agonist into the cerebro-spinal-fluid

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In this issue of the *Scandinavian Journal of Pain*, Thierry C. Mastenbroek and co-workers at the Department of Anaesthesiology, Pain and Palliative Medicine at Nijmegen Medical Center, The Netherlands, publish an important observational study on intrathecal spinal analgesia [1]. They demonstrate that terminal cancer pain that was intractable by conventional pain management can be relieved by intrathecal administration of a local anaesthetic plus an opioid and an alfa$_2$-agonist.

1. Additive pharmacodynamics effects between drugs causing spinal cord analgesia by different mechanisms

Pharmacological theory predicts that two or more drugs that have positive effects on the same process, but via different mechanisms, should cause additive, sometimes even supra-additive, analgesic effects [2]. When such drugs have different and dose-dependent side-effects, a reduction of doses will be possible with maintenance of analgesia with less side-effects, compared with trying to achieve the same degree of pain relief with only one of the drugs. This principle has been successfully applied in epidural analgesia by combining bupivacaine (or ropivacaine) with fentanyl and adrenaline, the superior effect clearly demonstrated on dynamic pain after major abdominal and thoracic surgery when the patients are mobilized out of bed soon after surgery [3,4].

2. The principle of multimodal analgesia applied to intrathecal pain relief in terminal cancer patients

Mastenbroek and co-workers [1] now confirm that effective pain relief can be achieved with intrathecal analgesia in palliative care of patients with terminal cancer having severe pain that is refractory to systemic multimodal analgesia.

It is well documented that about 10–15% of patients with severe pain from advanced cancer are refractory, or unresponsive, to the conventional WHO-guidelines using the "analgesic ladder" approach with non-opioid and opioid analgesia, as well as co-analgesic drugs [1,5]. Administering morphine alone (or other opioids) intrathecally or epidurally has been shown not to be more effective than intravenous or oral opioids in such patients [6–8].

The local anaesthetic drug is the clue to the striking effect from intrathecal analgesia [1]. However, using only a local anaesthetic drug like bupivacaine intrathecally requires doses that will be equal to giving the patients spinal anaesthesia with the accompanying unwanted effects, such as complete motor-blockade of the legs (= paraplegia), complete loss of sensations including pain from the lower part of the body, low blood-pressure, loss of urinary and rectal continence. This is not a tolerable situation.

By adding an opioid-agonist and an alfa$_2$-agonist, because of the additive analgesic effects between these three drugs, the dose of local anaesthetic drug needed is much reduced for intrathecal as well as epidural analgesia [3,4,9]. Muscle paralysis, low blood pressure, urine and faecal incontinence can all be avoided. For in-depth discussion on these positive interactions in the dorsal horn of the spinal cord between low doses of a bupivacaine, an opioid agonist, and an alfa$_2$-agonist, see [9].

3. A systematic review of low quality intrathecal pain-relief in cancer patients with dubious conclusions

Kurita and co-workers in the European Palliative Care Research Collaborative (EPCRC) published a systematic review of randomized controlled trials (RCTs) studying effects of intrathecal and other neuraxial blocks performed on cancer patients with severe pain [8]. They found few RCTs, all of low scientific quality, and concluded that there is no evidence for analgesic effects of intrathecal opioids with or without "adjuvant drugs". They even concluded

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that neuraxial opioids should not be used in palliative care until "large multicentre RCTs investigating the clinical efficacy of neuraxial analgesics etc. justify their use in the treatment of cancer-related pain" [8]. In effect, these authoritative palliative care experts condemn the use of opioids epidurally or intrathecally for pain related in advanced cancer diseases [8].

4. Absence of evidence from poor quality RCTs of effect is not evidence of absence of effect of intrathecal analgesia

With such a strong, negative statement [8], they have almost "killed" the highly effective practice of intrathecal multimodal relief of otherwise "intractable" pain in 10–15% of patients with advanced cancer disease [5]. Their conclusion has led to treatment-nihilism in palliative care teams without an experienced anaesthesiologist: requests for intrathecal pain relief to pain-teams of anaesthesia-departments have dwindled to almost zero in some places (Audun Stubhaug, Chairman of the Department of Pain Management and Research – personal communication). The only alternative then is palliative sedation with propofol and midazolam with major ethical and practical difficulties.

One reason they came to this negative conclusion is that they focused on opioids without local anaesthetics. It is old news that opioids alone given epidurally or intrathecally is not superior to opioids given parenterally or orally, documented by Vainio and Tigerstedt already in 1988 [6] and in Finland again by Kalso et al. in 1996 [7].

5. "Seeing is believing": intrathecal local anaesthetic with an opioid and an alfa$_2$-agonist is effective when conventional pain management fails

The present study by Mastenbroek and co-workers [1] is valuable because they focus on helping cancer patients with severe pain refractory to conventional pain management. They used intrathecal analgesic drugs aiming directly at the pain transmitting neurones in the "pain-control-gate" of the spinal cord. They use a low dose of bupivacaine and the hydrophobic morphine that is transported in the cerebro-spinal fluid (CSF) over several segments of the spinal cord. Sub-anaesthetic doses of bupivacaine hinder synaptic processes as does morphine acting on pre- and postsynaptic opioid-receptors between the primary and the secondary afferent neurons. They also added clonidine, a potent alfa$_2$-receptor agonist, also active at pre- and postsynaptic receptors. These three drugs inhibit the transfer of pain-signals from the primary afferent nociceptive neurones to the secondary afferent pain neurone in the posterior horn of the spinal cord [9].

Although they report on their experience with nine patients only, their results confirm my experience of clinically impressive pain relief with minimal adverse effects of appropriately performed and monitored intrathecal therapy. They experienced slight hypotension in one patient due to clonidine, and slight leg weakness in one patient due to bupivacaine, both side-effects resolved by adjusting dose of clonidine and bupivacaine, respectively [1].

Nitescue's group in Gothenburg also published convincing results with intrathecal bupivacaine and morphine, focusing on the importance of paying attention to details and having a well trained team that help the patients receive this treatment at home [10–13].

6. We do not need large prospective studies to verify the findings of Mastenbroek et al.!

I disagree with Mastenbroek and co-authors in their concluding remarks "*that large prospective randomized controlled studies are needed to verify these results*" [1]. Pain that is intractable by "conventional pain treatment" increases tremendously the already difficult terminal phase of cancer-diseases, difficult for the patients as well as their relatives and friends.

When we already have this effective treatment, why do we need to do large prospective RCTs to prove that it is effective? This is not ethical! Such a study comparing an effective treatment with something else that is less effective – how can you explain to the patient and relatives that you want to do a study to compare an effective pain treatment with something that is less effective, often with severe and difficult to treat adverse effects, especially nausea and vomiting - in order to prove that the effective treatment in fact is effective? Such considerations are the extreme results of "evidence-based medicine", a philosophy that can have such strange consequences.

7. Adrenaline is superior to clonidine as an alfa$_2$-agonist in the spinal cord dorsal horn

When clonidine is added to the intrathecal multimodal infusion, there is a tendency to sedation and hypotension [1,14]. This may be of minor importance for bed-ridden terminal cancer-patients. However, in less sick cancer patients who can ambulate, hypotension and sedation from clonidine is a problem. The hypotensive and sedative effect of clonidine is not a problem when another alfa$_2$-receptor agonist is used instead of clonidine: Adrenaline (epinephrine), has been widely used with bupivacaine and fentanyl for epidural analgesia, the direct spinal cord effects being emphasized also when this triple component mixture is administered epidurally [3,4,9]. When the epidural catheter occasionally moves through one of the many naturally occurring holes in the dura mater, the subarachnoid infusion rate needed is about 10–20% of the epidural dose [9]. Therefore the well documented triple epidural mixture (containing bupivacaine 1 mg/ml, fentanyl 2 μg/ml and adrenaline 2 μg/ml) functions just as well in an intrathecal infusion, but the infusion rate should be reduced from about 10 ml/h to 1–2 ml/h [4,9]. Adrenaline is easily oxidized and inactivated in solutions with a local anaesthetic and opioid unless details of producing such an adrenaline containing solution are observed [15]. Adrenaline does not cause vasoconstriction in the spinal cord vessels [9].

8. Obtaining informed consent from terminal cancer patients to take part in a pain study?

If I were such a patient in agonizing pain and I were able to consider the information, I certainly would not take part. Especially if I were told that I would be randomized to intrathecal triple component analgesia that Mastenbroek and co-workers have documented to be effective for up to several weeks, long enough for the remaining time I had left [1], or to a less effective treatment with more adverse effects.

Conflict of interest

None declared.

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