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Editorial comment

Severe side effects from intrathecal morphine for chronic pain after repeated failed spinal operations

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In this issue of the *Scandinavian Journal of Pain*, Kehua Zhou and co-workers present a case report on two patients treated for several years with intrathecal (IT) morphine due to chronic pain after multiple failed spinal operations [1]. Despite this treatment, the patients had insufficient pain relief and compromised function for activities of daily living. This was emphasized by the use of additional opioids (per oral, transdermal) and willingness to undergo further back surgery during the ongoing IT morphine treatment. Additionally, the patients experienced severe side effects, including respiratory complications that caused visits at hospital emergency departments. One of the patients was also transferred to a nursing home after developing dementia-like symptoms. The two patients were finally included in a pain programme based on education, physiotherapy and tapering of opioids via conversion to methadone. After discontinuation of opioids both interestingly described better pain-control and improved function, and the patient showing symptoms of dementia improved and could be discharged home.

1. Post-surgical chronic back and leg pain (CBLP)

The term post-surgical CBLP, formerly known as failed back surgery syndrome, describes a condition with persistent or recurring low back pain, with or without sciatica following one or more spine surgeries [2]. The condition is complex, involving biological, psychological and social factors, and the incidence of post-surgical CBLP is commonly described as occurring between 10 and 40% [2]. A broad rehabilitation approach seems to be important. In a Cochrane review from 2015 multidisciplinary rehabilitation programmes for chronic low back pain were found superior to usual care or physical treatments with respect to long-term pain and disability [3]. Spinal cord stimulation (SCS) is a treatment modality offered to patients with post-surgical CBLP, and RCTs including this patient population show better outcome for SCS compared with reoperation and with conventional management [4,5].

2. Intrathecal opioids in chronic pain

Many patients with post-surgical CBLP become chronic opioid users although the evidence for pain relief and function improvement is insufficient for this treatment [6]. In the USA, a more liberal prescription of opioids for chronic pain has caused an epidemic of abuse and overdose fatalities during the last decades [7,8]. The intention with IT drug delivery (ITDD) is to achieve adequate concentration of a drug by administration close to the site of action in the spinal cord, and then reduce the side effects compared with systemic administration [9]. The International Neuromodulation Society regularly organizes consensus conferences and publishes guidelines for ITDD, with the last update this year [10]. In the USA only morphine, ziconotide, and baclofen have been approved for intrathecal use by the Food and Drug Administration [11], but other drugs are used off-label, e.g. clonidine and several opioids [10]. In severe cancer pain IT opioids in combination with a local anaesthetic have been described as a safe and effective treatment [10,12,13]. For chronic pain, support for IT opioid administration is based on prospective and retrospective non-controlled trials [10], while ziconotide has tested positive in placebo controlled RCTs, although with short follow-up periods [14–16]. Severe complications of ITDD have been described, including deaths due to respiratory depression by opioids or other central nervous depressant drugs [9,17], and drug leakage in connection with the refilling process can be life-threatening [18,19]. Long-term IT opioid therapy has also profound effects on the neuroendocrine functions [20], and can lead to catheter-tip granuloma with spinal cord compression, particularly after high concentrations and high dosages [21]. In addition, severe infections (meningitis and epidural abscess) and neurological damage have been reported [9].

3. Opioid weaning

In Zhou and colleagues' case report, IT morphine weaning was done with a conversion to methadone before tapering the opioid treatment. An advantage with methadone is the possibility to

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stabilize the analgesic effect, but the conversion ratios from morphine to methadone vary considerably [22]. It is also possible to taper IT morphine treatment directly by reducing the infusion rate regularly, for instance by 5% every week, but often there will be a need of systemic opioids for a period after the IT infusion has been stopped. When IT morphine fails, the pain can be considered to be opioid-resistant and it would be reasonable to taper and discontinue the systemic opioids as well.

4. Conclusions and implications

Chronic pain is difficult to treat, and when all other treatments fail, some patients receive IT morphine as a last resort, but the evidence for this treatment is limited, as it is for long-term systemic opioids for chronic pain [6]. A placebo-controlled RCT needs a double-dummy design, but would still be difficult to blind. Due to the limited evidence and the potential severe side effects, IT morphine for chronic (non-cancer) pain should be restricted to a few and highly selected patients, and importantly, continuation requires substantial function improvement, not only pain reduction [8]. Most of our chronic pain patients treated with IT morphine have reported disappointing effect, and in our experience IT morphine infusion should not be combined with systemic opioid administration. Zhou and co-workers' case report underlines the importance of a tight follow-up of patients receiving IT morphine, and they emphasize the importance of stopping treatment if the effect is not significant or severe side effects occur.

Conflict of interest

None declared.

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