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Observational study

Multimodal intrathecal analgesia in refractory cancer pain

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HIGHLIGHTS

- 10% of cancer pain patients are not effectively treated according to WHO-guidelines.
- Multimodal intrathecal analgesia is effective in treating refractory cancer pain.
- No severe adverse events occurred in our study with multimodal intrathecal therapy.

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ABSTRACT

Background and aims: Cancer pain treatment has improved over the last decades. The majority of this population can be treated effectively with analgesics following the Guidelines of the original World Health Organisation (WHO). Unfortunately 10–15% of these patients still suffer from severe and refractory cancer pain, especially in the terminal phases of disease and require additional pain management modalities. Therefore, end-stage clinical interventions are particularly needed to minimize the perception of pain. With intrathecal therapy (ITT), drugs are delivered close to their site of action in the central nervous system avoiding first-pass metabolism and blood–brain barrier. It may improve analgesia with a smaller dose and possibly achieve a reduction in systemic or cerebral side effects compared to oral supplied medication alone. Multimodal analgesia enables further dose reduction with improved analgesia and fewer side effects.

Methods: In this retrospective research we investigated the effectiveness and side-effect profile of intrathecal morphine, bupivacaine and clonidine. Patients were followed until death occurred. Pain scores and side effects were recorded before initiating ITT (T0), just after initiating ITT (T1), at hospital discharge (T2), in the ambulant setting (T3) and the last obtained scores before death occurred (T4).

Results: Nine patients were included who suffered from severe and refractory cancer pain, not reacting to conventional pain management or had intolerable side effects. Primary tumour location was pancreatic (4), urothelial (3) and prostate (2). Primary pain was considered neuropathic or mixed neuropathic-nociceptive. The treatment team consisted of an anaesthetist, specialized nurse in coordination with primary physician, treating oncologist and specialized home care.

All patients were free of pain after initiation of the intrathecal therapy. The average follow-up period was 11 weeks in which there was a slight increase in NRS-score. In the last days before death occurred, half the patients were still free of pain. There were no problems during insertion of the catheter, device malfunction or infection. No severe adverse events defined as hypotension requiring inotropes, respiratory depression or neurological deficits were observed. Three patients experienced mild hypotension which gradually decreased after clonidine dose adjustment. Lower extremity weakness occurred in three patients as well. After bupivacaine dose adjustment the weakness disappeared in two patients and in one patient the lower extremity weakness persisted as a result of conus compression by tumour.

Conclusion and implications: Multimodal IT treatment with morphine, bupivacaine and clonidine is effective and safe for treating refractory cancer pain in the terminal phase of disease.

The study offers an important contribution to literature where there is still lack of convincing evidence about the benefits and harms of this type of pain management in patients with otherwise refractory cancer pain.

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1. Introduction

Cancer pain impacts all aspects of patients well-being. Although cancer pain treatment has been improved, it is often inadequately treated, despite it being a major fear and concern of many patients [1]. Failure to respond to treatment not only impacts cancer pain but is also associated with depression, morbid mood and reduced quality of life [2]. Management of pain related complications with additional hospital admissions are of major health and economic concern in this growing population.

The prevalence of cancer pain has been reported to be as high as 60–70%, particularly in the terminal phases of the disease. After cure, chronic pain may still be around 21–46% [3]. This high prevalence in combination with an increasing cancer survival rate makes this a growing population that requires extensive pain modulation. The majority of this population (85–90%) can be treated effectively with analgesics following the Guidelines of the original World Health Organisation (WHO). Unfortunately 10–15% of the patients suffer from severe and refractory cancer pain and require additional pain management modalities [4].

In 1973, specific opioid receptors were discovered in the substantia gelatinosa of the spinal cord [5], followed by the first intrathecal injection of morphine [6]. Spinal opioids exert their analgesic effect by reducing nociceptive transmission in the dorsal horn of the spinal cord. Since the late 1980s, IT analgesic therapy has become an alternative for oral and parenteral pain treatment with opioids.

The implantation of an IT drug delivery system offers many advantages by improving analgesia with reduction of systemic or cerebral side effects compared to oral or parenteral opioids [7]. Because IT opioids are still associated with side effects like respiratory depression, opioid dose escalation, granuloma formation, pruritus and myoclonus, a wide variety of drugs are currently being used either single, or in a combination to optimize the therapeutic benefit. Non-opioids like bupivacaine [8,9], clonidine [10], ziconotide [11,12], ketamine [13], baclofen and ketorolac have been used neuraxial to minimize these opioid associated side effects.

Multimodal therapy in perioperative analgesia has become common practice. Combinations of different analgesics, acting at various points in the neurochemical pathway results in additive analgesia. This synergistic effect allows a reduction in the individual drug dose and thus lower the incidence of medication-related adverse effects. Unfortunately, multimodal IT analgesia for intractable cancer pain is not common practice. Tumber described a case in which severe cancer pain was controlled by IT infusion of morphine, bupivacaine and clonidine but no large case series are published [14].

Single use of clonidine, an α2-adrenergic agonist, has shown to provide effective reduction in intractable cancer pain, particular in neuropathic type of pain [10]. The use of clonidine is limited as well, because of potentially side effects like hypotension, bradycardia and sedation.

In this retrospective research, the trialling combination of morphine, bupivacaine and clonidine was investigated in a group of terminal patients with refractory cancer pain, in order to gain a preliminary insight in effectiveness of this regime of multimodal analgesia in attenuating cancer pain and side effect profile.

2. Methods

2.1. Patients and procedure

In this retrospective research, 9 patients were given an IT-catheter in the period between August 2012 and August 2013. All patients suffered from severe and refractory cancer pain, not reacting to conventional pain management (WHO) or had intolerable side effects. Numeric rating scale (NRS)-score had to be at least 4 out of 10 and patients were required to be over the age of 18. Exclusion criteria were patient refusal, systemic infection, infection at the site of catheter placement and an existing uncorrectable coagulopathy.

All patients received an externalized pump system with patient-controlled intrathecal analgesia (PCIA) function (PCA-Legacy CADD, Smiths Medical, London). A full surgical scrub with antiseptic cleanser was performed. Access was obtained in the lumbar region under local anaesthesia before placement of the IT-catheter. The IT-catheter was tunnelled subcutaneously to the anterior flank hereafter it was connected to the pump system. All procedures were performed under strict sterile conditions in the operating room of the Rijnstate hospital in Arnhem.

Supplied medication consisted of a combination of morphine, bupivacaine and clonidine, converted to the analgesic requirement before placement of the IT-catheter (T1). Starting dose was based on previous experience in our centrum. For morphine the starting dose ranged between 2.4 and 4.8 mg/day. Patients using more than 240 mg morphine a day (or equivalent), the IT starting dose of morphine was 4.8 mg/day. In case the patient used less than 240 mg morphine, the IT starting dose was 2.4 mg/day.

Starting dose of bupivacaine ranged between 7.2 and 16.2 mg/day and clonidine maximum clonidine starting dose was 350 mcg/day but most patients start with a dose between 72 and 144 mcg/day.

During hospital stay further dose adjustment took place (T2) to optimize the analgesic effect and limiting the side effects. Besides continuous IT analgesia, patients were able to use a PCIA function to control breakthrough pain. A bolus was equivalent to what the patient received continuously in 1 h. For the first 24 h after placement, standard lockout period was 4 h. After this, the lockout period was 1 h. In case the PCIA-function was used more than two times a day, dose adjustment took place.

After initiation of the intrathecal therapy (ITT), anti-neuropathic medication were stopped directly. Oral opioids were halved every day and stopped about 2–3 days after initiating the ITT.

After hospital discharge patients remained under strict control by specialized nurses. Further dose adjustment (T3) is regulated by these nurses following a detailed doctors order. When the maximum IT-dose was reached according to the execution request, consultation with the pain department of the Rijnstate hospital took place. Patients were followed until they passed away. The last control and NRS-score taken by the specialized nurses was designed as T4.

NRS-scores and adverse events were recorded after placement of IT catheter (T1), at hospital discharge (T2), after hospital discharge (T3) and at the last NRS-score before dying (T4).

Opioid dose escalation index (OEI) was used to index the mean increase of the starting opioid dosage during ITT, expressed as a percentage. The OEI was calculated as the difference between the maximal morphine dose (T4) and starting dose after dose adjustment (T2) using the following formula: [(Morphine T4 – morphine T2)/morphine T2]/days $\times$ 100. These indices have already been validated to monitor opioid requirement [15,16]. Increasing OEI with increasing NRS-score >4 indicates dose escalation.

2.2. Ethical aspects

The study protocol, judged by the local ethics committee does not require ethical review and approval. The patients were informed about the procedure and could refuse intrathecal pain relief.