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Review

PALLIATIVE TREATMENT OF INTRACTABLE CANCER PAIN

Lidija Fumić Dunkić[1], Vedran Hostić[1] and Antonia Kustura[1]

[1]Division of Anesthesiology, Intensive Care and Pain Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

ABSTRACT – In 10% to 30% cancer-pain cases standard analgesic therapy fails to provide effective pain relief. Interventional techniques, such as peripheral nerve blocks, neuraxial analgesia along with neurolytic blocks may be used for such refractory pain. Peripheral nerve blocks can be used when pain occurs in the territory of one or more peripheral nerves, but rarely as main therapy. Neuraxial analgesia is a valid option for progressive cancer pain, and healthcare possibilities and costs call into question the utility of intrathecal infusion pumps. Neurolysis is the targeted destruction of a nerve or nerve plexus, using chemicals, radiofrequency ablation (RFA), cryoablation, and neurosurgical procedures; however, it rarely completely eliminates pain because patients frequently experience coexisting somatic and neuropathic pain as well. Complex conditions of palliative patients along with limited high-quality randomized controlled trials limit the use of interventional procedures. Even so, some cancer patients benefit from interventional procedures to achieve pain alleviation and consequently improve quality of life.

Keywords: *palliative care; cancer pain; refractory pain; nerve block; spinal anesthesia; neurolysis*

Introduction

Palliative care aims to alleviate suffering of patients at the end of their life with pain control as an integral part of it. Cancer pain is often severe and progressive with time. It is estimated that in 10% to 30% cases, standard analgesic therapy fails to provide effective pain relief or due to side effects, patients cannot tolerate systemic therapy (1). Such pain is referred to as refractory pain and interventional techniques, a diverse set of procedural techniques, may be used for pain relief. Interventional techniques for treatment of cancer-related pain can include peripheral nerve blocks, neuraxial analgesia, sympathetic blocks and neurolytic blocks among others. Moreover, it can involve sophisticated technology such as implanted neurostimulation and neuraxial drug infusion devices (2).

However, every intervention with all benefits and complications must be considered in the context of the individual patient. Nowadays neuraxial approaches are used in only a small percentage of cancer patients with refractory pain and consequently, there are limited high-quality randomized controlled trials (3). Experience in treatment of acute and chronic pain suggests that only carefully selected subset of patients with cancer pain may benefit from these procedures.

Today, there is controversy about the timing of interventional procedures in the treatment of pain. It is often misunderstood that intervention techniques are applied after exhaustion of other options due to the potential risk of serious complications (4). Such attitudes lead to untimely referral of patients to pain clinics where procedures are performed.

Nevertheless, invasive techniques effectiveness has been recognized and they have a place in the pain con-

Correspondence to: *doc.prim.dr.sc. Lidija Fumić Dunkić, MD,* Division of Anesthesiology, Intensive Care and Pain Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia
E-mail: lidija.fumic.dunkic@gmail.com

trol algorithm as an efficient treatment modality. This review aims to provide evidence on interventional refractory pain management in palliative cancer patients.

Peripheral blocks

Peripheral nerve blocks or plexus blocks can be used when pain occurs in the territory of one or more peripheral nerves. The role of a peripheral nerve block will very seldom be as the sole or even the principal treatment (5). Given that today, with various options for oncological treatment, the life of patients is extended, over 50% of patients survive up to 10 years, there is a question of long-term use of opioids in the treatment of cancer pain. Currently, traditional methods of peripheral blocks are used in the treatment of cancer pain with continuous infusions of local anesthetics and adjuvant drugs. Regional blocks are also used as diagnostic blocks with local anesthetics to confirm the efficacy and side effect profile before deciding on neurolytic blocks.

In the review from 2020, Bhaskar points out that the use of peripheral blocks for cancer pain is based on anecdotal evidence (4). The low number of reports argues that there is a selection bias for which cases are reported. According to some authors, long-term use of peripheral blocks is not recommended, but only short-term treatment, and the reason refers to side effects that can develop, numbness and motor blockade, and potential systemic side effects (4).

Neuraxial control of cancer pain

Neuraxial analgesia represents delivery of medicine into the epidural or intrathecal (spinal) space using percutaneous approach or implanted catheter. Generally, a mixture of drugs is used to reduce side effects, including opioids, local anesthetics and adjuvant analgesics.

With neuraxial analgesia, reduction of pain may be accomplished, but the evidence for the use of epidural versus intrathecal therapy is limited. The choice must be made by taking in consideration the patient's needs and requirements of care. However, by switching to regional therapy, oral opioid intake and its adverse effects are usually reduced, which can greatly contribute to a patient's quality of life.

Contraindications to neuraxial approach include coagulation defects, allergy to medications, and infection at the injection site, unstable spinal fracture, spinal cord compression, raised intracranial pressure, patient refusal and altered mental status or incapacity to make an informed decision (3). In addition, since life expectancy of palliative care patients is limited, cost-benefit assessment is necessary.

When considering complications, often fragile patients at the end-of-life are at great risk for harm of spinal cord during both punction and catheter placement, catheter migration, epidural hematoma, headache after dural puncture, infections and meningitis, among others (6). Therefore, a marginal group of palliative patients is suitable candidates for neuraxial therapy.

Intrathecal analgesia

Opioid pain control in intrathecal analgesia is achieved by binding at presynaptic and postsynaptic receptors in the spinal cord, which reduces or blocks the nociceptive signal conduction. Additionally, opioids interfere with descending pathways and modulate the pain pathway in the midbrain. Morphine, being the most studied along with extensive experience in clinical practice, is recommended as an opioid of choice for intrathecal administration in cancer pain control. Due to its hydrophilic character, it results in long-term pain relief, even on higher dermatomes and has great stability and receptor affinity (6).

Fentanyl and sufentanil, are lipid-soluble opioids, have more rapid onset and shorter duration of action, because of which are more effective for continuous application. Because of potency, sufentanil is a valuable alternative for morphine-induced adverse effects because efficacy is achieved through fewer spinal opioid receptors and therefore it has less side effects. Other opioid therapy such as pethidine due to its metabolite accumulation and CNS excitation is not often recommended.

Addition of local anesthetic drugs such as bupivacaine, levobupivacaine, lidocaine and ropivacaine in combination with opioids may improve analgesic effectiveness and reduce opioid requirement. Local anesthetic drugs produce effects by sodium channel blockade, inhibiting the action potential in the dorsal horn. Due to their non-specific activity, they can cause adverse effects, including sensory deficits, motor weakness/paresis, autonomic dysfunction and neurotoxicity. Bupivacaine, which has a long duration of action and low toxicity together with low costs, is beneficial and may especially be useful in patients with neuropathic pain.

Adjuvant analgesics such as clonidine, ketamine, neostigmine, ziconotide, dexmedetomidine and others may improve analgesia with possible reduction of opioid dosing (6). A wide range of adjuvant medications is used, but only a few have been subjected to well-conducted randomized controlled trials (7).

To manage cancer-related pain, an often used approach is intrathecal infusion using a drug delivery system. The selection of type usually depends on survival expectancy, patient's needs, organizational staff possibilities and costs.

Study by Zheng and et al. from 2017 evaluated patient-controlled analgesia pump using intrathecal drug delivery system (IDDS) and showed statistically significant decreases in pain scores and toxicity scores in comparison to conservative medications (8).

However, it requires specialized equipment, the participation of interventional pain specialists and staff infrastructure for 24/7 care of the patient and the delivery system. Although generally safe, it can be associated with technical problems and adverse effects and for every patient the decision about intrathecal drug delivery system (IDDS) should be made individually.

Some studies have shown the cost efficacy of IDDS for longer periods due to decreasing hospitalizations and other medical interventions. On the contrary, Health Quality Ontario published a report in 2016 estimating that the cost of intrathecal drug delivery system (IDDS) for refractory cancer pain was over $100,000 in the first year and growing. (9)

Considering cost-effectiveness, a reliable wireless analgesia pump system may be used. In the study from 2017 conducted in China it has been shown as a valuable alternative option for long-term intrathecal analgesia in the home care of patients (10).

Epidural analgesia

Epidural analgesia is the administration of analgesics into the epidural space, outside the dura mater. Analgesics can be given either as a single injection or as a continuous infusion via catheter. Potency of epidural opioid therapy is inversely proportional to its lipophilicity. Just like with intrathecal use, opioids delivered by epidural route can show tolerance and may need dose escalation over time. Additionally, one author suggested that tumor progression, psychological factors, development of pseudotolerance caused by dural thickening and reactive fibrosis among others were potential causes of reduced effectiveness over time (11).

Bupivacaine-morphine combination often presents more effective analgesic effect than morphine alone, more effective relief of the neuropathic component of pain with low neurotoxicity risk in long-term infusion (12).

Side effects and complication rates are variable, but even at lower doses patients can experience significant opioid-induced problems, the most common being constipation, pruritus, nausea, vomiting and urinary retention. Epidural analgesia may be preferred for in-hospital treatment and intrathecal analgesia for home care settings (13). In palliative care, an external pump system is more suitable for both the epidural and intrathecal route with a percutaneous catheter.

Celiac plexus block

Celiac plexus block (CPB) has been broadly used as a treatment option for reducing pain originating from upper abdominal organs. It is mostly indicated to treat pancreatic cancer pain, yet also to relieve pain because of chronic pancreatitis. Pain relief is achieved in 70-80% of patients with pancreatic cancer and in 50-60% of those with chronic pancreatitis (14). The average length of relief for patients with CPB is approximately 3 months in most studies, and CPB is therefore seen as a temporary measure (15). Factors associated with successful response to celiac plexus block in patients with upper abdominal cancer-related pain are celiac plexus metastases, absence of diabetes, and absence of prior upper abdominal surgery (16). The celiac plexus transmits pain from the pancreas and most of the abdominal viscera, except for the left colon, rectum, and pelvic organs (17).

CPB can be achieved by several approaches: transaortic, transcrural, anterior, or a bilateral splanchnicectomy approach. There is no advantage in the degree of immediate or long-term pain relief of one block approach over the other when compared, nor is there any significant difference in degree of complications (17). Bilateral multiple blocking of celiac plexus and splanchnic nerves is often required achieving optimal analgesia (18).

The celiac plexus block can be performed percutaneously under fluoroscopic guidance or guided CT. Nevertheless, an endoscopic ultrasound (EUS) guided approach has also been applied. No statistically significant difference was noted in pain relief and complications for EUS and percutaneous – CPB (19). Both

techniques are safe, effective and should be utilized according to the expertise and resources available at each facility (20). Absolute contraindications for CPB are a lack of patient cooperation, coagulopathy or low platelet count.

Complications resulting from CPB have been long reported and include diarrhea, back pain, paraplegia, postural hypotension, pneumothorax, and local anesthesia toxicity. Diarrhea and postural hypotension are two most common complications with studies reporting incidents occurring in 44% to 60% and 10% to 52% of patients, respectively (21).

Neurolysis for intractable cancer pain

Neurolysis is the targeted destruction of a nerve or nerve plexus. It can be achieved with chemicals, radiofrequency ablation (RFA), cryoablation, and neurosurgical procedures, all of which disrupt transmission of pain signals by causing Wallerian degeneration distal to the lesion. Pain associated with cancer may be somatic, visceral, or neuropathic in origin. The goals of performing a neurolytic block of the sympathetic axis are to maximize the analgesic effects of opioid or nonopioid analgesics and reduce the dosage of these agents to alleviate side effects. Neurolysis rarely eliminates cancer pain because patients frequently experience coexisting somatic and neuropathic pain as well (22). The most used chemicals for neurolysis are alcohol (50%–100%) and phenol (5%–10%) and they usually produce a block that lasts 3 to 6 months (23). RFA of peripheral nerves may last 3 to 12 months until axonal regeneration occurs and cryoanalgesia may provide variable relief lasting weeks to months (22). Contraindications to the procedure include patient refusal, active infection at the site of injection, allergy to a chemical neurolytic agent and uncorrectable coagulopathy. The technique consists of identification of target nerve (via ultrasound, nerve stimulation, fluoroscopy or CT), diagnostic block with a local anesthetic and finally, neurolysis procedure.

Superior hypogastric plexus neurolysis

The superior hypogastric nerve plexus is a bilateral retroperitoneal structure located at the level of L4-S1, positioned anteriorly to the bifurcation of the aorta. It provides innervation to structures within the pelvis, including the bladder, urethra, vagina, vulva, ovaries, prostate, penis, testicles, uterus, ureter, pelvic floor, descending colon, and rectum. Superior hypogastric plexus neurolysis is indicated for visceral pelvic pain treatment related to malignancy and is associated with 55.5% success rate, significant VAS reduction of 49.55% and reduction in opioid consumption of 12.55% at 3 months (24).

Celiac plexus neurolysis

Celiac plexus is situated closely to the origin of celiac artery and consists of parasympathetic nerves, sympathetic nerves, visceral sensory afferent nerves, and ganglia. Celiac plexus neurolysis is frequently used for pain originating from upper abdominal malignancy, particularly pancreatic cancer. CPB is an effective modality for pain relief in tumors originating from the head of the pancreas, the analgesic and opioid-sparing effect of this block is maximum when given early in the disease trajectory, and all approaches and radiological techniques to guide needle placement are useful with no specific contraindication of a single approach (25).

Intercostal nerve neurolysis

Primary or secondary neoplasms invading the chest wall and pleura originate from the lung, colon, or breast and are often incurable with treatment targeted toward palliation and control of pain (26). A majority of patients can benefit from neurolytic blockade, although the failure rate is relatively high at more than 30% (27).

Conclusion

Although interventional techniques represent a valuable option for pain management, there is scarcity of good quality randomized controlled trials (RCTs) evaluating their safety and efficacy in cancer pain. Consequently, it limits evidence-based practice guidelines for interventional therapies in cancer pain, which can be used for everyday practice. Moreover, interventional techniques imply risks for complications.

For now, interventional techniques are a valuable option for limited use in refractory cancer pain with individual assessment against the complexity of care and the risk of serious complications for every single patient. Oncologists and palliative care physicians are to be educated on the usefulness and timing of interventions in the management of complex cancer pain.

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Sažetak

PALIJATIVNO LIJEČENJE INTRAKTABILNE KARCINOMSKE BOLI

L. Fumić Dunkić, V. Hostić i A. Kustura

U 10% do 30% slučajeva karcinomske boli standardna analgetska terapija ne pruža učinkovito ublažavanje boli. Interventne tehnike, kao što su blokovi perifernih živaca, neuraksijalna analgezija zajedno s neurolitičkim blokovima mogu se koristiti za takvu refraktornu bol. Blokada perifernih živaca može se koristiti kada se bol javlja u području jednog ili više perifernih živaca, ali rijetko kao glavna terapija. Neuroaksijalna analgezija je valjana opcija za progresivnu karcinomsku bol, a mogućnosti zdravstvene skrbi i troškovi dovode u pitanje korisnost intratekalnih infuzijskih pumpi. Neuroliza je ciljano uništavanje živca ili živčanog pleksusa, korištenjem kemikalija, radiofrekventne ablacije (RFA), krioablacije i neurokirurških zahvata, međutim rijetko u potpunosti eliminira bol jer pacijenti često doživljavaju i somatsku i neuropatsku bol. Složena stanja palijativnih bolesnika uz ograničena visokokvalitetna randomizirana kontrolirana ispitivanja ograničavaju korištenje intervencijskih postupaka. Unatoč tome, neki karcinomski pacijenti imaju koristi od intervencijskih postupaka za ublažavanje boli i posljedično poboljšanje kvalitete života.

Ključne riječi: *palijativna skrb; karcinomska bol; refraktorna bol; blok živca; spinalna anestezija; neuroliza*