



MINIMALLY-INVASIVE PAIN MANAGEMENT TECHNIQUES IN CANCER PAIN

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SUMMARY – The indication for the application of invasive procedures in the therapy of cancer pain is lack of response to opioids or patients who have side effects to opioid therapy that significantly impair the quality of life. Invasive treatment of cancer pain should not be the last resort but should be an integrative part in the treatment of cancer pain in combination with opioid therapy as a part of multimodal therapy. For visceral pain, interventional techniques represent a minimally invasive and reliable option for many diagnoses where active treatment options have been exhausted. There is evidence for the effectiveness of the celiac plexus block in pain treatment for pancreatic cancer and some upper abdominal cancers. According to research, the hypogastric neurolytic block is an option for pelvic visceral pain treatment and has proven to be more effective than oral opioid pain treatment. Recently, progress has been made with intrathecal and epidural analgesia as safe and effective therapeutic options with a positive risk-benefit ratio for cancer pain treatment over a long period of time and in home settings. Invasive procedures are a safe and effective option for cancer pain therapy, thus significantly affecting the quality of life.

Key words: *cancer pain; intrathecal analgesia; epidural analgesia; celiac plexus block; hypogastric plexus block*

Introduction

Cancer pain is one of the most frequent causes of suffering and distressing side effects of cancer. A meta-analysis revealed that nearly two-thirds of patients who have been diagnosed with advanced cancer suffer moderate or even severe pain¹. Quality of life may be greatly improved by effective pain control, and pain management should therefore be a high priority in the care of patients with cancer. Typical first-line treatment consists of medication therapy, includ-

ing opioids. However, in 10% to 30% of cases this treatment does not achieve adequate pain control, or patients develop limiting systemic toxicities and/or side effects². Interventional techniques include either peripheral or central termination of nociceptive pathways. Today, there are various controversies about the timing of invasive procedures. Research has shown that patients with fatigue or symptoms of depression benefit less from procedures, which may indicate that invasive treatments may be more efficient as an integrative part of therapy for cancer pain, rather than leaving interventions for later stages³. This review aimed to describe the current development of principles regarding minimally-invasive pain management techniques in cancer pain: sympathetic nerve blocks for abdominal pain, neurolysis of the peripheral nerve and neuraxial analgesia.

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Celiac plexus block

The celiac plexus is formed by parasympathetic but also sympathetic nerves. Innervation of the sympathetic part emerges from the splanchnic nerves rising from Th5 to Th12. Celiac plexus block (CPB), first performed as early as 1990, is used today as a treatment for pain associated with cancer coming from upper abdominal viscera – mostly pancreatic cancer pain in which patients are often nonresponsive to high-dose opioid therapies. Pain relief is estimated to be achieved in 70-80% of patients⁴. Celiac plexus block success is based on individual anatomical distribution. Because of the spread of the malignancy and propagation to somatic parts such as the diaphragm or peritoneum, the block may have lower effectiveness in those situations and can obstruct only sympathetic pathways for visceral origin of pain. Local anesthetics in combination with opioids and often steroids are commonly used in patients who have benign pathology, whereas on the other hand, neurolytic celiac plexus blocks are mostly used to treat pain associated with pain⁵. In a study from 2021, the presence of diabetes was related to worse response to the block, probably due to the prolonged microvascular effect and chronic neuropathic changes caused by elevated glucose levels⁶. Additionally, the study showed that the positive effect of neurolytic celiac plexus block may have been correlated with patients with confirmed celiac plexus metastasis who did not undergo upper abdominal surgery. CPB can be achieved using several approaches with no particular advantages for any one approach, being performed percutaneously under fluoroscopic or CT guidance or by an endoscopic ultrasound (EUS) guided approach. CPB can be performed during laparotomy or thoracoscopy or using different percutaneous techniques: the anterior or posterior paraspinous approach, intradiscal, trans-aortic and para-aortic, and with retrocral being the one most often mentioned, with unilateral or bilateral needle placement. The choice of approach and technique should be made according to physician expertise and available resources⁷. General contraindications include malignancy invasion or infection at the insertion site, coagulopathy and bowel obstruction. Complications resulting from CPB include diarrhea, back pain, paraplegia, postural hypotension, pneumothorax, retroperitoneally positioned hematoma, bladder injury and unintended damage to the somatic nerve⁸. As an adjunct to celiac plexus blocks for the relief of intractable cancer pain, a superior hypogastric plexus block has been used.

Hypogastric neurolytic block

The superior hypogastric nerve plexus has a retroperitoneal location, level L4-S1. It supplies innervation for structures located in the pelvis, including the bladder, uterus, pelvic floor, descending colon, rectum and others. The superior hypogastric plexus block (SHPB) can be used for visceral pelvic pain treatment, either with a benign underlying cause such as endometriosis and pelvic inflammatory disease or a malignant cause such as gynecologic, colorectal and genitourinary cancer⁹. Pain control is achievable because innervation of pelvic organs travels along the sympathetic nerves, allowing inhibition with neurolytic agents¹⁰. Some ongoing studies are assessing the block for postoperative pain management after hysterectomies¹¹. The classic approach for SHPB is a fluoroscopy-guided approach, posterior, with a two-needle technique. In 2020, Rocha *et al.* carried out a study to assess the safety and efficacy of the classic approach¹². Results showed 48.8% pain reduction at 6 months, and it has been shown that the procedure can be considered safe and effective. Some studies have shown that the transdiscal approach, fluoroscopy-guided, with single-needle technique, is safer and faster when compared with the classic approach. On the other hand, the approach guided by ultrasound is increasingly used due to the real-time imaging free of radiation¹³. The injectate should be chosen carefully, with the goal of enhancing the analgesic effect of the solution and an emphasis on reducing side effects. The superior hypogastric plexus block is a reproducible and beneficial solution for pain management.

Peripheral nerve neurolysis

Peripheral nerve blockage interrupts the signaling of nociceptive input to the central nervous system. Today, peripheral blocks used to control cancer pain entail blocks of the brachial plexus, blocks of nerves in the head region, blocks of intercostal nerves and paravertebral blocks. The highly innervated head and neck area contains a myriad of anatomic structures in a limited region⁶. While the overall prevalence of pain in any malignant disease is enormous, patients with neck cancer have the highest prevalence of 70%⁴. The medication most commonly used for blocks are local anesthetics, which must be administered continuously or intermittently because of their limited duration of action. Most commonly applied local anesthetics include bupivacaine, ropivacaine and lidocaine. With the

use of additives such as epinephrine or clonidine, their duration may be altered, which varies between different types of block. With all the adjuvants, local anesthetics are still a short-term relief and their usefulness in peripheral blocks for cancer pain is limited. On the other hand, medications typically used for neurolysis are chemical agents such as phenol (5-10%) and sometimes ethanol (50-100%), with anesthetic bupivacaine. Both phenol and ethanol act by denaturing proteins, causing Wallerian degeneration leading to distal degeneration that can last up to 6 months¹⁵. Studies have shown there is no significant difference between phenol and ethanol when comparing the efficacy of neurolysis. Phenol is more commonly used because it has lower water solubility and has a better safety profile than alcohol. Additionally, patients do not report pain upon injection of phenol, and there is a lower risk of neuritis. Nevertheless, axonal regeneration takes place earlier with phenol when compared to ethanol, which may cause shorter effect duration. Given that alcohol injection is highly painful, it is often recommended to inject a small dose of local anesthetics before using an alcohol-based block to reduce severe pain⁹. Peripheral nerve neurolysis should be used only for an intense pain that is precisely localized and does not respond to pharmacological treatment, with previously proven positive diagnostic blocks. Complications from local anesthetic are not a major clinical problem because motor function returns to normal with dose reduction or discontinuation of infusion. Peripheral neurolytic blocks, on the other hand, if wrongly performed may result in permanent loss of motor and sensory capabilities, but even if correctly performed there is a possibility of neuropathic pain due to reinnervation⁸. Therefore, neurolytic block treatment should not be used as the first-choice treatment for cancer pain. It should be performed rarely and only to alleviate pain from incurable cancer with expected survival above 3 months.

Neuraxial analgesia

The mechanism of neuraxial analgesia is based on delivery of drugs into the epidural or intrathecal (spinal) space using the percutaneous approach or an implanted catheter. Pain management in spinal analgesia is primarily achieved by attaching medications at receptors located in the spinal cord with the resulting reduction or total blockade of nociceptive signal conduction, while epidural analgesia uses delivery of medication into the epidural area, either by single in-

jection or by continuous application using a catheter. With the goal of reduction of side effects, a combination of drugs is used such as opioids, together with local anesthetics and adjuvant analgesics. Anesthetic agents such as bupivacaine have prolonged duration of action as well as with lower toxicity and costs. At the same time, opioids hinder descending pathways and modulate the pain pathway in the mesencephalon. Other possible agents used as adjuvants include ketamine, clonidine or neostigmine, among others, which may advance analgesia and reduce opioids dosage. The selection of neuraxial therapy (epidural or intrathecal) and the usage of delivery systems is based on location, mechanism of pain as well as survival expectancy and the patient's needs and costs. When there is longer probability of survival (>3 months) many favor the intrathecal route for prolonged infusions, due to the catheter obstruction or migration, fibrosis, and loss of analgesic efficacy which has been described with prolonged epidural infusions⁸. In contrast, patients with shorter estimated survival can be treated with an epidural approach connected to an implantable or external pump. There are many choices regarding the medication delivery system, but economic cost-benefit analysis has shown that for patients with at least 3-month life expectancy or longer there is lower cost with an implanted pump than the external system^{16,17}. Before administration, each patient should be assessed to determine whether this method of administering the drug is appropriate for them. Assessment should include an extensive estimation of symptoms, underlying disease, social and psychological factors, preceding treatment procedures and possible treatment options. Patient education increases their understanding of the risks and benefits of procedures, thereby increasing the motivation for participation and adherence. Appropriate arrangements for continuous care must be in place. Patient treatment goals must be taken into account when applying intrathecal therapy and managing complications and side effects in patients in a hospital setting. Contraindications to the neuraxial approach comprise coagulation defects, unstable spinal fracture, spinal cord compression and raised intracranial pressure¹⁸. Because patients with cancer are often underweight and cachectic, there is an increased risk of harm to the spinal cord, catheter migration, epidural hematoma and infection, among others^{8,19}. Therefore, neuraxial therapy as a method of pain control is suitable for only a small group of patients with cancer.

Conclusion

Today, minimally-invasive pain management techniques represent a wide range of possibilities for pain control, where more precise applications are to be expected with the advancement of technology. Invasive methods are a valid option in pain control, but only with appropriate timing and after precise assessment of each patient beforehand. Cost-benefit analysis helps determine the best-suited option for each patient in order to ensure that their quality of life is at a satisfactory level.

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Sažetak

MINIMALNO INVAZIVNE TEHNIKE U LIJEČENJU KARCINOMSKE BOLI

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Indikacija za primjenu invazivnih postupaka u liječenju karcinomske boli je kod bolesnika koji nisu responderi za opioide ili su prisutne nuspojave na opioidnu terapiju koje u značajnoj mjeri narušavaju kvalitetu života. Invazivno liječenje karcinomske boli ne bi trebao biti posljednji pokušaj već bi trebao biti integrativni dio u kombinaciji s opioidnom terapijom u okviru multimodalne terapije u liječenju karcinomske boli. U liječenju visceralne boli intervencijske tehnike predstavljaju minimalno invazivnu i pouzdanu opciju kod mnogih dijagnoza kod kojih su iscrpljene opcije aktivnog liječenja. Dokazano je da je blok celijačnog pleksusa vrlo učinkovit u kontroli boli kod karcinoma gušterače te kod nekih karcinoma gornjeg abdomena. Prema istraživanjima hipogastrički neurolitički blok predstavlja opciju u liječenju visceralne boli u maloj zdjelici i pokazao se učinkovitiji u odnosu na peroralno liječenje boli opioidima. U posljednje vrijeme se prati napredak kod intratekane kao i epiduralne analgezije kao sigurne i učinkovite terapijske opcije s pozitivnim omjerom koristi i rizika u svrhu liječenja karcinomske boli kroz duže vrijeme i u kućnim uvjetima. Invazivni postupci predstavljaju sigurnu i učinkovitu opciju u liječenju karcinomske boli te time u značajnoj mjeri utječu i na kvalitetu života.

Ključne riječi: karcinomska bol, intratekalna analgezija, epiduralna analgezija, blok celijačnog pleksusa, blok hipogastričkog pleksusa