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Review and Meta-analysis

Role of Interventional Techniques in the Management of Cancer Pain

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Pain is the major cause of morbidity in cancer patients. Interventional techniques should be considered for the management of pain that is refractory to traditional analgesics or when patients are unable to tolerate opioids. Interventional techniques are intended to stop pain signals through neural pathways from the periphery to the brain. This article deals with major interventional pain management techniques such as central neuraxial block, sympathetic block, peripheral nerve block, percutaneous cordotomy, percutaneous vertebroplasty and kyphoplasty, radiofrequency ablation, and cryoablation. Besides this, the role of radiotherapy and radionuclides in cancer pain have also been discussed. Central neuraxial block can effectively reduce pain while preventing opioid toxicity. It involves a percutaneous epidural or intrathecal catheter, an external syringe pump, or a fully implanted intrathecal drug delivery system to give medication. Sympathetic blocks such as celiac plexus and superior hypogastric block have role in patients with visceral abdominal pain. Peripheral nerve blocks may be employed when the distribution of somatic pain is restricted to a single nerve or plexus. Percutaneous cordotomy could be useful for any unilateral cancer pain below C4 dermatome. Percutaneous vertebroplasty (PV) treatment is used to alleviate axial back pain due to osteoporotic wedge fracture or malignant vertebral body disease. RFA and cryoablation techniques are now widely used for back pain due to osteoporotic and malignant vertebral collapse that are resistant to conservative treatment. External beam radiotherapy and radionuclides are useful in relieving cancer pain due to bone metastasis. This article aims at summarizing the indications, mechanisms, drug agents, contraindications, and complications of interventional pain management techniques that may offer benefits to patients coping with cancer and its terrible symptoms. Even though there is some risk involved with the techniques discussed in this article, the advantages of reduced pain and enhanced quality of life usually outweigh the risk.

Introduction

Pain is the major cause of morbidity for cancer patients [1-2]. Between 20% and 50% of cancer patients report experiencing pain in the early stages of the disease. Most of the cancer patients with advanced stage disease experience pain at multiple sites, with about 75 percent of them reporting moderate to severe pain [3-4]. Pain negatively affects the quality of life of cancer patients, and nearly 32% will have pain that is not adequately addressed [2, 5]. According to estimates, 66% of people with advanced cancer will feel pain as a result of their condition or its treatment.

The WHO Cancer Pain Ladder for Adults has been used as a model for the management of cancer-

related pain since 1986. Their three-step approach suggests using non-opioids for early pain management, then mild opioids (such as codeine) for mild to moderate pain, and finally strong opioids (such as morphine) for moderate to severe pain. Most cancer patients who experience pain obtain effective results with drugs included in the WHO analgesic ladder [6].

Treating physicians believed that the WHO's three- step pain management ladder had not kept up with the quickly developing breakthroughs in oncology and pain research. To make the 3-step WHO analgesic ladder effective after drugs fail, a fourth "interventional" step that included nerve blocks, intrathecal drug delivery systems, and palliative surgery was required to make the three-step WHO analgesic ladder effective [7].

In 80% to 90% of these patients, pain can be effectively managed with the help of oral, conventional analgesics. However, it has been estimated that in 10–20% of individuals with advanced disease, systemic analgesics and opiates are found to be ineffective in treating the pain [8]. Such a type of pain is known as refractory pain. Interventional techniques intended to stop pain signals through neural pathways from the periphery to the brain may be quite helpful for some patients. Additionally, opioid use is linked to side effects like cognitive impairment, nausea, and constipation; as a result, patients sometimes find it difficult to tolerate a dose increase, even when they need improved pain management [9].

Interventional pain management approaches can reduce opioid use and its negative effects. When conventional analgesics fail to provide sufficient pain relief or have severe side effects, interventional techniques should be taken into account, whether the disease process is early or late. This article aims at summarizing the indications, mechanisms, drug agents, contraindications, and complications of interventional pain management techniques that may offer benefit to patients coping with cancer and its terrible symptoms.

Central Neuraxial Blocks

The binding of an opioid to its spinal cord receptor inhibits or blocks the conduction of nociceptive signals, which is the basis for neuraxial analgesia. Opioids may also alter the pain pathway in the midbrain by disrupting the descending pathways. Although it can effectively reduce pain while preventing opioid toxicity, it should only be used on patients for whom simpler approaches have failed to adequately control their pain. Approximately 2% of patients will benefit from these techniques, depending on the population under consideration.

A percutaneous epidural or intrathecal catheter, an external syringe pump, or a fully implanted intrathecal drug delivery system can all be utilized to give medication. Patients with shorter life expectancies (<3 months) may benefit from epidural therapy using implanted systems such as a catheter or port-a-catch connected to an external patient-controlled analgesia (PCA) pump, while patients with cancer-related pain and longer survival expectancies (>3 months) may benefit from neuraxial therapies using implantable systems as a permanent intrathecal catheter and subcutaneous pump [10]. The likelihood of survival, patient demands, and cost are typically taken into account while choosing a type of device. Other anaesthetics, such as bupivacaine, can be used instead of or in addition to opioids because of their long duration of action, low toxicity, and affordable price. Other agents such as clonidine, ketamine, and neostigmine may enhance analgesia and lower opioid dosages [10]. It is crucial to choose patients carefully and to educate the people who will be caring for patients who receive these infusions [11-12]. Complications of neuraxial therapy include damage to the spinal cord or fibers during catheter insertion, dural puncture headache, epidural hematoma, infection, and meningitis [13].

Kurita et al. in a systematic review, analyzed the analgesic efficacy and adverse effects of opioids with and without adjuvant analgesics when administered through the neuraxial route (epidural and subarachnoid) to adults with cancer pain. They demonstrated better pain control for all interventions analyzed [14]. However, the review concluded with a weak recommendation for the

neuraxial administration of opioids in adult cancer patients, which might be attributed to the heterogeneous characteristics and many methodological flaws in the study.

Sympathetic nerve block

Despite the fact that abdominal pain frequently coexists with other pathophysiological symptoms, patients with visceral abdominal pain are advised to undergo neurolytic inhibition of sympathetic pathways at various levels [15]. The celiac plexus receives the sympathetic fibres from greater and lesser splanchnic nerves from T5 to T12 [16]. These nerve fibers extend inferiorly to the level of the superior and inferior mesenteric plexus and surround the celiac trunk.

Most of the abdominal viscera, including the stomach, liver, biliary tract, pancreas, spleen, kidneys, adrenals, omentum, small bowel, colon to the splenic flexure, are innervated by the celiac plexus. Celiac plexus block (CPB) is used to treat cancer-related pain arising from the upper abdominal viscera while the superior hypogastric plexus block (SHPB) is used to treat lower abdominal pain. In order to eliminate or lessen pain, these blocks interfere with neural conduction. The effectiveness of CPB is probably dependent on each patient's anatomical distribution, which is probably going to change as the tumor grows locally. The block is probably going to be less effective when tumor spread involves other somatic regions like the peritoneum or diaphragm.

The general contraindications for neurolytic blocks of sympathetic pathways include tumor penetration into the insertion site, coagulopathy, systemic or localised infection, complicated anatomy, and bowel obstruction [17,18]. The main complications of sympathetic block are back pain, orthostatic hypotension, diarrhoea, retroperitoneal hematoma, bladder or ureteral injury, and unintentional somatic nerve damage [17,18]. CPB is believed to be safer than neurolytic somatic blocks because, when carried out under CT guidance, neurological complications are infrequent and mostly transient.

With total pain relief reported in up to 48% of patients in randomised controlled trials, celiac plexus neurolysis (CPN) has been demonstrated to be effective in reducing overall pain. Other randomised controlled trials have demonstrated that celiac plexus blocks and neurolysis lessen the overall need for opioids as well as their negative effects, such as nausea, vomiting, constipation, and hypotension [16]. Patients receiving CPN are advised to have post-procedure monitoring. The most frequent adverse effects are transitory diarrhoea and hypotension, with risk ratios of 5.88 and 7.43, respectively, according to a recent comprehensive review [18]. Compromised respiratory function (pneumothorax and pleural effusion), neurologic issues (transient dysesthesias or paraplegia), increased pain, alcohol intoxication, peritonitis, and hematuria are rare but potentially dangerous consequences of CPN [19].

In a systematic review by Mercadante et al, compared to standard analgesic care, celiac plexus blocks have been shown to increase analgesia, reduce opioid intake, and mitigate opioid-induced side effects [20]. Patients with painful, inoperable pancreatic adenocarcinoma may benefit from endoscopic ultrasonography guided celiac plexus neurolysis, as described by Wyse et al. in a randomised controlled trial [21]. Okumaya et al, have shown that that intraoperative celiac plexus block is an effective and safe, method for the management of pain caused by unresectable pancreatic cancer [22].

There is a lack of available data on superior hypogastric block. A study based on the use of anterior USG-guided superior hypogastric plexus neurolysis has reported that it is a useful technique in relieving pelvic pain in gynaecological malignancies. However, it requires expertise to perform the block [23]. The origin of pelvic cancer-related pain, is even more complex, because of different mechanisms involved due to the various overlapping structures, including muscles and nerves [24]. The study reported that patients with pelvic cancers with a neuropathic component showed worse pain relief. The evidence from the literature is weak in support of employing this intervention.

Other autonomic blocks

For pain with an autonomic component in the head or arm, a stellate ganglion block may be employed. As catheter procedures are challenging and neurolytic block poses major risks in light of the anatomical relations of the ganglion, single or repeated injections are carried out. For ischemic leg pain, pain mediated by the sympathetic nervous system, and bilaterally for tenesmus, a lumbar sympathetic block can be performed [25]. The superior hypogastric plexus neurolytic block [26] or the ganglion of impar can reduce pain from pelvic structures [27].

Peripheral nerve block

When the distribution of somatic pain is restricted to a single nerve or plexus, peripheral nerve blocks may be employed. The pain may be due to primary or secondary tumor deposits or as a result of treatment e.g. post-radiation pain, or due to secondary complications like pathological fracture or vascular blockage.

Peripheral nerve blocks are rarely used as the sole or even the primary form of treatment. Most people will have pain at multiple sites. However, when used in conjunction with other forms of therapy like systemic analgesics, radiotherapy, and chemotherapy, they may be able to effectively relieve one component of a patient’s overall pain while also facilitating other types of treatment like physiotherapy and lymphedema care.

Local anaesthetics are the medications used for nerve blocks, and due to their short duration of action, they must be used continuously or intermittently. Lidocaine, bupivacaine, and ropivacaine are a few examples of local anaesthetics in use. The analgesic effect is similar despite the potential toxicity in connection to cardiac events and other local anaesthetic toxic reactions. The risk of toxicity is negligible, nevertheless, provided the local anaesthetic is administered in accordance with the recommended doses. Each local anaesthetic has a distinct duration of action. as a different duration. Bupivacaine and ropivacaine are long-acting local anaesthetics (4-18 h), but lidocaine has an intermediate action and takes 1.5 to 3 hours to have effect [28]. The duration of action may vary depending on the location of the nerve block and may be affected by addition of other agents like epinephrine or clonidine [29]. Therefore, long-term treatment with local anaesthetics is best achieved by bupivacaine or ropivacaine; bupivacaine has been the most often reported drug for this purpose. According to some reports, peripheral nerve blocks were used with neurolytic agents such as glycerol, phenol, or alcohol. These substances irreversibly damage the neuron and need a single injection for a long-term block of the signalling of nerve impulse.

Most frequently, local anaesthetics are administered as single injections or catheter infusions to target the peripheral nervous system as part of a perioperative anaesthetic regimen [30]. Deep analgesia can be achieved by injecting local anaesthetics into the nerve supply of the affected extremities without the adverse side effects of parenteral medications like opioids [31]. The technique used for the management of acute postoperative pain might be applied for the treatment of cancer related pain. Although a single injection of local anaesthetic is sufficient for short-duration analgesia, such as during an imaging test, surgery, or rapid treatment of a pain crisis, continuous infusion via an indwelling catheter provides a longer period of analgesia.

The peripheral nerve blocks that have been reported in several studies include femoral nerve block, sciatic nerve block, paravertebral block, brachial plexus block, suprascapular, psoas compartment, distal lumbar plexus, and intrapleural blocks [32-39]. However, there are not many clinical studies on the usage of peripheral nerve blocks. Most of them are case reports or small case series containing a description of what has worked.

Contraindications to upper-extremity peripheral nerve block techniques include infection, deranged

coagulation profile, past history of nerve injury, including exposure to certain chemotherapeutic medications that are neurotoxic [40]. Pneumothorax, spinal cord injury, nerve damage, respiratory depression secondary to phrenic nerve block, [41] and Horner's syndrome are risks associated with interscalene blocks. Other methods of upper-extremity blocks carry similar risks. However, as one proceeds distally along the plexus, the risk of respiratory depression and Horner's syndrome decreases.

A systematic review by Klepstad et al. which reported on the existing evidence of analgesic efficacy for peripheral nerve blocks in adult patients with cancer found that most cases experienced pain relief. The duration of efficacy lasted for several weeks even till death. However, peripheral blocks for cancer-related pain are currently only supported by anecdotal data [42].

Percutaneous Cordotomy

Percutaneous cordotomy is a technique in which a thermal lesion is created by radiofrequency electric current in the spinothalamic tract contralateral to the side of the pain. This interrupts conduction fibres and eliminates pain and temperature sensation from the affected half of the body. Its mechanism is unknown, however, alteration on descending impulse or dorsal horn modulation, C fiber damage, and immunomodulatory effects could all affect how pain is transmitted. Pulsed radiofrequency needle tips are maintained at 43 °C to minimize tissue injury, however typical radiofrequency needle tips are 80–90 °C [17].

Cordotomy can only alleviate pain below the C4 dermatome since certain second-order spinothalamic fibers decussate multiple spinal segments above or below their distal synaptic connections (i.e., below the clavicle). Radiofrequency current is typically used to achieve it percutaneously. However, open surgical techniques are an option. It is effective, as in 83% of patients undergoing the procedure opioid use is cut to half, and 38% of the patients can stop it altogether [43]. It is primarily utilised for refractory chest wall pain secondary to mesothelioma and infrequently for Pancoast tumours, although theoretically it could be useful for any unilateral cancer pain below C4. Percutaneous cordotomy by radiofrequency has emerged as a practical alternative because of developments in fluoroscopy that allow for treatment under sedation instead of general anaesthesia. These benefits are especially advantageous for frail patients with terminal cancer. Risks and outcomes should be carefully taken into consideration because this technique disrupts nerve conduction irreversibly. Cancer patients who are candidates for this procedure must have unilateral pain that is resistant to systemic analgesics and other non- destructive interventions, have a life expectancy of a few years or less taking into account the possibility of pain recurrence, and anatomic location of the intervention that permits a safe procedure [44].

Percutaneous cordotomy can be used for the treatment of brachial plexus pain associated to pancoast tumour, breast cancer, malignant pleural mesothelioma, unilateral leg pain, and pain related to breast cancer. Besides this, it can also be used for bilateral cancer-related pain, but bilateral treatments raise the risk of complications and mortality [45].

Some people may experience numbness or dysesthesias below the level of the lesion as a result of this procedure. Contraindications are abnormal coagulation, infection, severe respiratory dysfunction, and advanced disease that prevents optimal positioning of the patient during the procedure [45]. The complications include hemiparesis, respiratory irregularities, bladder and bowel dysfunction (usually temporary), and ataxia [44]. Studies have shown it to be safe and effective in reducing cancer related pain [46-49].

Percutaneous vertebroplasty and kyphoplasty

Percutaneous vertebroplasty (PV) treatment is used to alleviate axial back pain due to osteoporotic

wedge fracture or malignant vertebral body disease. In this procedure, bone cement is injected into the vertebral body under fluoroscopic supervision. It is believed to function by preventing painful aberrant macro- or micromovement of bony ends and stabilising fracture sites. The underlying mechanism of action is that the thermogenesis produced by the setting cement may have a neurolytic effect.

Despite the reported efficacy and low risk associated with these interventions, only a few patients have access to such minimally invasive procedures because of a shortage of skilled staff, imprecise indications, and higher costs [50]. Therefore, these treatments should only be used on a specific group of patients who have severe and incapacitating cancer-related back pain that is resistant to systemic analgesic therapy. In PV, a cement called polymethylmethacrylate is injected percutaneously into the vertebral bodies. This cement can mechanically stabilize the lesion or compression fracture, boost bone strength, and reduce pain.

In a related surgery called kyphoplasty, the height of the vertebral body is restored with the injection of cement into the cavity created by the repeated inflation of a balloon inserted into the vertebral body. Both PV and kyphoplasty have comparable indications and contraindications, and neither provides better pain relief than the other [51].

Several studies have suggested a potential therapeutic function for these treatments, but the available data are generally hampered by small sample sizes, retrospective designs, or a lack of comparability across study groups. A systematic review has reported that both vertebroplasty and kyphoplasty significantly and rapidly lowered pain severity in cancer patients with vertebral compression fractures. They also lowered the requirement for opioid pain medication, and functional limitations related to back and neck pain [52]. A systematic review involving five studies, recommended to perform kyphoplasty in patients with vertebral tumors or metastases [53]. However, a number of flaws and a poor study design compromise the validity of this recommendation, which is based on a single randomized controlled trial.

Radio frequency ablation and Cryoablation

Radio frequency ablation (RFA) ablates bone tumor or metastasis using the heat produced by medium frequency alternating current. Cryoablation (CA) is an alternative to radiofrequency ablation (RFA) for treating metastatic bone disease. It is performed with the use of cryoprobes that circulate cold, thermally conductive fluids. These techniques are now widely used for back pain due to osteoporotic and malignant vertebral collapse that is resistant to conservative treatment [50].

The use of these techniques, particularly in individuals with advanced cancer, is still debatable. Several studies have suggested a possible therapeutic role of these approaches, despite the fact that current data are limited to series with a small number of patients, retrospective designs, or mixed populations. Due to the small patient population and poor data quality, there is currently no evidence of efficacy of these techniques for cancer patients with spinal metastases or tumours.

Radiotherapy and Bisphosphonates

An external beam radiotherapy is a treatment option for metastatic bone pain [54-57]. According to a meta-analysis, external beam radiation provided partial pain relief in up to 60% to 90% of the patients with uncomplicated bone metastasis and about a quarter of these patients reported complete pain relief within 3-4 weeks [58]. According to various studies, single fraction radiation is just as efficient at relieving bone pain as fractionated radiation [59-60]. In other words, short course palliative radiation with a greater dose per fraction produce outcomes that are comparable to those of longer courses that with a small dose per fraction. Patients receiving unfractionated

radiation appear to have a higher re-treatment rate and a higher incidence of pathological fractures. The minimal total dose of radiation required for pain relief is still unknown.

After radiation, patients who experience improvement in pain may also experience better emotional functioning, decreased insomnia, less constipation, and an overall increase in quality of life scores [61]. In order to alleviate pain and prevent additional symptoms, radiation therapy should be a crucial component of palliative care for bone metastases [62].

The absence of a dose-response relationship shows that the initial pain relief mechanism is more likely due to change in the local environment resulting in activation of bone resorption by osteoclasts rather than a decrease in tumour load [63]. This explains the seemingly paradoxical comparison of relief in pain between single-dose treatment and longer-course treatment.

The most appropriate treatment for patients with a poor performance status having difficulty in making multiple trips for treatment, extensive bony metastases, and/or a short life expectancy is a single fraction of 8 Gy. Patients with a limited expectancy (<3 months) also experience pain relief, and palliative radiotherapy should still be considered for such patients [64-65]. While patients with a good performance status, longer life expectancy and bone-only metastases, a longer course of treatment (30 Gy in 10 fractions) may be a better option to minimize the risk of retreatment. Treatment with a higher dose may be necessary for some patients with a single bone metastasis (referred to as a “oligometastasis”), although this must be balanced against the possibility of potential weakening of surrounding normal bone.

Reirradiation to the painful metastatic sites can be administered for some patients who do not respond to the initial course of treatment or for those who experience pain recurrence after an initial successful treatment [66]. Approximately 60% of retreated patients reported an improvement in their pain, with 16% to 28% of patients reporting a complete resolution of pain [67]. Patients also reported an improved overall quality of life and decrease in pain-related functional limitations with the retreatment of painful bone metastasis [68].

Patients with osseous metastases typically have multiple lesions. Radiation therapy can relieve pain in a few specific sites, but it cannot treat widespread disease. Wide-field radiation treatment, also known as hemibody irradiation, is a method of treating a sizable area of the body with an external beam of radiation. Although the term hemibody irradiation is used, the field normally treats around one-third of the body, rather than the entire body. The treatment has been used as an adjuvant to stop the development of new bone metastases as well as to relieve symptoms. Patients with diffuse, extensive bone metastases benefit the most from the treatment for pain relief.

Trials evaluating multifraction courses of HBI were conducted by both the RTOG and the International Atomic Energy Agency [69-70]. The total dosage ranged from 8 to 20 Gy, with doses per fraction varying from 2.5 to 4 Gy. On the RTOG 88-08 study, 17.5 Gy in seven fractions was the highest tolerated dose. According to the study by the International Atomic Energy Agency, 3 Gy twice day for 2 days (12 Gy total) or 3 Gy every day for 5 days (15 Gy total) were more efficient than 4 Gy every day for 2 days. The use of bisphosphonates is recommended as they have a role in reducing skeletal morbidity in bony metastatis [64-65,71]. Although a thorough study found little evidence of an analgesic effect, bisphosphonates may delay the onset of pain [72]. In a study by Vassiliou et al., bone density in the area of the metastases increased by 73% by 10 months after treatment [73].

Radionuclides

Radionuclide therapy is as effective as external radiation therapy in relieving cancer pain due to bone metastasis. The concept of radiopharmaceutical treatment is compelling [74]. Calcium (and to a lesser extent phosphorous) analogs will preferentially accumulate in bone in areas of active bone turnover. A targeted treatment in the regions where the radiopharmaceutical accumulates will be

possible using a radioactive isotope that is beta emitter or low-energy gamma emitter. This reduces side effects and provides an excellent therapeutic ratio. A single injection is used to administer the radiopharmaceuticals, making it simple to administer. It is possible to combine the therapy with other approaches, such as chemotherapy or external radiation therapy.

Phosphorus-32 was the first radiopharmaceutical used to treat bone metastases (P-32). Subjective pain alleviation with P-32 treatment for diffuse bone metastases was achieved, albeit at the expense of significant bone marrow damage. With a better therapeutic ratio than P-32, several radioisotopes have been applied to the palliation of diffuse osseous metastases.

Chemically comparable to calcium, strontium-89 (Sr-89) is deposited in the bone matrix, preferentially in areas where osteogenesis is actively taking place. Sr-89 is a pure beta emitter with a half-life of 50.6 days and an energy of 1.4 MeV [75]. Although samarium-153 (Sm-153) is largely beta emitter, it also possesses a gamma emission component that is useful for imaging purposes.

Multiple prospective trials have been conducted to assess these two isotopes. Other, more recent isotopes like tin-117m, rhenium-186, and rhenium-188 are being studied. Radium-223 may also increase overall survival in individuals with castrate-resistant metastatic prostate cancer in addition to pain relief. All of these isotopes accumulate in areas of osteoblastic activity, especially in areas of increased uptake on bone scintigraphy. This is the reason why most of the patients entered on prospective trials have metastatic prostate cancer.

In a study by Porter and McEwan, after receiving involved-field radiation treatment, the patients were assigned to receive 400 MBq of Sr-89 or a placebo. Even while there was no statistically significant difference in the primary objective of pain alleviation, the Sr-89 had superior results in a number of secondary end points. In the patients who got Sr-89, more patients (17% vs. 2%) were able to stop using their analgesics, and there were fewer sites of new pain requiring radiotherapy [76]. Studies have reported significant improvement in pain relief, decrease in the average opioid dose in the patients receiving Sm-153 [77-78].

In conclusion, the treatment of a patient with refractory pain due to cancer may be incredibly challenging. Those patients who do not respond well to the systemic opioids and adjuvant analgesics should be actively examined for more advanced pain treatment alternatives. It is crucial to pay close attention to the selection of the technique, skill to perform the procedure, logistics, appropriate indication, type of pain if well-defined/localized, benefits and risks involved. Besides this, patient’s health status, estimated survival time, and requirements should be taken into account when treating cancer-related pain in order to prevent complications and ensure that the right intervention is chosen. Even though there is some risk involved with the advanced interventional techniques discussed in this article, the advantages of reduced pain and enhanced quality of life usually outweigh the risk.

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