Sympathetic Blockade for Pain Associated With Nonaxial Bone Lesions in Patients With Cancer: An Uncontrolled Cohort

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Abstract

Background: Cancer-related bone pain remains a prevalent and frequently incapacitating ailment. Although conventional approaches effectively alleviate pain in most individuals, a subset of patients may continue to experience intractable pain. Current recommendations for treating cancer-related bone pain include oral analgesics and multimodal adjuvants, radiation therapy, and, in selected cases, intrathecal therapy. Cancer-related bone pain is mediated by a proliferation of sensory and sympathetic fibers. Thus, we believe that this pain can be successfully managed with minimally invasive sympathetic blockade (SB). **Methods:** In a retrospective observational cohort, we reviewed patients who underwent single-shot SB for uncontrolled cancer-related bone pain despite receiving opiate analgesics and other interventions. We documented the Edmonton Symptom Assessment Scale (ESAS) ratings, the numeric rating scale (NRS) pain scores, and the morphine equivalent daily dose (MEDD) before and after SB. **Results:** The final cohort included 43 patients (median age, 58 years [range, 23–86 years]) with a history of bone pain experienced for a median of 6 months (IQR, 3–12 months). Comparing before and after the SB, patients had pain reduction –6 (IQR, –7 to –4; $P<.001$), reduction of ESAS scores of –17 (IQR, –23 to –3; $P<.001$), and reduction of MEDD –57 mg (95% CI, –79 to –34; $P<.001$). The treatment was well tolerated. **Conclusions:** Blockade of sympathetic afferent innervation is an effective and cost-effective modality that can be safely used to palliate intractable pain in patients with malignant bone pain.

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Background

Bone cancer is categorized as primary or secondary (also referred to as *metastatic*). The 4 most prevalent primary bone cancers are multiple myeloma, osteosarcoma, Ewing sarcoma, and chondrosarcoma.[1] In contrast, metastatic bone cancer has a higher prevalence, and bone is the third most common site of metastasis after the lung and liver.[2,3] Notably, certain malignancies, such as breast, lung, prostate, thyroid, and kidney cancers, exhibit a heightened tendency to metastasize to bone, accounting for approximately 80% of distant bone lesions.[4] Skeletal metastasis tends to occur in hematopoietically active bone marrow in adults, such as in the axial skeleton, pelvis, ribs, proximal humerus and femur, and skull[5] (Figure 1), with less frequent occurrences in sites like the sternum.

Bone pain is considered the most common type of pain in patients with cancer.[6–8] Even hematologic malignancies, such as acute leukemia, can give rise to bone pain due to marrow infiltration.[9] The intensity of bone pain is related to the degree of tissue destruction, invasion of surrounding structures, and the adverse impact on the function of the compromised bone (eg, torso erection in vertebrae, breathing in ribs, load-bearing in pelvic or femur bones). The pain caused by bone metastasis is further confounded by systemic therapies (eg, chemotherapy, hormonal therapies, colony-stimulating agents, systemic steroids) and localized treatment (eg, radiation therapy, surgical stabilization).

Among general practitioners, pain management in patients with bone cancer is traditionally based on the WHO analgesic ladder. Despite their known side effects, administration of escalating doses of opioids is a common strategy for malignant bone pain, frequently yielding suboptimal results.

The pathophysiologic mechanism of metastatic bone pain remains incompletely elucidated. However, advances in basic science have shed light on different pathways of pain mechanisms, including tumor-induced osteolysis, tumoral production of growth factors and cytokines, stimulation of ion channels, and tissue production of endothelins and nerve growth factors.[10] Furthermore, laboratory observations of phenotypic alterations in sympathetic fibers have been associated with increased bone pain and associated neural activity.[11]

Currently, blockade of sympathetic innervation is indicated for various pain syndromes, including complex regional pain syndrome, phantom limb pain, groin and testicular pain, postherpetic neuralgia, neuropathy, ischemic limb pain, radiation-induced plexopathy, and tumor-related bladder spasms.[12] However, the involvement of the sympathetic nervous system in pain mechanisms suggests a potential neuroanatomical pathway for cancer-related bone pain. Thus, the sympathetic pathway involved in this nociception process cannot be peripherally blocked with conventional nerve blocks, or systemically with intrathecal therapy.

This study highlights the potential utility of sympathetic blockade (SB) in pain management in individuals experiencing cancer-related bone pain. Consequently, increasing interest has been shown in targeting the sympathetic component of bone

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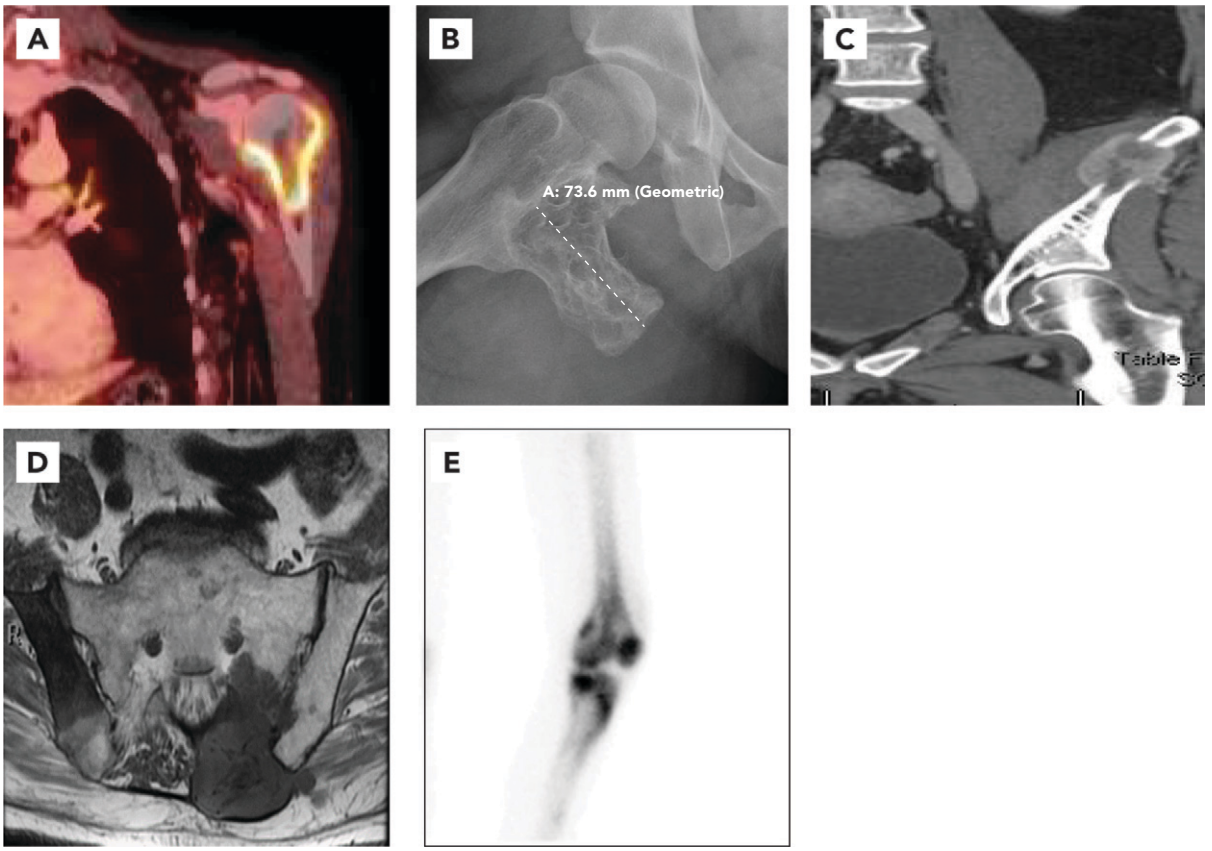

Figure 1. Typical diagnostic images of bone lesions with radiographic reports. **(A)** PET/CT scan of a metabolically active metastatic bone lesion involving the left humeral head-neck demonstrating cortical disruption. **(B)** Plain radiographs of the hip showing large exostosis of the proximal right femur and a cartilaginous lesion of the right ilium. **(C)** CT scan of a metastatic lesion arising from the left iliac bone infiltrating the iliacus muscle. **(D)** MRI of the large left sacral ala mass invading the left S1–S3 foramen with effacement of the fat surrounding the S2 and S3 nerves. **(E)** Nuclear medicine bone scan showing focal tracer uptake worrisome for metastatic disease in left distal femur and left proximal tibia.

pain refractory to conventional treatments.[13] Our observational data support the effectiveness of SB in the treatment of cancer-related bone pain.

Methods

Study Setting and Patient Population

This retrospective cohort was performed at our academic tertiary care cancer center and was approved by the MD Anderson Cancer Center Institutional Review Board (2021-0506). No written informed consent from participants was required.

Data Collection

Utilizing billing codes in our electronic medical records, we identified and retrospectively reviewed study candidates seen in our pain department undergoing cancer therapy evaluated for intractable pain related to metastatic bone lesions in the upper or lower limbs. Patients experienced incident or movement-related bone pain, as well as pain at rest. We included patients treated between December 1, 2020, and June 1, 2022.

Selection and Description of Participants

Patients of any age, sex, cancer type, disease stage, and treatment modality were included. All reported suboptimal pain control; many reported this despite the use of antineuropathic agents, bisphosphonates, and receptor activator of nuclear factor-κB ligand (RANKL) inhibitors, and all of them received opiate analgesics. There was evidence that controlled pain can have a negative impact on their quality of life despite undergoing cancer treatment and pain management. Physical examinations revealed no differences in local temperature, perfusion, sweating, edema, or allodynia when compared with the opposite limb. Extremity temperature is not commonly measured in a clinical setting and therefore was not documented. Completion of records was defined as adequate documentation from the initial evaluation and procedure performance to the follow-up visit(s).

Procedures for Pain Management

Within our pain clinic, we routinely attend to patients experiencing pain associated with bone lesions. Before the lumbar sympathetic blockade, patients were encouraged to continue other modalities of pain management, including systemic analgesics, if deemed necessary or beneficial. Our safety checkpoints consisted of an assessment of documented drug allergies, current medications, laboratory tests, and imaging results. All patients were presented with the option of undergoing a sympathetic nerve block, and willingly consented to this intervention. The block injectate consisted of a mixture of 0.25% bupivacaine and 40 mg/mL triamcinolone. Most patients underwent a unilateral

fluoroscopy-guided lumbar plexus sympathetic block (9:1 mL) (see Appendix 1 in the Supplementary Materials, available online with this article). Two patients underwent an ultrasound-guided stellate ganglion block (3:1 mL) (see Appendix 2).

Outcome Measures

We used the validated patient-reported numerical rating scale (NRS) for bone pain using a 11-point Likert scale from 0 (no pain) to 10 (worst possible pain). We also used the patient-reported Edmonton Symptom Assessment Scale (ESAS), ranging from 0 (absence) to 10 (worst possible), to measure the severity of common symptoms among patients with advanced cancer (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath; the "other symptoms" option is not routinely recorded), and assessed the changes on morphine equivalent daily dose (MEDD) with treatment. We aimed to compare those scores before and after SB. In addition, we calculated the duration of the analgesic effect experienced with the intervention and any adverse effects reported. All results were based on a single sympathetic nerve block. Some of the patients were already deceased and no patient had undergone a repeat block at the time of completing this cohort.

Statistical Analysis

Median with IQR for ordinal data, mean with 95% confidence intervals (CIs) for continuous data, and percentages for count data were used to present descriptive analysis. The Student t test was used for comparing continuous data assuming normal distribution and the Wilcoxon rank sum test was used for comparing ordinal data. The Spearman correlation test was used to assess the relationship between 2 continuous or at least ordinal variables.[14] Bonferroni correction was used to account for multiple independent comparisons, with initial P values multiplied by the number of comparisons for final adjusted P values and presented as $P=1.0$ when the adjusted P value was >1.0 (6 total comparisons).[15] All CIs were set at 95% and the significance level α was set at 0.05. Statistical analysis was completed via GraphPad Prism 10.0.2 (GraphPad Software).

Results

Patient Characteristics

We identified 43 adult patients who were seen in our pain clinic between December 1, 2020, and June 1, 2022, for intractable pain related to metastatic bone lesions in the upper or lower limbs. Among these patients, 6 died and 2 entered hospice care, but all had previous documented postprocedure visits. The remainder of the cohort (n=35) was still undergoing active follow-up.

Demographic Characteristics

As summarized in Table 1, the median age was 58 years (IQR, 50–67 years); 22 patients were female and 21 were male. The most common diagnoses were sarcoma (n=9; 20.6%) and renal cell carcinoma (n=8; 18.6%). The most common combination of cancer therapy used was chemotherapy plus radiation plus surgery (n=13; 30%) and the least common cancer therapy included tumor ablation (n=1; 2%). The most common area of pain reported by patients included combined hip and thigh (n=18; 42%).

Table 1. Patient Demographics (N=43)

Characteristic	n (%)
Sex	
Female	22 (51)
Male	21 (49)
Age, median (IQR), y	58 (50–67)
Pain duration, median (IQR), mo	6 (3–12)
Primary tumor	
Sarcoma	9 (20.6)
Renal cell carcinoma	8 (18.6)
Breast	6 (14.0)
Lung	4 (9.3)
Prostate	4 (9.3)
Myeloma	3 (7)
Gastrointestinal	3 (7)
Gynecologic	3 (7)
Thyroid	3 (7)
Treatment modality	
Ch/Rad/Sx	13 (30)
Ch/Rad	9 (21)
Ch alone	8 (19)
Ch/Sx	3 (7)
Rad alone	3 (7)
Sx alone	3 (7)
Sx/Im	2 (4)
Im/Rad	1 (2)
Ch/Rad/Abl	1 (2)
Pain location	
Hip/Thigh	18 (42)
Hip/Buttock	15 (35)
Hip/Pelvis	4 (10)
Shoulder/Arm	2 (5)
Hip/Low back	1 (2)
Hip/Thigh/Knee	1 (2)
Knee alone	1 (2)
Leg alone	1 (2)

Abbreviations: Abl, ablation; Ch, chemotherapy; Im, immunotherapy; Rad, radiation; Sx, surgery.

Clinical Characteristics

Most patients described their pain as "ache and dull" in nature (n=35; 81%) (data not shown). Pain was constant and/or present even at rest in all patients. Dynamic pain was not well defined; however, it was presumed that these patients would present with worsened pain with activity or weight-bearing (n=28; 65%). The median duration of the pain before SB was 6 months (IQR, 3–12 months) (Table 1).

Efficacy of SB on Reported Pain

NRS pain scores were reported both before and after the SB (Table 2). Among the 43 patients, 36 (84.4%) had a baseline NRS pain score of ≥7. The NRS median pain score before SB was 8 (IQR, 7 to 9) and after the procedure was 2 (IQR, 0 to 3). The change in NRS pain score (delta) was –6 points (IQR, −7 to −4). Many patients had pain reduction of >5. Bonferroni corrected P value indicated that the change in pain score from before to after treatment was significantly different even after adjustment ($P<.001$; Table 2, Figure 2A). The duration of pain prior to SB did not correlate with amount of NRS pain relief achieved (Spearman's $r=0.01$; adjusted $P=1.0$), implying that patients with a long duration of pain prior to SB may experience similar pain relief as those with shorter duration of pain.

Table 2. Outcome Effect Sizes for Pre- and Post-Sympathetic Blockade

Variable	n	Pre-Sympathetic Blockade	Post-Sympathetic Blockade	Delta (Δ)	*P* Value	*P* Value[a]
NRS (0–10)	43	8 (7 to 9)	2 (0 to 3)	−6 (−7 to −4)	<.0001	<.001
ESAS (0–100)	43	35 (28 to 56)	22 (16 to 38)	−17 (−23 to −3)	<.0001	<.001
MEDD (mg)	27	130 (75 to 186)	74 (27 to 120)	−57 (−79 to −34)	<.0001	<.001

Ordinal data presented as medians with interquartile range (NRS and ESAS). Continuous data presented as mean with 95% confidence intervals (MEDD).
Abbreviations: ESAS, Edmonton Symptom Assessment Scale; MEDD, morphine milligram equivalent daily dose; NRS, numeric rating scale for pain.
[a]Bonferroni corrected *P* value.

Efficacy of SB on Reported Symptoms

ESAS scores were reported both before and after SB (Table 2, Figure 2B). Median ESAS score before SB was 35 (IQR, 28 to 56) and after SB was 22 (IQR, 16 to 38). The change in ESAS score (delta) was −17 (IQR, −23 to −3). Bonferroni corrected *P* value indicated that the change in pain score from before to after treatment was significantly different even after adjustment ($P<.001$).

Descriptively, most patients (n=41; 95%) reported maximum pain relief immediately after the procedure. Two patients claimed no changes in pain scores after SB; however, their ESAS scores were 20% better on follow-up. Six patients were deceased at the completion of this data collection; however, 2 completed a 6-month follow-up—one with 100% and the other with 75% pain improvement. The others had 75% to 100% pain relief reported at 2 months post SB. Similarly, 2 patients were discharged to hospice; however, their 2 months post SB described pain relief of 75% to 100%. The median duration of the analgesic effect of SB was 3 months (IQR, 2–4 months) (Figure 3). The duration of pain prior to SB did not correlate with amount of ESAS symptom improvement achieved (Spearman's $r=-0.13$; adjusted $P=1.0$), implying that those with a long duration of pain prior to SB may experience similar symptom improvement as those with shorter duration of pain.

Effect of SB on Opioid Use

MEDD comparison could only be conducted for 27 of the 43 individuals due to incomplete data on methadone dosages. MEDD amounts were reported both before and after SB (Table 2, Figure 2C). The MEDD showed a reduction from 130 mg (95% CI, 75 to 186 mg) to 74 mg (95% CI, 27 to 120 mg) after SB, with a delta of −57 mg (95% CI, −79 to −34 mg) and adjusted $P<.001$. The immediate and sustained improvement after the procedure suggests that no other confounders were responsible for this attribute. Multiple patients reported complete pain relief of the targeted bone lesions. To assess whether missing analgesic data may affect final comparison, unknown methadone dosages were set to 0 and Student *t* test was performed for all 43 individuals, showing a reduction of –58 mg (95% CI, –76 to –39 mg), implying that patients on low doses of methadone, which had minimal impact in overall MEDD, may likely experience similar reduction in MEDD after SB.

Discussion

The sympathetic nervous system is an essential component of neuropathic, vascular, and visceral pain.[16] As opposed to blockade of the nociceptive somatic pathways, the blockade of sympathetic nervous system attenuates the transmission of nociceptive impulses, providing analgesia without influencing somatic sensory or motor activity.[17,18] Physicians have

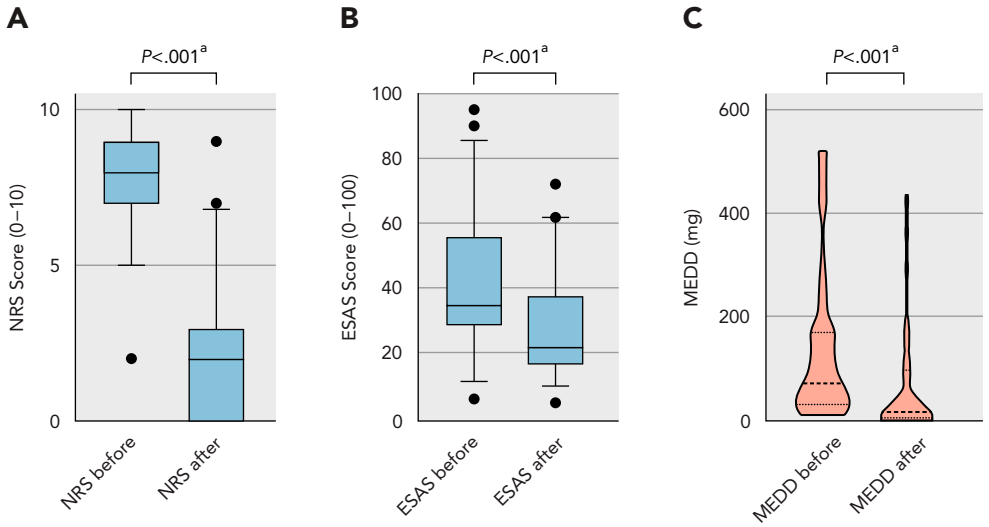

Figure 2. Charted outcomes pre- and post-sympathetic blockade. Box-and-whisker plots for **(A)** NRS (n=43) and **(B)** ESAS (n=43) outcomes, displaying median with IQR as box and 5% to 95% range as whiskers. Dots represent outliers from the 5% to 95% range. **(C)** MEDD (n=27) violin plot displays continuous data density, with thick dotted line representing median and thin dotted lines representing IQR.
Abbreviations: ESAS, Edmonton Symptom Assessment Scale; MEDD, morphine milligram equivalent daily dose; NRS, numeric rating scale for pain.
[a]Bonferroni corrected *P* values.

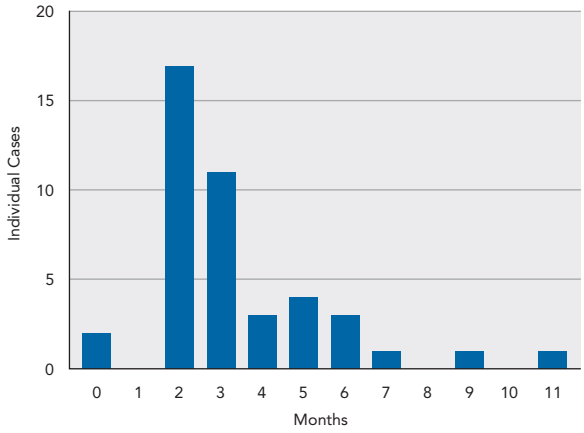

Figure 3. Histogram of pain relief duration (n=43).

previously used chemical or thermal blockade of the sympathetic chain to treat complex regional pain syndrome, ischemic limb pain, phantom limb pain, neuropathic pain, and cancer-related visceral pain.[19,20]

Stretching of the periosteum, releasing of inflammatory mediators and growth factors, microfractures, and nerve root infiltration are common mechanisms of cancer-related bone pain.[21,22] A better understanding of the pathways compromising the sympathetic nervous system in patients with chronic bone pain would elucidate potential therapeutic strategies for pain management. Although the periosteum is composed of densely innervated tissue, animal studies have revealed that most sympathetic and sensory fibers, including large Aβ fibers, are in the marrow.[23] Studies of animal models have suggested that bone tissue has an innervation pattern that differs from other human tissues. The density of these fibers is variable, and a significant proportion (50:1) of nerve fibers residing in the periosteum are myelinated (Aδ fibers) and unmyelinated (C fibers).[24,25] In mouse studies, tumor cells invade the sensory and sympathetic nerve-rich periosteum wherein sensory nerve fibers sprout and give rise to intricate structures of disordered axon endings, resembling interlacing-like neuromas.[26]

Other studies have demonstrated that osseous tumors induce inflammatory cells to release nerve growth factors, sensitizing afferent neurons and inducing neural tissue formation.[27] This formation resulted in a 10- to 70-fold increase in fiber density in the bone marrow due to progrowth factors produced by the tumor environment.[13] Tumor cells release multiple signaling molecules, including protons, which promote an acidic environment.[28] As a result, the transient receptor potential vanilloid 1 receptor (TPRV-1) is upregulated in tumors. Low pH induces thermal hyperalgesia and mechanical allodynia.[29,30] Furthermore, neurotrophins such as nerve growth factors are upregulated in tumors and facilitate the release of substance P and calcitonin gene-related peptide (CGRP) and activate ion channels such as TRPV-1 and sodium, leading to the sprouting of sensory and sympathetic nerve fibers.[31,32] These changes collectively bring about phenotypic alterations in sensory and sympathetic fibers, which in turn increase spontaneous and dynamic (movement-related) neural activity (eg, spontaneous and ectopic discharges) and result in bone pain.[33–36] Therefore, SB is a reasonable treatment option for cancer-related bone pain. Although the precise timing of the emergence of these phenotypic alterations remains uncertain, their gradual onset may not have a significant impact on acute bone lesions. This neuroanatomical framework in patients with nonacute cancer-related bone pain highlights SB as a possible alternative for pain relief in these cases, which has not been previously explored.

Sympathetic blocks were described as early as the 1800s. In a series of 300 patients with cancer, researchers reported the successful use of cocaine to treat cancer pain attributed to the lumbar, thoracic, and cervical sympathetic ganglia.[37] Further experimentation has identified various sympathetic chain targets, ranging from the sphenopalatine ganglion to the ganglion impar (ganglion of Walther).

The lumbar sympathetic chain blockade can affect the hip and lower limb regionally, and the stellate ganglion affects the head, neck, shoulder, thorax, and upper limb.[20,38] The efficacy and duration of the SB may depend on the technique (eg, single-shot, ablation, neurolysis), medications (eg, local anesthetic, ethanol, phenol), and patient-related variables (eg, age, comorbidities, physical therapy, concomitant medications). In previous studies, a >50% reduction in leg pain intensity was reported and patients experienced pain relief for up to 5 weeks. However, they failed to show details of the specific pathology or characteristics of the pain.[39] To the best of our knowledge, our study is the first to elucidate the efficacy of SB to treat cancer-related bone pain. In the future, prospective studies would aid in validating the strength of these retrospective findings, ideally with eventual progression to randomized controlled trials. Additionally, it is important to recognize that patients with cancer pain often have multisite pain, and although SB aids in alleviation of pain in one site or limb, patients will likely remain on analgesics or require additional interventions for other sites of pain. With this being the case, the outcome changes seen in this retrospective sample that includes patients with multiple cancer pain sites likely underestimates the true outcomes for patients with only single-site cancer pain who may potentially experience greater benefits from SB.

Due to the retrospective nature of the study, we were unable to rectify deficiencies in the original data collection and medical record documentation. In addition, the limited sample size constrained our ability to accurately estimate the treatment's effectiveness, potentially posing a risk of false-positive findings. Many patients could potentially benefit from this interventional approach, but might be contraindicated in clinical conditions, such as the presence of bacteremia or infectious processes, cytopenias, active anticoagulation, or poorly controlled diabetes; patient preference against procedural interventions; and the avoidance of steroid use as restricted by some clinical trials in cancer treatment.

Conclusions

Reports in the literature suggest the existence of a pathophysiologic mechanism of cancer-related bone pain. Our clinical observational data support the use of sympathetic nerve blocks to treat cancer-related bone pain. SB is a safe, effective, readily accessible intervention. Demonstrating the effectiveness of blocking the sympathetic pathway for the treatment of this pain syndrome might open new horizons for neuromodulation.

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References

1. Rajani R, Quinn RH. OrthoInfo: bone tumor. Accessed September 19, 2020. Available at: https://orthoinfo.aaos.org/en/diseases–conditions/bone-tumor/
2. Middlemiss T, Laird BJ, Fallon MT. Mechanisms of cancer-induced bone pain. Clin Oncol (R Coll Radiol) 2011;23:387–392.
3. Jimenez-Andrade JM, Mantyh WG, Bloom AP, et al. Bone cancer pain. Ann N Y Acad Sci 2010;1198:173–181.
4. Ballantyne J, Fishman S, Rathmell J. Cancer-related bone pain. In: Ballantyne JC, Fishman SM, Rathmell JP, eds. Bonica's Management of Pain, 5th ed. Wolters Kluwer; 2019:744–750.
5. Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastases. Bone 1991;12(Suppl 1):S9–10.
6. Brescia FJ, Adler D, Gray G, et al. Hospitalized advanced cancer patients: a profile. J Pain Symptom Manage 1990;5:221–227.
7. Morris JN, Mor V, Goldberg RJ, et al. The effect of treatment setting and patient characteristics on pain in terminal cancer patients: a report from the National Hospice Study. J Chronic Dis 1986;39:27–35.
8. Twycross RG, Fairfield S. Pain in far-advanced cancer. Pain 1982;14:303–310.
9. Jonsson OG, Sartain P, Ducore JM, et al. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. J Pediatr 1990;117:233–237.
10. Sabino MA, Mantyh PW. Pathophysiology of bone cancer pain. J Support Oncol 2005;3:15–24.
11. Black JA, Nikolajsen L, Kroner K, et al. Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas. Ann Neurol 2008;64:644–653.
12. Gulati A, Puttanniah V, Bruel BM, et al, eds. Essentials of Interventional Cancer Pain Management, 1st ed. Springer International Publishing; 2019.
13. Mantyh P. Bone cancer pain: causes, consequences, and therapeutic opportunities. Pain 2013;154(Suppl 1):S54–62.
14. du Prel JB, Röhrig B, Hommel G, et al. Choosing statistical tests: part 12 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2010;107:343–348.
15. Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt 2014;34:502–508.
16. Sanvictores T, Jozsa F, Tadi P. Neuroanatomy, Autonomic Nervous System Visceral Afferent Fibers and Pain. StatPearls Publishing; 2021.
17. Osterweis M, Kleinman A, Mechanic D. The anatomy and physiology of pain. In: Osterweis M, Kleinman A, Mechanic D, eds. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. National Academies Press; 1987.
18. Yam MF, Loh YC, Tan CS, et al. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci 2018;19:2164.
19. Doroshenko M, Turkot O, Horn DB, et al. Sympathetic nerve block. Accessed February 15, 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK557637/
20. Day M. Sympathetic blocks: the evidence. Pain Pract 2008;8:98–109.
21. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997;69:1–18.
22. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27–37.
23. Mach DB, Rogers SD, Sabino MC, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. Neuroscience 2002;113:155–166.
24. Ivanusic JJ, Mahns DA, Sahai V, et al. Absence of large-diameter sensory fibres in a nerve to the cat humerus. J Anat 2006;208:251–255.
25. Mahns DA, Ivanusic JJ, Sahai V, et al. An intact peripheral nerve preparation for monitoring the activity of single, periosteal afferent nerve fibres. J Neurosci Methods 2006;156:140–144.
26. Mantyh PW, Jimenez-Andrade JM, Stake JI, et al. Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. Neuroscience 2010;171:588–598.
27. Mantyh PW, Koltzenburg M, Mendell LM, et al. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. Anesthesiology 2011;115:189–204.
28. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–674.
29. Asai H, Ozaki N, Shinoda M, et al. Heat and mechanical hyperalgesia in mice model of cancer pain. Pain 2005;117:19–29.
30. Shinoda M, Ogino A, Ozaki N, et al. Involvement of TRPV1 in nociceptive behavior in a rat model of cancer pain. J Pain 2008;9:687–699.
31. Honore P, Rogers SD, Schwei MJ, et al. Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 2000;98:585–598.
32. Idris AI, Landao-Bassonga E, Ralston SH. The TRPV1 ion channel antagonist capsazepine inhibits osteoclast and osteoblast differentiation in vitro and ovariectomy induced bone loss in vivo. Bone 2010;46:1089–1099.
33. Devor M. Neuropathic pain: what do we do with all these theories? Acta Anaesthesiol Scand 2001;45:1121–1127.
34. Devor M, Govrin-Lippmann R, Angelides K. Na+ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci 1993;13:1976–1992.
35. England JD, Happel LT, Kline DG, et al. Sodium channel accumulation in humans with painful neuromas. Neurology 1996;47:272–276.
36. Lindqvist A, Rivero-Melian C, Turan I, et al. Neuropeptide- and tyrosine hydroxylase-immunoreactive nerve fibers in painful Morton's neuromas. Muscle Nerve 2000;23:1214–1218.
37. Dargent M. Role of sympathetic nerve in cancerous pain; an inquiry on 300 cases. BMJ 1948;1:440–442.
38. Jeon Y. Therapeutic potential of stellate ganglion block in orofacial pain: a mini review. J Dent Anesth Pain Med 2016;16:159–163.
39. Spiegel MA, Hingula L, Chen GH, et al. The use of L2 and L3 lumbar sympathetic blockade for cancer-related pain, an experience and recommendation in the oncologic population. Pain Med 2020;21:176–184.