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ORIGINAL ARTICLE

Multimodal analgesia in primary bone tumors

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Abstract

Introduction: A worrying increase in the number of bone tumors that appear at younger ages justifies the efforts aimed at optimizing perioperative management practices in orthopedic tumor surgery. Pain control is critical in the prognosis and postoperative outcome of these procedures.

Material and methods: Our study included a group of 11 patients diagnosed with bone malignancies. These patients were hospitalized in the Orthopedic Clinic of the University Emergency Hospital Bucharest. Under our supervision, they underwent surgical treatment of the tumor under combined general anesthesia and epidural anesthesia for the pelvic limb, and general anesthesia only for the upper limb. We performed perioperative pain management with multimodal analgesia (continuous epidural analgesia with ropivacaine 0,2% and fentanyl 2 mcg/ ml in association with systemic analgesics). Following this procedure, we measured the intensity of the postoperative pain at intervals of 48 hours and one week after surgery and compared with preoperative pain intensity using the visual analogue pain scale (VAS).

Results: Multimodal analgesia (epidural analgesia associated with systemic analgesics – paracetamol, COX2 inhibitor, gabapentinoids) was performed well in the postoperative pain of the tumor prosthesis, with a significant decrease in VAS from a mean value of 7.63 preoperatively to an average of 3 in the first 48 hours postoperatively. After the removal of the epidural catheter, which also coincided with patient mobilization, the level of pain registered a slight increase to a mean value of 3.23.

Conclusions: Multimodal analgesia is currently considered the gold standard in perioperative pain management. The use of multimodal analgesia during perioperative period in patients with bone tumors has been shown to decrease the length of hospital stay, improve surgical outcome, reduce the number of systemic complications, and improve the long-term prognosis of the patient. Efficacy of analgesia correlates with tumor site and vascularization.

Keywords: epidural analgesia, bone malignancies, pain, outcome

Introduction

Bone tumors are a group of malignancies that include a wide range of histopathological variants. Of these, the most common are osteosarcoma. In Europe, these tumors are found especially in young people, with an estimated annual incidence of 0.3 per 100,000

inhabitants. Another example is chondrosarcoma, which is more prevalent in the elderly population and has an annual incidence of 0.2 per 100,000 inhabitants. The increasing number of tumor prostheses in the last decade has shown the advance in musculoskeletal oncology [**1**]. Presently, limb sparing surgery is critical in preserving the quality of life of patients [**2**]. To our knowledge, it appears to be feasible in 90% of cases. The psychological factor of limb amputation still represents a hardly manageable subject [**3**].

Prognosis depends on the histological type of tumor, size, and local extension. Another important factor in prognosis is the degree of pain associated with different types of bone tumors, which can vary in intensity and character. Being the leading symptom, pain is strongly correlated with the quality of life [**4**].

In bone tumors, pain is due to a complex pathophysiological mechanism involving both the central and the peripheral nervous system. It can often be related to a traumatic event, especially in young active patients. In young patients, a persisting pain around the knee, with a pulsatile character, which awakens them at night, should be considered crucial in the tumor pathology. As the tumor grows, depending on its site (extra- or intra-compartmental), pain changes its character. Consequently, fast growing tumors lead to the evolution of pain from mild to severe in a relatively short period of time (2-3 months). At first, pain usually responds to nonsteroid anti-inflammatory drugs (NSAIDs). We reckon this may be one important reason why patients do not seek medical help early. In bone tumors, pain has both a neuropathic and a nociceptive pain component. In late stages, when the tumor invades the surrounding soft tissues, pain becomes non-respondent to usual NSAID therapy and opioids, due to the direct stimulation of the sensory nerve endings [**5**].

The character of pain depends on the localization of the tumor. Periosteal involvement leads to localized pain with faster appearance, while central localization will determine diffuse pain with late appearance. The reason for this aspect of pain is based on the physiological innervation of the bone where significantly more nerve endings can be found at the level of the periosteum compared to the bone marrow [**6**]. In order to prevent pain related complications, pain management needs to be personalized until specific surgical and/ or oncological treatment is conducted. Furthermore, pain management should be specifically adapted to tumor grade, localization, and the underlying neural mechanisms [**7,8**].

Conventional treatment of pain with NSAIDs and opioids in primary bone tumors, often requires administration of high doses. As a result, there is an increased occurrence of side effects such as nausea, vomiting, ileus, respiratory depression, and digestive ulcers.

The aim of this study was to evaluate pain by visual analog scale (VAS) in patients with primary bone sarcomas, before and after surgery, with multimodal analgesia (combination between neuraxial and systemic analgesia). Our purpose was to compare the level of pain to the histological grade and localization of the tumor, in order to obtain a better bone pain control while reducing opioid doses and their side effects.

Material and methods

This study was conducted on patients admitted in the University Emergency Hospital of Bucharest, Orthopedics and Traumatology Department. A total number of 11 patients with primary bone sarcomas (osteosarcoma and chondrosarcoma) were included in the study. Before the oncological surgical treatment, these patients underwent routine radiological examinations, computer tomography (CT scan), magnetic resonance imaging (MRI), whole body bone scintigraphy, angiography, and biopsy of the affected limb.

Pain was quantified by Visual Analog Scale (VAS) before surgery, 48 hours after surgery and during the following hospitalization days. Patients were asked to describe their pain at the early onset to compare the evolution of VAS with the results obtained after biopsy and surgery. Preoperative planning was based on the Enneking classification for primary malignant bone tumors [**9**].

We performed a total of 4 surgical wide resections followed by reconstruction with modular tumor prostheses. Due to the localization and extra-compartmental localization of the tumors, we were forced to carry out 3 lower limb amputations above the knee, and one shoulder disarticulation for an extra-compartmental grade 3 chondrosarcoma (proximal humerus). In 3 cases of pelvic tumors, we performed Enneking type III resection of the obturator ring (**Fig. 1**).

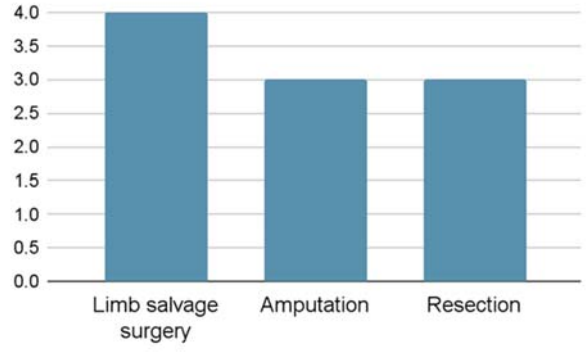

Fig. 1 Type of surgery

We performed perioperative pain management with a combination of neuraxial analgesia (epidural analgesia with ropivacaine 0.2%) with systemic analgesia. We used a combination of 3 drugs, each with a different mechanism of action: NSAID (Celecoxib 200 mg oral route, twice daily, started from the day before surgery and continued two weeks after surgery), analgetic (Paracetamol intravenous 1000 mg every 8 hours, for one week) and gabapentinoids for neuropathic pain component (Gabapentin 300 mg twice daily, oral route). We started systemic analgesia on the day before surgery.

Surgical interventions were performed under general anaesthesia with continuous epidural anaesthesia/ analgesia, as none of the patients presented major contraindications for neuraxial anaesthesia, such as coagulopathy. General anesthesia was provided for only one upper limb case. In the first group, epidural catheter was placed for analgesia before surgery. General anaesthesia was maintained with volatile anesthetic (sevoflurane). We administered 8 mg dexamethasone intravenously (iv) in each case and conducted prophylactic antibiotherapy with third generation cephalosporine and vancomycin. All patients received LMWH in prophylactic dose.

Postoperative pain control in the first 48 hours was achieved with continuous infusion over an epidural catheter of 0.2% ropivacaine and 2 mcg/ ml fentanyl with a rate varying between 3-6 ml/ hour, celecoxib orally, and paracetamol iv, to a maximum dose of 4 g/ 24 hours. Pain was quantified using Visual Analog Scale (VAS) over 4 hours and if VAS was ≥ 4 then we used ketorolac supplemental 30 mg iv to a maximum dose of 120 mg. In addition, gabapentinoids therapy was initiated on the day before surgery.

Epidural catheter was removed after 48 hours and we designed a pain management plan, which consisted of a combination of 4 drugs that were administered orally: paracetamol 1000 mg 3 times a day, tramadol 100 mg twice daily, celecoxib 200 mg twice daily, and gabapentin 300 mg twice daily. Early mobilization was made after epidural catheter removal. All opioids used postoperatively were converted to equivalent doses of oral morphine.

Pain intensity was evaluated using VAS score at mobilization and rest (supplemental analgesia with ketorolac 30 mg iv to a maximum dose of 120 mg if VAS ≥ 4).

Results

A total number of 5 patients with osteosarcoma and 6 patients with chondrosarcoma were included. Out of the 11 patients, 7 males had a mean age of 32 and 4 females had a mean age of 50. 4 cases of osteosarcomas and 5 cases of chondrosarcoma (totally, 9 cases out of 11) had extra-compartmental localization based on the Enneking classification (**Table 1**).

Table 1. Histological results, tumor localization and local invasion using the Enneking classification system for primary malignant bone tumors

Histopathologic type	Age	Localization	Stadialization
Osteosarcoma	25	Distal Femur	IIB
Chondrosarcoma	23	Proximal Femur	IB
Chondrosarcoma	74	Distal Femur	IB
Osteosarcoma	17	Proximal Tibia	IIB
Osteosarcoma	57	Distal femur	IIB
Chondrosarcoma	62	Proximal Humerus	IIB
Osteosarcoma	23	Distal tibia	IIB
Chondrosarcoma	60	Distal Femur	IIB
Osteosarcoma	17	Ilio-pubic ramus	IA
Chondrosarcoma	46	Ilio-pubic ramus	IIA
Chondrosarcoma	23	Ilio-pubic ramus	IIB

Multimodal analgesia was used for pain control in the postoperative period. Within the first 48 hours, analgesia was performed using an epidural catheter by continuous infusion of ropivacaine 0,2% and fentanyl 2 mcg/ ml at a rate of 5 ml/ h in combination with paracetamol, COX2 inhibitors and gabapentin. In the case of the patient with shoulder disarticulation, pain control was achieved with multimodal systemic analgetic protocol, which included intravenous morphine 20 mg/ day for the first 2 days (60 mg oral morphine), AINS, gabapentinoids and paracetamol.

The average VAS score obtained in the first 48 hours was 3, a significantly smaller value compared to 7.63 before surgery. We removed the epidural catheter at an interval of 48 hours after surgery and subsequently, management of pain was made using a combination of paracetamol, celecoxib, gabapentin, and tramadol. Patients with epidural analgesia needed 20 mg oral morphine per day starting from the third day after surgery to one week (no morphine in the first 2 days after surgery) and the patient with shoulder disarticulation needed 60 mg oral morphine per day in the first 2 postoperative days and 30 mg oral morphine from day 3 to one week. The average VAS score from 48 hours to one week of hospitalization was 3.27 (**Fig. 2**).

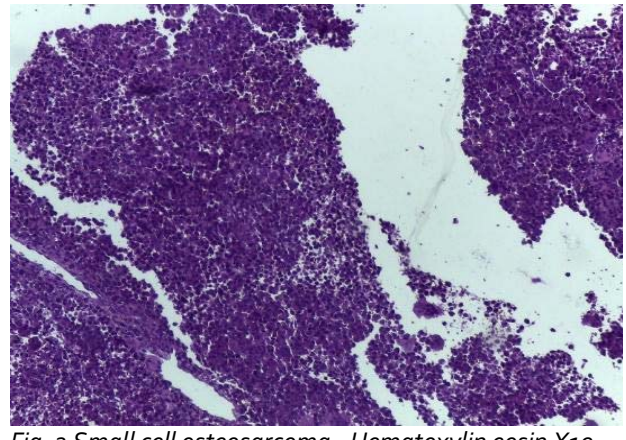

Fig. 2 Small cell osteosarcoma - Hematoxylin eosin X10

Pain control was heavily dependent on the tumor's staging. There was an increase in the analgesic requirement in the case of extracompartmental tumors before surgical intervention, because of the pathophysiological mechanism of bone pain transmission. However, in the postoperative 48 hours period, patients with extracompartmental tumors had similar VAS scores (<4) with those with intracompartmental tumors (**Fig. 3**). We noted that both categories of patients incurred a similar analgetic protocol. Patients with tumoral prostheses and obturator ring resection had slightly higher VAS and needed anti-inflammatory drug supplementation (ketorolac). The patient who had an extensive tumoral growth that required amputation surgery, had good pain control with epidural and systemic analgesia, without supplemental anti-inflammatory drugs. A special case was the shoulder disarticulation with higher consumption of opioids (60 mg oral morphine in the first 2 days) and supplemental ketorolac, versus neuraxial analgesia combined with multimodal systemic analgesia.

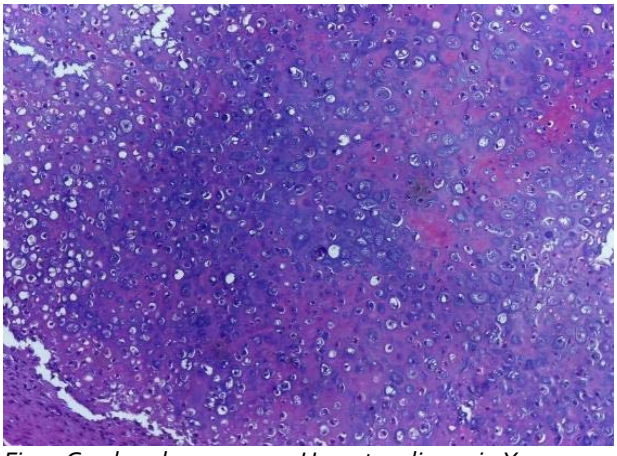

Fig. 3 G2 chondrosarcoma - Hematoxylin eosin X10

During the postoperative period, continuous epidural ensured a similar and good quality analgesia in both osteosarcomas and chondrosarcomas. Therefore, no significant differences were noticed regarding the VAS score based on the histopathological type of the tumor (**Fig. 4-6**) in the postoperative period.

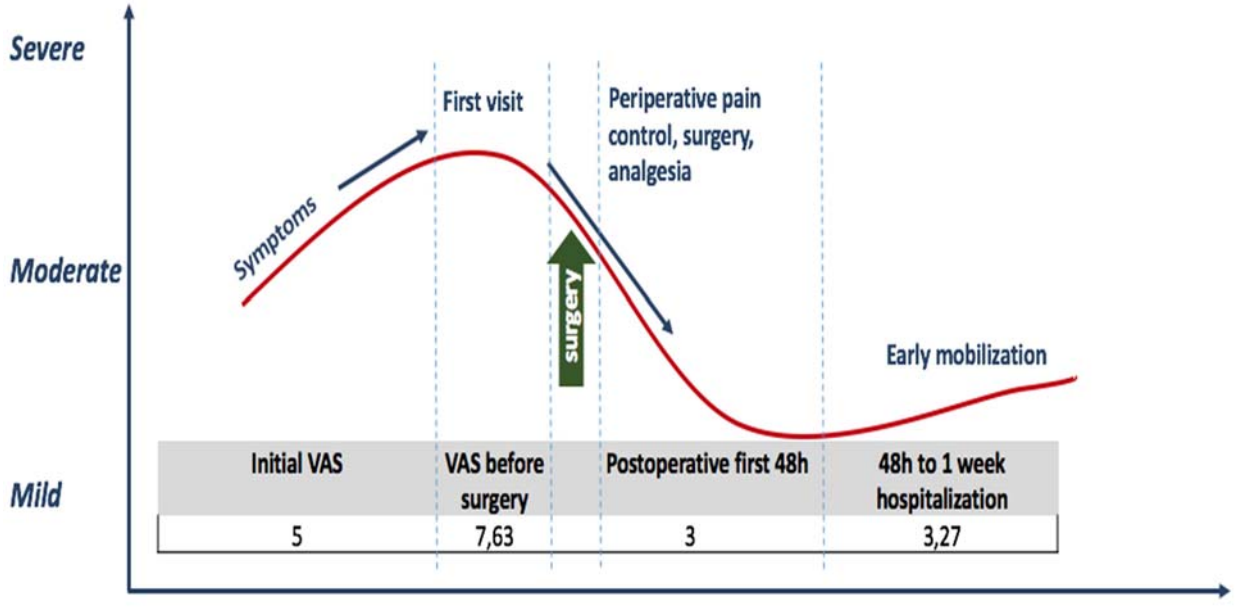

Fig. 4 VAS score in patients with primary bone tumor

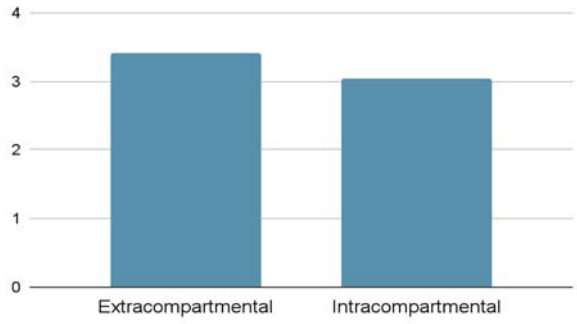

Fig. 5 Postoperative VAS score related to tumor extension

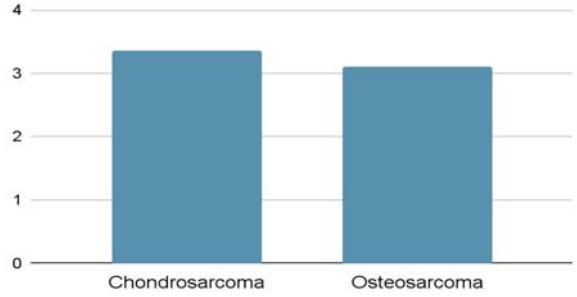

Fig. 6 Postoperative VAS score related to histopathological tumor type

Discussions

Previous studies showed that regional anesthesia has lower rates of cardiovascular and pulmonary complications, lower thromboembolic events, lower rates of intraoperative blood loss and transfusion requirements, less nausea and vomiting and excellent pain relief and increased patient satisfaction [**10**].

Our findings reinforce previous results in literature that pain management in primary bone malignancies is often challenging, especially in late stages of the tumors, when it is generated by mechanical compression on the surrounding soft tissues and nervous endings. In these cases, we measured a higher preoperative VAS level compared to the intra-compartmental tumors in which pain had a moderate level and responded to NSAIDs. NSAIDs associated or not with opioids are the cornerstone of analgesic regimens in bone tumors, on the one hand by centrally mediated analgesia, and on the other hand by inhibiting prostaglandin synthesis with consequent decrease in bone edema and periosteal pressure [**11**].

VAS recordings during follow-up did not show significant differences in the postoperative period in terms of pain intensity between patients with intracompartmental and extracompartmental tumors and opioid use was similar. Moreover, many of our sample patients presented themselves in advanced stages of the disease, with invasive tumors and extracompartmental localization. Thus, it was difficult to compare these 2 groups (only 2 patients had intracompartmental tumors).

Vascularization of the tumor also has an impact on the pain management. In the case of systemic analgesia, a higher distribution of drugs can be found in tumors with increased vascularity, compared to minimally vascularized tumors like chondrosarcomas, where higher doses of analgesics may be needed preoperatively. This pathophysiological mechanism constitutes an explanation for better response of osteosarcomas to chemotherapeutic treatment [**12**]. The intense vascularization of osteosarcomas ensures a better penetrability of intravenous drugs at the site of tissue injury [**13**].

Although we did not find any significant differences in postoperative pain control between patients with osteosarcomas and those with chondrosarcomas, it is important to keep in mind that pain was measured after tumor removal. We believe that some of the painful stimuli were mainly initiated by the surgical trauma, rather than by the tumor itself.

The surgical removal of the tumors had a serious impact on the entire biological status of the patients. The appearance of a higher level of stress hormones (cortisol, catecholamine, growth hormone, glucagon) increases the risk of infection, stresses the

cardiovascular system, enhances the possibility of cardiac events, and prolongs immobilization with lower ventilation, gastrointestinal complication (ileus), and thromboembolic events. All these result in a longer hospitalization period [**14**].

Analgesia before oncological surgery should be preemptive (should be initiated before surgery) and multimodal (the use of more than 2 drugs or modalities) [**15**]. The use of COX2 inhibitors, acetaminophen and gabapentin starting the day before surgery and continuing 2 weeks after surgery significantly reduced pain, improved the functional outcome after resection and modular prosthesis reconstruction and increased the overall satisfaction of the patients [**16**].

Many studies confirm the existence of sensory neurons that fulfill the function of innervation of the periosteum and medullary channel and implicitly, with an important role in nociception. However, their physiology is insufficiently known. They appear to be particularly sensitive to stimuli offset by stretching forces and are responsible for transmitting nociceptive information to the central nervous system [**17**]. In addition, bone tumors release mediators that activate the nociceptive pathways through different mechanisms than in other types of inflammation [**4**]. All these aspects explain why pain management in patients with bone tumors is often a difficult challenge.

The main objectives of analgesia in primary bone tumors are to reduce the rate of complications from perioperative pain, improve the quality of life of patients and decrease the opioid consumption during perioperative period, thus lowering the complications' rate due to opioids use [**18**].

Conclusions

Perioperative pain management in painful tumors should be customized to the localization and local soft tissue invasion of the tumor, especially in the preoperative period. In the late stages of sarcomas or local recurrence, conventional analgesics can be inefficient. Early diagnosis and surgical removal of these tumors is the most important objective for a good prognosis.

Patients' education also plays an important role, since a doctor visit is often delayed.

Multimodal analgesia is currently considered the gold standard in perioperative pain management. The use of multimodal analgesia during perioperative period in patients with bone tumor has been shown to decrease the length of hospital stay, improving surgical outcome, reducing the number of systemic complications, and improving long-term prognosis of the patient. Efficacy of analgesia correlates with tumor site and vascularization mostly during the preoperative period with small differences on the postoperative period.

Conflict of Interest statement

Authors state no conflict of interest.

Informed Consent and Human and Animal Rights statement

Informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration and was approved by the review board of University Emergency Hospital, Bucharest, Romania.

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Disclosures
None.

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