International Journal of Anaesthesia & Research
IJAR, 2(3): 67-73
www.scitcentral.com

ISSN: 2641-399X

Case Report: Open Access

Midazolam Use as the Adjuvant of Epidural Bolus Analgesia for Persistent Post-Operative Pain After Lower Limb Orthopedic Surgery

Gusti Ayu Pitria Septiani*, Aninda Tanggono, Marilaeta Cindryani and Tjokorda Gde Agung Senapathi

*Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Udayana University, Indonesia.

Received May 22, 2019; Accepted June 04, 2019; Published December 05, 2019

ABSTRACT

The persistence of pain after surgery has become a major concern due to its variable debilitating consequences. Epidural analgesia is widely used for postoperative pain in a variety of surgical procedures and recognized to provide excellent quality of analgesia when compared with systemic opioid use.

Midazolam belongs to benzodiazepine/type Gamma-aminobutyric acid (GABA)-A which produces an analgesic action through GABA-A receptor complex; it can be used as a promising adjuvant in postoperative epidural analgesia.

In 2013, researchers have conducted the prospective study to compare the effectiveness of 2 mg Midazolam as an adjuvant in combination with 0.5% Bupivacaine and 5 mg Morphine as an intermittent bolus of epidural for postoperative analgesia after an elective lower limb orthopedic surgery. It showed a satisfying prolonged analgesia duration (up to 23.04 h) compared to bupivacaine with pethidine or morphine alone. It also exhibited better pain control without any significant drowsiness effect, nausea/vomiting and pruritus.

This case report described a 20 year old male who underwent mayor orthopedic surgery due to comminutive open fracture of the right tibia and fibular bone. He has achieved a satisfying postoperative pain scale after having a 12 hourly intermittent bolus of Epidural with 1 mg preservative-free of midazolam as an adjuvant of 0.1% plain Levobupivacaine, 1 mg morphine and 30 mcg clonidine for treating his ten days of persistent postoperative pain condition. For the last five days of his hospital stays after the adjuvant therapy has been given, it was successfully produced bearable pain (at rest and a light degree of mobilization) without any significant undesirable side effect recorded.

Keywords: Persistent postoperative pain, Midazolam adjuvant, Intermittent epidural bolus

INTRODUCTION

The Persistent Postoperative Pain (PPP) reflects an evolving complex constellation of processes involving several neurotransmitters, modulators and immune system at peripheral, spinal and cerebral levels. Normally, acute surgical pain in most patients declines over the first few days after surgery. Unfortunately, in a proportion of patients, the pain can persist and become chronic, severe and long-lasting disabilities. The consequences of PPP can be variable and significant, not only in terms of suffering and reducing quality of life (QoL) but also the subsequent cost to the health care and social support [1-3]. Genetic factors appear to account as one of the risk factors for the transition from acute pain to PPP and have contributed to a significant degree of inter-individual pain sensitivity and treatment response. Phenotypes variants in pain perception and modulation together with genetic variation during drug uptake, transport, action at the effector site and during the metabolism and excretion, plays a role in perpetuating postoperative pain. Poor metabolism showed in a frequency of about 7-10% in Caucasian populations. Moreover, 3-5% of them are ultra-rapid metabolizer, in whom the therapeutic effect cannot be obtained with conventional dose only [1].

There is no definition of persistent or Chronic Post-Surgical pain (CPSP) that distinguishes its mechanism from acute pain. Its definition for chronicity relates only with the time duration, which International Association for the Study of

Corresponding author: Gusti Ayu Pitria Septiani, Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Udayana University, BIMC Ubud Medical Centre, Jl. Sanggingan No. 21 Kedewatan, Ubud-Gianyar 80561, Indonesia, E-mail: pitriaseptianigustiayu@gmail.com

Citation: Septiani GAP, Tanggono A, Cindryani M & Senapathi TGA. (2019) Midazolam Use as the Adjuvant of Epidural Bolus Analgesia for Persistent Post-Operative Pain After Lower Limb Orthopedic Surgery. Int J Anaesth Res, 2(3): 67-73.

Pain (IASP) defines as persistent pain after surgery of greater than three months [1,4]. The incidence of PPP varies ranging from 5% to 50%, depending on the definition and surgical procedure. Despite the availability of multiple analgesic drugs and techniques, to relieve persistent postoperative pain, specifically movement-associated pain remains a challenge in some 30% of the patients [2,3].

Postoperative pain is a potent trigger for the stress response; it has resulted from not only local tissue injury but also from sensitization of central nervous system which creates pain from a wider area (secondary hyperalgesia).

Secondary hyperalgesia is thought to be a basis for chronic postoperative pain which has many mechanisms related to memory at supraspinal sites. It is defined as mechanical hypersensitivity in uninjured tissue surrounding the wound, amplifies postoperative pain and contributes to chronic pain [1,2,5].

In human pain research, the anterior cingulate cortex of the brain has been implicated in a number of persistent or chronic pain syndromes. The thalamus is frequently activated as well in the process. The potentiation of anterior cingulate cortex neuronal activity induced by thalamic bursting suggests that short-term synaptic plasticity enable the processing of nociceptive information from the medial thalamus. This variability of temporary response is particularly important in pain because it maintains the response which supports cortical integration and memory formation related to noxious events. Moreover, these modifications of cingulate synapses appear to regulate afferent signals associated with persistent peripheral noxious stimulation that may be important in the transition from acute to chronic pain [1].

Some meta-analysis studies have shown that epidural analgesia is recognized to provide excellent quality of analgesia for each postoperative day, for all types of surgeries and all types of pain assessment methods. It showed a relative lower complication rate, more superior to parenteral opioids following upper abdominal, thoracic, pelvic and lower extremities orthopedic procedures [6-10]. In the study conducted by Kaynar et al. [9] showed that intermittent bolus of the epidural catheter has a wider spread of sensory analgesia compared to the continuous epidural infusion (CEI), which probably contributes to the better quality of the nerve block in the clinical setting.

Despite the advantages in intermittent epidural boluses in managing persistent postoperative pain, a higher dose of local anesthetics is required for effective epidural analgesia when it is used alone. It may be associated with its limited duration of action and dose-dependent deleterious adverse effects on the cardiac and central nervous system. To decrease these “dose-dependent” side effects and prolong the duration of analgesia of local anesthetics, opioids are commonly added [10-15]. However, since epidural opioids may be associated with distressing side effects for instance nausea, vomiting, pruritus, urinary retention and respiratory distress, therefore, the non-opioid drugs like midazolam, clonidine and others, have been investigated as the promising adjuvants to epidural local anesthetics. Potential advantages of these agents include a reduction in the dose of individual drugs, opioid requirements and opioid-related side effects [10].

Midazolam, a water-soluble benzodiazepine/type Gamma-aminobutyric acid (GABA)-A produces an analgesia action through GABA-A receptor complex and reducing the excitability of the spinal cord. Midazolam can be used as an ideal epidural and intrathecal analgesic for persistent postoperative pain due to its widespread availability, low cost and excellent patient tolerance [6].

Intrathecal (preservative-free) midazolam produces spinally mediated analgesia by the effect in the type benzodiazepine/GABA-A receptors which distributed in a consistently similar fashion in the gray matter of the cervical, lumbar and sacral regions within lamina II of the dorsal horn human spinal cord. This region plays a prominent role in processing nociceptive and thermoceptive stimulation along with a possible role in pain modulation [14,16-18]. The GABA-A receptors and the GABAergic system have been proposed to play an important role in the presynaptic inhibition of primary afferents nervous system. GABA binding results in a change of receptor configuration, opening an ion channel which allows an influx of chloride ions down their electrochemical gradient into the cell. This results in hyperpolarization of the neuron and reduces action potential propagation and by reducing the glutamate release in the spinal cord. Thus, it modulates gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain [17-19]. The intrathecal midazolam is also been shown to act at opioid receptors which may potentiate the anti-nociceptive effect of morphine-like agents by acting as a direct agonist at kappa (κ) and delta (δ) opioid receptor site in the spinal cord [7,11]. The epidural midazolam also exerts antiemetic action through an unknown mechanism. It is probably due to glycine mimetic inhibitory effect, enhancement of the inhibitory effect of GABA, inhibition of dopamine release, and augmentation of adenosine-mediated inhibition of dopamine in the chemoreceptor trigger zone [20-22]. The incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and differed from placebo (odds ratio 1.2, 95% CI 0.22 to 6.68, p=0.84) [7]. Although, concerns with the possibility of epidural midazolam toxic effects, particularly in neonates continue to persist. Recently available evidence suggests that a small diluted dose of less than 1 mg/mL preservative-free midazolam (Dormicum® F, Hoffmann-La Roche Ltd., Basel, Switzerland) or Midazolam Torrex, Torrex Chiesi Pharma GmbH, Vienna, Austria) shows no neurotoxicity [13]. Previous studies have found that epidural midazolam in a dose of 50 mcg/kg diluted in 10 mL of saline co-

administered with local anesthetics has been shown to be effective in providing prolonged postoperative analgesia without significant adverse effect in adults undergoing orthopedic, urological, lower abdominal surgeries, cesarean sections and children undergoing the urologic procedure [12,13]. In 2005, Agrawal et al conducted a study on postoperative pain relief following intrathecal administration of 1 mg preservative-free midazolam with bupivacaine in patients scheduled for elective lower abdominal, lower limb orthopedic procedure and endoscopic urological surgeries. Time to the first rescue analgesic in patients who received bupivacaine alone was significantly earlier than the patient who received bupivacaine and midazolam combination (4 ± 3.5 h vs. 17.6 ± 8.87 h, $p<0.0001$). They concluded that intrathecal midazolam and bupivacaine provides a longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone without extending the time for dermatomal regression [14,16].

CASE REPORT

A 20 year old Caucasian male with ASA I was admitted and planned to have an urgent debridement and surgical stabilization with an open reduction external fixation due to a comminuted open fracture of right proximal shaft tibia and fibular bone after having been involved in a motor vehicle accident. He had two times of surgeries due to his complexity-comminuted fracture. For the first surgery, an epidural catheter was placed initially before induction in general anesthesia at the level of L3-L4 intervertebral space. After the completion of the first uneventful surgery, the patient received postoperative analgesia with continuous epidural infusion at 5 ml/h (Regiments containing 20 ml of 0.5% bupivacaine, epinephrine 1:200.000 + 2 mg morphine + NaCl 0.9% to 50 ml) and intravenous Fentanyl 25 mcg/h for 48 h postoperatively. Unfortunately, he kept on having moderate pain Numerical Rating Scale (NRS) (5-6 out of 10) scale at resting and severe NRS (>6 out of 10) by the light degree of ambulation. Thus, the regiment has been changed by the addition of 75 mcg clonidine hydrochloride, without any significant improvement in postoperative pain scale for the following 48 h before he proceeded to the second surgery. The second surgery conducted to stabilize his fracture by putting the external fixator. The postoperative epidural analgesia was continued, however, the technique of continuous epidural infusion (CEI) has been changed to the intermittent twelve-hourly epidural bolus regiment of 10 ml of 0.1% plain levobupivacaine + 1 mg morphine + 30 mcg clonidine. We also added 0.5 mg preservative-free midazolam (Dormicum®) as the adjuvant. Another pharmacological approach as multimodal analgesia was given with paracetamol 1000 mg/8 h intravenously, 25 mcg fentanyl patch, oral gabapentin 400 mg/12 h and oral duloxetine 60 mg/24 h at night. The patient has a significantly reduced pain in the NRS scale since the epidural technique was changed and preservative-free midazolam (Dormicum®) was added as the adjuvants. He did not complain about any severe pain sensation as before. This postoperative modality has successfully reduced the pain scale into the 2-3 out of 10 scales in the 48 h following the operation. In the third day, the intermittent epidural bolus was tapered off and given every 24 h. The 25 mcg fentanyl patch has also been switched into a lower dose of 12 mcg as the pain scale at rest remained low with the scale of 3 out of 10. This patient was planned to be escorted back to his home country by commercial flight according to his family request, thus the epidural catheter was maintained until the fourth day. In the fifth day following the second operation, he has had very bearable pain at resting and light degree mobilization in bed, with the scale, 2-3 out of 10, thus the epidural catheter and fentanyl patch were removed and he has been returned to his home country escorted by a nurse on the same day. Throughout or during his hospital stay, we recorded no significant hemodynamic changes or any potential adverse effects (i.e., drowsiness, hypotension, nausea, vomiting, pruritus, motor blockade or infection at the catheter insertion site) from adjuvant midazolam administration. He continued to have oral medication regiment consisted of MST morphine 15 mg/8 h, Oxycodone 20 mg/12 h, Gabapentin 200 mg/12 h and Paracetamol 500 mg/6 h after being discharged from the hospital **(Figures 1 and 2)**.

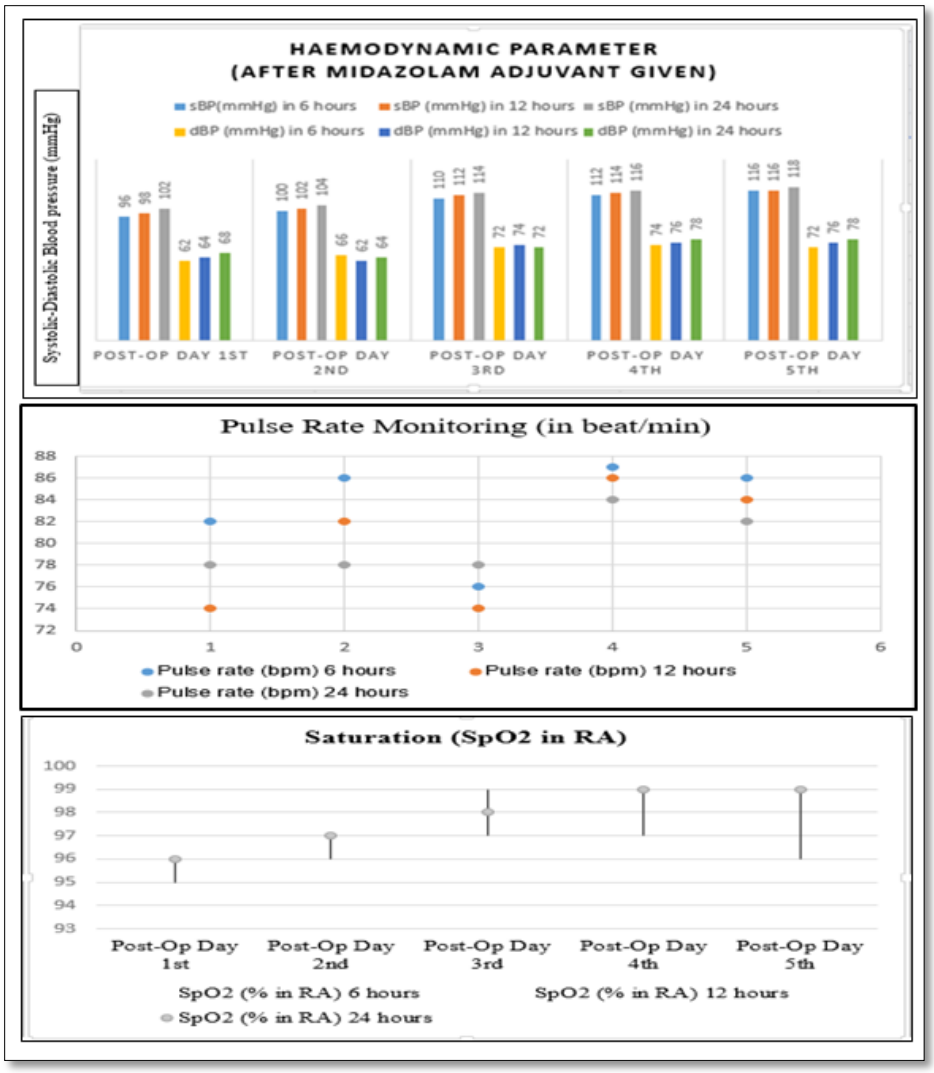

Figure 1. Hemodynamic and respiratory parameter (blood pressure, heart rate and saturation SpO_2 after midazolam adjuvant was given).

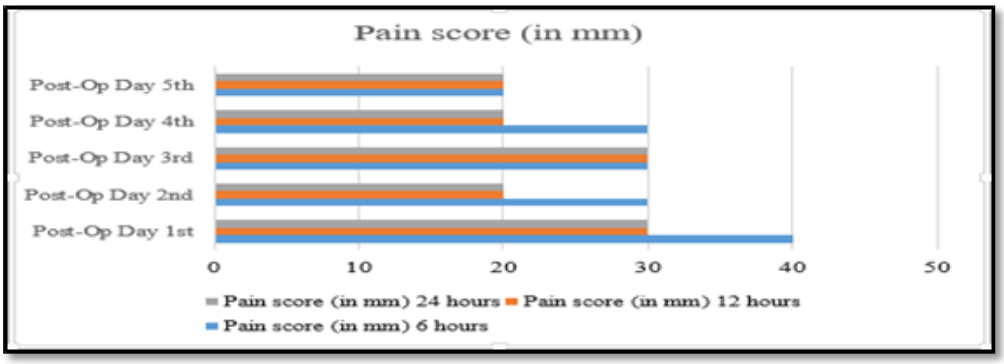

Figure 2. Pain NRS during 5 days after 2nd surgery (after midazolam adjuvant was given).

DISCUSSION

In recent days, despite extensive progress in our understanding of pain physiology and availability of multiple analgesic drugs and techniques, relieving persistent postoperative pain specifically movement-associated pain remains unsatisfactory and becomes a challenge in one-third of the patients. The concept of multimodal or balanced analgesia Offers more advantage by creating additive or

synergistic effects of combining multiple technique and medications [2,3,20]. Epidural analgesia is widely used for postoperative pain in a variety of surgical procedures and recognized to provide excellent quality of analgesia when compared with systemic opioids [6]. Recently, midazolam use has been extended to the epidural and intrathecal route with considerable success as an adjuvant to decrease "dose-dependent" side effect of local anesthetics. It also minimizes opioids associated-distressing potential effect when it is used as the regiment of postoperative epidural analgesia [9,10].

The comparison between literature reviews and current evidence or studies support with the application of this case are shown in **Table 1**.

Table 1. Comparison between reference, current evidence or study support with the application of this case.

No.	Reference/Current evidence or study support	Application in this patient
1.	Some preoperative risk factors are posed a significantly greater risk in developing persistent postoperative pain includes younger age and genetic variations, for example, poor and ultra-rapid metabolizers as showed by Caucasian populations.	The patient is a 20 year old Caucasian male who underwent major orthopedic surgery.
2.	Meta-analysis studies have shown that Epidural analgesia is widely used for postoperative pain in a variety of surgical procedures and recognized to provide excellent quality of analgesia when compared with systemic opioids.	This patient has received postoperative epidural analgesia started from his first surgery.
3.	The efficacy of epidural analgesia requires an adequate spread of the anesthetic solution to produce sensory blockade of the appropriate dermatome. The most uniform spread of epidural analgesia occurs with large volume and high injecting pressures near the site of injection. It also tends to spread more evenly when injected as a bolus, which likely explains why more effective analgesia was achieved in the intermittent epidural bolus rather than in continuous epidural infusion (CEI).	Initially, He was in a CEI technique for postoperative analgesia, unfortunately, he did not have a satisfactory pain scale reduction either at rest or light degree of mobilization. Since the epidural technique has been changed into intermittent boluses, this patient has a significantly reduced of his pain NRS subsequently.
4.	Recently, midazolam has been extended used to an adjuvant of epidural postoperative analgesia with considerable success in a dose of 1 or 2 mg with concentration <1 mg/ml.	After the 2nd surgery, the patient received an additional of 2 mg/24 h of Dormicum®, which resulted in significant improvement of his pain NRS.
5.	The incidence of neurotoxicity symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo (odds ratio 1.2, 95% CI 0.22 to 6.68, p=0.84). Many preservatives, antioxidants, or excipients used in the drug given spinally can cause neurotoxic changes in animal models even though they are safe when administered intravenously or intramuscularly.	This patient has received preservative-free midazolam (Dormicum®) and during his hospital stay, there were no neurological symptoms appeared.
6.	The additional of epidural midazolam can be successfully combined with other drugs such as opioid and clonidine for additive effect in a patient with PPP.	After the epidural analgesia has been changed to intermittent bolus, and adjuvant midazolam was given, he successfully

	The data extracted from the literature regarding dose recommendation of Morphine is ranged between 1-5 mg has exhibited good analgesic efficacy. Meanwhile, epidural clonidine in a dose 25-50 mcg/h has a beneficial effect in various procedures such as spine instrumentation and orthopedic surgeries.	achieved bearable pain NRS with significantly reduced half doses of opioid adjuvant from 4.8 mg/24 h into 2 mg/24 h. It has also reduced the dose of clonidine hydrochloride from 180 mcg/24 h into 60 mcg/24 h.
7.	Current evidence in human studies suggested that the administration of preservative-free midazolam (Dormicum®) in epidural with doses of 1-2 mg is beneficial in the treatment perioperative and chronic pain without evidence of a deleterious neurologic and respiratory effect. Moreover, midazolam added to epidural analgesia exert its antiemetic action.	Throughout his five days of hospital stay, he did not show any undesirable side effect (i.e., drowsiness, hypotension, respiratory depress, nausea/vomiting or pruritus) after midazolam adjuvant was given.

CONCLUSION

The addition of preservative-free midazolam (Dormicum®) to the intermittent bolus epidural seems to be a promising adjuvant to persistent postoperative pain. Since midazolam is also favored with its widespread availability, low cost and excellent patient tolerance, it would be an ideal analgesic approach for persistent postoperative pain. There was no significant adverse effect (neurotoxicity, sedation effect, hypotension, respiratory depression, nausea/vomiting, motor and sensory deficits, bowel and bladder dysfunction) of midazolam use has been observed in this orthopedic surgery. This is in accordance with the outcome of previous studies which showed that the potential neurotoxicity of Midazolam can be avoided if the dosage is kept within the safety range.

REFERENCES

1. Shipton EA (2011) The transition from acute to chronic post-surgical pain. Anesth Intensive Care 39: 824-836.
2. Lavand'homme P (2011) The progression from acute to chronic pain. Curr Opin Anesthesiol 24: 545-550.
3. Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: Risk factors and prevention. Lancet 367: 1618-1625.
4. Pereira LG, Valdoleiros I, Reis P, Abelha F (2016) Evaluating persistent postoperative pain in one tertiary hospital: Incidence, quality of life, associated factors and treatment. Anesth Pain Med 6: e36461.
5. Eckhardt MRB (2018) From acute to chronic postsurgical pain: The significance of the acute pain response. Danish Med J 65: B5326.
6. Shamim MS, Enam SA, Tahir MZ, Khan M (2012) Prospective case-control evaluation of epidural midazolam for improving pain and ambulation after a microdiscectomy. J Pak Med Assoc 62: 561-565.
7. Bharti N, Batra YK, Negi SL (2015) Efficacy of intrathecal midazolam versus fentanyl for endoscopic urology surgery. S Afr J Anesth Analg 21: 13-16.
8. Senapathi TGA, Widnyana IMG, Wiryana M, Aribawa IGNM (2017) Programmed intermittent epidural bolus improves the efficacy of patient-controlled epidural analgesia in postoperative pain management. Bali J Anesthesiol 1: 44-47.
9. Kaynar AM, Shankar KB (1999) Epidural infusion: continuous or bolus? Anesth Analg 89: 531-538.
10. Virmani R, Ghai A, Singh DK (2008) A study to compare continuous epidural infusion and an intermittent bolus of bupivacaine for postoperative analgesia following renal surgery. S Afr J Anesth Analg 14: 19-22.
11. Christiansson L (2009) Update on adjuvants in regional anesthesia. Periodicum Biologorum 111: 161-170.
12. Swain A. Nag DS, Sahu S, Samaddar DP (2017) Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases 5: 307-348.
13. Adetoye AO, Adenekan AT, Faponale AF, Sowande OA, Owojuyigbe AM, et al. (2017) Caudal bupivacaine and midazolam versus bupivacaine alone for pain relief in pediatric ambulatory groin surgeries. Pediatr Anesth Critical Care J 5: 95-102.
14. Chattopadhyay A, Maitra S, Sen S (2013) Midazolam in subarachnoid block: Current evidence. Anesthesiology 202835: 1-7.
15. Wheatley RG, Schug SA, Watson D (2001) Safety and efficacy of postoperative epidural analgesia. Br J Anesth 87: 47-61.
16. Prochazka J, Hejcl A, Prochazkove L (2011) Spine section-original research articles intrathecal midazolam

as supplementary ankgesia for chronic lumbar pain - 15 years' experience. Pain Med 12: 1309-1315.

17. Pathak L (2015) Effect of postoperative epidural analgesia after major orthopedic surgeries, a retrospective study. J Universal College Med Sci 3: 20-25.
18. Zencirci B (2014) Midazolam in spinal anesthesia - Intrathecal or intravenous? IntechOpen 6.
19. Ansari A, Rizk D, Whinney C (2017) Multimodal pain strategies guide for postoperative pain management. The Society of Hospital Medicine.
20. Kehlet H, Wilmore DW (2002) Multimodal strategies to improve surgical outcome. Am J Surg 183: 630-641.
21. Sharma NR, Timalsena P, Sundip DC (2013) Comparison of epidural analgesia provided by Bupivacaine plus Pethidine, Bupivacaine plus Morphine or Bupivacaine plus Morphine plus Midazolam for lower limb orthopedic surgery. J Kathmandu Med College 2: 117-121.
22. Elsharkawy H, Naguib MA (2015) Centrally acting non-opioid analgesics. In: Stoelting's Pharmacology & Physiology in Anesthetic Practice. Fifth edition. Flood P, Rathmell JP, Shafer S (Eds). Philadelphia, Wolter Kluwer Health, pp: 258-268.