Egyptian Journal of Anaesthesia

Vol. 41, 2025
ISSN: 1110-1849 (print))
ISSN: 1687-1804 (online)
DOI: 10.21608/EGJA.2025.385255.1083

LETTER OF THE EDITOR

Epidural Oxycodone for Prevention of Phantom Limb Pain in Patients Undergoing Major Lower Limb Amputation: A Randomized Controlled Trial

Mohamed Mamdouh Kotb, Ahmed Abdalla Ghareeb, Mohamed Hassan Osman, Heba Fouad Dawood, Gamal Hendawy Shams

Lecturer in Anaesthesia and Surgical Intensive Care, Kafrelsheikh Faculty of Medicine, Kafrelsheikh, Egypt.

Correspondence to *Mohamed Mamdouh Kotb; Lecturer in Anaesthesia and Surgical Intensive Care, Kafrelsheikh Faculty of Medicine, Kafrelsheikh, Egypt.*
E-mail: mohamedkotb@med.kfs.edu.eg

Background Postoperative care for patients undergoing major lower limb amputations carries special challenges for both the anaesthetist and pain therapist. In our study we assessed the efficacy of epidural oxycodone in postoperative pain control and prevention of phantom limb pain in patients undergoing major lower limb amputation under general anesthesia.

Settings and Design Prospective randomized controlled trial.

Methods This work enrolled 40 patients undergoing lower limb amputation under general anaesthesia with epidural analgesia. Patients were randomized into two groups. Group O received a bolus dose of 0.15mg/kg plus 20ml bupivacaine 0.25% followed by an infusion 0.03mg/kg/h oxycodone plus 0.1ml/Kg/h bupivacaine 0.125% and group C were given a bolus 20ml bupivacaine 0.25% followed by an infusion 0.1ml/Kg/h bupivacaine 0.125%. Vital signs were recorded. Visual analogue scale was recorded postoperatively at 2, 4, 6, 12, 18, 24, 36 and 48 hours. Postoperative total dose of rescue analgesic morphine and timing of first analgesic request were recorded. Incidence of phantom limb pain up to 3 months after surgery was assessed. Postoperative opioid related adverse reactions were recorded in both groups.

Results Mean heart rate in patients of group O was significantly lower at 6- and 12-hours intervals postoperatively than in patients of group C (P_2= 0.002 and 0.003). Mean arterial blood pressure in patients of group O was significantly lower at 6- and 12-hours intervals postoperatively than in patients of group C (P_2= 0.027 and 0.001 respectively). Group O showed significantly lower VAS scores at 6, 12 and 18 hours post-operatively in comparison with patients group C (p= 0.002, 0.021 and 0.002 respectively). Patients of group O showed less total morphine consumption and later request for rescue analgesia than patients of Group C in a statistically significant way (p= 0.001 and 0.001). Phantom limb pain at 3 months post-operatively was found to be statistically less in patients of group O (p= 0.021). Patients of group O showed statistically significant less incidence of PONV and pruritis in comparison to the patients of group C (p= 0.046 and 0.022 respectively).

Conclusions Epidural oxycodone infusion may be beneficial in both control of acute postoperative pain and prevention of phantom limb pain in patients undergoing major lower limb amputations.

Keywords Epidural oxycodone, lower limb amputation, phantom limb pain.
Received: 14 May 2025, Accepted: 14 June 2025
Egyptian Journal of Anaesthesia 2025,

INTRODUCTION

Following major lower limb amputation, patients often experience significant postoperative pain, a complex phenomenon involving nociceptive and neuropathic components. This acute pain, characterized by both somatic and visceral elements arising from the surgical site and amputation stump, necessitates multimodal analgesia to optimize patient comfort and facilitate early rehabilitation. Effective management aims to preempt chronic pain development and improve functional outcomes [1].

The experience of pain in an amputated limb stump is known as phantom pain. Phantom pain may start in the initial days following amputation. The feeling could be static or intermittent. Even while the sensation usually affects the limb that is farthest from the body, like the foot of an amputated leg, it can still impact the arm or hand, which are closer to the brain. Sensations can be characterized as searing, throbbing, squeezing, boring, stabbing, or shooting [2,3].

Smaller limbs and digits, such fingers or toes, typically experience less intense sensations. It can occasionally feel like the phantom portion is being pushed into an awkward position. In general, mental stress or pressure on the remaining portion of the limb may cause the feelings [4].

PLP pain prevention techniques are challenging to implement, and if left untreated, they can result in chronic pain. In order to treat somatic and occasionally neuropathic postoperative pain, the anesthesiologist and acute pain physician play a crucial perioperative role. It should be properly recognized and treated if neuropathic or hyperalgesia symptoms begin to appear [5].

PLP has been shown to be effectively prevented by preoperative epidural infusion of bupivacaine and opioids. Although the success of epidural clonidine as a postoperative analgesic was reported, drowsiness and hypotension are among its marked adverse effects [6].

Oxycodone, a semi-synthetic narcotic analgesic, is a common drug of abuse. It is administered intravenously or orally [7].

Oxycodone's effects include drowsiness, cough suppression, constipation, respiratory depression, pain alleviation, and papillary constriction. Chronic or long-term use of acetaminophen containing oxycodone can seriously affect the liver. On the brain, Oxycodone's most common effects include relaxation, and euphoria [8].

By binding to both peripheral and cerebral opioid receptors, opioids (oxycodone, methadone, morphine, and levorphanol) produce analgesia without impairing touch, proprioception, or awareness. They might also interfere with one of the hypothesized processes of PLP and reduce cortical remodeling [9].

We conducted this work aiming to assess the efficacy of epidural oxycodone in acute postoperative pain control and the prevention of PLP and secondarily to investigate the impact of epidural oxycodone on the overall incidence of intravenous opioid related adverse effects.

PATIENTS AND METHODS

Our double blinded RCT was approved by the Ethics committee in the faculty of medicine in Kafrelsheikh university (KFSIRB200-97). We enrolled 40 patients from Kafrelsheikh University Hospital from November 2023 to December 2024. The purpose of the study was explained to all patients and an informed written consent was obtained. A secret code number and a private file was assigned for each patient to maintain confidentiality. All collected data were used for the current medical research only.

Patients included were between 20 and 80 years of age, of both sexes, physical status II-III according to American Society of Anesthesiologists (ASA) and receiving general anesthesia with epidural analgesia for major lower limb amputation.

Patients with acute asthma or other obstructive airways disease, cardiac arrhythmias hypersensitivity to local anesthetics or opioids, severe renal impairment, severe diabetic neuropathy and pregnancy were excluded from the trial.

Computer generated random numbers in closed-sealed, opaque envelopes were used for randomization. The sealed envelope containing each patient's group allocation was opened before the patient was taken into the operating room. Patients were randomly categorized into two equal parallel groups.

• Group O (Oxycodone group) (n= 20): An epidural bolus dose of 0.15mg/kg and 20ml bupivacaine 0.25% was given to patients followed by an infusion 0.03mg/kg/hr oxycodone and 0.1ml/kg/hr bupivacaine 0.125%.

• Group C (Control group) (n= 20): An epidural bolus 20ml bupivacaine 0.25% was given to patients followed by an infusion 0.1ml/kg/hr bupivacaine 0.125%.

Patients and outcome assessors were blinded to the group of the patients. The study solutions were prepared by a clinical pharmacist to ensure blindness.

Preoperative history taking, clinical examination and routine laboratory investigations were done. Patients were informed about visual analogue scale (VAS) and instructed to circle the number from 0 and 10, where 0 means no pain and 10 means the worst pain [10].

In the operating room, standard monitoring was connected to record non-invasive arterial blood pressure (NIBP), electrocardiography (ECG), capnography, pulse oximetry, and temperature probe. An epidural catheter was introduced before surgery.

The technique of epidural block

While the patient was seated, an 18G Tuohy needle was used to identify the epidural space (L3-L4 or L4-L5 in midline approach) using the loss of resistance to air technique, under aseptic conditions. After inserting the 18G portex epidural clear catheter 5cm past the needle tip, the needle was taken out. Two milliliters of 0.25% bupivacaine were administered as test dose after the catheter was confirmed patent and secured with a fixator. Next, patients were placed in supine position and an 18ml of 0.25% bupivacaine were given, then 0.1mL/kg/hr bupivacaine 0.125%.

We considered the disappearance of pinprick sensation on the block's dermatomal site 30 minutes after injection as successful block and excluded patients with failed blocks.

Standardized general anesthesia by 1-2mcg/kg fentanyl, 1-2mg/kg propofol and 0.5mg/kg cis-atracurium was given to all patients and after confirming adequate anesthesia an endotracheal tube was introduced.

To maintain anesthesia, Sevoflurane 2% in air/oxygen was used with the minimum alveolar concentration (MAC) adjusted for patient's age. For neuromuscular block, cis-atracurium 0.1mg/kg top-up doses were administered every 20 minutes.

Volume-controlled mode was set on the ventilator which was adjusted to deliver a tidal volume of 6–8ml/kg. An inspiratory-to-expiratory ratio of 1:2 and a respiratory rate (RR) of 12/minute were established. The RR was adjusted to maintain normocapnia (end-tidal CO_2 between 30-35mmHg). By a forced-air warming system, the body temperature was maintained at 36–37°C and was measured using an esophageal temperature probe. All patients received; 1gm paracetamol infusion intraoperatively. Operations were performed by the standard technique by the same team.

At the end of the surgery, anesthesia was discontinued, and neostigmine (0.08mg/kg) and atropine (0.02mg/kg) reversed residual neuromuscular blockade followed by extubation. Patients were transferred to the post anesthesia care unit (PACU) after full awakening.

Heart rate (HR) (beats/minute) and mean arterial pressure (MAP) (mmHg) were recorded before surgery, intraoperatively and post operatively after 2, 6, 12, 24 and 48 hours. Scoring of acute pain using VAS was done immediately post-operative at PACU then at 2h, 4h, 6h, 12h, 18h, 24h, 36h and 48h after surgery. A regimen of standardized analgesia was prescribed in the post-operative period when all patients received paracetamol 1gm every 6hrs. Rescue analgesia in the form of intravenous morphine 2mg were administered if VAS is more than 3. Morphine consumption in the 1st 48 post operative hours, time to the first request for the rescue analgesia (from end of surgery to first administered dose of morphine) were also recorded. Patients were observed for the occurrence of any adverse events related to opioids. The incidence of PLP was followed up in patients up to 3 months after surgery.

Sample size calculation

The sample size was determined using G*Power 3.1.9.2 (Universitat Kiel, Germany). A pilot study enrolling five cases for each group was done recorded the mean (±SD) pain score (VAS) was 1.6±1.14 in group O and 3.6±1.95 in group C. The following factors were considered: The study had a 1.252 effect size, 95% confidence limit, 95% power, a 1:1 group ratio, and two cases were added to each group to account for dropout. As a result, we recruited 20 patients for each group.

Statistical analysis of the data

Computer software program (IBM SPSS version 24.0) was used for data analysis. Numbers and percentages described qualitative data. The Fisher Exact test compared categorical variables across groups. Mean and standard deviation were used to describe normally distributed quantitative data. The independent *t*-test was used to compare normally distributed data from two different populations. Significance test findings are shown as two-tailed probabilities. The significance of the results was determined at the 5% level.

RESULTS

A total of 45 patients were enrolled in the research, while 10 were excluded due to ineligibility. Five patients withdrew from the trial during its duration. A total of 40 participants completed the three-month research length (Figure 1).

The two studied groups were perfectly matched regarding age, gender, BMI, ASA class, type of surgery and the surgical duration (Table 1).

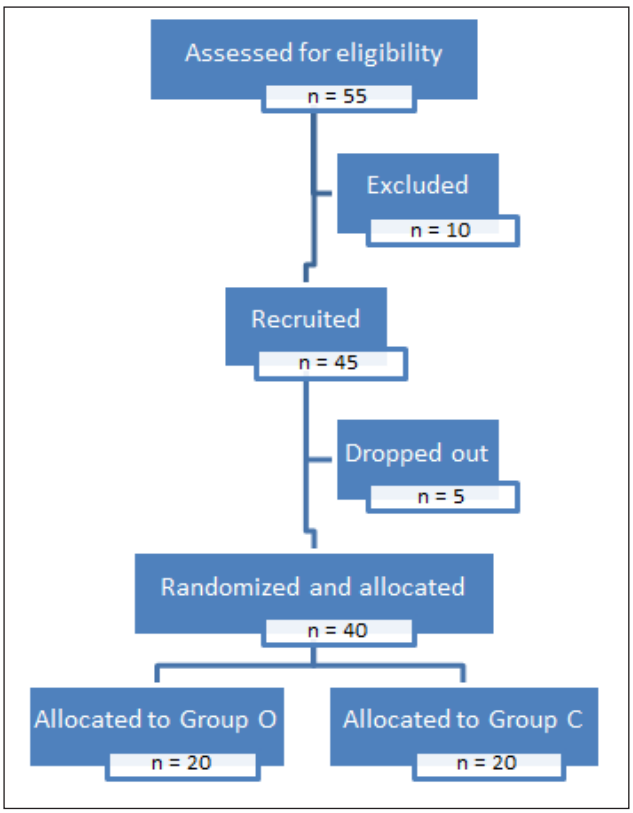

Figure 1: Flow chart of patients.

Table 1: Comparison between the two groups studied regarding basic demographic and clinical data:

	Group O	Group C	*P* value
Age (years)			
Mean	56.4	59.9	0.144 N.S.
SD	11.7	8.9	
Gender			
Male	16(80.0%)	16(80.0%)	1.000 N.S.@
Female	4(20.0%)	4(20.0%)	
BMI (kg/m^2)			
Mean	27.4	26.7	0.318 N.S.
SD	5.3	4.6	
ASA class			
II	17(85.0%)	18(90.0%)	0.632 N.S.
III	3(15.0%)	2(10.0%)	
Type of surgery			
AKA	7(35.0%)	8(40.0%)	0.894 N.S. @
BKA	12(60.0%)	10(50.0%)	
High AKA	1(5.0%)	1(0.0%)	
Duration of surgery (min)			
Mean	56.4	60	0.166 N.S.
SD	12.6	10.8	

T: Student *t*-test; @ *p* was calculated by Fisher exact test: *P* was significant if ≤0.05; N.S.= Not significant.

Regarding HR, patients of group O showed no significant difference in all time intervals in comparison to the baseline readings, while in group C, heart rate was significantly elevated during 6- and 12-hours intervals post-operatively (*p* value= 0.002 and 0.003 respectively) (Figure 2).

Comparing the two groups, mean HR in patients of group O was significantly lower at 6- and 12-hours intervals postoperatively than in patients of group C (mean±SD 73.9±10.61 and 74±9.71 vs 95.9±10.98 and 101.35±9.04 respectively. *P*= 0.002 and 0.003) (Figure 2).

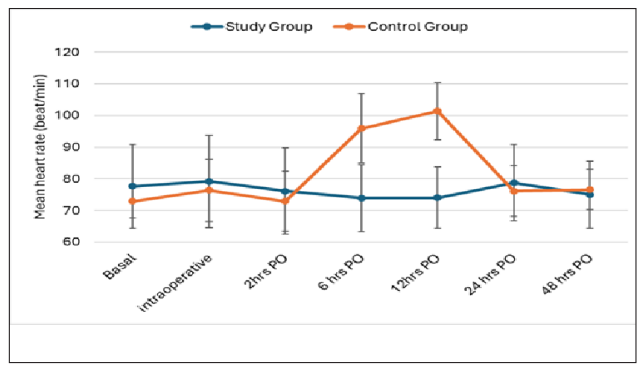

Figure 2: Comparison between the two studied groups regarding heart rate at different periods of follow-up.

Regarding MAP, patients of both groups showed no significant difference in all time intervals in comparison to the baseline readings except at 12 hours post operatively when group C showed significant elevation in MAP in comparison to the baseline measurement (mean±SD 101.6±6.11 vs 97.46±6.64 *P*= 0.022) (Figure 3).

Comparing the two groups, MAP in patients of group O was significantly lower at 6- and 12-hours intervals postoperatively than in patients of group C (mean±SD 94.85±11.51 and 94.1±7.87 vs 101.45±9.31 and 101.6±6.11. *P*= 0.027 and 0.001 respectively) (Figure 3).

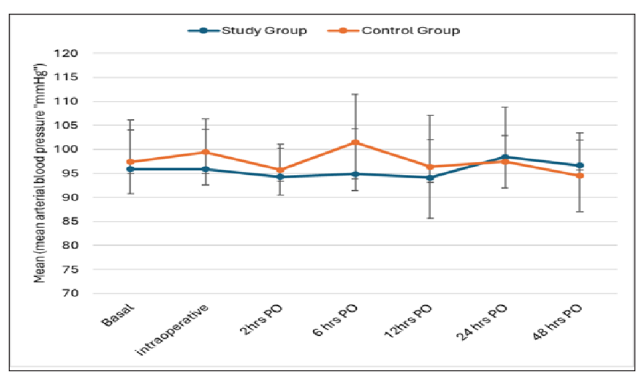

Figure 3: Comparison between the two studied groups regarding mean arterial blood pressure at different periods of follow-up.

Comparing VAS scores between the two groups during the post-operative period patients of group O showed significantly lower scores at 6, 12 and 18 hours post-operatively in comparison with patients group C (mean±SD 1.95±1.00, 2±0.73 and 2.5±0.76 vs 4.05±1.23, 2.65±1.18 and 3.5±1.24 *p*= 0.002, 0.021 and 0.002 respectively) (Figure 4).

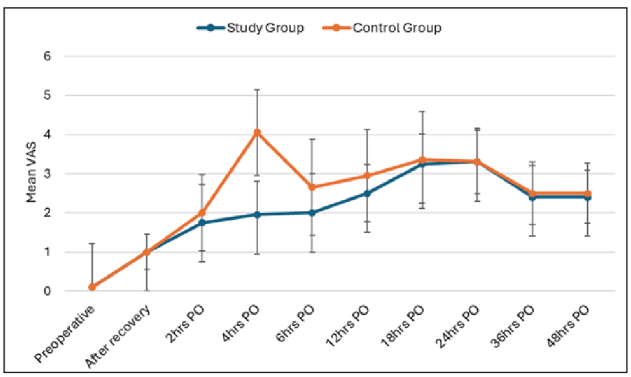

Figure 4: Comparison between the two studied groups regarding VAS at different periods of follow-up.

Patients of group O showed less total morphine consumption (20% of group) than patients of group C (100% of group) in a statistically significant way (mean±SD 2.70±2.27 vs 8.85±3.70 *p*= 0.001) (Table 2).

Also, patients of group O requested analgesia later than patients of group C (mean±SD 27.13±8.91 vs 6.20±3.17 *p*= 0.001) (Table 2).

Phantom limb pain at 3 months post-operatively was found to be statistically less in patients of group O (0% vs 30% *p*= 0.021) (Table 2).

Table 2: Comparison between the two studied groups regarding total morphine consumption, time to first analgesia request and incidence of phantom limb pain 3 months post-surgery:

	Group O	Group C	*P* value
Total morphine consumption 48hrs (mg)			
Mean	2.7	8.9	0.001*
SD	2.3	3.7	
Time of first analgesia request (hours postoperative)			
Mean	27.1	6.2	0.001*
SD	8.9	3.2	
Phantom limb pain 3 months post-surgery			
No	20(100.0%)	14(%70.0)	0.021*#
Yes	0 (0.0%)	6 (%30.0)	

#: *p* value was calculated by using Fisher exact test.

Patients of group O showed statistically significant less incidence of PONV and pruritis in comparison to the patients of group C (*p*= 0.031 and 0.008 respectively), while there was no statistically significant difference between patients of both groups regarding urine retention and dizziness, sedation or respiratory depression (Table 3).

Table 3: Comparison between the two studied groups regarding post operative complicationy:

	Group O	Group C	*P* value
Post-operative nausea and vomiting (PONV)	2(10.0%)	9(45.0%)	0.031
Urine retention	0(0.0%)	2(10.0%)	0.487 N.S.
Dizziness, sedation or respiratory depression	0(0.0%)	4(20.0%)	0.106
Pruritis	1(5.0%)	9(45.0%)	0.008*

@: *p* was calculated by Fisher exact test.

DISCUSSION

The results of our study showed significantly lower HR and MAP values at 6 and 12 hours and much better pain scores at 6, 12 and 18 hours postoperatively, in patients who received epidural oxycodone in addition to bupivacaine. In addition, the total consumption of rescue analgesia was significantly lower and the call for it was later than the other group in the postoperative period. The patients were followed for the existence of PLP for 3 months post-surgery and the incidence was markedly lower than the group that received epidural bupivacaine in addition to general anesthesia.

The first article about the use of epidural opioids was published in 1979 by Behar *et al.,* when they used 2mg of epidural morphine for the management of acute and chronic pain, their results demonstrated great improvement in pain scores with the 'novel technique' [11]. Years later, the use of epidural opioids was thoroughly studied, and the spinal opioid receptors were fully discovered. Today, the spinal administration of opioids became routine for intraoperative and postoperative analgesia and in labor, as well as for chronic pain, especially that associated with cancer [12].

We also showed that Pain scores postoperatively were significantly lower up to 18 hours in the epidural oxycodone group when assessed using VAS. Consequently, Group O showed markedly lower intravenous opioid consumption and later call for rescue analgesia also lower opioid related side effects. These findings match the results of the studies performed by Backlund M. *et al.,* [13] and Yanagidate F. *et al.,* [14] who used epidural oxycodone in lower abdominal and gynecological surgeries respectively.

The exact pathophysiology and definitive treatment of phantom limb pain are still not well established [15],

but the results of our study provide possible effective management line for it and pave the way for future work in this field, the pre-emptive blockage of spinal opioid receptors may lead to significant reduction of the occurrence of PLP among major lower limb amputees.

CONCLUSION

The use of epidural oxycocdone in addition to bupivacaine may provide better post operative analgesia and reduce the incidence of PLP in patients undergoing major lower limb amputations.

LIMITATIONS

The difficulty in patient follow-up, the small sample size, and the short time of this study all limited its scope.

ABBREVIATIONS

PLP: Phantom limb pain; **GA:** General Anesthesia; **MAP:** Mean Arterial Pressure; **HR:** Hear rate; **VAS:** Visual Analogue Scale.

ACKNOWLEDGMENTS

The authors are thankful to Anesthesia and Surgical Intensive Care Department and Vascular Surgery Unit, Faculty of Medicine, Kafrelsheikh University.

FUNDING DETAILS

No funding was received by the authors for conducting this study.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Ahuja V, Thapa D, Ghai B. (2018). Strategies for prevention of lower limb post-amputation pain: A clinical narrative review. Journal of Anaesthesiology Clinical Pharmacology. Oct 1;34(4):439-49.
2. Browne JD, Fraiser R, Cai Y, Leung D, Leung A, Vaninetti M. (2022). Unveiling the phantom: What neuroimaging has taught us about phantom limb pain. Brain Behav Immun. 12(3):509-16.
3. Rierola-Fochs S, Varela-Vásquez LA, Merchán-Baeza JA and Minobes-Molina E. (2021). Development and validation of a graded motor imagery intervention for phantom limb pain in patients with amputations (Grami protocol): A delphi study. Int J Environ Res. 18(22):240-8.
4. Borrell JA, Manattu AK, Copeland C, Fraser K, D'Ovidio A, Granatowicz Z, *et al.* (2023). Phantom limb therapy improves cortical efficiency of the sensorimotor network in a targeted muscle reinnervation amputee: a case report. Front Neurosci. 17:777-82.
5. Ahuja V, Thapa D, Ghai B. (2018). Strategies for prevention of lower limb post-amputation pain: A clinical narrative review. J Anaesthesiol Clin Pharmacol. 34(4):439-49.
6. Valero EG, Acosta Acosta CDP, Vargas Useche W, Orozco Sandoval L, Seija-Butnaru D, Sánchez-Flórez JC, *et al.* (2023). Perioperative Management of Painful Phantom Limb Syndrome: A Narrative Review and Clinical Management Proposal. J Pain Palliat Care Pharmacother. 37(2):194-208.
7. Hutt-Williams S and Mackinney C. (2023). Peripheral nerve blocks for ischaemic limb pain. BMJ Support Palliat Care. 642-9.
8. Kiyatkin EA. (2019). Respiratory depression and brain hypoxia induced by opioid drugs: Morphine, oxycodone, heroin, and fentanyl. Curr Neuropharmacol. 151:219-26.
9. Tian H, Hu H, Li X, Liu J, Guo Q, Li Y, *et al.* (2021). Auricular therapy for treating phantom limb pain accompanied by jumping residual limb: A short review and case study. Pain Ther. 10:739-49.
10. Sahli L, Hagenbuch N, Ballmer PE, Rühlin M, Imoberdorf R. (2021). NRS-2002 components, nutritional score and severity of disease score, and their association with hospital length of stay and mortality. Swiss Med Wkly. 151:517-8.
11. Behar M, Magora F, Olshwang D, *et al.* (1979). Epidural morphine in treatment of pain. Lancet. 1(8115): 527-529.
12. Bujedo BM, Santos SG, Azpiazu AU. (2012). A review of epidural and intrathecal opioids used in the management of postoperative pain. J Opioid Manag. Mar;8(3):177-92.
13. Backlund M, Lindgren L, Kajimoto Y, *et al.* (1997). Comparison of epidural morphine and oxycodone for pain after abdominal surgery. J Clin Anesth. 9(1): 30-35.
14. Yanagidate F, Dohi S. (2004). Epidural oxycodone or morphine following gynaecological surgery. Br J Anaesth. 93(3): 362-367.
15. Urits I, Seifert D, Seats A, Giacomazzi S, Kipp M, Orhurhu V, Kaye AD, Viswanath O. (2019). Treatment strategies and effective management of phantom limb–associated pain. Current pain and headache reports. Sep; 23:1-7.