

Evaluation of the postoperative morphine-sparing effect of oral premedicants used as pre-emptive analgesics in breast-conserving cancer surgeries: A randomised placebo-controlled trial

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ABSTRACT

Background and Aims: Breast cancer surgeries are associated with both nociceptive and neuropathic pain, requiring strong analgesics. We aimed to evaluate the postoperative morphine-sparing effect of pre-emptive oral premedication with tramadol versus pregabalin in patients undergoing breast-conserving cancer surgeries (BCCS). **Methods:** This prospective, randomised, placebo-controlled trial was carried out at tertiary care centre on 90 patients undergoing BCCS randomised into three groups of 30 each. Group C received placebo, Group T received tramadol 100 mg and Group P received pregabalin 75 mg as oral premedication, 1 hour before surgery. General anaesthesia was administered. Postoperatively morphine 1 mg.h⁻¹ through intravenous PCA was started at a visual analogue scale score ≥ 4 . Total morphine consumption in 24 hours was calculated and its sparing effect was evaluated as the primary outcome. **Results:** The median with interquartile range (IQR) of total postoperative morphine consumed in 24 hours, was found to be 22 mg (IQR 0-25.77), 15 mg (IQR 0-16) and 17.50 mg (IQR 0-19.25) in groups C, T, P respectively, ($P = 0.000, 0.003, 0.060$). The median duration of analgesia in group C was 5.40 hours (IQR 3.30-11.40), 11.6 hours (IQR 9.30-24.0) in group T and 8.60 hours (IQR 6.97-16.27) in group P (P value C/T = 0.000, C/P = 0.007, T/P = 0.002). The postoperative side effects were comparable. **Conclusion:** Oral tramadol 100 mg and oral pregabalin 75 mg as premedication reduced the 24 hours postoperative morphine requirement as compared to placebo in BCCS. However, tramadol 100 mg provided superior analgesia for longer duration than pregabalin 75 mg and was associated with more side effects.

Key words: Morphine, patient-controlled analgesia, postoperative pain, pregabalin, premedication, tramadol

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INTRODUCTION

Breast cancer is associated with moderate to severe nociceptive as well as neuropathic pain. After breast-conserving cancer surgery (BCCS), the postoperative pain depends upon the extent and duration of surgery.^[1] Inadequate treatment of postoperative pain can lead to delayed recovery and hence post-surgery stress disorder. Morphine through patient control analgesia (PCA) provides standard mode of postoperative analgesia following breast surgery, but is associated with various distressing side effects.^[2] BCCS or simple mastectomy does not

involve extensive dissections, therefore more invasive modalities like epidurals or paravertebral blocks

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may not be required. So, whether the use of simpler alternative such as pre-emptive oral premedication helps in controlling postoperative pain in BCCS remains much unexplored.^[3] This study aimed to evaluate the 24 hour postoperative requirement of morphine in BCCS with tramadol or pregabalin as pre-emptive pre-medicants as compared to the placebo as the primary outcome. The incidence of adverse effects was the secondary outcome.

METHODS

This prospective, randomised, double-blind placebo-controlled trial was conducted as per the Declaration of Helsinki in the Department of Anaesthesia for one year (August 2018-July 2019). Ninety adult patients (18–65 years) of American Society of Anesthesiologists physical status I and II undergoing elective BCCS were enrolled at a tertiary care hospital in North India. Criteria for exclusion included the patient's refusal to take part in the study, pregnant and lactating women, prior usage of study drugs, known hypersensitivity to study drugs, history of drug abuse or mental retardation, inability to understand the functioning of PCA pump and visual analogue scale (VAS) and surgery requiring extensive dissection. The study was registered with the Government of India Clinical Trial Registry (CTRI/2018/08/015232), after being approved by the Institutional Ethics Committee. After getting full information about the procedure in their language, the patients signed the written consent form. Patients were explained the use of PCA pump a day prior to the surgery. VAS was explained on paper as a ten point 11-cm line for pain assessment, 0 standing for no pain and 10 standing for the worst imaginable pain.

Randomisation was carried out using random numbers table generation which were then assigned to different groups. The coded slips which were then made were put in a sealed envelope. A registered nurse practitioner administered study drug capsule after opening the code from the sealed envelope to the patients with sips of water, orally 1 hour before surgery. For the purpose of blinding, the hospital pharmacy prepared capsules identical in size, shape and colour. These bottles encoded as A, B and C contained placebo, tramadol 100 mg and pregabalin 75 mg capsules, respectively. The patients and the assessor remained blinded to the study drug. Thirty patients were allocated in each group. Group C (n = 30) patients received multivitamin capsules as placebo, Group T (n = 30) received oral tramadol 100 mg capsule and Group P (n = 30)

received oral pregabalin 75 mg capsule.

A comprehensive pre-anaesthetic evaluation of the patients was done and they were kept nil per oral for 6 hours before surgery. Baseline non-invasive blood pressure (NIBP), heart rate (HR) and oxygen saturation (SpO₂) were checked in the pre-operative room. Same general anaesthesia technique was followed and all the patients were induced with intravenous morphine 0.1 mg.kg⁻¹, propofol 2 mg.kg⁻¹, and the trachea intubated using vecuronium 0.1 mg.kg⁻¹. Anaesthesia was maintained with oxygen, nitrous oxide (66:33) and isoflurane. HR, NIBP, SpO₂, Electrocardiography (ECG) and end-tidal carbon dioxide (EtCO₂) were monitored throughout at a regular interval of 10 min. Intraoperatively, if the patient felt pain as judged from hypertension, tachycardia or lacrimation, an additional dose of 2 mg morphine was administered. Injection ondansetron 8 mg was injected 30 min before the completion of surgery. At the end of surgery, neuromuscular blockade was reversed with intravenous neostigmine 0.05 mg.kg⁻¹ and glycopyrrolate 0.01 mg.kg⁻¹ and the trachea was extubated. The patients were shifted to the post-anaesthesia care unit and assessed for pain and vitals every 15 min for the first 2 hours, then every two hourly till VAS ≥4. Then programmed PCA with background infusion of 1 mg.h⁻¹, a bolus of 1 mg, lockout time 12 min and a maximum dose of 6 mg per hour was started up to 24 hours postoperatively. For VAS ≥4 with dose more than 6 mg per hour of morphine, intravenous diclofenac 75 mg was kept as a rescue analgesic.

The total duration of analgesia was considered from the time of oral premedication to the first demand of the patient, i.e., VAS ≥4. During 24 hours of observation, the total postoperative morphine consumption was recorded in each group. For evaluation of sedation, Ramsay sedation scale was used; Grade '0' being fully awake; 1 = slightly drowsy; 2 = asleep but easily arousable; 3 = fully asleep but arousable; 4 = fully asleep and not arousable.^[4] Post-operative nausea and vomiting (PONV) was assessed using a 4-point scale, where 0: for none, 1: for slight, 2: for moderate and 3: for severe.^[4] Other side effects such as respiratory depression, nausea, vomiting, pruritus and chest wall rigidity were also assessed.

The sample was determined using G Power version 3.1.9.2, program written by Franz, Universitat, from the results of the pilot study conducted in 10 patients in each group, and these patients were

excluded from the study. An effective difference of >20% in the consumption of total dose of morphine was considered significant. So, considering alpha error 0.05, beta error 0.90 and the standard deviation (SD) of 5.45, the sample size of 87 was required. To compensate for dropouts, 90 patients with 30 patients in each group were considered [Figure 1].

After the completion of the study, the data were collected, compiled, decoded and statistically analysed to draw relevant conclusions using Statistical Package for Social Sciences-22 (2013, Armonk: International Business Machines Corporation). The observations were then tabulated in the form of mean ± SD for parametric data and median and interquartile range (IQR) for non-parametric data. The non-parametric data were further analysed using Mann–Whitney U test for intergroup comparison amongst the three groups. Parametric data were evaluated using the analysis of variance and categorical variables were analysed using the Chi-square test. The results with *P* value < 0.05 were considered as significant and *P* < 0.001 was considered as highly significant.

RESULTS

Out of 95 patients assessed for eligibility, only 90 could

participate in the study [Figure 1]. All the 90 patients, 30 in each group, were comparable for age, weight, height and had similar duration of surgery [Table 1]. Perioperative vitals such as systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, SpO₂, EtCO₂ and HR were also found statistically comparable (*P* > 0.05).

Total postoperative morphine requirement in 24 hours was 22.00 mg (IQR 0-25.77), 15 mg (IQR 0-16) and 17.50 mg (IQR 0-19.25) in group C, T and P, respectively. Groups C versus T as well as groups C versus *P* revealed statistical significance on intergroup comparison but not between the study drug groups T versus *P* (*P* values C/T = 0.000, C/P = 0.003, T/P = 0.060) [Figure 2].

The duration of analgesia was found to be 5.40 hours (IQR 3.30-11.40) in group C, 11.6 hours (IQR 9.30-24.0) in group T and 8.60 hours (IQR 6.97-16.27) in group *P*. (*P* value C/T = 0.000, C/P = 0.007, T/P = 0.002) [Figure 3].

There was a statistically significant difference in the time to start morphine PCA, and time to receive first morphine top-up bolus amongst the various groups [Table 2].

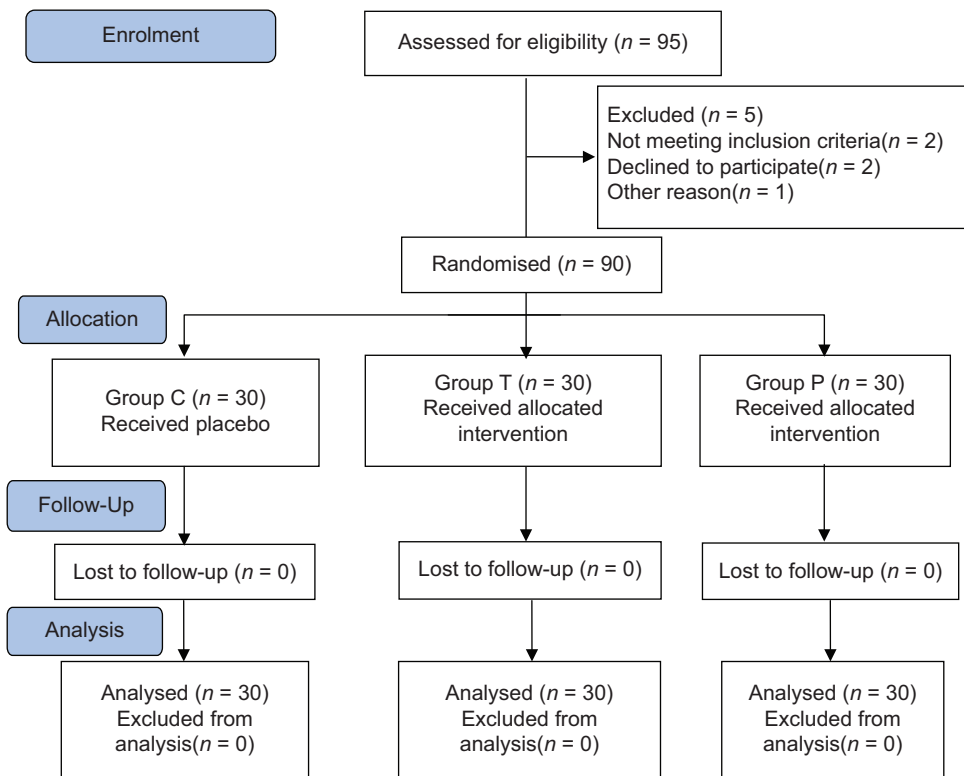


Figure 1: CONSORT flow diagram

Variables	Group C (n=30) Mean±Standard Deviation	Group T (n=30) Mean±Standard Deviation	Group P (n=30) Mean±Standard Deviation	P
Age (years)	51.13±8.98	50.43±6.71	49.45±8.95	0.831
Weight (kilograms)	59.20±8.59	59.43±6.71	58.68±7.75	0.918
Height (centimetres)	156.83±3.21	157.00±3.11	155.24±3.46	0.891
Duration of surgery (minutes)	86.50±16.98	93.00±17.05	85.16±22.54	0.064

n=no. of patients, insignificant (P>0.05), *Significant (P<0.05), †Highly Significant (P<0.001)

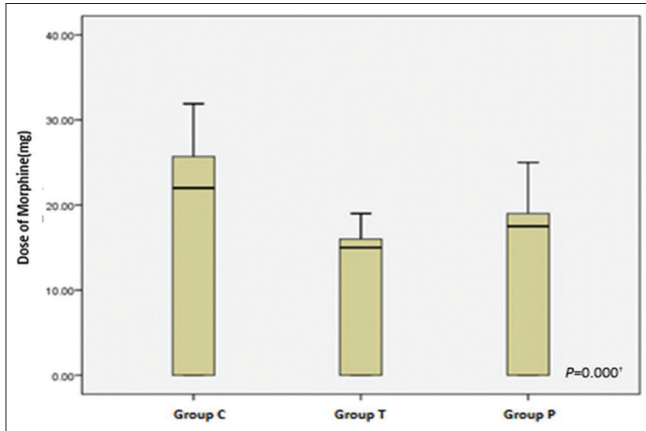


Figure 2: Distribution of the total postoperative morphine requirement(mg) in 24 hours

The mean number of boluses from morphine PCA, in group C was more than group T and P. A statistically significant difference was observed amongst all three groups on intergroup comparison (P < 0.001) [Table 2].

The haemodynamic parameters were within the normal physiological range at all-time intervals in both the groups.

No serious adverse effects were reported in any patient during the entire study period. The minor complications that occurred showed no statistical difference (P > 0.05) amongst the three groups [Table 3].

DISCUSSION

Nowadays, BCCS has become the standard of care in early stages of breast cancer because of which the long-term survival rate has improved. Post-mastectomy pain still remains a major concern as it increases the morbidity, duration of hospitalisation and the risk of chronic persistent postoperative pain. However, the analgesic requirement varies with the extent of surgery, the patient’s built, nutritional status and advancement of the disease process.^[5] Hence, the requirement

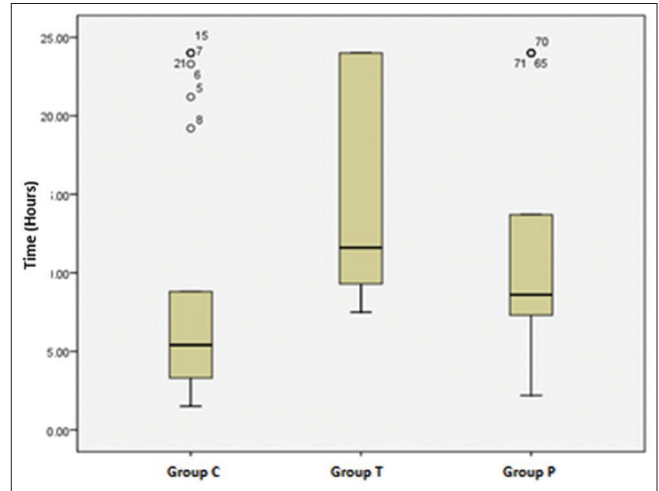


Figure 3: Duration of analgesia (hours) in all the three groups

of analgesia during BCCS would be much less as compared to radical mastectomies. Morphine has been widely studied for its use especially through intravenous PCA pump and remains the gold standard.^[6] So in a quest to find the effective alternatives to opioids, various non-opioids such as pregabalin, gabapentin, ketamine, dexmedetomidine and non-steroidal anti-inflammatory drugs have been used pre-emptively as a part of multimodal analgesic regimen to reduce the postoperative pain and help in early postoperative recovery in different types of surgeries.^[7-9]

In the present study, patients in the tramadol group had significant reduction in the dose of morphine during the postoperative period as well as a lesser requirement of rescue analgesia compared to the patients receiving pregabalin and placebo. A single dose of intravenous tramadol 1 mg kg⁻¹ appeared effective in relieving postoperative pain while decreasing morphine requirements after coronary bypass surgery.^[10] In another study, oral tramadol 50 mg was found to have morphine-sparing effect in patients undergoing open cholecystectomy under general anaesthesia.^[11] But at the same time, pregabalin 75 mg had better morphine-sparing effect than placebo. Pregabalin and tramadol have been

Table 2: Analgesic Requirement in All the Three Groups

Variables	Group C (n=30)	Group T (n=30)	Group P (n=30)	F	P
	Mean±Standard Deviation	Mean±Standard Deviation	Mean±Standard Deviation		
Time to the first top-up (h)	2.86±0.30	0.83±0.12	1.53±0.23	19.193	0.000†
Total no. of a boluses of morphine	5.05±1.15	9.5±0.51	6.0±0.63	7.005	0.002*

n=no. of patients, h=hours, insignificant ($P>0.05$), *Significant ($P<0.05$), †Highly Significant ($P<0.001$)

Table 3: Incidence of Adverse Effects in Various Study Groups

Complications	Group C (n=30)	Group T (n=30)	Group P (n=30)	Total	P
Respiratory depression	0	0	0	0	--
Pruritus	0	2	0	2	0.129
Nausea	2	5	2	9	0.329
Vomiting	1	2	1	4	0.770
Chest wall rigidity	0	0	0	0	N.A
Urinary retention	0	2	0	2	0.129

n=no. of patients, insignificant ($P>0.05$)

compared for postoperative pain management for lumbar laminectomies by Kumar KP *et al.*^[4] and they reported results similar to our study. As such, there is no study comparing these two drugs during breast cancer surgeries.

Nevertheless, in a meta-analysis, pregabalin both in single as well as multiple doses of 75–300 mg showed statistically significant opioid-sparing effect than placebo.^[12] The meta-analysis included studies using pregabalin in doses ranging from 50 to 300 mg and implied that the opioid-sparing effect is limited to 100-150 mg and 300 mg but not ≤ 75 mg at 2 hours postoperatively, but these doses had no statistically significant difference at 24 hours. The reduction in pain scores with pregabalin evaluated at rest and irrespective of dosing could be explained on the basis of its estimated elimination half-life ranging from 5.5 to 6.7 hours. It was also observed that pain on movement was not reduced with a single dose of pregabalin compared with placebo; however, reduction had been observed rather with multiple doses. Nevertheless, in our study, we did not evaluate pain at rest or on movement separately. So, the optimal dose or frequency of administration remains obscure.

Sensitisation of nerves induced by surgery-related neuroplastic changes can lead to allodynia and hyperalgesia postoperatively which is prevented by the meticulous use of analgesics.^[13,14] During BCCS or mastectomy, injury to the intercostobrachial and intercostal nerves is usually unavoidable which leads to pain and discomfort.^[15] Oral tramadol and pregabalin have been used as premedicants in other

types of surgeries for controlling postoperative pain. Tramadol is being prescribed for treating acute and chronic pain as a substitute for the high affinity opioids, the world over. Its opioid receptor agonist activity coupled with monoamine reuptake inhibitory action make it a unique analgesic.^[16] More recently, pregabalin also has emerged rapidly as an efficient non-opioid analgesic. It binds potently to the $\alpha 2$ - δ subunit and modulates calcium influx at nerve terminals, thus, reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P.^[17,18] It prevents central sensitisation, hyperalgesia and is effective against neuropathic pain with lesser inter-subject variability. Mahran E *et al.*^[19] studied the efficacy of oral pregabalin 150 mg and intravenous ketamine 0.5 mg/kg in postoperative pain management in breast cancer surgeries and found oral pregabalin to be effective in reducing the postoperative morphine consumption. The analgesic efficacy of oral pregabalin premedication in varied doses of 75 mg to 300 mg per day has been studied in patients with spinal cord injury, postherpetic neuralgia, dental surgery and gynaecological surgery.^[20-23]

Both the study groups showed stable haemodynamic profiles. The sedation increased with the use of PCA morphine in all the groups, but none of the patients reported undesirable sedation levels. However, Kumar KP *et al.*^[4] reported significantly lower sedation scores in patients undergoing laminectomies with tramadol as compared to pregabalin and placebo groups as they did not use continuous intravenous opioid PCA for postoperative analgesia. In their study, the degree of sedation in the pregabalin group was more than the placebo group. From this, they inferred that pregabalin has a good anxiolytic effect without excessive sedation. Preoperative pregabalin prolongs post-spinal analgesia too and is an important component in multi modal therapy.^[24]

Two patients complained of urinary retention, and two patients presented with pruritus in the tramadol group. Nausea and vomiting was more in the tramadol group as compared to other two groups ($P>0.05$). In

literature, higher incidence of nausea and vomiting with oral tramadol has been reported even when used as an oral pre-medicant.^[4,11,25] A reduction in opioid-related side-effects such as PONV and pruritus was observed in various studies with pregabalin.^[4] We did not observe any common side effects of pregabalin such as higher incidence of sedation, dizziness and visual disturbance relative to placebo which could be due to lesser dose of pregabalin used, i.e., 75 mg versus 100–300 mg used in other studies. The dose-response effect with pregabalin led to a greater incidence of these adverse effects when used in higher doses.

The limitation of this study was that we did not evaluate pain at rest and on movement separately. Moreover, we could not follow-up our patients beyond 24 hours, so, we cannot comment upon the effect of the study drugs on persistent post-mastectomy pain. Further studies can be carried out for evaluating optimal dose of pregabalin or tramadol to be used as oral pre-medicant drugs.

CONCLUSION

To conclude, oral tramadol 100 mg or oral pregabalin 75 mg as pre-medicants would be useful as a part of multimodal analgesia in breast conservative surgeries. Patients receiving either a single dose of tramadol or pregabalin had a significant reduction in morphine requirement, lesser postoperative pain, better VAS scores and prolonged duration of analgesia compared to placebo.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Kokosis G, Chopra K, Darrach H, Dellon AL, Williams EH. Re-visiting post-breast surgery pain syndrome: Risk factors, peripheral nerve associations and clinical implications. *Gland Surg* 2019;8:407-15.
- Elsabeeny WY, Shehab NN, Wadod MA, Elkady MA. Perioperative analgesic modalities for breast cancer surgeries: A prospective randomized controlled trial. *J Pain Res* 2020;13:2885-94.
- Mishra AK, Afzal M, Mookerjee SS, Bandyopadhyay KH, Paul A. Preemptive analgesia: Recent trends and evidence. *Ind J Pain* 2013;27:114-20.
- Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: A randomized, double-blinded, placebo-controlled study. *J Pain Res* 2013;6:471-8.
- Moo TA, Sanford R, Dang C, Morrow M. Overview of breast cancer therapy. *PET Clin* 2018;13:339-54.
- Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005;101:44-61.
- Karri SR, Jayaram K, Kumar A, Durga P. Comparison of efficacy of gabapentin and memantine premedication in laparoscopic cholecystectomies for postoperative pain relief – A randomised placebo controlled trial. *Indian J Anaesth* 2021;65:539-44.
- Kaur G, Kaur P, Gupta R, Kullar K, Bhangu GS, Sandhu SS. Discharge readiness after minor gynaecological surgeries comparing dexmedetomidine and ketamine premedication in bispectral index (BIS) guided propofol-based anaesthesia. *Indian J Anaesth* 2021;65:34-40.
- Bajwa SJ. Dexmedetomidine and Ketamine - Comrades on an eternal journey! *Indian J Anaesth* 2021;65:1-4.
- But AK, Erdil F, Yucel A, Gedik E, Durmus M, Ersoy MO. The effects of single-dose tramadol on postoperative pain and morphine requirements after coronary artery bypass surgery. *Acta Anaesthesiol Scand* 2007;51:601-6.
- Zavareh SM, Kashefi P, Saghaei M, Emami H. Pre emptive analgesia for reducing pain after cholecystectomy: Oral tramadol vs. acetaminophen codeine. *Adv Biomed Res* 2013;2:12.
- Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and postoperative pain: A systemic review and meta-analysis. *Br J Anaesth* 2015;114:10-31.
- Bajwa SJ, Halder R. Pain management following spinal surgeries: An appraisal of the available options. *J Craniovertebr Junction Spine* 2015;6:105-10.
- Nolte MT, Elboghdady IM, Iyer S. Anaesthesia and postoperative pain control following spine surgery. *Semin Spine Surg* 2018;30:154-9.
- Chen VE, Greenberger BA, Shi Z, Gajjar S, Shi W, Mourad WF, et al. Post-mastectomy and post-breast conservation surgery pain syndrome: A review of etiologies, risk prediction, and trends in management. *Transl Cancer Res* 2020;9:S77-85.
- Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: Pharmacology, metabolism and misuse. *Anesth Analg* 2017;124:44-51.
- Shneker BF, McAuley JW. Pregabalin: A new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005;39:2029-37.
- Chizh BA, Gohring M, Troster A, Quartery GK, Schmelz M, Koppert W, et al. Effects of oral pregabalin and arepitan on pain and central sensitization in the electrical hyperalgesia model in human volunteers. *Br J Anaesth* 2007;98:246-54.
- Mahran E, Hassan ME. Comparison of pregabalin versus ketamine in postoperative pain management in breast cancer surgery. *Saudi J Anaesth* 2015;9:253-7.
- Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *J Neurosurg Anesthesiol* 2012;24:121-6.
- Cappuzzo KA. Treatment of postherpetic neuralgia: Focus on

- pregabalin. *Clin Interv Aging* 2009;4:17-23.
22. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathé H, Murray G. Pregabalin in patients with postoperative dental pain. *Eur J Pain* 2001;5:119-24.
 23. Chotton T, Singh NR, Singh LC, Laithangbam PS, Singh HS. The effect of pregabalin for relief of postoperative pain after abdominal hysterectomy. *J Med Soc* 2014;28:18-21.
 24. Saraswat V, Arora V. Preemptive gabapentin vs pregabalin for acute postoperative pain after surgery under spinal anaesthesia. *Indian J Anaesth* 2008;52:829-34.
 25. Nain P, Kundra S, Singh T, Singh MR, Kapoor R, Singh A. Comparative evaluation of oral tramadol and gabapentin for prophylaxis of post-spinal shivering. *Indian J Anaesth* 2021;65(Suppl 1):5-11.