Clinical Investigation

Premedication with gabapentin, alprazolam or a placebo for abdominal hysterectomy: Effect on pre-operative anxiety, post-operative pain and morphine consumption

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ABSTRACT

Background and Aims: Utility of gabapentin for pre-operative anxiolysis as compared to commonly administered alprazolam is not evident. The aim of the present study was to compare the effects of pre-operative oral gabapentin 600 mg, alprazolam 0.5 mg or a placebo on pre-operative anxiety along with post-operative pain and morphine consumption. **Methods:** Seventy five patients scheduled for abdominal hysterectomy under general anaesthesia were included. Groups gabapentin, alprazolam and placebo, received oral gabapentin 600 mg, alprazolam 0.5 mg and one capsule of oral B-complex forte with Vitamin C respectively, on the night prior to surgery and 2 h prior to surgery. Visual analogue scale (VAS) was used to measure the anxiety and post-operative pain. All patients received patient-controlled analgesia. Statistical tests used were Kruskal–Wallis test, Wilcoxon signed rank test and one-way ANOVA. **Results:** Alprazolam provided significant anxiolysis (median [interquartile range] baseline VAS score 35 [15.5, 52] to 20 [6.5, 34.5] after drug administration; $P = 0.007$). Gabapentin did not provide significant decrease in anxiety (median [interquartile range] VAS score 21 [7.5, 41] to 20 [6.5, 34.5]; $P = 0.782$). First analgesic request time (median [interquartile range in minutes]) was longer in group gabapentin (17.5 [10, 41.25]) compared to group placebo (10 [5, 15]) ($P = 0.019$) but comparable to that in group alprazolam (15 [10, 30]). Cumulative morphine consumption at different time periods and total morphine consumption (mean [standard deviation]) at the end of study period (38.65 [18.04], 39.91 [15.73], 44.29 [16.02] mg in group gabapentin, alprazolam and placebo respectively) were comparable. **Conclusion:** Gabapentin 600 mg does not have significant anxiolytic effect compared to alprazolam 0.5 mg. Alprazolam 0.5 mg was found to be an effective anxiolytic in the pre-operative period. Neither alprazolam nor gabapentin, when compared to placebo showed any opioid sparing effects post-operatively.

Key words: Alprazolam, anxiety, gabapentin, pain, post-operative prevention and control, psychological responses

INTRODUCTION

Anxious patients react differently to anaesthesia and stress of surgery. Larger doses of anaesthetics are required to induce anaesthesia, and associated autonomic fluctuations may ensue.[1-3] Anxiety leads to a surge of catecholamines associated with the stress response leading to tachycardia, hypertension and haemodynamic instability. The relationship between anxiety and pain has previously been identified. Psychological stress, measured over several post-operative days, revealed that anxiety and pain are well correlated.[4] Thus, alleviation of pre-operative anxiety as an adjunct to post-operative pain management seems a promising approach.

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Gabapentin, a structural analogue of gamma amino butyric acid, is used as an analgesic adjunct to reduce the post-operative pain and post-operative morphine consumption. Initially introduced as an antiepileptic, it soon found use in treating neuropathic pain associated with post-herpetic neuralgia, post-poliomyelitis neuropathy and reflex sympathetic dystrophy.[5] Ménigaux *et al*. suggested the anxiolytic effect of gabapentin.[6] A single drug providing pain relief as well as anxiolysis is desirable favouring better perioperative results. Alprazolam, a triazolo-analog of the 1,4 benzodiazepine is a widely used pre-operative anxiolytic drug in anaesthetic practice. There are no studies comparing gabapentin and alprazolam with regard to their anxiolytic properties. Hence, we conducted this placebo controlled study with a primary objective to compare the anxiolytic properties of gabapentin and alprazolam and a secondary objective of evaluating the effects of these drugs on post-operative analgesia.

METHODS

This randomised, placebo controlled study was approved by the Institutional Ethics Committee (Ref: IEC 072/2010) and registered at Clinical Trial Registry, India (Ref: CTRI/2010/091/002830). Seventy five consenting patients belonging to age group 30–65 years and American Society of Anesthesiologists Physical status 1 or 2, weighing 45–85 kg scheduled for elective abdominal hysterectomy with a lower abdominal incision under general anaesthesia were included. These patients were scheduled first in the list in the morning to maintain uniformity in the timing of administration of study drugs to the patients. Patients with major psychiatric disorders, known hypersensitivity to gabapentin/alprazolam/morphine, hepatic or renal disorders, body mass index >35 kg m^{-2}, drug or alcohol abuse, chronic pain syndrome, patients already on analgesic therapy, those unable to understand pre-operative instructions regarding the use of patient controlled analgesia (PCA) and visual analogue scale (VAS) were excluded. Patients were randomised to three groups, group gabapentin, group alprazolam and group placebo, using a computer generated random number table with allocation concealed in sequentially numbered opaque sealed envelopes. Patients received following premedication with sips of water, on the night prior to surgery and 2 h prior to surgery: Group gabapentin – oral gabapentin 600 mg (Capsule Gabantin® 300, Sun Pharma Sikkim, East Sikkim, Sikkim, India); group alprazolam – oral alprazolam 0.5 mg (Tablet Alprax®-0.5, Torrent Pharmaceuticals Limited, Solan, Himachal Pradesh, India); group placebo – oral B-complex forte with Vitamin C 1 capsule (Becosules*Capsules, Pfizer Limited, Navi Mumbai, Maharashtra, India).

The patients and investigators involved in the evaluation of pre-operative anxiety and post-operative pain were blinded to the study drug. The numbered envelope for a patient included in the study was opened by an anaesthesiologist not involved in the study. The respective medication as revealed by the randomisation was prescribed by this anaesthesiologist and administered to the patient by the ward nurse (not involved in the study) the night prior to surgery and 2 h prior to surgery. The patient could see only the tablet or capsule that he received, but not the package from which it was drawn to ensure blinding. Documentation of the drug prescription and administration to the patient in the case record were concealed by opaque tapes to blind the investigators to the study drug, before the patient arrived at the pre-operative holding area.

The VAS was used to measure the anxiety of the patient. During the pre-operative visit (evening prior to surgery), the patients were explained and familiarised with the concept of VAS, comprising of a 100 mm vertical straight line with bottom indicating no anxiety and top indicating maximum anxiety. The pre-operative baseline anxiety of the patient was then assessed on VAS after counselling the patient privately and explaining to them that it was normal to have fear and anxiety about anaesthesia and surgery. We encouraged them not to be hesitant or ashamed to mark their level of anxiety. They were explained that similar VAS scale would be used to assess post-operative pain. Patients were also trained to use the PCA pump during this visit.

Just prior to surgery, in the pre-operative holding area, patients' anxiety was assessed using the VAS. Sedation level was assessed using Ramsay sedation score. Anaesthetic technique was standardised for all the patients. Standard anaesthesia monitoring comprising of pulse oximetry, 5 lead electrocardiogram, automated non-invasive blood pressure were initiated and continued to the post-operative period up to 24 h. End tidal carbon dioxide, train-of-four neuromuscular response and nasopharyngeal temperature were monitored after induction of anaesthesia. Following pre-oxygenation, anaesthesia was induced with intravenous (IV) fentanyl

2 μg/kg and propofol (loss of verbal response taken as end point of induction). Ability to mask ventilate was checked before injecting 0.1 mg/kg of vecuronium for neuromuscular blockade. Following 3 min of ventilation with 1–2% isoflurane in 100% oxygen, trachea was intubated with appropriate sized tracheal tube. Anaesthesia was maintained with isoflurane in 33% oxygen and 66% nitrous oxide aiming a minimum alveolar concentration of 1.3. Vecuronium was repeated as appropriate. Concerned consultant anaesthesiologist started an infusion of morphine at 20 μg/kg/hr through a dedicated IV line, 30 min after induction of anaesthesia and stopped infusion at start of skin closure. Non-steroidal anti-inflammatory drugs, local anaesthetic infiltration of the wound or epidural analgesia were not used as analgesic modalities. In the post-operative anaesthesia care unit (PACU) PCA was started using PCA pump (Graseby 3300 PCA Pump, Graseby Medical Ltd., UK) through the dedicated IV line. A loading dose of 2 mg was set. The demand bolus dose of morphine was set at 1 mg (1 mg/ml) with a lock out period of 10 min. No background infusion of morphine was administered. Only during the 1st h following surgery, the PACU nurse was allowed to give morphine boluses upon patient's request via the PCA pump. Time to first analgesic request was recorded (duration between completion of surgery and request for first analgesic). VAS was used to assess post-operative pain. Pain was assessed at intervals of 1, 2, 6 and 24 h following surgery by the blinded investigator. The ward nurse also assessed the pain every hour, when the patient was not sleeping; and encouraged the patient to use PCA if pain score was ≥4. Total morphine consumed at the end of 24 h was recorded. Sedation level was assessed at each interval. Patients were encouraged to report any side effects experienced by them. Specific enquiry was made regarding nausea, vomiting, dizziness, headache and pruritus. PCA was terminated at the end of 24 h and the subsequent analgesia was managed by the treating gynaecologist.

Data were analysed with SPSS version 11.5.0. Based on the incidence of anxiety scores ranging from 30 to 60 in our pilot study it was estimated that 22 patients have to be included in each group to detect a difference in anxiety VAS score of at least 10 with the power of study being 80% and the level of significance fixed at 5%. To account for drop-out and exclusion, we randomised 25 patients into each group. Anxiety scores and time to first analgesic request were compared between the groups using Kruskal–Wallis test. Anxiety before premedication (on the night prior to surgery) and after premedication (on the day of the surgery just before shifting the patient into the operating room) were compared within the groups using Wilcoxon signed ranks test. Kruskal–Wallis test (a non-parametric test) was applied to compare the VAS pain score between the groups at 1 h because Barlett's test suggested that the differences among the standard deviations (SDs) are significant. At all other time intervals, the SDs were comparable (Barlett's test), and the data had a normal distribution. So, one-way ANOVA (parametric test) was applied. Post-operative morphine consumption was compared using one-way ANOVA. $P < 0.05$ was considered as significant.

RESULTS

The CONSORT flow diagram details the conduct of the study in Figure 1. Patient characteristics and duration of anaesthesia are given in Table 1. Anxiety scores before administering the study drug (on the night prior to surgery) were comparable between the groups ($P = 0.353$). Anxiety scores after the administration of the study drug were also comparable between the three groups ($P = 0.277$). Table 2 depicts the median (interquartile range) anxiety scores in the three groups and the comparison between anxiety scores before and after administering the drug within each group. Only in the alprazolam group, there was a significant decrease in anxiety after administration of the drug, thus confirming the anxiolytic properties of alprazolam. Patients in group gabapentin did not show any significant decrease in anxiety. First analgesic request time was longer in group gabapentin (17.5 min [10, 41.25]) compared

Table 1: Patient characteristics and duration of anaesthesia*

Patient characteristics	*n*=25		
	Group gabapentin	Group alprazolam	Group placebo
Age (years)	43.32 (8.62)	46.12 (9.29)	44.44 (5.55)
Weight (kg)	55.36 (6.72)	55.54 (9.47)	55.52 (7.55)
BMI (kg m^{-2})	24.01 (3.91)	24.23 (4.35)	23.93 (3.32)
Duration of surgery (min)	152.71 (31.83)	160.00 (41.23)	155.00 (41)

*Data are mean (SD). SD – Standard deviation; BMI – Body mass index

Table 2: Comparison of anxiety before and after premedication within groups*

Group (*n*=25)	Anxiety score before premedication	Anxiety score after premedication	*P*
Group gabapentin	21 (7.5, 41)	20 (6.5, 34.5)	0.782
Group alprazolam	35 (15.5, 52)	20 (6.5, 34.5)	0.007
Group placebo	33 (15, 51.5)	26 (17, 46.5)	0.417

*Data are median (interquartile range)

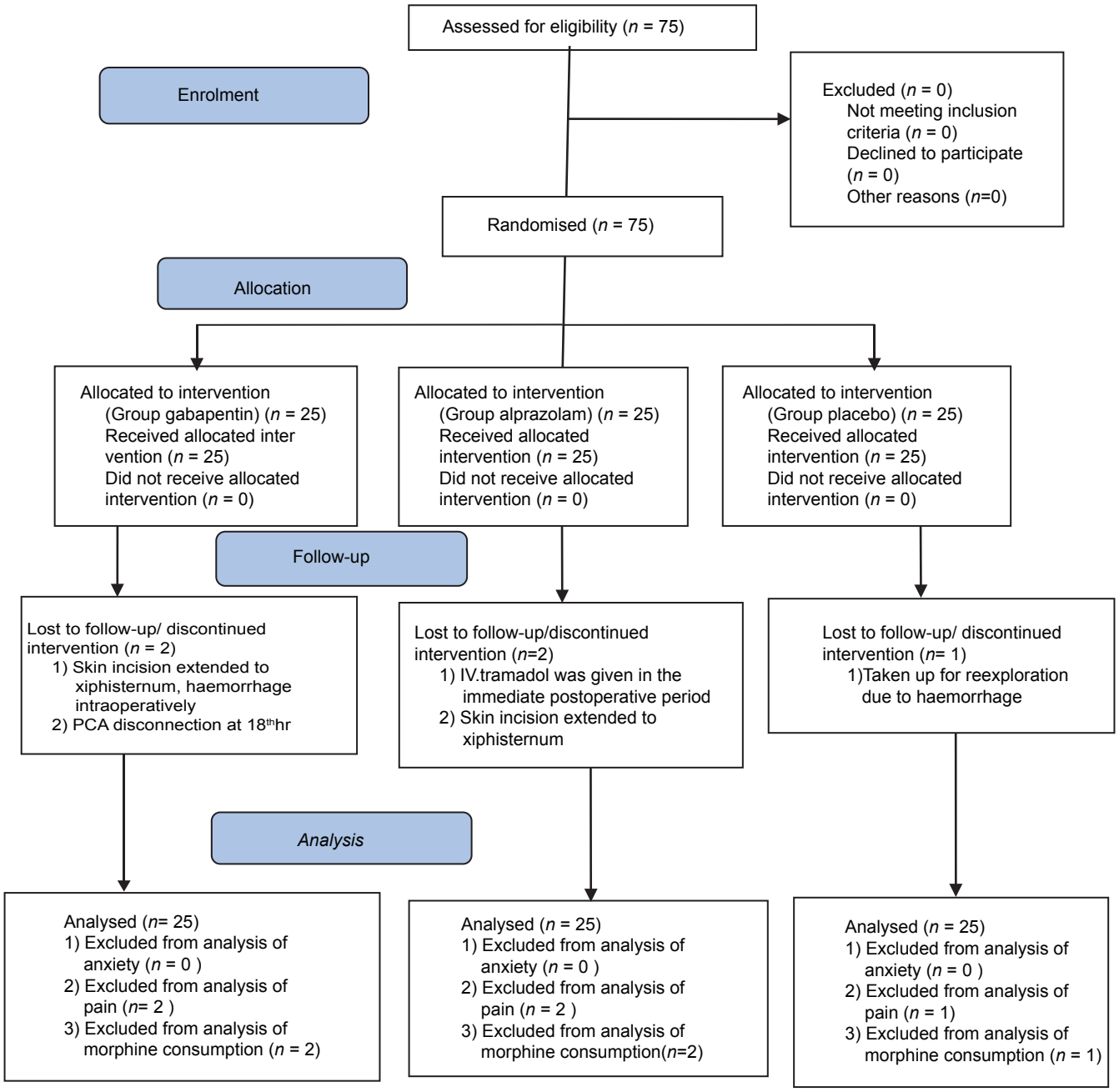

Figure 1: CONSORT 2010 flow diagram

with group placebo (10 min [5, 15]) but comparable to that in group alprazolam (15 min [10, 30]); data are median (interquartile range) $P = 0.019$. VAS pain scores at rest and movement at different time intervals were analysed. There was no significant difference in pain scores at rest and movement at all the time intervals between the groups [Figures 2 and 3]. The mean (SD) of cumulative morphine consumption at the end of 24 h among the three groups, gabapentin 38.65 (18.04) mg, alprazolam 39.91 (15.73) mg and placebo 44.29 (16.02) mg were comparable. None of the groups showed excessive sedation. There was no significant difference in the median sedation scores measured using Ramsay sedation score at the different time intervals among the three different groups [Kruskal–Wallis test, Table 3].

The incidence of side-effects was similar in the three groups.

DISCUSSION

Several studies have shown the utility of gabapentin in decreasing the post-operative analgesic requirements.[7-11] However, the anxiolytic properties

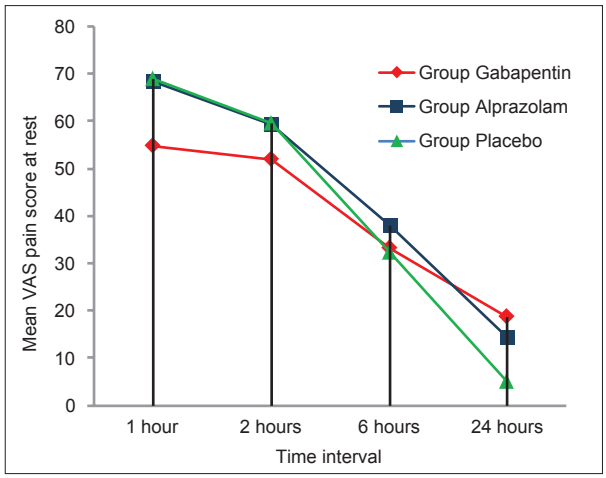

Figure 2: VAS pain scores at rest at different time intervals in the three groups

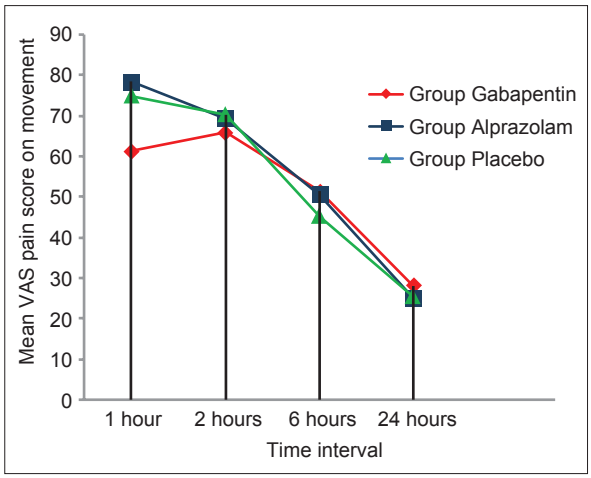

Figure 3: VAS pain scores on movement at different time intervals

Table 3: Sedation level at different time intervals

Ramsay sedation score (h)	Group gabapentin (*n*=23)	Group alprazolam (*n*=23)	Group placebo (*n*=24)	*P*
1	2	3	2	>0.05
2	2	2	2	
6	2	2	2	
24	2	2	2	

Data are median sedation score

of gabapentin are not well documented. Hence, we sought to find an answer to the question 'is there a need to use another anxiolytic when gabapentin is used as an analgesic adjunct?' Although the exact percentage of patients who are anxious pre-operatively is unknown, literature suggests an incidence between 60% and 80%.[12] A sedative drug given as a premedication to relieve fear and anxiety has become common practice. Alprazolam is widely used for pre-operative anxiolysis. Hence, we wanted to evaluate the anxiolytic properties of gabapentin against the commonly used anxiolytic alprazolam in a controlled manner.

We found that gabapentin does not have anxiolytic effects, when compared with alprazolam and is similar to placebo. Only alprazolam was found to have a significant anxiolytic property, when compared with placebo. So, even when gabapentin is used as an analgesic adjuvant starting in the pre-operative period, another anxiolytic drug needs to be used for anxiolysis. Contrary to our findings Ménigaux *et al*. found that gabapentin 1200 mg provided significant anxiolysis compared with placebo in patients of either gender who underwent arthroscopic anterior cruciate ligament repair.[6] Contrary to this, in another study 15 mg oxazepam was found to be more effective in relieving pre-operative anxiety than 1200 mg gabapentin in patients undergoing vaginal hysterectomy.[13] Our study supports this finding that a benzodiazepine is a better anxiolytic than gabapentin. In patients undergoing total hip arthroplasty under spinal anaesthesia Clarke *et al*. found that gabapentin 600 mg did not reduce the pre-operative anxiety compared to a placebo.[14] In a recently published study (published after the completion of our study), the investigators found that gabapentin 1200 mg was effective in decreasing the pre-operative anxiety in highly anxious patients prior to a major surgery.[15] The dosage of gabapentin evaluated in these studies is 600 mg and 1200 mg. Gabapentin has been used in a dose range of 300 mg to 1200 mg in the various studies evaluating post-operative pain in literature.[7-10] The absorption of gabapentin has been found to be inversely related to the dose administered.[16-18] Considering the average body weight of the patients that we come across in our clinical practice and to keep the side effects of gabapentin to a minimum we selected to use this dosage in our study. We had observed unacceptably high sedation in patients administered 1200 mg of gabapentin during our pilot study. The usual dose of alprazolam used for pre-operative anxiolysis is 0.5 mg and we chose the same dosage in our study. Since patients knew that they were receiving a medication to allay anxiety pre-operatively there would have been a possible placebo effect. To eliminate this confounding factor, we included a control group which received a placebo. Anaesthetic technique and intraoperative analgesia were standardised for all the patients and the possible confounding factors like patient gender and type of surgery were addressed by the study design.

Visual analog scale is the gold standard tool to measure post-operative pain. The same tool was used to measure pre-operative anxiety. VAS for anxiety has

been validated against the six-question Amsterdam pre-operative anxiety and information scale and the state portion of the Spielburger state-trait anxiety inventory (STAI). STAI is considered as the gold standard tool for measurement of anxiety, but has an extensive collection of 20 questions.[19,20] We found this tool to be cumbersome and difficult to understand for patients during our pilot study. Hence, we chose the simpler VAS to assess anxiety. The pain scores at all intervals studied and the post-operative morphine consumption were comparable among all the three groups. This refutes the role of gabapentin as a post-operative analgesic adjunct. Our findings support the results of Adam *et al*. who found that a single pre-operative dose of gabapentin 800 mg did not augment post-operative analgesia in patients given interscalene brachial plexus block for arthroscopic shoulder surgery.[21] Similarly, Short *et al*. found that a single pre-operative dose of gabapentin, 300 mg or 600 mg, did not improve post-caesarean delivery pain management.[22]

It is not clear whether this lack of efficacy of gabapentin is due to the lower dose (600 mg) of gabapentin used in our study. The median effective analgesic dose of gabapentin has been found to be 21.7 mg/kg.[23] This dose of gabapentin is higher than the generally used dose of gabapentin in clinical practice. This lower dose of gabapentin that we chose might have been the cause for lack of anxiolytic, opioid sparing effect and post-operative analgesic augmentation effects of gabapentin. At the same time, there are several studies in the literature that have found gabapentin dose of as low as 300 mg to be effective in reducing post-operative pain. No study has established the equipotent doses of gabapentin and alprazolam. Hence, we compared the doses of these drugs that are commonly used in clinical practice.

Patients in our study had low pre-operative anxiety in general. Though there was no selection bias while recruiting the patients for the study (consecutive patients scheduled for elective abdominal hysterectomy were assessed for eligibility irrespective of their anxiety levels) patients in group gabapentin had lower pre-operative anxiety level. Hence, enrolling only a set of patients with a higher level of pre-operative anxiety and evaluating a larger dose of gabapentin in future studies may be required.

CONCLUSION

Only alprazolam as permedication was found to be an effective anxiolytic in the pre-operative period. Alprazolam and gabapentin did not show any opioid sparing effects post-operatively and any reduction in the post-operative pain.

REFERENCES

1. Goldmann L, Ogg TW, Levey AB. Hypnosis and daycase anaesthesia. A study to reduce pre-operative anxiety and intra-operative anaesthetic requirements. Anaesthesia 1988;43:466-9.
2. Williams JG, Jones JR. Psychophysiological responses to anesthesia and operation. JAMA 1968;203:415-7.
3. Tolksdorf W, Schmollinger U, Berlin J, Rey ER. The preoperative psychological state and its correlation to psychophysical parameters important to anaesthesia. Anasth Intensivther Notfallmed 1983;18:81-7.
4. Johnston M, Vogele C. Benefits of psychological preparation for surgery: A meta analysis. Ann Behav Med 1993;15:245-56.
5. Kong VK, Irwin MG. Gabapentin: A multimodal perioperative drug? Br J Anaesth 2007;99:775-86.
6. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394-9.
7. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97:560-4.
8. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, *et al*. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Can J Anaesth 2004;51:986-9.
9. Turan A, Karamanlioglu B, Memis D, Hamamcioglu MK, Tükenmez B, Pamukçu Z, *et al*. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004;100:935-8.
10. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004;51:358-63.
11. Pandey CK, Singhal V, Kumar M, Lakra A, Ranjan R, Pal R, *et al*. Gabapentin provides effective postoperative analgesia whether administered pre-emptively or post-incision. Can J Anaesth 2005;52:827-31.
12. Norris W, Baird WL. Pre-operative anxiety: A study of the incidence and aetiology. Br J Anaesth 1967;39:503-9.
13. Rorarius MG, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R, *et al*. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 2004;110:175-81.
14. Clarke H, Kay J, Orser BA, Gollish J, Mitsakakis N, Katz J. Gabapentin does not reduce preoperative anxiety when given prior to total hip arthroplasty. Pain Med 2010;11:966-71.
15. Clarke H, Kirkham KR, Orser BA, Katznelson R, Mitsakakis N, Ko R, *et al*. Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: A blinded randomized placebo-controlled trial. Can J Anaesth 2013;60:432-43.
16. Vollmer KO, Anhut H, Thomann P, Wagner F, Jahncken D. Pharmacokinetic model and absolute bioavailability of the new anticonvulsant gabapentin. Adv Epileptol 1989;17:209-11.
17. Turck D, Vollmer KO, Bockbrader H, Sedman A. Dose-linearity of the new anticonvulsant gabapentin after multiple oral doses. Eur J Clin Pharmacol 1989;36 Suppl: A310.
18. Richens A. Clinical pharmacokinetics of gabapentin. In: Chadwick D, editor. New Trends in Epilepsy Management: The Role of Gabapentin. London: Royal Society of Medicine Services; 1993. p. 41-6.
19. Boker A, Brownell L, Donen N. The Amsterdam preoperative anxiety and information scale provides a simple and reliable

measure of preoperative anxiety. Can J Anaesth 2002;49:792-8.
20. Kindler CH, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesth Analg 2000;90:706-12.
21. Adam F, Ménigaux C, Sessler DI, Chauvin M. A single preoperative dose of gabapentin (800 milligrams) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. Anesth Analg 2006;103:1278-82.
22. Short J, Downey K, Bernstein P, Shah V, Carvalho JC. A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: A randomized, double-blind, placebo-controlled dose-finding trial. Anesth Analg 2012;115:1336-42.
23. Van Elstraete AC, Tirault M, Lebrun T, Sandefo I, Bernard JC, Polin B, *et al*. The median effective dose of preemptive gabapentin on postoperative morphine consumption after posterior lumbar spinal fusion. Anesth Analg 2008;106:305-8.

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