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Efficacy of Single Dose Oral Gabapentin in Day Care Laparoscopic Surgeries - A Randomized Double-blinded Placebo Control Study

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ABSTRACT

Gabapentin, an anticonvulsant, reduces postoperative pain and has an anti-emetic property by diminishing central sensitisation. We studied the effect of oral gabapentin on the recovery profile of daycare laparoscopic surgeries. One hundred patients undergoing daycare laparoscopic surgeries were randomly divided into two groups: Group G - Gabapentin 300mg and Group P - Placebo tablet was given orally one hour before surgery. General anaesthesia was standardized in both groups. The time taken to achieve a Modified Aldrete score of nine and duration of postoperative analgesia was observed. The Visual analogue score(VAS), hemodynamics, additional intraoperative fentanyl consumption and complications were also recorded. If VAS $\geq$ 3, Paracetamol 1g and if VAS $\geq$ 6, Tramadol 100mg was used. The total consumption of analgesics was noted. The continuous and categorical variables were assessed by unpaired student t-test and chi-square test, respectively. Both groups were demographically similar. The recovery time in the gabapentin group (5.18$\pm$1.53 min) was similar to the control group (5.05$\pm$1.62 min). The duration of analgesia was significantly prolonged in gabapentin (297.4$\pm$120.86 min) than in the control (148.63$\pm$48.92) group. The hemodynamics was significantly reduced during the first hour in the gabapentin group than in the control group. The additional fentanyl requirements, PONV were also significantly reduced in gabapentin while an increased incidence of dry mouth was observed. The use of a single dose of oral gabapentin in laparoscopic surgeries significantly prolonged the duration of postoperative analgesia with similar recovery time, reduced intraoperative fentanyl consumption, better hemodynamic stability and fewer complications.

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INTRODUCTION

Laparoscopic surgeries entail small incisions with minimal post-operative pain, better cosmetic results, shorter recovery time, early enteral feeds, reduced perioperative morbidity, intraoperative bleeding and postoperative respiratory complications. Laparoscopic surgeries have certain demerits, either due to physiological changes during pneumoperitoneum and positioning or risks associated with individual techniques of laparoscopy. [1, 2] Sympathetic stimulation due to laryngoscopy and pneumoperitoneum and pain management forms

the major part of laparoscopic surgery especially done on a daycare basis.

Gabapentin has a structural similarity to gamma-aminobutyric acid (GABA). It has anti-epileptic action, also been shown to lessen pain, opioid requirement and post-operative nausea and vomiting. Gabapentin decreases the stress response to laryngoscopy and intubation by an unknown mechanism. [3] Gabapentinoids lack opioid side effects, decrease anxiety, decreases pain sensitivity and can be used in decreasing the stress response to laryngoscopy and intubation. [4, 5] Hence, we designed our study to compare a single oral dose of Gabapentin (300mg given 1 hour before surgery) with a placebo for recovery in daycare laparoscopic surgeries. The primary objectives were to assess recovery time and duration of postoperative analgesia. The secondary objectives were to compare the intraoperative hemodynamic parameters, additional total fentanyl consumption, and complications, if any.

MATERIALS AND METHODS

After getting institutional ethical committee approval (1228/IEC/2017), this study was registered in Clinical Trial Registry – India (CTRI/2017/12/010776). The informed written consent was obtained from all the patients. One hundred patients of age 18 to 60 with ASA I ASA II scheduled for elective laparoscopic surgeries were included in the study. We excluded patients with hypersensitivity to any drugs, uncontrolled medical diseases (hypertension, bronchial asthma, diabetes mellitus, impaired kidney or liver function), cognitive dysfunction and dizziness, on treatment with gabapentinoids, who had any reaction to gabapentinoids drugs, patients with chronic pain, suicidal depression, [6] pregnancy, ataxia, glaucoma with a narrow-angle, sleep-related respiratory event, respiratory depression, gastric bypass surgery in the past. [7] Computer-generated random numbers obtained corresponding randomization log sheets generated based on one surgeon/surgery combination and two equal groups formed. The patient's information was documented and placed inside the envelope, and sealed. The patients were randomly divided into two groups: Group G patients received Tab. Gabapentin 300mg 1h before surgery with sips of water, and Group P got placebo tablet 1h before surgery with sips of water. Both the tablets were similar, looking to maintain blinding. The patient and the anesthesiologist monitoring the patient were blinded to the study drug.

All the patients received alprazolam 0.5mg orally on the previous night and two hours before surgery. Inj. Glycopyrrolate 0.2mg and ondansetron 4mg IV were administered. Fentanyl 2 mcg/kg was used as the intraoperative analgesic. The patient was induced with propofol 2 mg/kg, atracurium 0.5mg/kg IV and an appropriate size cuffed endotracheal tube was used to secure the airway. The anaesthesia was maintained with desflurane 3-4%, O2/N2O mixture. Inj. Fentanyl 0.5 mcg/kg in bolus doses was given intravenously if there was 20% from the baseline in hemodynamics. The total fentanyl consumption was documented. At the end of the surgery, the patient was extubated after reversal with neostigmine and glycopyrrolate. After recovery from anesthesia, patients were monitored in the post-anesthetic care unit (PACU) for monitoring and discharged. The time taken to achieve a Modified Aldrete score of 9 was taken as the recovery time and was noted. The Visual analogue score (VAS) was monitored at PACU every two hours before discharge. The duration of postoperative analgesia was taken as the time from extubation to VAS $\geq$ 3. Inj. Paracetamol 1g IV bolus was used as rescue analgesic if VAS $\geq$ 3 and tramadol 100 mg IV if VAS $\geq$ 6. The total consumption of analgesics was recorded. The incidence of postoperative nausea and vomiting (PONV) were observed, and ondansetron 4mg IV was used as a rescue antiemetic. The incidence of any other adverse effects was observed.

To detect a 20% difference in duration of analgesia with 80% power and alpha error at 0.05, assuming a standard deviation of 1.5. 43 patients were needed in each group. Assuming 10% drop out, 48 patients were required in each group. We included 50 patients in each group. The normality of the distribution of continuous data was tested using the Kolmogorov-Smirnov test. Graphpad Prism statistical software was used for statistical analysis. Mean $\pm$ standard deviation was used for continuous variables, and an unpaired student t-test was used for analysis. Not normal data were expressed as median with interquartile range and analyzed using the Mann-Whitney U test. Categorical variables were expressed as a percentage and statistical significance was analyzed by Pearson's chi-square. P-value < 0.05 was considered to be statistically significant.

RESULTS

The Consolidated Standard of Reporting trials depicting the passage of patients were given in Figure 1. There was no significant difference in demographic characteristics, and the type of surgeries between the two groups and the results

were tabulated in Table 1. The recovery time in the gabapentin group (5.18 ± 1.53 min) was similar to the control group (5.05 ± 1.62 min). The p-value was 0.6809 and was found to be statistically insignificant. The duration of postoperative analgesia was significantly prolonged in gabapentin (297.4 ± 120.86 min) than in placebo (148.63 ± 48.92 min). The p-value was < 0.001 and was statistically significant.

The difference in heart rate, systolic blood pressure, and diastolic blood pressure were significantly reduced until 30, 40, and 50 min, respectively, in the gabapentin group than in the control group (Figure 2). The additional fentanyl requirement was significantly reduced in the gabapentin than in the control group. In group G, about 46% of patients did not require any additional dose of fentanyl, 28% needed one dose, 20% had two doses, and only 6% required three additional doses. In the control group, 42% of patients required one dose, 40% needed two doses, and 10% required three additional doses of fentanyl. This was statistically significant, with a p-value of 0.028.

There was significant reduction in paracetamol (p-value = 0.01) and tramadol (p-value <0.001) consumption. There was no statistically significant difference in VAS scores and RSS between the two groups (Figure 3, Figure 4). The incidence of vomiting is significantly less in the gabapentin (6%) than control (26%) group. In our study, we had found a significantly higher incidence of dry mouth in the gabapentin (30%) group when compared to the placebo (4%) group. The results were summarized in Table 2.

DISCUSSION

Though Gabapentin has a structural resemblance to GABA, it has no activity at GABA A or GABA B receptors of the brain. Its effects are due to its action via auxiliary subunit of voltage-sensitive calcium channel subunits modulation. Gabapentin modulates glutamic acid decarboxylase (GAD) and the glutamate synthesizing enzyme, branched-chain amino acid transaminase GABA and glutamate synthesis. Gabapentin was found to prolong the duration of postoperative analgesia, reduce opioid consumption, reduce preoperative anxiety and increase patient satisfaction. In our study, we evaluated the efficacy of oral gabapentin for daycare laparoscopic surgeries.

Verret et al. conducted a meta-analysis on 281 randomized controlled trials studying postoperative pain control by using gabapentin in the perioperative period. [8] The pain was assessed at 6, 12, 24, 48, and 72 h after surgery. The results were clinically less significant though statistically significant. In our study, the duration of postoperative analgesia was significantly prolonged in gabapentin (297.4 ± 120.86 min) than in placebo (148.63 ± 48.92 min), which was both statistically and clinically significant during the 24h observation period. They had shown that many studies had associated less postoperative nausea and vomiting. In our study also, vomiting was significantly less in the gabapentin (6%) than control (26%) group.

Liu et al. conducted a meta-analysis on the treatment of acute postoperative pain following spinal surgery following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. [9] They selected sixteen clinical studies and found out that Gabapentin was associated with reduced pain scores at 6, 12, 24, and 48 hours and a reduction in cumulative morphine consumption at 24 and 48 hours. Furthermore, gabapentinoids can significantly reduce the occurrence of nausea, vomiting, and pruritus. These results were similar to our study. In our study, the gabapentin group had a significantly less VAS score when compared to the placebo group. Side effects like nausea, vomiting, and pruritus were significantly less with gabapentinoids which was similar to our study. None of the studies has shown an increased incidence of sedation, dizziness, headache, visual disturbances, somnolence, or urine retention following gabapentinoids usage.

The consumption of analgesics was significantly reduced with oral gabapentin. Chiu et al. conducted a retrospective study on Enhanced Recovery After Surgery (ERAS) in patients who underwent a skin-sparing total mastectomy. [10] In the ERAS pathway, preoperative gabapentin was given along with paracetamol, scopolamine, regional block (pecs or paravertebral block) and intraoperative dexamethasone and ondansetron. This retrospective study compared ERAS group (n=96) patients to retrospective cohort (n=276) patients called the Pre group. Total intravenous anesthesia using Propofol and fentanyl or Hydromorphone was given at the anesthesia provider's discretion. The ERAS group showed significantly lower opioid consumption compared to the cohort (mean ±SD): 111.4 ± 46.0 mg and 163.8 ± 73.2 mg with p < 0.001). The hospital stay was similar between the two groups.

Pandey et al. on 459 patients, compared the preemptive effects of oral gabapentin (300mg) with tramadol (100mg) and placebo. [11] They found that less fentanyl was consumed when gabapentin (221.16 ± 52.39 mcg) was used than in the tra-

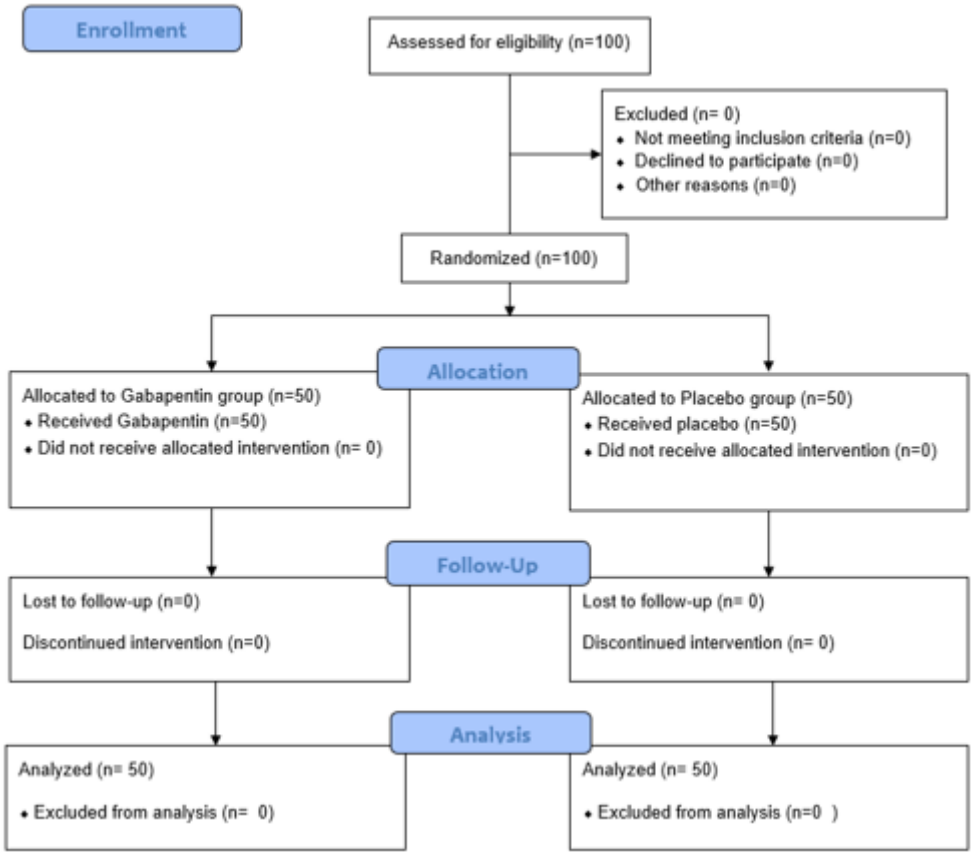

Figure 1: Consolidated Standard of Reporting trials (CONSORT) flow diagram

Table 1: Demographic characteristics

Patient characteristics	Group G	Group P	P-value
Age (years)	37.92 ± 11.83	36.84 ± 5.87	0.564*
Body weight (kg)	66.65 ± 7.46	68.73 ± 8.34	0.054*
Height (cm)	166.34 ± 10.45	164.42 ± 11.23	0.378*
ASA physical status I/II	36/14	33/17	0.668*
Gender (M/ F)	11/39	14/36	0.644*
Mean duration of surgery (min)	89.4 ± 29.23	84.54 ± 24.42	0.369*
Type of surgery (Cholecystectomy/ appendicectomy/ inguinal hernia repair)	12/ 22/ 16	14/ 24/ 12	0.666*

Values are Mean ± SD or number of patients.
Statistical analysis: Continuous data by student t-test, categorical data by chi-square test.
*p-value not significant.

madol (269.60 ± 44.17 mcg) and placebo groups (355.86 ± 42.04 mcg; P < 0.05), which was similar to our study. They had shown significantly prolonged analgesia throughout the study period in gabapentin when compared to the tramadol and placebo groups. In our study, the pain scores (VAS Score) were less during the first eight hours period in the gabapentin group when compared to placebo for 24h, though not statistically significant. They had shown a high incidence of PONV (24.8%) with gabapentin than with tramadol and placebo, which was in contrast to our study.

Siddiqui et al. conducted a retrospective cross-sectional study in the PACU on 228 patients to analyse if gabapentin administration delays the discharge of patients. [12] They were divided into those who received 300 mg (n=108), 600 mg (n = 41) and no gabapentin (n = 139).

They all underwent elective surgical procedures and stayed in PACU for more than two hours. Opioid consumption, respiratory depression and

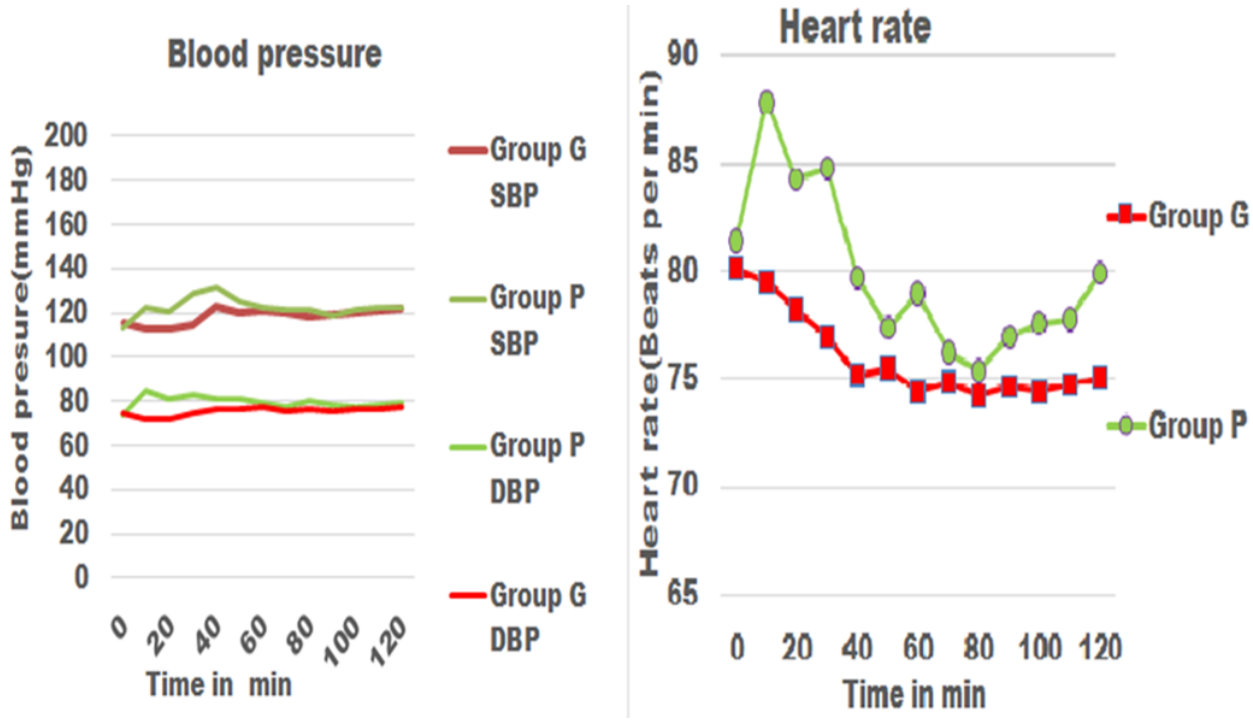

Figure 2: Changes in Heart rate and blood pressure (Values are in mean)

Table 2: Anaesthetic data

	Group G	Group P	P-value
Duration of postoperative analgesia (min)	297.4 ±120.86	148.63 ± 48.92	< 0.001 ŧ
Additional fentanyl requirement (Number of doses)	0=23(46%) 1=14(28%) 2=10(20%) 3=3(6%)	0=9(18%) 1=21(42%) 2=15(30%) 3=5(10%)	0.028 ŧ
Recovery Time (min)	5.18 ± 1.53	5.05 ± 1.62	0.68*
Total paracetamol consumption (Number of doses)	0-14(28%) 1-17(34%) 2-19(38%	0-3(6%) 1-23(46%) 2-24(48%)	0.01 ŧ
Total tramadol consumption (Number of doses)	0-29 1-17 2-4	0-3 1-26 2-21	<0.001 ŧ
Adverse effects:			
Nausea	2 (4%)	11(22%)	0.014 ŧ
vomiting	3 (6%)	13(26%)	0.012 ŧ
dryness of mouth	15(30%)	2 (4%)	<0.001 ŧ

Statistical analysis -continuous variable by student t-test, categorical data by chi-square test.
Values are Mean ± SD or Number of doses, ŧ= Significant p-Value.

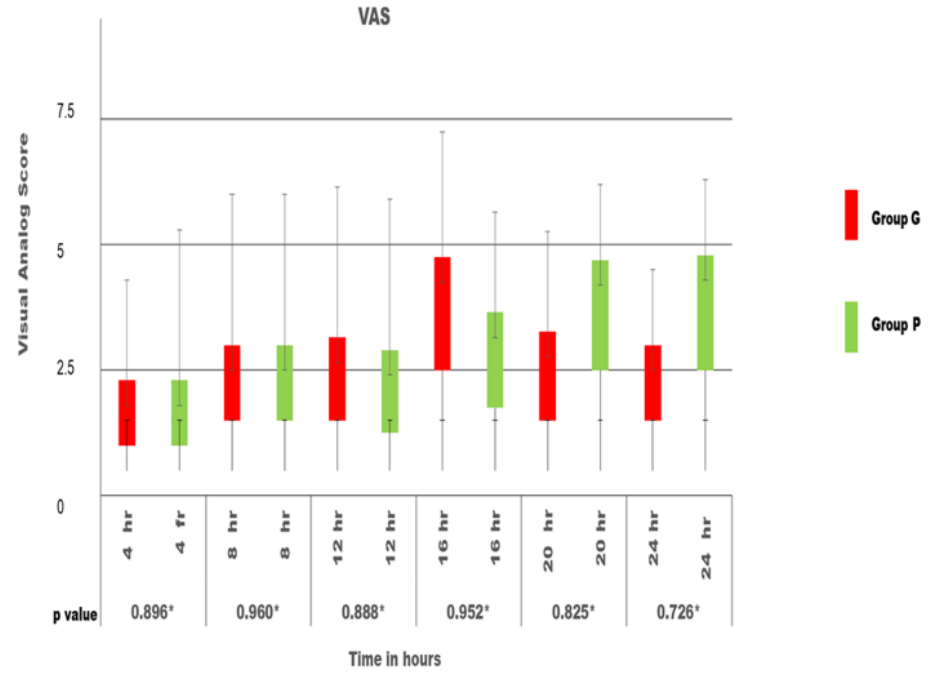

Figure 3: Visual analog scores (*P-value not significant)

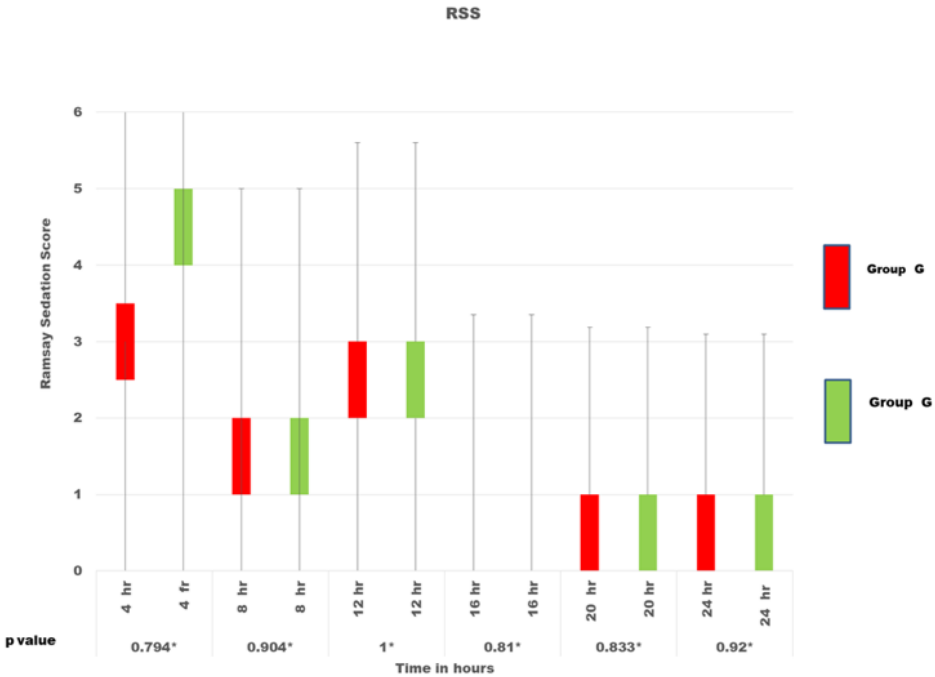

Figure 4: Ramsay sedation score (*P-value not significant)

PONV were similar. Patients who were administered gabapentin had less VAS ($P < 0.001$). There was a dose-dependent depression in consciousness leading to a longer stay in the PACU ($P < 0.001$) in patients who had received 600mg gabapentin. They emphasized that in enhanced recovery after surgery, gabapentin delayed the discharge from the recovery room. In contrast, the PACU stay was not prolonged in our study as we used 300mg of gabapentin.

Wang et al. conducted a meta-analysis on perioperative pain control and PONV on nine studies with 966 patients and showed that the gabapentin group had less VAS score in 12 and 24h, reduced morphine consumption with less incidence of PONV (10% when compared to placebo 48%) similar to our study. [13] Arumugam et al. also, in their meta-analysis of 1793 patients, found reduced consumption of opioids in the first 24h but with no effect on PONV. [14]

Our study had few limitations. First, the sample

size was less to generalize the results. Secondly, the follow-up period of the study was 24h. The more prolonged follow-up would have given us more data. Finally, the comparison of cost-effectiveness between the groups was not done.

CONCLUSION

The use of a single dose of oral gabapentin in laparoscopic surgeries significantly prolonged the duration of postoperative analgesia, better hemodynamic stability, less VAS scores, and fewer complications with no significant change in the recovery time.

Conflict of Interest

The authors declare that they have no conflict of interest.

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