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A Comparative Study between Oral Pregabalin 150mg and Gabapentin 300mg for Postoperative Analgesia in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

This study designed to test the hypothesis that the preoperative use of pregabalin will reduce the consumption of analgesics after laparoscopic cholecystectomy and to compare its efficacy and side effects with that of gabapentin. It is observed that preoperative single-dose pregabalin (150mg) was comparable to gabapentin (300mg) in reducing both the static and the dynamic components of postoperative pain along with postoperative analgesic consumption in subjects undergoing laparoscopic cholecystectomy. A decrease in VAS pain scores was found in patients who received pregabalin one hour before surgery in comparison to patients who received gabapentin. Although pregabalin was found more effective than gabapentin in the present study, usage of both was associated with decreased analgesic consumption. In conclusion, oral Pregabalin 150 mg administered before surgery was effective than Gabapentin 300mg in reducing postoperative pain and postoperative analgesic consumption in patients undergoing laparoscopic cholecystectomy. Gabapentin and Pregabalin, both can be an effective tool in the armamentarium of anaesthesiologist in treatment of postoperative pain. They can be used as part of multimodal therapy if not as sole analgesic.

Keywords: Gabapentin; VAS Pain Score; Pregabalin.

Introduction

Pain is defined by International Association for Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage".

Anaesthesia as a subject by itself originated in an endeavor to offer pain relief to the patient during surgical procedures. But acute pain following surgery has been managed inadequately because of wide variety of myths and fears. The incidence of postoperative pain has been found to be between 25%-76%. This uncontrolled pain in postoperative period has some adverse physiologic responses and effects like delayed recovery and chronic pain. Surgical stimulation is associated with central and peripheral sensitization. Antihyperalgesic drugs improve postoperative pain by preventing the development of central sensitization [1].

Most patients undergoing elective surgery experience pre-operative anxiety which is an unpleasant emotion adversely influencing anaesthetic induction and patient . Controlling anxiety being a modifiable aspect can be considered as a part of treatment of pain.

In the earlier periods analgesia was restricted to surgical and postoperative period. However this was associated with lots of morbidity to the patient in terms of surgical stress and increased requirements for analgesics in the postoperative period which were associated with various adverse effects.

The concept of preemptive analgesia which has been recently introduced is nothing but administering an analgesic drug prior to a noxious stimulus such as surgical skin incision. This analgesic administration is supposed to decrease surgical stress response as well as postoperative analgesic requirements. Primarily, three different classes of drugs are

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utilized for the treatment of postoperative pain (anti-inflammatory, local anesthetics, and opioids). Unfortunately long-term clinical use of these agents is limited by their side effects. Gabapentinoids (Gabapentin & pregabalin) are novel drugs used for the treatment of postoperative pain with antihyperalgesic properties and a unique mechanism of action, which differentiates it from other commonly used drugs.

Gabapentin is a GABA analogue which was introduced as an anti-epileptic (AED) in 1994 and later proved to be effective in neuropathic pain related to post herpetic neuralgia (PHN) [2], post poliomyelitis neuropathy [3], reflex sympathetic dystrophy [4] and diabetic neuropathy[5]. Meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain scores[5,6]. Its unique potency in reducing opioid requirements, prevention of opioid tolerance, enhancing the quality of opioid analgesia, decreased respiratory depression and anxiolysis, make it an attractive drug to consider for control of pain in the post-operative setting. Pregabalin and its developmental predecessor gabapentin were originally developed as spasmolytic agents and adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies [7]. Gabapentin has been found to be useful for neuropathic pain [8] and postoperative pain after breast surgery [9], spinal surgery [10], and laparoscopic cholecystectomy[11]. Similarly, pregabalin has a proven role in treating neuropathic pain [7]. It is claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery, to produce more opioid sparing effect and for amelioration of perioperative anxiety. The efficacy of pregabalin for treating symptoms of generalized anxiety disorder has been demonstrated in several clinical trials [12].

Pregabalin is also a GABA analogue and has anticonvulsant, anti-hyperalgesic and anxiolytic properties similar to gabapentin, but pregabalin has a more appropriate pharmacokinetic profile than gabapentin, including dose-independent absorption and far more potent than gabapentin while producing fewer adverse effects [13]. In recent years, pregabalin has been used widely as an adjunct for the treatment of acute post-surgical pain. Established role of pregabalin as an analgesic adjuvant as a part of multimodal analgesia for acute pain control is in progress [13,14]. There were initial studies showing some evidence that it may have efficacy in acute pain similar to that of gabapentin [15]. However, evidence supporting the postoperative analgesic efficacy of pregabalin is limited to randomized controlled trials in patients undergoing dental surgery [15], spinal fusion surgery [16], laparoscopic hysterectomy [17] and day-case gynaecological laparoscopic surgery [18].

Having looked at these two drugs from different angles and aspects, one comes to this understanding that these multi-purpose drugs have found a strong and reliable place in acute pain service setting. So far, evidence of the analgesic properties of these drugs in postoperative pain is limited to controlled randomized trials conducted in patients of dental pain, minor and day-case gynecological surgery, laparoscopic hysterectomy and hip arthroplasty [19].

This study designed to test the hypothesis that the preoperative use of pregabalin will reduce the consumption of analgesics after laparoscopic cholecystectomy and to compare its efficacy and side effects with that of gabapentin.

Materials and Methods

This prospective study was conducted after approval from Institutional Ethical Committee. Conducted at Department of Anaesthesiology & Critical care, Narayana Medical College, Nellore.

Adult patients 18 and 65 years of physical status American society of Anaesthesiologists (ASA) I and II scheduled for elective laparoscopic cholecystectomy under general anaesthesia from January 2015 to June 2016.

60 patients satisfying all the inclusion criteria were enrolled in the study.

Patients belonging to ASA grade I and II, Adults aged between 18-65 years of both sexes, Weight between 40-80 kg, Patients undergoing elective laparoscopic cholecystectomy under general anaesthesia and Haemodynamically stable patients were included.

Patient who were not willing to participate in the study, Patient with history of uncontrolled concomitant medical diseases (hypertension, bronchial asthma, diabetes mellitus), Patient with acute or chronic renal disease or liver disease, Patient with known neurological disease, Pregnant, lactating and menstruating females, Patients with chronic pain, psychiatric disease, peripheral vascular disease, Patients with known history of hypersensitivity to study drugs, History of drug or alcohol abuse, Patients on sedatives, hypnotics, antidepressants, and drugs with effects on the nervous system, Patient

already taking oral gabapentin or pregabalin, Patients with history of drug or alcohol abuse, Laparoscopic cholecystectomy converted into open cholecystectomy were excluded.

Pre-anaesthetic evaluation was done on the evening before surgery.

Investigations like Hemoglobin estimation, Complete urine routine examination, Standard 12-lead electrocardiogram, X-ray chest / Screening of chest, Random blood sugar, Blood urea, Serum creatinine were analysed.

All the patients received Tablet Alprazolam 0.5 mg night before surgery. Patients were allowed for a period of absolute fasting of 8 hours.

Patients were randomly assigned in to two groups as Group G and Group P with the help of a computer generated table of random numbers.

1 Tablet of Gabapentin (300 milligrams) was given for Group G patients .

1 Tablet of Pregabalin (150 milligrams) was given for Group P patients per oral.

Visual analogue anxiety score was explained to them.

The study drug was given to the patient by the attending anaesthesiologist who was not in the study team, with sips of water 60 minutes before induction in the preoperative ward. The identity of the tablet was not revealed to the patient. No other premedication was given other than the study drugs.

Upon arrival in the operating room, baseline reading of all vital parameters were taken. Then intravenous access was secured by an 18G venous catheter inserted into a peripheral vein and infusion of crystalloids like Ringer lactate was started.

Monitoring of vital parameters like non-invasive blood pressure (NIBP), heart rate, electrocardiogram and Peripheral oxygen saturation (Spo2) was done. For pre-medication, Midazolam 0.07 mg / kg, Glycopyrrolate 0.004 mg / kg and Fentanyl 2mcg / kg were administered intravenously on the table. After adequate pre-oxygenation for 3 min, anaesthesia was induced with Thiopentone 5mg / kg and Vecuronium 0.1 mg / kg and maintained with O_2 & N_2O and Vecuronium 0.02 mg / kg on closed circuit mechanical ventilation. At the end of surgery, neuromuscular block was antagonized with neostigmine 0.05 mg / kg and glycopyrrolate 0.008 mg / kg. Surgeries lasting for more than 1 hr were given a repeat dose of fentanyl 1μg / kg at the end of the first hour of induction. Any increase in the HR and MAP when not settling down by deepening the plane of anaesthesia was managed by giving fentanyl 0.05 μg / kg subsequently. Total duration of the surgery in both the groups was studied.

After tracheal extubation, patients were observed in the PACU (post anaesthesia care unit) for 1 hr and then transferred to the post operative surgical ward. After surgery, pain score was recorded at rest on a visual analogue scale, immediately on extubation (0 h) and at 2, 4, 6, 12, and 24 hours post-operatively. Visual analogue score (VAS), (0-10cm) was interpreted as 0 cm - "no pain" and 10 cm - "worst pain imaginable."

Post-operative rescue analgesia was provided with Injection Diclofenac 75mg intramuscularly for the body weight more than 50kgs and 50mg for the body weight less than 50 kgs. The first dose (Rescue Analgesic) was given when patients experienced pain with VAS score above 3.

Time since extubation to first dose of rescue analgesic, number of doses and total dose of analgesia in 24hrs in both the groups were studied and compared. We avoided opioids like Tramadol, Fentanyl, Pentazocine and Butorphanol because of additive sedative effect they produce.

Any complications like dizziness, somnolence, diplopia, nausea & vomiting, confusion, pain were recorded in first 24 hours of post- operative period.

Results on continuous measurements were presented as Mean and Standard deviation (SD) and results on categorical measurements were described as counts and percentage (%). Student-t test (two tailed, independent) was used to find the significance of study parameters between two groups.

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value: $0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

The SPSS 15.0 Statistical software was used for the analysis of the data.

Results

The mean age of Group G and Group P observed as 47.87 and 48.53 years. 16 females and 14 males were enrolled in Group G and 17 females and 13 males were enrolled in group P respectively. The demographic data revealed that the two groups were comparable in age, gender, weight and ASA status ratios. In 31-40 age group, 7 in group G and 6 in group P were observed. In 41-50 age group, 13 in group G and 11 in group P were observed. In 51-60 age group,

10 in group G and 13 in group P were observed. There was no statistically significant difference between the two groups with regard to demographic data. In ASA I, 20 were Group G and 18 were Group P. In ASA II, 10 were Group G and 12 were Group P. The prevalent weight group was between 61 and 70 kgs in both the groups (Table 1).

There were 9 persons in group G and 6 persons of group G had surgery duration 60-80 minutes. There were 19 persons in group G and 21 persons of group G had surgery duration 81-100 minutes. There were 2 persons in group G and 3 persons of group G had surgery duration 101-120 minutes. There was no statistically significant difference between the groups in Mean duration of surgery (P value > 0.05).

There is no statistically significant difference between the groups in Mean heart rate at baseline, 20min, 40min, 60min, 80min, 100min and 120min.

Table 1: Demographic data

Variables	Group G	Group P	P value
Age (Yrs)	47.87±6.7657	48.53±6.7657	P= 0.7042
Gender (F / M)	16 / 14	17 / 13	
Weight (Kgs)	62.67±7.63537	62.97±7.536	P= 0.8788
ASA Status(I / II)	20 / 10	18 / 12	

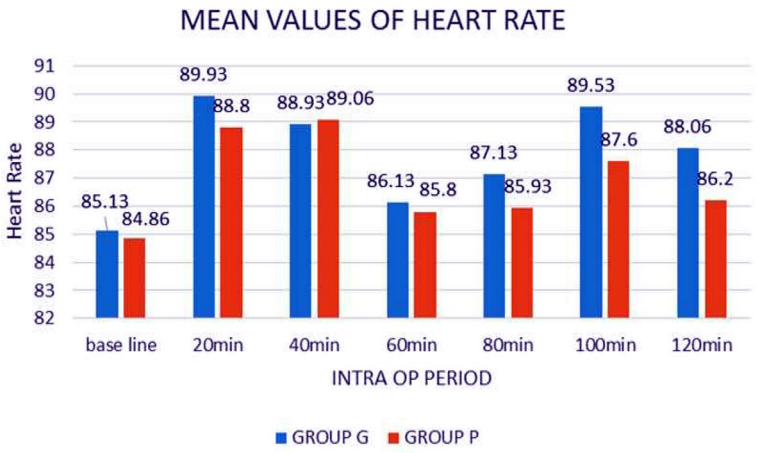

Fig. 1: Changes in Heart rate among two groups

(P value > 0.05) (Figure 1).

There was no statistically significant difference between the groups in mean arterial pressures except at 100min (P value < 0.05)(Figure 2)(Table 2).

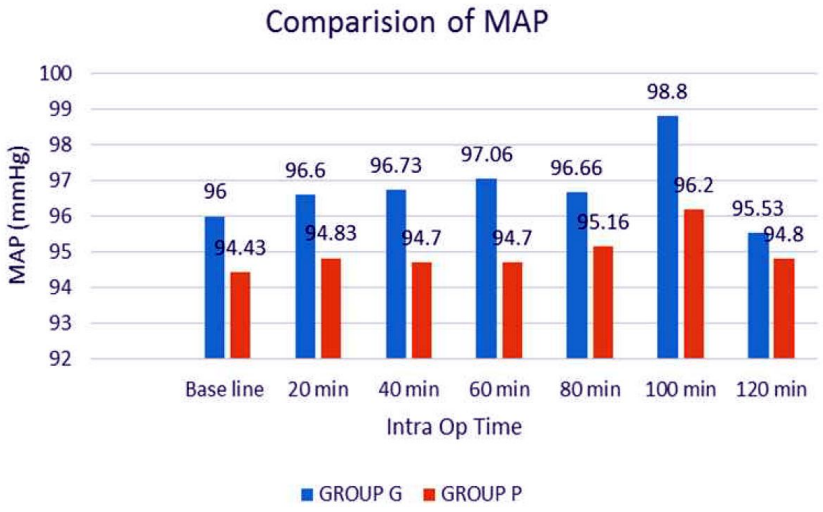

Fig. 2: Comparision of Mean BP among two groups

Table 2: Variations in Mean Arterial Blood Pressure in Two Groups

MAP(mm of Hg)	Group G Mean± SD	Group P Mean± SD	P value
Base line	96±6.335	94.43±9.302	0.449
20 min	96.6±4.598	94.83±6.878	0.2496
40 min	96.73±4.689	94.7±7.423	0.2112
60 min	97.06±5.619	94.7±6.454	0.1362
80 min	96.66±5.188	95.16±5.663	0.2874
100 min	98.8±5.115	96.2±4.254	0.037
120 min	95.53±5.649	94.8±4.978	0.5978

The VAS score in the pregabalin group was less in comparison to gabapentin group except at the six hour, suggesting that the preoperative administration of pregabalin had a more prolonged analgesic effect than gabapentin (Table 3) .

In gabapentin group, more no of patients required first dose of rescue analgesia at 4th hour, so there was decrease in VAS score up to 8th hour.

In pregabalin group, more no of patients required first dose of rescue analgesia after 6 hours, so there was increase in VAS score at 6th hour when compared to gabapentin group (Figure 3).

Table 3: Comparison of VAS score between the Groups

Post op Pain Assessment	Group G (Mean VAS)	Group P (Mean VAS)	P value
0 HR	1.77±0.626	1.76±0.568	0.9484
2 HR	2.6±0.498	2.46±0.507	0.285
4 HR	2.97±0.556	2.86±0.345	0.364
6 HR	2.83±0.98	3.33±0.479	0.0162
8 HR	3.3±0.749	2.96±1.098	0.168
12 HR	2.03±0.999	1.96±0.927	0.7788
24 HR	1.13±0.345	1.16±0.379	0.7486

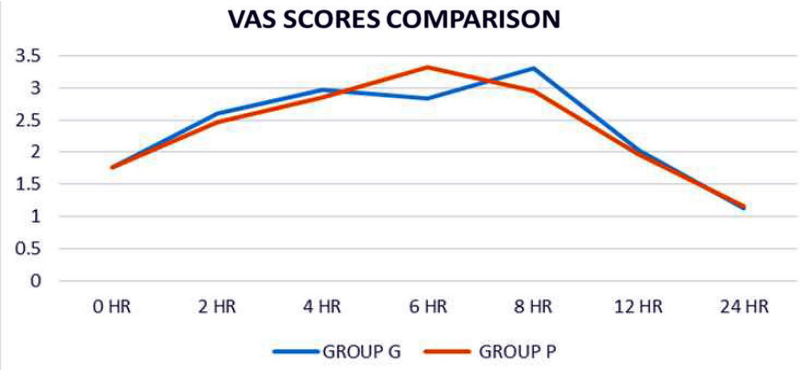

Fig. 3: Comparison of VAS score between the Groups over time.

Table 4: Profile of side-effects

Side Effects	Group G	Percentage	Group P	Percentage
Dizziness	2	6.67%	2	6.67%
Somnolence	3	10%	2	6.67%

The mean duration for first rescue analgesia was more in pregabalin group (7.03448±1.972) compared to gabapentin (7.7037±1.814) group even though there is no statistical significant difference in duration.

The overall Analgesic (Diclofenac) consumption (mg) over 24h in gabapentin group (75±34.114) was more than pregabalin group (70±27.386). But there was no statistical significant difference (P >0.05).

The side-effect profiles were comparable in both the groups (Table 4).

Discussion

Preoperative administration of gabapentin is efficacious for postoperative analgesia, preoperative

anxiolysis, attenuation of the haemodynamic response to laryngoscopy and intubation, and preventing chronic post-surgical pain, postoperative nausea and vomiting, and delirium.

Dose of Gabapentin

Christophe et al., in 2005 showed that premedication with 1200 mg gabapentin improved preoperative anxiolysis, postoperative analgesia, and early knee mobilization after arthroscopic anterior cruciate ligament repair under general anaesthesia [20].

Hurley et al., in 2006 in a meta-analysis on 896 patients concluded that perioperative use of oral gabapentin is a useful adjunct for the management of post-operative pain by providing analgesia through a different mechanism than opioids and therefore would make a reasonable addition to a multimodal analgesic treatment plan [21].

Saraswat and Arora et al., in 2008 studied with single dose of preemptive gabapentin 1200mg and pregabalin 300mg for acute post-operative pain after surgery under spinal anaesthesia. Gabapentin and pregabalin, both have been effective in prolongation of post-spinal analgesia [22].

Most of the previous studies have reported 1200 mg of gabapentin [11, 22, 23]. A study conducted by Ghai A et al. in 2011, compared gabapentin 900 mg, pregabalin 300mg and placebo for pain management after abdominal hysterectomy. Both the drugs are better than placebo [24].

Chandra Kant Pandey et al., compared 300 mg gabapentin with 100 mg tramadol or placebo in a patients with laparoscopic cholecystectomy under general anaesthesia. There was significantly less fentanyl consumption in the gabapentin group than tramadol and placebo group [11].

In our study, we selected 300 mg of gabapentin because the bioavailability of gabapentin is not dose proportional i.e., as dose increases bioavailability decreases. The bioavailability of a single 300 mg oral dose of gabapentin is 60% and for 400 mg is 40% and decreases with an increasing dose and higher doses are associated with adverse effects like sedation and dizziness. This decreases to 35% at steady state with 1600 mg [25].

Dose of Pregabalin

Pregabalin demonstrates highly predictable and linear pharmacokinetics, a profile that makes it easy to use in clinical practice. It is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentration occurring within 1 h after single or multiple doses, and steady state being achieved within 24–48 h after repeated administration. It can be started at an effective dose of 150 mg/day the dose of pregabalin used in the present study. The oral bioavailability of pregabalin is high at ≥ 90% and is independent of dose [26].

The use of pregabalin in acute postoperative pain management has been evaluated in following recent studies. These studies sought to determine whether perioperative pregabalin was effective in reducing postoperative pain and whether it had opioid-sparing effects.

Hill et al., found 300 mg pregabalin to be more effective than 50 mg pregabalin or 400 mg ibuprofen in attenuating pain after dental extraction [27].

On the contrary, in a recent study [19] reported that a single preoperative dose of 100 mg pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery involving only the uterus. The difference in the results from the present study could possibly be because Paech and colleagues administered a smaller dose (100 mg) against the recommended starting dose of 150 mg [18] or because of the difference in the nature of surgery.

Differences in the pregabalin dosages and types of surgery have yielded contrasting results; from the above studies it was considered that the optimum dosage of pregabalin is 150 mg to attenuate the postoperative pain without any adverse effects. So we conducted this study with pregabalin 150 mg. Both drugs, in earlier clinical trials, have been used as a preemptive analgesic and found to be safe and effective.

The administration of drugs 1–2 hours prior to surgery appeared rational in order to attain maximal plasma concentration at the time of surgical stimuli though pregabalin is rapidly absorbed (peak: within 30 minutes to 2 hours) and gabapentin is slowly absorbed (peak: 45 minutes to 2 hours). There is sufficient data supporting the evidence of gabapentin and pregabalin in comparison with placebo in postoperative pain relief in various surgical procedures, but there is paucity of literature regarding controlled studies comparing gabapentin with pregabalin in acute pain states. None of the trials available in literature have compared the efficacy of gabapentin with pregabalin in laparoscopic cholecystectomy.

In our study the groups were comparable with respect to age, gender, body weight, ASA status and duration of surgery. Haemodynamic parameters are

also comparable in both the groups.

VAS Score

In our study, we followed all patients for 24 hr. In gabapentin group more no of patients had early requirement of rescue analgesia around 4th hour compared to pregabalin group which is around 6th hour. The VAS score in the pregabalin group was lesser than gabapentin group till 4th hour but it is not statistically significant (P>0.05). As gabapentin group patients received early rescue analgesia, the VAS score was lesser than pregabalin group around 6th hour. It suggests that the preoperative administration of pregabalin has a more prolonged analgesic effect than gabapentin.

In the study on 90 patients done by Induja Rajendran et al [28], it was observed that preoperative single dose of pregabalin (300 mg) resulted in significant reduction in postoperative analgesic requirement compared to gabapentin (900 mg) and placebo in infraumbilical surgeries under spinal anaesthesia. The VAS scores were significantly reduced in the initial hours of recovery. There was significant difference (P < 0.001) between all groups from first hour to 8 hour. The VAS scores of gabapentin (P = 0.206) at 12 hour was not significantly reduced compared to control. The total VAS score of pregabalin was significantly less (P = 0.023) compared to gabapentin.

Time to Rescue Analgesia

In our study the mean duration of post-operative analgesia in Gabapentin group is 7.03448±1.972 and in Pregabalin group 7.7037±1.814. Time to first analgesic was significantly longer with pregabalin due to its quicker and consistent action compared to gabapentin.

V Saraswat et al. [22] in their study observed that the total postoperative analgesic duration (time from spinal analgesia to first dose of analgesic) was 8.98h in Group G whereas 14.17h in Group P, which was highly significant (P < 0.001)

In our study the total dose of analgesia (Inj diclofenac IM) over 24hrs consumed in gabapentin group is 75 mg ±34.114 and in pregabalin group is 70 mg ±27.386 which is not statistically significant. In gabapentin group, 3 patients received double dose of diclofenac and one patient did not require any analgesia during first 24 hrs. In Pregabalin group only one patient received double dose of diclofenac and 3 patients did not require any of analgesic during first 24hrs. Total dose of analgesic required in gabapentin group was higher than pregabalin group, but it is not statistically significant.

V Saraswat et al. [22], in their study observed that total dose of analgesics i.e diclofenac in first 24h was 62.5mg in Group P and 72.5mg in Group G Although total dose of analgesics in first 24h was less in pregabalin group, but it was not statistically significant (P>0.05).This study is comparable to our study.

Adverse Effects

In our study of 60 patients the incidence of somnolence was 10% (3 patients) in gabapentin and 6.67% (2 patients) in pregabalin groups, similarly incidence of dizziness was 6.67% (2 patients) in gabapentin and 6.67%(2 patients) in pregabalin. The side-effect profiles were comparable in both the groups. The incidence reported in present study is similar to earlier studies.

V Saraswat et al. [22] in their study in 2008 found Somnolence and dizziness are the two most common side effects associated with gabapentin and pregabalin. Six patients in either group experienced somnolence and hence was not significant. Dizziness was experienced in five patients (17%) in gabapentin group as compared to four patients (14%) in pregabalin group, which was again not significant (P<0.05).

Anju Ghai et al., [24] in 2011 compared pregabalin with gabapentin for postoperative pain in 90 patients of abdominal hysterectomy and found that the incidence of somnolence was 40% in pregabalin group, 33.3% in gabapentin group, 3.3% in control group (P = 0.002). Six patients (20%) reported dizziness in pregabalin group, eight (26%) in gabapentin group and one (3%) in control group (P = 0.093).

Conclusion

Oral Pregabalin 150 mg administered before surgery was effective than Gabapentin 300mg in reducing postoperative pain and postoperative analgesic consumption in patients undergoing laparoscopic cholecystectomy. Gabapentin and Pregabalin, both can be an effective tool in the armamentarium of anaesthesiologist in treatment of postoperative pain. They can be used as part of multimodal therapy if not as sole analgesic.

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