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To Evaluate the Effectiveness of Oral Pregabalin during Laparoscopic Cholecystectomy

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I. Introduction

There has been a rapid growth in the interest of Anaesthesiologists in the management of acute pain and postoperative pain[1] over the past few decades.

More focus on procedure-specific effects of Gabapentin in postoperative pain, demonstrated that preoperative Gabapentin reduces 24-h postoperative opioid consumption for patients in abdominal hysterectomy and spinal surgery[2].Pregabalin is a structural analog of gamma aminobutyric acid, which shares some characteristics with its predecessor, Gabapentin. Its mechanism of action is probably the same as Gabapentin but it has a superior pharmacokinetic profile[3].

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 the amelioration of perioperative anxiety. The efficacy of Pregabalin for treating symptoms of generalized anxiety disorder has been demonstrated in several clinical trials.[4,5]

Postoperative pain after laparoscopic cholecystectomy (LC) is the most prevailing complaint.[6] Although, LC is assorted with less postoperative pain compared with the conventional open Cholecystectomy, effective postoperative pain management remains a clinical challenge.[7] Intense acute pain after LC might predict the development of chronic pain e.g., Post Laparoscopic Cholecystectomy Syndrome (PLCS).[8]

Pregabalin is a γ-aminobutyric acid (GABA) analogue that binds to α2 subunits of the voltage-gated calcium channels.[9] The mechanisms of action of Pregabalin is different from either opioids, nonsteroidal anti-inflammatory drugs or local anaesthetics and it may be useful as an adjunct to control post surgical pain.[10]Pregabalin is rapidly absorbed orally with bioavailability of 90%, attains peak plasma levels within 30 min to 2 h and shows linear pharmacokinetics.[11] It has an elimination half-life estimated to range from 5.5 to 6.7 hours, which is independent of the dose and frequency of administration[12]

Pregabalin has been investigated in laparoscopic surgery patients for postoperative pain relief and analgesic consumption with variable results.[13] Study using low-dose Pregabalin shows limited analgesic benefit and those with higher dose in various combinations, found it to have an analgesic and opioid sparing effect but associated with an increased incidence of side effect.[14]

The aim of this study is to evaluate postoperative analgesic benefit in patients administered with oral Gabapentin or Pregabalin as premedication for laparoscopic cholecystectomy under general anaesthesia and to compare their postoperative efficacy with respect to increase in duration of analgesia, reduction in postoperative pain scores, total postoperative requirements of analgesics, study side effects and complications, if any attributable to these drugs.

II. Materials and Methods

The study was prospective, randomized placebo control study. Data was collected from 60 ASA I and II patients scheduled for laparoscopic Surgeries aged between 20 – 50 years at Katuri Medical College and Hospital, Guntur. Both study group and control were selected from these patients. The study was conducted over a period of eighteen months. The patients satisfying inclusion criteria were randomly allocated into two groups each containing 30 patients. Computer based randomization was done.

Inclusion criteria

1. ASA I and II patients
2. Both genders
3. Age 20-50yrs

Exclusion criteria
1. Pre-existing cardiac disease
2. Known case of Systemic Hypertension
3. Renal dysfunction
4. Hepatic dysfunction
5. Anticipated difficult intubation
6. Patient refusal
7. Allergic to any of the study drug

Materials
1. Pregabalin tablet 100mg
2. Placebo tablets
3. Drugs- Injection Midazolam, Injection Glycopyrrolate, Inj Fentanyl, Inj.propofol, Inj. Vecuronium, Inj. Neostigmine, Isoflurane, emergency drugs, Normal Saline and Ringer Lactate.
4. Monitors- ECG, NIBP, SPO2, EtCo2.

Pre - anaesthetic Evaluation
1. History
2. Clinical examination
3. Relevant investigations
4. Informed consent from patients

Pre- anaesthetic medication was given with Tab Ranitidine 150 mg and Tab Diazepam 10 mg the night before surgery. Patients were randomly allocated into two groups.

- Group 1– Those who receive placebo tablets (sugar pills).
- Group 2- Those who receive Pregabalin tablets (100 mg)

The tablets given orally with sips of water 60 mins before induction of general anaesthesia. Before administration of oral premedication, each patient's baseline heart rate, systemic blood pressure, diastolic blood pressure and mean arterial pressure and SpO2 recorded. After shifting the patient to the operation table SpO2, NIBP, ECG monitors were attached. The baseline values were recorded. IV access was established. Inj.midazolam 0.05mg/kg and inj.glycopyrrolate 0.01 mg i.v. given and patient pre-oxygenated for 3 minutes. Anaesthesia was induced with inj.propofol 2mg/kg, inj.fentanyl 2 microgram/kg and inj.vecuronium 0.1 mg/kg. Proper sizecuffed PVC endotracheal tube was inserted orotracheally. Anaesthesia was maintained with NitrousOxide 67%, Oxygen 33% ,isoflurane 1% and intermittent doses of inj.vecuronium and inj.fentanyl. Ventilation was controlled mechanically and was adjusted to keep ETCO2 between 30 to 35 mm of Hg. The intra abdominal CO2 pressure was kept between 12 -14 mm of Hg. Hemodynamic instability was defined as "Heart rate and blood pressure fall or rise more than 15% from baseline" and was treated accordingly. Systemic arterial pressure including the systolic, diastolic and mean arterial pressure, heart rate, SpO2 were recorded. Post operative pain and sedation of the patient was monitored for 6 hours using the visual analog scale and the Ramsay sedation score respectively. Pain quantification was done on a modified Visual Analog Scale score between 0 and 10 (0 = no pain to 10 = worst imaginable pain. Descriptive statistics like frequencies, percentages, mean and standard deviation were calculated. Un paired test was the test statistic used and p value at <0.05 is considered statistically significant. Microsoft excel 2013 and SPSS version 16 were used for statistical analysis.

III. Results

The mean age of the control group was 37.53 ± 8.36 and Pregabalin Group was37.73± 8.832. There was no significant difference between the 2 groups. (P>0.05). In the control group and Pregabalin group majority of the study participants were female 60% and 56.7% respectively. In the Control group 60% with ASA Grade 1 where as 53.3% in the Pregabalin group. The parametric data of pregabalin and control group baseline data was calculated. There was no statistically significant difference between the two groups. (P>0.05). Mean and Standard Deviation of Heart rate among the study group and control group were calculated. Since the p value of heart rate pre op, AI 1 min, AP 1 min, AP 5min, AP 15 min, AP 30 min, AP 45 min, and AE are lesser than 0.05, there is significant relationship between the group 1and 2 and the variable. Mean and standard Deviation of SBP among the study group and control group were calculated. Since the p value of Systolic blood pressure pre op, SBP AI 1 min, SBPAP 1 min, SBP AP 5 min, SBP AP 15 min, SBP AP 30 min, SBP AP 45

min and SBPAE are lesser than 0.05, there is significant relationship between the group 1 and 2 are variable. Mean and standard Deviation of DBP among the study group and control group were calculated. Since the p value of Diastolic blood pressure pre op, DBP AI 1 min, DBPAP 1 min, DBP AP 5 min, DBP AP 15 min, DBP AP 30 min, DBP AP 45 min andDBP AE are lesser than 0.05, there is significant relationship between the group 1and 2 and the variable. Mean and standard Deviation of MAP among the study group and control group were calculated and there is significant relationship between the two groups. There is a significant relationship between the VAS score of group 1 and 2. A significant relationship between the Sedation score was observed between the two groups. 3 (10%) study participants in the control group presented with nausea where as 5(16.66%) in the Pregabalin group presented with nausea 3 (10%) study participants in the control group presented with Vomiting whereas 5(16.66%) in the Pregabalin group presented with Vomiting. 3 (10%) study participants in the control group presented with drowsiness whereas 13(43.33%) in the Pregabalin group presented with drowsiness.

IV. Discussion

Haemodynamic changes during laparoscopic surgery is attributed to the stress response to pneumoperitonium. We studied sixty patients of both sexes coming to Katuri Medical College & Hospital for elective Laparoscopic surgeries. The patients were randomized in to two groups to receive placebo tablet in group I and 100 mg of Pregabalin in group II about 60 mins before induction of anaesthesia. Patients were observed for intraoperative heart rate, systolic BP, diastolic BP and mean BP. Hemodynamic instability was defined as heart rate and blood pressure fall or rise not more than 15% from base line.

Pregabalin is effective in producing intra operative hemodynamic stability as compared to the control group by blunting the stress response to pneumoperitoneum but the hemodynamic stability is better with pregabalin group, which itself is better than placebo group. The pain scores were significantly reduced in pregabalin groups when compared to the placebo. The visual analogue scale for pain at rest was comparable with placebo group, which points out to no improvement in the quality of analgesia with Pregabalin premedication. This finding is in contradiction with the observation made by Jokela.Rand colleagues that VAS score was lesser in patients who received 150mg Pregabalin with 800mg Ibuprofen, which indicates better quality of analgesia.[15] This difference could be because of difference in the rescue analgesic method used. With multimodal analgesia the quality of pain relief could have been better in this study.The sedation score is higher in Pregabalin group when compared to placebo group. Intraoperative fentanyl requirement is more with placebo group than pregabalin group. Drowsiness is more with Pregabalin group than placebo. Post operative nausea and vomiting incidence was similar in all groups. This study showed that an oral premedication dose of oral dose of pregabalin100 mg attenuated the hemodynamic stress response produced by Laryngoscopy and Pneumoperitonium in patients undergoing Laparoscopic surgeries. It showed that oral Pregabalin 100mg produced better hemodynamic stability than oral placebo.Intra operative opioid requirement and postoperative pain score was reducedin pregabalin than placebo group. The sedation score was high with pregabalin group than placebo. Post op drowsiness was more with Pregabalin group than placebo. This study concluded that oral premedication with Pregabalin 100mgproduces better hemodynamic stability in laparoscopic surgeries than placebo group. Pregabalin has significantly reduces intraoperative and post operative analgesic requirements without significant post operative respiratory depression. Mathieson concluded that 300mg pregabalin reduced postoperative morphinerequirement by 50% but with greater sedation, nausea and vomiting.[16] whereas in our study 100mg Pregabalin reduced the post operative fentanyl consumption. Pregabalin lacks GABAnergic activity which explains the lack of optic nerve toxicity.[17] Pregabalin has got the novel mechanism of action on alpha 2delta subunit of neuronal calcium channels which helps in blunting the release of excitatory neuro aminoacids. Although the exact mechanism of attenuation of hemodynamic response to laryngoscopy and intubation by Pregabalin is not known, this must be because of calcium channel blocking caused by pregabalin. Gabapentin reduced catecholamine release from adrenal chromaffin cells.[18]Calcium channels are not completely blocked to the influx of calcium, but the calcium is not able to facilitate vesicular fusion. In the method done, this study observed that premedication with 100mg pregabalinan hour before induction as a single dose attenuated hemodynamic response to laryngoscopy and tracheal intubation. It produced pre-operative sedation without prolonging the recovery from general anaesthesia in patients undergoing abdominal surgery. Preoperative pregabalin 100mg reduced patient controlled fentanyl requirement in the first 12hours after surgery.

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