

EFFICACY OF ORAL PREGABALIN AS PRE-MEDICANT IN ELECTIVE-LAPAROSCOPIC INTRAABDOMINAL PROCEDURES: A CLINICAL DISCUSSION

Authors

Dr. Sanath Kumar S G

Specialist

Cloud physician Healthcare Pvt Ltd

Bangalore, Karnataka, India.

Dr.Varghese Zachariah K

Consultant,

Sultan Qaboos Cancer Care centre,

Muscat, Oman.

Dr. Priyanka Pushpavathi

Consultant

Bangalore Baptist Hospital

Bangalore, Karnataka, India.

I. INTRODUCTION

Preemptive analgesia is a continuously evolving concept. Preemptive analgesia has the following three definitions: It is defined as the treatment that “(1) starts before surgery; (2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and (3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covering the period of surgery and the initial postoperative period).”⁽¹⁾

Similarly, in the field of surgery, laparoscopy has evolved over decades as an option to reduce the postoperative pain and the duration of stay in hospital. Laparoscopic intra-abdominal, surgeries are associated with stress response due to peritoneal insufflation, sympathetic stimulation due to hypercarbia, in addition to the intubation response. The pain associated with laparoscopy can be due to various factors. Mainly, the source of pain is the port site, the inflammation due to the stretch of the peritoneum and residual pneumoperitoneum^(3,4). So, even laparoscopic surgeries are still associated with considerable amount of postoperative pain and it is extremely important that this pain be controlled effectively.⁽⁵⁾

An ideal premedication drug should relieve anxiety, produce amnesia and sedation, decrease secretions, prevent nausea and vomiting and suppress hemodynamic responses to laryngoscopy and intubation. Benzodiazepines are the most commonly used premedication.⁽⁶⁾ With evolving concepts in premedication, it has now been extended to cover

intra-operative and post-operative pain. But It is of concern that benzodiazepines provide only amnesia and sedation, without analgesia.

Pregabalin, a gabapentinoid, is a time proven drug in treating chronic neuropathic pain. It is structural analogue of Gama amino butyric acid (GABA), acts on presynaptic voltage gated calcium channels and inhibit the release of excitatory neurotransmitters in central nervous system and peripheral nervous system. Also, had shown a clear reduction in post-operative opioid requirements and sedative effect ⁽⁷⁾. It may also provide better hemodynamic stability in laparoscopic surgeries and hence, lead us to newer uses of pregabalin in addition to preventive analgesia.

Though the starting dose of pregabalin for chronic pain is 75mg, for acute pain, the safest dose with maximum efficacy has not been determined. White PF et al in his study, demonstrated an increase in sedation levels with increase in pregabalin dose to 300mg. however, analgesia property has not been studied ⁽⁸⁾. We had taken up a clinical study to look for an alternative premedication to the conventional diazepam, with an added property of intraoperative hemodynamic stability and post-operative analgesia. Premedication with such properties can be useful in decreasing the incidence of chronic post-surgical pain.

II. MATERIALS AND METHODS

The study was Randomized open label trial performed in operating theatres of Bangalore Baptist hospital which is a referral hospital for a period of 3 years by including 88 patients of either gender, aged between 18 to 65 years, Patients posted for elective laparoscopic intra-abdominal surgeries and under American Society of Anaesthesiologists (ASA) grade I and II patients.

Pregnant, lactating women, the patients with history of Alcohol or drug abuse, chronic pain and on long term analgesics or opioids, psychiatric disease with inability to comprehend pain assessment, patient on antiepileptic drugs and anti-depressants were excluded from the study. The patients with known or been tested positive presently for pregabalin test dose were also excluded.

All patients who were posted for elective laparoscopic intraabdominal surgeries, fulfilling the above- mentioned criteria during the pre-anesthetic consultation, were explained about the study. Written informed consent was obtained from them. Patients were shifted into the Operation Theatre, one hour before surgery. The recruited participants were block randomized by a computer-generated random number sequence into one of the two groups, Group PG received Four tablets of Pregabalin 75mg, one hour before surgery. Group-D received One tablet of Diazepam 10mg, one hour before surgery

All other premedication orders were as per the standard protocol. Sedation scoring was done by the principal investigator using Ramsay sedation score at 15 min, 30min and 60 min after administration of the drugs in the preoperative holding area. All baseline vital parameters were also noted in the preoperative holding area prior to the administration of study drugs

Standard preoperative anesthetic procedures were done, and all the patients received standard intraoperative anesthetic care.

Plan for first rescue analgesic in the recovery room was:

VAS Score between 3-5: Inj diclofenac 75mg in 100ml NS iv infusion was given, VAS score >5: fentanyl 0.5mcg/kg was given. Ramsay sedation score of 1: Midazolam 1mg iv was given
Nausea or vomiting: Inj ondansetron 0.15-0.2mg/kg will be given

If pain did not decrease (VAS ≥ 3) in thirty minutes or had already received rescue analgesic, it was followed by Inj. Pethidine 0.5mg/kg iv, given by the ward nurse, repeated every fifteen minutes till relief obtained.

III. IMPORTANT OBSERVATIONS AND DISCUSSION

Recent studies have shown that pregabalin is effective in acute pain also. Anudeep Saxena et al, have conducted a study which showed lesser stress response for intubation and peritoneal insufflation in the patient who received pregabalin. Also, studies by Rajesh Meena et al, and Godret et al,^{9,10} showed a better post-operative analgesia in those who received pregabalin.

The age wise distribution of the enrolled patients between the two groups were similar and the variation was not statistically significant.

Similarly, the gender distribution between the two groups were equal with 36 females and 8 males in each group. However, females (81.8%) were represented more in this study than males (18.2%). This could be because of the types of surgeries considered in this study, with gynecological laparoscopic surgeries forming the bulk, and, the need for laparoscopic cholecystectomy being higher in females. Hence, the profile of drugs obtained by this study is better applicable to females than males.

IV. STRESS RESPONSE TO INTUBATION

The heart rate (in beats per minute) following intubation in group pregabalin (PG) increased from baseline of 80.32 to a high of 85.39, which was statistically significant with a pvalue of 0.031. then it reduced to below the baseline i.e. 77.39 at 5minutes, which was suggestive of statistical significance. It continues to drop further to 72.61 till 15minutes post intubation which was statistically highly significant. However, in diazepam group (D), though the heart rate increased from baseline 81.27 to at one-minute post intubation, and further increased to 82.86 at three minutes post intubation, none of this rise was statistically significant but at no point of time was the heart rate difference between the two groups was statistically significant.

Our results are similar to that in the study conducted by Anudeep Saxena et al,¹¹ which also showed an immediate statistically rise in heart rate in heart rate in all the groups while diazepam group showed a sustained raise in heart rate for a longer time than in diazepam group. However, our results contrast with the study by Meena Rajesh et al,⁹ in which the rise in heart rate was less in the group which received pregabalin 300mg compared to the group which received diazepam, and, our study showed a significant drop in heart rate

in pregabalin group (PG) which was not there in their study. Also, in their study, the difference in heart rate between the groups receiving diazepam and pregabalin 300 mg were statistically significant while in our study it was not statistically significant.

1. Systolic Blood Pressure and Diastolic Blood Pressure: Although there was sharp fall in both SBP and DBP at 5th and 15th minute in Pregabalin and Diazepam groups respectively, there was no statistically significant difference in the values between the two groups at any point of time.

Unlike our results, in the study conducted by Anudeep Saxena et al,¹¹ there was a statistically significant rise in mean arterial pressure in the group receiving diazepam, which came back to baseline only at fifteen minutes post intubation, while in the group receiving pregabalin 300mg, the rise in heart rate was not statistically significant and reached baseline value at three minutes post intubation.

Also, our results, are in contrast to the results of the study by Rajesh Meena et al,⁹ in which the mean arterial pressure was significantly high for the entire fifteen minutes post intubation in the group which received diazepam, while in the group which received pregabalin 300mg, the rise in mean arterial pressure became statistically insignificant by ten minutes and almost reached baseline by fifteen minutes. Also, unlike in our study, the difference in mean arterial pressure between the two groups was significant throughout the fifteen minutes.

Hence, the ability of pregabalin to blunt the hemodynamic perturbations following intubation seems to be equivocal compared to diazepam. Though there was a small rise in vital following intubation in group pregabalin (PG), It was not significantly high compared to that in diazepam group (D) but in group pregabalin (PG), there was more profound decrease in vitals with progress of time, which was also not statistically significant.

This difference in results between our study and the studies conducted by Anudeep Saxena et al and Rajesh Meena et al^{11,9}, is probably because of the difference in the protocol of induction. Both the studies used Inj. Fentanyl citrate 1mcg/kg and Inj Thiopentone Sodium 3- 5mg/kg, while we used Inj Fentanyl citrate 2mcg/kg and Inj Propofol 1-2mg/kg. this higher dose of opioid and the usage of propofol against thiopentone sodium could be the reason for the pattern of hemodynamics obtained.

Our results in intra-operative hemodynamics contrasts with that obtained by Anudeep Saxena et al,¹¹ who demonstrated minimal rise in vitals compared to baseline in the two groups which received pregabalin, while the rise in vitals in the group which diazepam was significantly higher. This disparity could be due to, firstly, two doses of pregabalin been given preoperatively in their study while in our study a single dose was administered. Secondly, use of vasopressors and atropine been more in the pregabalin group, might have falsely given a higher mean value for the vitals. Also, we use isoflurane for maintenance of anesthesia intraoperatively, while Anudeep Saxena et al used sevoflurane for the same.

2. **Post-operative Analgesia:** Time for first rescue analgesia was highly statistically significantly lower in the pregabalin group (PG) than in the diazepam group(D). We also analyzed the type of first rescue analgesic required, which would indirectly suggest the severity of break through pain. We found that more patients in the pregabalin group (PG) received paracetamol as first rescue analgesic than that in the diazepam group(D). Also, more patients in diazepam group(D) received diclofenac or fentanyl as first rescue analgesic than that in the pregabalin group (PG). thus, higher analgesics was required in the diazepam group (D) and this was suggestive of statistical significance. We could not find any study comparable to our study which had analyzed time for first rescue analgesic or type of first rescue analgesic.
3. **VAS scores:** VAS scores at various points of time post extubation was statistically highly significantly high at most of the time in group diazepam (D) than in group (PG). only at sixty minutes post extubation, the VAS score was higher in pregabalin group (PG) than in the diazepam group(D). This could be because the patients in pregabalin group (PG) had not received any analgesia for a longer time than those in the diazepam group(D) who had already received their first rescue analgesic.

Our results with respect to VAS scores is comparable to that in the study by H. Bornemann-Cimenti et al.¹² in which they have used average NRS score. Even they have demonstrated a lower average NRS score in the first 48 hours in those who received pregabalin than those who received placebo. Rajesh Meena et al. also demonstrated a lower VAS score in immediate post-operative period in those who received pregabalin 300 mg than those who received diazepam. In another study by Godret et al,¹⁰ VAS scores analyzed at different intervals post operatively till 24 hours, showed a consistently lower VAS scores in the group which received pregabalin compared than that which received placebo, and it was statistically highly significant.

4. **Post-operative opioid requirements:** Also, requirement of Fentanyl in the recovery room was statistically significantly lower in the pregabalin group (PG) than that in the diazepam group(D). also, post-operative pethidine requirements in terms of number of doses was higher in the diazepam group than in the pregabalin group. However, this was not statistically significant.

This finding is in accordance with the study by H. Bornemann-Cimenti et al¹² who has demonstrated a statistically significant lower piritramide consumption in first 48 hours in those who received pregabalin than those who received diazepam.

5. **Perioperative sedative scores:** We found that patients in the pregabalin group (PG) had lower sedation scores preoperatively than that of diazepam group(D). this is in contradiction to the results in the study by Anudeep Saxena et al.¹¹ who found higher pre-operative sedation scores in the patients who received pregabalin. In our study, majority of PG group had RSS of 2 whereas D group had RSS of 3, preoperatively, which was statistically significant. When compared to 30 min post administration of study drug, at 60 min, there were more patients with RSS of 3 in PG group. Even though the onset time of both drugs was 30-60 min, we had given only single dose of the drugs but 10mg of Diazepam whereas in other studies, drugs were given at night and morning of surgery and the dose of Diazepam was 5mg.

However, we found higher sedation scores in the pregabalin group (PG) post operatively up to 60 minutes post extubation than in the diazepam group(D). It could be due to the higher dose of PG used in our study which could have prolonged the duration of sedation.

Inference: On analysing the outcome of our clinical trial and the other studies, we found that the efficacy of Pregabalin in decreasing the stress response to laryngoscopy and intubation as well as in maintaining the intraoperative hemodynamics issimilar to Benzodiazepines. Pregabalin is superior even in providing postoperative analgesia and sedation.

REFERENCES

- [1] Kissin I. Pre-emptive analgesia. *Anaesthesiology* 2000;93:1138-43.
- [2] Kehlet H: Controlling acute pain—role of pre-emptive analgesia, peripheral treatment, balanced analgesia, and effects on outcome, *Pain* 1999—An Updated Review. Edited by Max M. Seattle, IASP Press, 1999, pp 459–62
- [3] Gilron I, Vandenberg E, Katz J, et al. Evaluating the association between acute and chronic pain after surgery: impact of pain measurement methods. *Clin J Pain* 2017;33:588-594. [PubMed]
- [4] Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A. Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1994; 79: 152– 154.
- [5] Gilron I, Vandenberg E, Katz J, et al. Evaluating the association between acute and chronic pain after surgery: impact of pain measurement methods. *Clin J Pain* 2017;33:588-594. [PubMed] Jaap vuyk et al., *Miller's Anaesthesia*, 8th edition, pg 837-838
- [6] Li Z, Taylor CP, Weber M, et al. Pregabalin is a potent and selective ligand for $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 calcium channel sub-units. *Eur J Pharmacol* 2011 Sep; 667(1–3): 80–90
- [7] White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: A dose-ranging study. *Anesth Analg* 2009;108:1140-5.
- [8] Asgari Z, Rouholamin S, Nataj M, et al. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: a randomized, double blinded, placebocontrolled, clinical trial. *J Clin Anesth* 2017;38:13–7
- [9] Meena R, Meena K, Prakash S. Study of Attenuation of Cardiovascular Response during Laryngoscopy and Intubation Using Two Different Doses of Pregabalin as Premedication in Controlled Hypertensive Patients- A RCT. *J Anesth Clin Res* 2016;7: 607.
- [10] Saxena A, Gupta P, Chaudhary L. Effect of Pregabalin Premedication on the Laryngoscopic Response and Intra-operative Hemodynamic Variables in Laparoscopic Cholecystectomy: A Randomized Comparison of Two Doses. *Int J Sci Stud* 2016;4(5):75-80.
- [11] Bornemann-Cimenti H, Lederer AJ, Weibora M. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. *Br J Anaesth.* 2012;108:845-849.