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Original Research Article

Effect of oral pregabalin on post operative analgesia in patients undergoing lumbar spine fusion surgeries under general anesthesia

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ABSTRACT

Background: Pregabalin has been used successfully as a component of multimodal analgesia regimen in a variety of surgical procedures. However, side effects such as dizziness and somnolence have been reported especially with doses ≥300mg. We hypothesized that using a lower cumulative dose of oral pregabalin in a divided dosing regimen would lower the incidence of side effects while providing adequate postoperative analgesia in patients undergoing lumbar spine fusion surgery.

Materials and Methods: Seventy adult patients of either sex of ASA 1-3, undergoing lumbar spine fusion surgery under general anesthesia were randomly divided into two equal groups. Group B received oral pregabalin 150mg one hour before induction and 75mg 2 hours after surgery. Group A received oral placebo at the corresponding time points. Pain was assessed using Visual Analogue Score (VAS) at extubation, 2, 4, 6, 12, 18 and 24 hours after surgery.

Results: In the first 24 hours after surgery, the mean VAS scores were significantly lower in Group B (P0.001) at all time points while tramadol consumption for rescue analgesia (P0.001) and postoperative nausea (P0.013) and vomiting (P0.011) were significantly higher in Group A. Preoperative anxiety and sedation scores and postoperative incidence of dizziness and somnolence were comparable between the two groups.

Conclusion: Low dose oral pregabalin preoperatively and postoperatively using a divided dose regimen can be safely used to provide adequate postoperative analgesia with low incidence of side effects after lumbar spine fusion surgeries.

1. Introduction

General anesthesia (GA) is the most common anesthesia technique employed in lumbar spine fusion surgeries. Patients undergoing spine surgeries experience acute pain of high intensity for the first 3 days postoperatively.[1,2] Adequate management of postoperative pain using a multimodal analgesia regimen comprising of opioid and non-opioid drugs, like NSAIDS, benzodiazepines, $\alpha 2$ adrenergic drugs etc.[3] is essential for early ambulation. It also reduces the duration of hospital stay and shortens the time taken for recovery following spine surgeries. However, many of these drugs have side effects like nausea, vomiting, hypotension, pruritus, sedation, respiratory depression, and urinary retention.[2]

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Gabamimetic drugs like gabapentin and pregabalin have been successfully used as a part of the multimodal analgesia technique to attenuate postoperative pain after various surgeries, including spine surgeries like laminectomies and microdiscectomies. Their use has demonstrated lower postoperative consumption of rescue analgesics like fentanyl, morphine etc.[1–9] However, pregabalin has been associated with dizziness and somnolence of mild to moderate severity with most side effects occurring with doses ≥300mg.[1,2]

Our study aims at assessing the efficacy of use of oral pregabalin in a divided dosing regimen- 150mg one hour prior to surgery and 75mg two hours postoperatively, on postoperative analgesia in patients undergoing lumbar spine fusion surgeries.

2. Materials and Methods

After obtaining institutional ethical committee approval (MSRMC/EC/PG-42/2018, dated 27/10/2018) and a written informed consent from patients, the study was conducted in accordance with the Declaration of Helsinki throughout the project. The trial is registered with CTRI with registration number CTRI/2019/10/021725.

Seventy ASA1-3 patients of either gender between 18-65 years undergoing lumbar spine fusion surgeries at our institute were randomly divided into 2 equal groups using a computer generated, block randomization table. This was a prospective, single blinded randomized control trial. The study was done over a period of 8 months from January 2020 to August 2020. Patients with pre-existing liver, renal and cardiovascular disorders, chronic obstructive pulmonary disease, known neurological or psychiatric illness or on neuro-psychiatric treatment, undergoing recurrent spine surgeries, BMI >30 kg/m^2, patients who have received pregabalin in the last 24 hours and who were allergic to the study drug were excluded from the study.

After thorough pre-anesthetic evaluation, patients were pre-medicated with intravenous (IV) pantoprazole 40mg and ondansetron 8mg on the night before surgery and half an hour before being shifted to OT. On the day of surgery, preoperative VAS score for pain was assessed. Vital parameters were recorded in the preoperative room before the study drug or placebo was given. Both sedation and anxiety were assessed 1 hour after giving the study drug, using Ramsay Sedation Scale (RSS). Group A received a placebo given orally with sips of water, 1 hour before induction and 2 hours postoperatively. Group B received pregabalin 150mg given orally with sips of water, 1 hour before induction and 75mg 2 hours postoperatively.

On arrival at the operating room, ASA standard monitors were connected and baseline vitals were recorded. All patients were induced with IV fentanyl 2mcg/kg and thiopental 5mg/kg. Muscle relaxation was achieved with vecuronium 0.1 mg/kg followed by endotracheal intubation with an appropriate size tube and positive pressure ventilation adjusted to an $ETCO_2$ of 28 to 32mmHg and peak airway pressures <25cm of H_2O with a PEEP of 5cm of H_2O. After intubation, patients' eyes and face were covered with cotton pads and patients were positioned prone on Wilson's frame, with head in neutral position over a horse shoe head rest. Before incision, surgical site skin was infiltrated with freshly prepared mixture of 0.125% Bupivacaine 10 cc with 100mcg adrenaline per level of fusion. Anesthesia was maintained on O_2, N_2O and Isoflurane titrated to MAC 1.0 with intermittent doses of vecuronium. Patients in both Group A and Group B were started on dexmedetomidine 0.5μg/kg/hr IV infusion as a part of standard practice in our institute for all patients undergoing lumbar spine fusion surgeries and titrated to maintain MAP between 60-70 mmHg intra operatively. Dexmedetomidine infusion was stopped at the beginning of skin closure. All patients received paracetamol 1gm IV after induction and ondansetron 4mg IV one hour prior to extubation.

The HR, SBP, DBP, MAP and SPO_2 were recorded pre-induction, post induction, post intubation and then every 15 minutes till the patient is shifted to recovery room. Intra operative use of fentanyl, decision of blood transfusion and amount to be transfused was made at the discretion of attending anaesthesiologist.

After completion of surgery, patients were reversed with IV neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg and extubated. In the recovery room, patient's vitals were monitored every 15 minutes for 2 hours and thereafter hourly in the ward for 8 hours. Pain was assessed using Visual Analogue Score at immediate postoperative, 2, 4, 6, 12, 18 and 24 hours after surgery. All patients received paracetamol 1gm IV TID and diclofenac 75mg IV BD for postoperative pain management. The first dose of diclofenac was administered within 30 minutes of shifting to the recovery room. Tramadol 50mg IV was used as a rescue analgesic in patients reporting VAS ≥4 at any time during the first 24 hours after surgery. Total number of doses of tramadol administered and the time of administration were recorded. Incidence of side effects like dizziness, somnolence, nausea and vomiting in the postoperative period were also noted. Data collection was performed by one of the authors blinded to the interventions received by the patient by patient interview, clinical examination and review of clinical records.

2.1. Statistics

Sample size was calculated using nMaster software V2.0 based on a previous study.[1] Assuming a confidence level of 95% and power of 90% to assess a mean difference of 10mm in the VAS score between the groups as significant, sample size was estimated to be 35 in each group.

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements and categorical measurements are presented as mean±SD and Number (%) respectively. Significance is assessed at 5% level of significance. Normality of the data was tested using Kolmogrov-Smirnov test.

Independent t-test was used to compare the baseline characteristics between the groups. Repeated measures for ANOVA were used to compare postoperative pulse and MAP at different times within each group. The significance of study parameters on a categorical scale between the two groups was analyzed using Chi-square test. The Fisher exact test was used when chi-square test assumption had failed. Data was analyzed using SPSS 18.0 (IBM Corporation, Armonk, NY, USA).

3. Results

Of the total 70 patients assessed for eligibility, all patients who were recruited completed the study. Patient baseline characteristics like age, gender, BMI, ASA physical status, preoperative VAS scores for pain and preoperative RSS scores were found to be comparable between the two groups (Table 1). There was no significant difference between Group A and Group B in the estimated blood loss (406.29 ± 130.03 vs 436.29 ± 86.20 ml) (P 0.259)and the duration of surgery (209.57 ± 39.933 vs 205.29± 44.966 min)(P0.675).

Intraoperative pulse was significantly higher at induction in Group B (Pregabalin) and at 285 min in Group A (Placebo). At all other time points the difference in the pulse rates between the two groups was statistically insignificant. Intraoperative Mean Arterial Pressure (MAP) was significantly lower in Group B at intubation, 10 min after intubation, at 195 min and at 210 min. At all other time points, the difference in the intraoperative MAP between the two groups was statistically insignificant.

Postoperative pulse was consistently lower in Group B when compared to Group A at all time points and the difference was statistically significant at 90 min, 2, 3, 6, 7 and 8 hours postoperatively (Figure 1). Postoperative MAP was consistently and significantly lower in Group Bas compared to Group A at all time points up to 8 hours after surgery (Figure 2).

The mean postoperative VAS scores were significantly lower in Group B than in Group A at all time points up to 24 hours postoperatively (P 0.001) (Figure 3). Intraoperatively, the mean fentanyl consumption was significantly lower in Group B (150.86±22.41) when compared to Group A (174.86±32.21) (P 0.001). Postoperative tramadol consumption for rescue analgesia was significantly higher in Group A (P 0.001). In Group A, 30 patients requested for tramadol rescue analgesia with 15 patients (42.9%) receiving 1 dose, 10 patients (28.6%) receiving 2 doses and 5 patients (14.3%) needing as many as 3 doses of rescue analgesic. In Group B, only 5 patients (14.3%) requested for 1 dose of rescue analgesic.

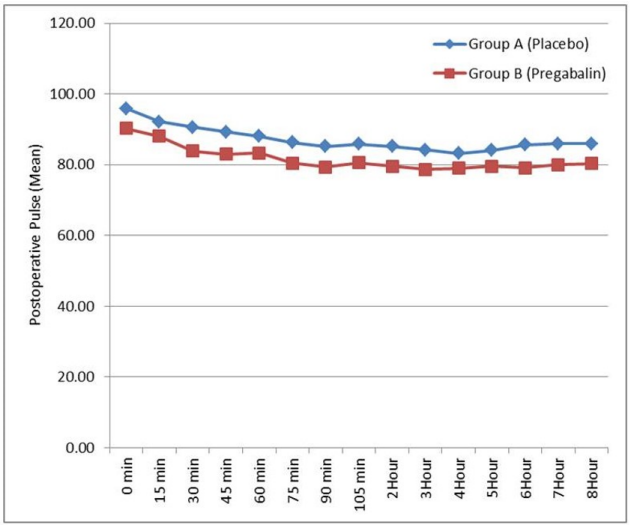

Fig. 1: Postoperative pulse changes

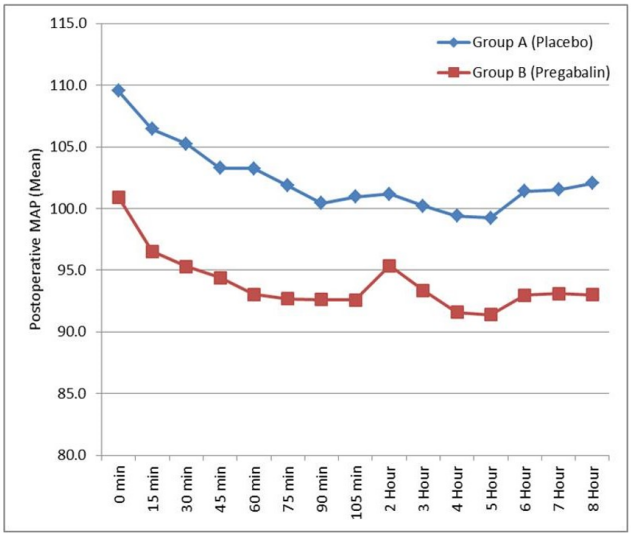

Fig. 2: Postoperative MAP changes

Dizziness was reported by 6 patients in Group B and 4 patients in Group A(P 0.495). Patients in Group A also reported significantly higher nausea (P 0.013) and vomiting (P 0.011) (Figure 4). Somnolence was not reported by patients in either of the groups.

4. Discussion

Our study primarily aimed to evaluate postoperative analgesia with administration of oral pregabalin in a divided dose regimen. Significantly lower VAS scores were seen with pregabalin group up to 24 hours postoperatively. This significantly reduced the need for tramadol as the rescue opioid analgesic in the postoperative period.

Table 1: Patient characteristics. (Data expressed as Mean±SD or numbers (%))

Patient Baseline Characteristics	Group A Placebo (n=35)	Group B Pregabalin (n=35)	P
Age (y)	51.14 ±9.397	50.03 ± 8.273	.600*
Sex (Male/ Female)	20 (57.1%) / 15 (42.9%)	19 (54.3%) / 16(45.7%)	.810Ď
BMI (kg/m^2)	25.89 ± 2.180	25.57 ± 2.933	.613*
ASA Class (1 / 2)	13 (37.1%) / 22 (62.9%)	16 (45.7%) / 19 (54.3%)	.467Ď
Preop RSS (1 / 2)	22 (62.9%) / 13 (37.1%)	15 (42.9%) / 20 (57.1%)	.094Ď
Preop VAS (1 / 2 / 3)	1(2.9%)/ 21(60%)/13(37.1%)	0(0)/20(57.1%)/ 15(42.9%)	.558Ď

*Independent t-test; ĎChi-Square Test

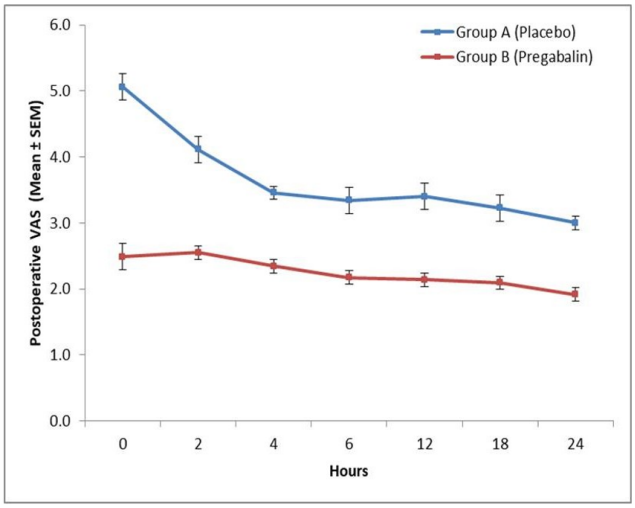

Fig. 3: Postoperative VAS changes

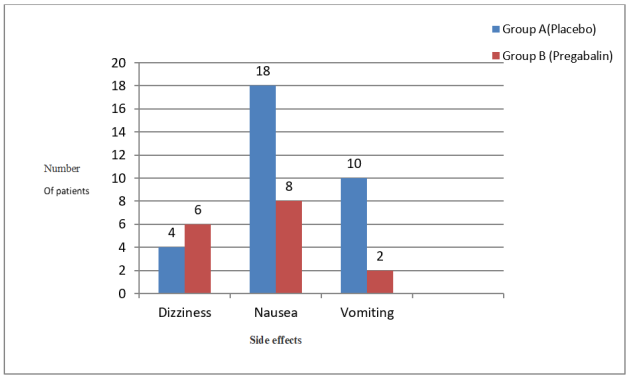

Fig. 4: Incidence of post-operative side effects

Pregabalin is structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid. It binds to presynaptic voltage-gated calcium channels at the alpha-2-delta subunit in central nervous system tissues, hence decreasing the depolarisation induced influx of calcium into neurons and reduces the release of excitatory neurotransmitters which accounts for analgesic effects of pregabalin.

A previous placebo-controlled, randomized trial in patients undergoing posterior lumbar interbody fusion reported similar results with lower postoperative VAS at rest and lower morphine consumption at 48 hours in the pregabalin (150mg)group.[7] A single pre-operative dose of pregabalin 150mg was reported to provide good analgesia with significantly lower VAS score in another randomized, placebo-controlled trial.[1] In the same study, postoperative side effects were found to be significant with pregabalin 300 mg.

Somnolence and dizziness are the most common adverse effect reported shortly after initiating pregabalin. A study by Hiroshi Kato et al.[10] found that age (≧65 years) and co-administration of strong opioids like fentanyl, oxycodone and morphine are the risk factors for somnolence or dizziness during pregabalin therapy. Our study has excluded geriatric age group and also co-administration of strong opioids. We did not find any significant difference in dizziness in pregabalin group but nausea and vomiting were significantly more in placebo groups which we attribute to higher consumption of tramadol used as a rescue analgesic. In our study, the total cumulative dose of pregabalin including preoperative and postoperative administration was 225mg. Side effects like dizziness and blurring of vision known to occur with pregabalin were probably avoided by using a lower cumulative dose and by dividing the dose between the preoperative and postoperative period.

Similar results were reported in a meta-analysis of clinical trials where use of gabapentinoids resulted in lower VAS scores with rest or mobilization at 6, 12, 24, and 48 hours postoperatively and decreased cumulative morphine consumption and morphine-related complications following spine surgery.[2]

Contrary results were seen in a study conducted by Urban MK et al.[11] where they were unable to demonstrate any benefit on prescribing pregabalin to patients undergoing posterior lumbar spinal fusion surgeries.

In the present study, no significant difference was noted in the anxiety and sedation scores between the groups, which was different from the findings of other studies using preoperative administration of pregabalin or other gabapentinoids.

We used dexmedetomidine infusion in both the groups to avoid blood loss intraoperatively, which explained the comparable MAP at almost all times intraoperatively except post induction. Repeat oral administration of pregabalin 75mg along with paracetamol 1g IV TID and diclofenac 75mg IV BD in the postoperative period helped to maintain lower VAS scores up to 24 hours in the study group thereby reducing the requirement of opioid medications.

The high oral bioavailability of pregabalin ensures rapid onset of action. Instead of using a single large dose of pregabalin preoperatively, it appears advantageous to administer it in divided doses during the pre and postoperative period as it prolongs the duration of postoperative analgesia and reduces the incidence of side effects of pregabalin. This also reduces the use of opioid based analgesics for postoperative analgesia and its associated complications.

The present study holds relevance in the field of perioperative pain management of patients with extensive surgical tissue trauma involved in spine instrumentation procedures. There are not many randomized trials on oral pregabalin administration in both pre and post-operative period, for pain management. We did not find any major limitations with our study. Probably, including a larger group of patients would have improved the power of the study.

5. Conclusion

We conclude that oral pregabalin is a safe option to provide acute postoperative pain relief for extended period following lumbar spine fusion procedures.

6. Source of Funding

None.

7. Conflict of Interest

None.

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