Pre-Emptive GABAPENTIN V/S PREGABALIN for Acute Postoperative Analgesia following Abdominal Hysterectomy under Spinal Anaesthesia: A Randomized Double Blind Study

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ABSTRACT

PREGABALIN is a potent ligand for alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system, which exhibits potent anticonvulsant, analgesic and anxiolytic activity. The pharmacological activity of PREGABALIN is similar to that of GABAPENTIN and shows possible advantages .Although it shows analgesic efficacy against neuropathic pain. We investigated its analgesic efficacy in patients experiencing acute pain after abdominal hysterectomy and compared it with gabapentin and placebo for pre-emptive analgesia.

Materials and Method: A randomized, double-blind, placebo-controlled study was conducted in 90 women undergoing abdominal hysterectomy under spinal anaesthesia were selected. Patients received 300 mg pregabalin, 900 mg gabapentin or placebo, 1 hours prior to surgery. Postoperative analgesia was administered at visual analogue scale (VAS) ≥3. The primary outcome was analgesic consumption over 24 hours and time to rescue analgesia, sedation score, side effects as secondary outcomes.

RESULTS: The Diclofenac consumption was statistically significant between pregabalin and gabapentin groups, and pregabalin and control groups The sedation score was statistically significant between pregabalin and gabapentin groups, and pregabalin and control groups. Time to first request for analgesia was longer in pregabalin group followed by gabapentin and control groups.

CONCLUSION: A single dose of 300 mg pregabalin given 1 hours prior to surgery is superior to 900 mg gabapentin and placebo after abdominal hysterectomy. Both the drugs are better than placebo.

Keywords: Abdominal hysterectomy, gabapentin, pregabalin, pre–emptive analgesia, post-operative analgesia,

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INTRODUCTION

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, 1979)[1]. High-quality pain control after surgery is still a major challenge. Although opioids have been the mainstay of postoperative pain management, they are not free from side effects.

A multimodal approach has been suggested to improve postoperative analgesia and to reduce opioid related side effects. Surgical stimulation is associated with central and peripheral sensitization.. Postoperative pain may be considered as a transient type of "neuropathic" pain. The concept of pre-emptive analgesia involves initiating an analgesic regimen before the onset of the noxious stimulus to prevent this central sensitization and limit the subsequent pain experience.[2,3] It has been seen that not only both the drugs provide postoperative pain relief, they also reduce the requirements of other analgesics.[3,4,5,6,7,8]

Pre-emptive Analgesia has been defined as treatment that starts before surgery; prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).[9]

GABAPENTIN and PREGABALIN, are structural analogues of the inhibitory neurotransmitter Gamma-Amino Butyric acid (GABA), but are functionally not related to it. Both drugs were introduced in the treatment of epilepsi, Gabapentin in 1993-94 and Pregabalin in 2004. Anecdotal reports were followed by randomized controlled trials proving these drugs to be useful in treating neuropathic pain like that of diabetic neuropathy, trigeminal neuralgias, post herpetic neuralgia and reflex sympathetic dystrophy. The mechanism of action of Pregabalin is probably the same as Gabapentin but it has a superior pharmacokinetic profile.[6,9]

Pregabalin has an amino acid substitution at third position, which allows increased lipid solubility and diffusion across blood brain barrier, better pharmacokinetic profile and fewer drug interactions due to the absence of hepatic metabolism.[10] It is a potent

and more effective analogue of gabapentin and acts as a better ligand for α2-δ protein subunit than gabapentin.[11] It has shown superior analgesic potency than gabapentin in rodent models of neuropathic pain.[12]

Pregabalin has been found to be equally effective to gabapentin, however, at much lower doses. It is due to much higher bioavailability. Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins.[13,14] This is not true with gabapentin as plasma concentrations have been found to have a nonlinear relationship to increasing doses. The elimination half-life is 5–9 hours.[15]

MATERIALS AND METHOD:

Following approval from our institutional Ethical Committee, informed written consent was obtained from all patients included in this study. Ninety patients of aged between 30 and 60 yr, ASA grade I–II, undergoing Abdominal Hysterectomy and were included in this randomized, double-blind study. After obtaining written informed consent and confirming inclusion and exclusion criteria, 90 Patients were randomly divided into three groups of 30 each. The study was randomized double blind and placebo controlled by slip in Box technique, Group G(n=30) received Oral Gabapentin, 900mg, Group P (n=30) received Oral Pregabalin, 300mg and Group C(n=30) received Oral Placebo capsule 1 hour prior to surgery, with a sip of water respectively.

Patients were explained about premedication, preoperative procedure of spinal anaesthesia, intra-operative management and post operative management. All patients were kept fasting overnight (6-8 hrs) prior to surgery. All Patients were pre-medicated with injection intravenous 10mg METOCLOPRAMIDE, 50MG RANITIDINE AND 0.2MG GLYCOPYRROLATE 1hour before induction. All doses of GABAPENTIN, PREGABALIN and PLACEBO has been given per oral one hour prior to administration of spinal anaesthesia. Patient was preloaded with an intravenous infusion of one litre of ringer lactate solution in preoperative area. Patients were monitored for basal heart rate (HR), respiratory rate,(RR) non invasive blood pressure (NIBP),mean arterial pressure (MAP) peripheral oxygen saturation (SpO2).

Spinal anaesthesia was performed with the patient in sitting position using a 25-gauge Quincke's needle at the L3–4 or L4–5 intervertebral spaces using midline approach. Dural puncture was recognized by the specific click and giving in filling followed by a free and uniform flow of CSF on withdrawal of

stylet. 3ml hyperbaric bupivacaine (0.5%) was administered over 30sec. Patient was turned gently , placed in supine position. After the spinal block, HR,RR, NIBP, MAP and SpO2 were measured every 5 min until operation and then every15 min in post operative period. Time to first complaint of pain and request for rescue analgesia was recorded. Patient's pain was assessed immediate postoperatively, and every two hourly, then at 4, 6, 12, 24 hours by visual analogue Scale (VAS) and dose of rescue analgesic drug was measured during these intervals of time. Patients were monitored till 24 hours.

Patients pain were assessed on 10cm linear visual analogue scale (VAS) for pain, where 0 denotes "no pain" and 10 denotes "worst imaginable pain.'' Any patient with VAS score of more than 3 was administered inj diclofenac 1mg/kg intramuscularly. Time since spinal anaesthesia to first complaint of pain and request for rescue analgesia was recorded. Sedation score was assessed by Ramsay sedation score[16] every two hourly, then at 4,6,12,24 hours. Modified Ramsay sedation score,

- anxious, agitated or restless
- co-operative, oriented & tranquil
- sedated, but responds to commands
- asleep, brisk glabellar reflex or response to loud noise
- asleep, sluggish glabellar reflex or response to loud noise
- asleep with no response to painful stimulus

Statistical method

Proper template was generated for data entry in Ms Excel. Data entry was done and 10% data were randomly checked to assure the quality of the data. Data analysis was done through SPSS (Statistical Package for Social Sciences) software. One way ANOVA (Analysis of Variance) was used to see the significance difference among the groups. Multiple Comparison Analysis was also used to see the significant difference between the groups. Statistical significance was defined as <0.05.

RESULTS: Patients were comparable in all three groups with regard to age, weight and duration of surgery

Table: 1 Demographic data and duration of surgery

	Group G (n=30)	Group P (n=30)	Group C (n=30)	P value
Age(yrs)	41.033±6.57	43.033±6.75	43.26±6.67	0.467
Mean weight(kg)	54.56±9.57	52.10±5.48	53.43±6.11	0.426
Duration of surgery(min)	80.16±3.34	79.16±3.49	81.33±3.45	0.138

Values are mean±SD. No statistical significant difference between the groups (p>0.05)

Table : 2 Comparison of Sedation score**,** Time request for analgesia, total Diclofenac consumption

Parameters	Group G	Group P	Group C	P value
Sedation score	1.76±0.817	3.50±0.508	1.50±0.508).	0.0001
Time request for analgesia (min)	218.00±52.81	372.00±53.20	217.00±26.92	0.0001
Total diclofenac Consumption (inj)	174.66±38.79	103.00±20.36	186.33±38.54	0.0001

Sedation score at time of rescue analgesia was maximum in group P (3.50±0.508) as comparison to group G (1.76±0.817) and group C (1.50±0.508). Time request for analgesia was maximum in group P (372.00±53.20) as comparison to group C (217.00±26.92) and group G (218.00±52.81). Diclofenac Consumption was lowest in group P, as comparison to group C and group G. The mean of diclofenac Consumption in group C was 186.33±38.54 , in group G was 174.66±38.79 and in group P was 103.00±20.36. These findings were both clinically and statistically highly significant. (P < 0.001).

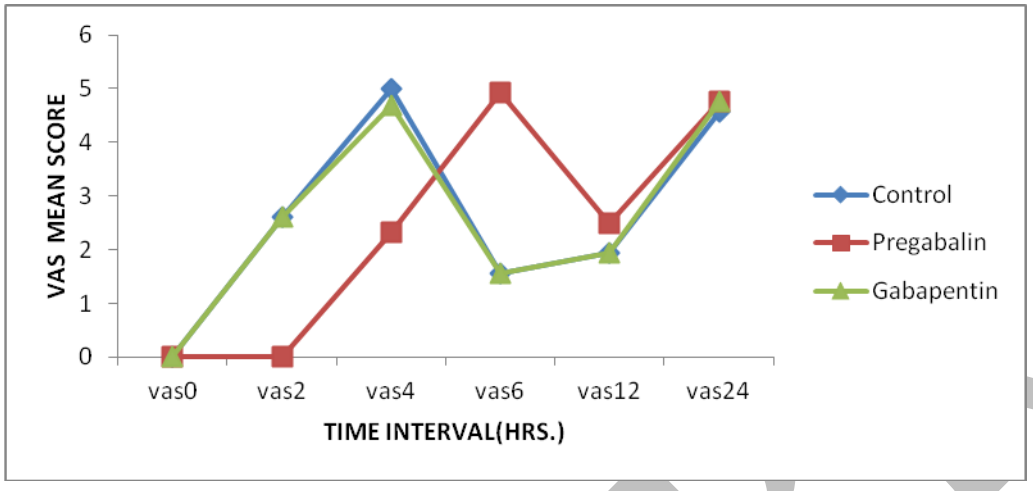

Figure: 1 Mean VAS score in the three groups

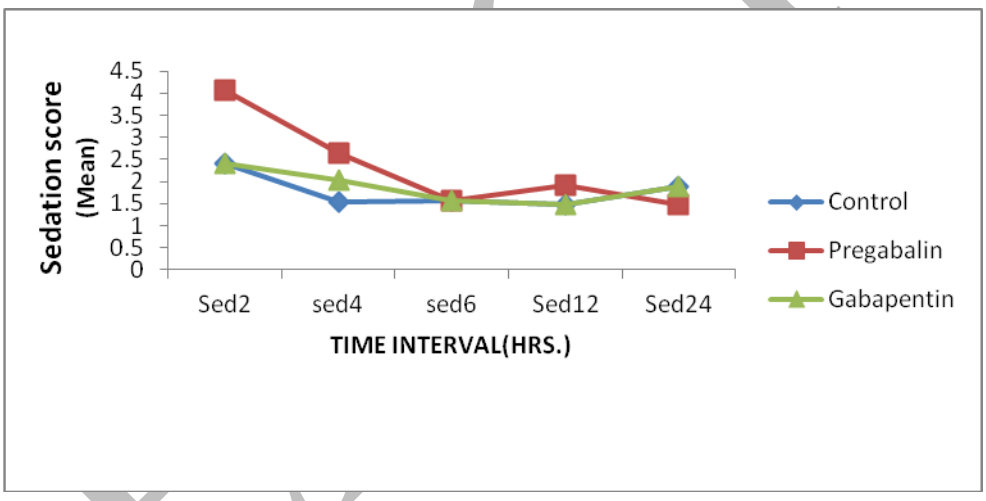

Figure: 2 Mean Sedation Score in the three Groups

DISCUSSION

Acute post-operative pain is an undesirable outcome that can delay functional recovery for patients undergoing surgical procedures. In this study, we have compared the effectiveness of orally administered Gabapentin and Pregabalin as pre-emptive analgesics for post-operative pain relief. We used Gabapentin in a single dose of 900 mg in accordance with a study conducted by **Pandey,C.K. et al.** (2005)[17] they found that Gabapentin 900 mg is the optimal dose for post-operative pain relief following lumbar diskectomy. **Hill *et al*.** (2001)[18] found 300 mg pregabalin to be more effective than 50 mg pregabalin or 400 mg

ibuprofen in attenuating pain after dental extraction.

The time to rescue analgesia was 218.00±52.81 minutes for Gabapentin as compared to 372.00±53.20 minutes for Pregabalin. These were similar to the findings of **Saraswat, V. et al.** (2008)[3] who while comparing the effects of Gabapentin and Pregabalin on post-operative pain after surgery under spinal anaesthesia also found Pregabalin to be more effective than Gabapentin. **Ghai,A. et al.** (2011)**[19]** reported that Pregabalin 300 mg is superior to both Gabapentin 900mg and placebo for postoperative pain relief following abdominal hysterectomy under spinal anaesthesia. **Chang, S.H. et al.** (2009)[20] reported an increase in sedation with 300 mg doses of Pregabalin. **Buvanendran, A. et al.** (2010)[21] also reported increased frequency of sedation in patients receiving Pregabalin preoperatively. **Pandey,C.K et al.** (2005)[22] who al reported an increase in PONV with Gabapentin in a 900mg dose.

CONCLUSION

We compared pre-emptive Gabapentin 900mg, Pregabalin 300 mg and placebo for postoperative pain relief following abdominal hysterectomy under spinal anaesthesia. postoperative analgesia was better with 300 mg pregabalin than 900 mg gabapentin and placebo during the early recovery after abdominal hysterectomy. The major side effect noted was sedation in the immediate post-operative period with both study drugs.. Gabapentin caused an increase in PONV.

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