



Anaesthesiology

PRE-EMPTIVE PREGABALIN AS AN ADJUVANT TO MULTIMODAL ANALGESIA, FOR OPIOID SPARING AND ANALGESIC EFFECTS FOR PATIENTS UNDERGOING LAPAROSCOPIC ASSISTED VAGINAL HYSTERECTOMIES (LAVH), A RANDOMIZED CONTROLLED TRIAL

Jain Amrita*

DNB, PDCC Assistant Professor Department of Anaesthesiology and Pain Medicine, Pt. J.N.M. Medical College & Dr. B.R.A.M. Hospital, Raipur (C.G.)*Corresponding Author

Shah Saurabh

DNB, IDCCM Senior Resident Department of Anaesthesiology and Pain Medicine, JLN Sector 09 Hospital Bhilai, CG

ABSTRACT

Background and aims- Pregabalin is a potent gabapentanoid with analgesic property. Preoperative pre-emptive administration of analgesics prevents central and peripheral sensitisation. Our study aims at studying the effect of pre-emptive administration of pregabalin as a part of multimodal pain regimen, on postoperative pain and opioid requirements in females undergoing laparoscopic gynaecological surgeries. **Materials and methods-** 66 female patients undergoing laparoscopic vaginal hysterectomy participated in this randomized, placebo controlled study. 150 mg of capsule pregabalin was orally administered 1hr prior to surgery along with other premedication drugs in Group P. Patients in the other arm of the study (Group C) received placebo capsules. Anaesthesia was standardised in both the groups. Post-operative VAS score, degree of sedation, time to demand of first analgesic, total frequency and amount of rescue analgesic required, and any side effects such as nausea/vomiting, burping of vision, were recorded for 24hr post-surgery. **Results-** Postoperative mean VAS score at all time periods (0,1,2,3,4,5,6,8, 10,12,16,20and 24hours) in Group P was significantly lower than those in Group C ($p<0.05$). this difference was significant at all time periods except at 5Hr. The mean post-operative sedation score in Group P (2.45 ± 0.50) was more than mean preoperative sedation score in Group C (1.48 ± 0.51 , $P<0.05$). The time to demand of first analgesic in Group P was 7.24 ± 2.06 hours as compared to 2.03 ± 0.77 hours in Group C ($p<0.05$). Total number of doses of rescue analgesia (frequency of rescue analgesia) was significantly less in Group P (0.64 ± 0.99) as compared to Group C (4.09 ± 1.04). Mean total amount Tramadol as rescue analgesic required in 24 hr. was significantly less in Group P (31.82 ± 49.39 mg) as compared to Group C (204.55 ± 52.08 mg). The incidences of side effects in both the groups were very minimal and comparable. **Conclusion:** In patients for LAVH, 150mg Pre-emptive pregabalin oral administration provided better pain relief, increased the duration of analgesia and lesser opioid consumption in first 24 hr. of postoperative period.

KEYWORDS : Laparoscopic surgery, Pregabalin premedication, pre-emptive analgesia.

INTRODUCTION:

Pain following surgery still remains a concern. High incidence of pain has been reported after surgery. 30% patient have reported to have moderate to severe pain following surgery, with higher incidence among female patients. (1) Pre-emptive analgesia and multimodal analgesia are widely used concepts for pain control after surgery. In multimodal analgesia 2 or more types of drugs with different mechanism of action are administered, and when these drugs are administered before the surgical stimulus is defined as pre-emptive analgesia. (2) Aim of multimodal analgesia is to achieve adequate pain control with lesser opioid use, thereby reducing opioid related side effects. Gabapentin and pregabalin can reduce acute pain after surgery, and has also opioid sparing effect. (3)

Materials and methods:

Study design: This was a prospective, randomized, controlled study.

Ethics clearance: Institutional review board clearance and written informed patient consent were obtained.

Inclusion criteria: Sixty six ASA I/II patients aged 30–60 years female patients, scheduled for laparoscopic assisted vaginal hysterectomy under general anaesthesia were included in this study.

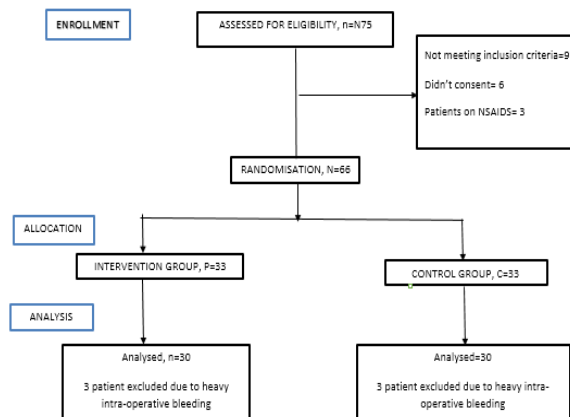
Exclusion criteria: Patients with h/o NSAIDS ingestion in last 24 hrs., on any sedative drugs, psychiatric medications, drug allergy, and pregnant were excluded from the study. All patients were explained about visual analogue scale a day before surgery. All patients were premedicated with oral Alprazolam 0.5mg the night before surgery and at 6 a.m. on the day of surgery.

Randomization: Patients were randomly allocated (using computer-generated number) to receive either pregabalin or placebo. For external uniformity of drugs, pregabalin capsules were emptied and filled with sugar powder to be used as placebo.

- Group P (pregabalin/Study Group): received capsule pregabalin 150 mg 1 h before surgery.
- Group C (placebo/Control Group): received matching placebo 1 h before surgery.

Blinding: Double blinding, both participants and the assessors were blinded of the intervention.

CONSORT FLOW DIAGRAM



Anaesthesia technique was standardized in all the groups. Patients were given injection fentanyl 2micrograms/kg and induced with appropriate dose of propofol. Orotracheal intubation was facilitated by vecuronium 0.08mg/kg IV. Anaesthesia was maintained with inhalational agent sevoflurane with 66% nitrous oxide and 33% oxygen. Intraoperative hemodynamic monitoring was done every 5 minutes and study data were collected every 15 minutes. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05mg/kg IV and glycopyrrolate 0.008mg/kg IV. After satisfactory recovery, the patients were extubated.

Time of completion of anaesthesia was recorded and after the patient became conscious oriented and responding to commands, this time was considered as zero hour for studying postoperative pain. VAS score was noted at this time. Patients were shifted to PACU. In the PACU, patients were assessed via visual analogue scale for pain every hour for 6 hours, then every two hourly for next 6 hours and every four hourly up to 24 hours.

When patient complained of pain for the first time in the PACU that time was noted along with VAS score, if VAS score was ≥ 4 or patient

demand analgesic, injection Tramadol 50 mg bolus were administered as rescue analgesia.

Sedation: was assessed in preoperative and postoperative period (2, 4, 6, 8, 12, and 24) via Ramsay sedation scale.

The Ramsay sedation scale was used to assess sedation. Ramsay sedation scale is as follows:-

1. Anxious, agitated, or restless;
2. Co-operative, oriented, and tranquil;
3. Awake and responds to command;
4. Asleep but has brisk response to glabellar tap or loud auditory stimulus;
5. Asleep but has sluggish response to glabellar tap and loud auditory stimulus;
6. Asleep and no response.

Patients with a sedation scale of ≥ 4 were considered as sedated.

Post-operative pain Assessment: was done by a 10 mm visual analogue scale (VAS). Patients were assessed via visual analogue scale for pain every hour for 6 hours, then every two hour for next 6 hours and every 4 hourly up to 24 hours.

"0" = no pain and "10" = worst pain.

Time for demand of first rescue analgesia, total doses and total amount of injection tramadol 50 mg required in 24 hours were recorded. Side effects and complications: dizziness, blurring of vision, post-operative nausea and vomiting were noted for 24 hrs.

All these outcomes were assessed by an independent anaesthesiologist blinded to group allocation.

Statistical analysis

Considering 5% dropout with $\alpha=0.05$ and 80% power, 66 patients undergoing LAVH were included in the study.

Statistical tools:

Quantitative data was analysed by mean, SD, 't' test. Qualitative data was analysed by Chi square test, Fisher exact test. $P<0.05$ was considered as statistical significance. The statistical analysis was done using SPSS (Statistical packages for Social Sciences) Version 16.0 software.

RESULTS-

Patients whose duration of surgery extended beyond 120 minutes were excluded from the study so sixty patients (thirty in each group) were studied. The demographic data of both the groups were similar and matched for age, weight, duration of surgery and total intra-op fentanyl consumption.

Table 1

	Group C	Group P
Age(years)	45.84 $\pm$ 6.19	44.09 $\pm$ 4.62
Weight (kg)	56 $\pm$ 3	55 $\pm$ 5
Duration of surgery (minutes)	154.54 $\pm$ 20.47	154.24 $\pm$ 19.41
Intra-op fentanyl consumption (μ g)	208 $\pm$ 11	202 $\pm$ 8

(Values are in mean)

Postoperative pain scores(VAS) at all time periods (0,1,2,3,4,5,6,8, 10,12, 16,20and 24hours) in Group P was significantly lower than those in Group C ($p<0.05$).

Graph 1

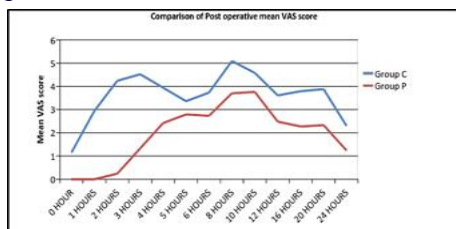


Table 2

POSTOPERATIVE VAS SCORE	Group C		Group P		P VALUE
	Mean	SD	Mean	SD	
0 HOUR	1.15	1.2	0	0	<0.001
1 HOURS	2.94	1.54	0	0	<0.001
2 HOURS	4.24	1.09	0.24	0.44	<0.001
3 HOURS	4.52	0.91	1.33	0.69	<0.001
4 HOURS	3.94	0.9	2.42	1.09	<0.001
5 HOURS	3.36	0.96	2.79	0.96	0.04
6 HOURS	3.73	0.91	2.73	1.31	<0.001
8 HOURS	5.09	1.18	3.7	0.92	<0.001
10 HOURS	4.58	1.41	3.76	1.06	0.01
12 HOURS	3.61	0.83	2.48	1.23	<0.001
16 HOURS	3.79	1.27	2.27	0.88	<0.001
20 HOURS	3.88	1.39	2.33	1.59	<0.001
24 HOURS	2.3	1.21	1.24	0.44	<0.001

The minimum time at which the first postoperative analgesic required was one hour in Group C with the mean time of 2.03 $\pm$ 0.77 hours. However the minimum time at which the first postoperative analgesic required was four hours in Group P with the mean 7.24 $\pm$ 2.06 hours. The time to requirement of first analgesic was significantly delayed in Group P.

All the patients needed analgesic (pain score >4) by 3 hour in Group C and by 10 hour in Group P.

Total number of doses of rescue analgesia (frequency of rescue analgesia) was significantly less in Group P (0.64 $\pm$ 0.99) as compared to Group C (4.09 $\pm$ 1.04).

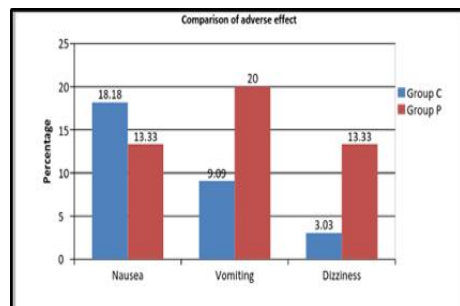
Mean total amount of injection tramadol in milligrams was significantly less in Group P (31.82 $\pm$ 49.39 mg) as compared to Group C (204.55 $\pm$ 52.08 mg) ($p<0.001$).

Table 3

	GROUP C	GROUP P	P value
TIME OF REQUIREMENT OF FIRST ANALGESIC	2.03 $\pm$ 0.77 HOURS	7.24 $\pm$ 2.06 HOURS	$P<0.05$
MEAN TOTAL NUMBER OF DOSES OF RESCUE ANALGESIA	4.09 $\pm$ 1.011	0.64 $\pm$ 0.96	$P<0.05$
MEAN TOTAL AMOUNT OF RESCUE ANALGESIA	204.55 $\pm$ 50.56 mg	31.82 $\pm$ 48.12 mg	$P<0.05$

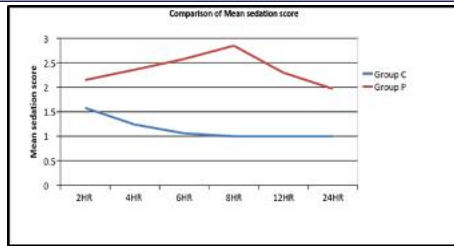
The incidences of side effects in both the groups were very minimal and comparable. Pregabalin 150 mg did not cause significant side effects as compared to placebo.

Graph 2



It was observed that post-operative sedation score at 2, 4, 8, 12 and 24 hours in the Group P was more as compared with Group C. The difference was statistically significant but none of the patient in intervention group was deeply sedated to require any intervention during study period.

Graph 3



DISCUSSION

Perioperative use of gabapentanoid provides better pain relief and decreases opioid consumption. Our results of this study are consistent with the results of the meta analysis by Peng et al and Hurley et al. (4)(5) patients who receive pregabalin preoperatively had better pain relief for prolonged period with less requirement of rescue analgesics and without any increase in side effects.

LAVH is performed by more and more centres as day care surgery, and better pain relief with less side effects is desirable in such subset of patients. Pain after laparoscopic gynaecological procedures may range from mild to severe. Visceral pain and incisional pain may be intense on the day of surgery (6)

Oral pregabalin premedication has been used as an adjunct in laparoscopic cholecystectomy with decrease in VAS score at rest and decreased morphine consumption in post-operative period (7)(8)

Jokela et al conducted RCT to evaluate analgesic efficacy of two doses of Pregabalin 300mg and 600 mg where the incidence of side effects were higher in patients who received 600 mg of pregabalin. Post-operative opioid consumption was less in pregabalin group (9)

In another study by Jokela et al, evaluated quality of analgesia with 75 mg and 150 mg Pregabalin in day care laparoscopic gynaecological procedure. The authors found better analgesia with 150 mg Pregabalin premedication. However they didn't find any difference in decrease in post-operative opioid requirement (10)

The main findings of our study are, 150 mg oral Pregabalin administration in women undergoing laparoscopic hysterectomy provides better post-operative pain relief, less frequency and amount of rescue analgesic requirements with delayed time to demand for first dose of rescue analgesia. These benefits were not associated with any increase in side effects or hemodynamic in stability. Our results are in consistency with the results of previous studies by Jokela et al.

This study was conducted in patients undergoing LAVH, randomisation, blinding and allocation concealment was followed properly.

Limitations: The calculated sample size of our study is 66 with power of 80%. Further studies are required with higher power and better sample size to prove the efficacy of pregabalin as part of multimodal analgesia package. We didn't followed up the patients beyond discharge from hospital to find out the incidence of chronic pain, and whether single dose of pre-emptive pregabalin has any effect on it. Further studies are required with follow up methods up to 6 month to find out effect of pregabalin in post-operative chronic pain in patients undergoing LAVH.

CONCLUSION

Single dose oral administration of Pregabalin may be considered in patients undergoing LAVH for better acute pain control. However, its effect on prevention of chronic pain needs further investigation.

Financial support and sponsorship: Nil

Conflict of interest:

REFERENCES

1. Elaqoul A, Obaid A, Yaqup E, Shahan I, Arraqap A, Alshatnawi I, et al. Postoperative Pain Among Patients After Day-Case Surgery. *Plast Surg Nurs*. 2017;37(4):130–6.
2. Rosero EB, Joshi GP. Preemptive, Preventive, Multimodal Analgesia. *Plast Reconstr Surg*. 2014 Oct;134(4 Suppl 2):85S–93S.
3. Rai AS, Khan JS, Dhaliwal J, Busse JW, Choi S, Devereaux PJ, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: A systematic review and meta-analysis of randomized controlled trials. *J Plast Reconstr Aesthetic Surg*. 2017 Oct;70(10):1317–28.
4. Peng PW, Wijesundera DN, Li CC. Use of Gabapentin for Perioperative Pain Control – a Meta-Analysis. *Pain Res Manag*. 2007;12(2):85–92.

5. HURLEY R, COHEN S, WILLIAMS K, ROWLINGSON A, WU C. The Analgesic Effects of Perioperative Gabapentin on Postoperative Pain: A Meta-Analysis. *Reg Anesth Pain Med*. 2006 May;31(3):237–47.
6. Choi JB, Kang K, Song MK, Seok S, Kim YH, Kim JE. Pain Characteristics after Total Laparoscopic Hysterectomy. *Int J Med Sci*. 2016;13(8):562–8.
7. Li S, Guo J, Li F, Yang Z, Wang S, Qin C. Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy patients. *Medicine (Baltimore)*. 2017 May;96(21):e6982.
8. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth*. 2008 Nov;101(5):700–4.
9. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative Gabapentinoids. *Anesthesiology*. 2013 Nov 1;119(5):1215–21.
10. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth*. 2008 Jun;100(6):834–40.