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A randomized placebo controlled trial on evaluation of the efficacy of two different doses of pregabalin as a pre-emptive analgesia in gynaecological surgeries

Priti M. Patel[1*], Rakesh D. Panchal[2], Bipin M. Patel[3]

[1]Assistant Professor, [2] Resident (MD), [3]Professor & HOD, Dept. of Anaesthesia, Gujarat Cancer & Research Institute, Civil Hospital Campus, Ahmedabad, Gujarat

***Corresponding Author:**
Email: doctorpreetipatel@gmail.com

Abstract

Background: Pre-incisional analgesia has been shown to be more effective in control of postoperative pain by protecting central nervous system from deleterious effects of noxious stimulus and resulting allodynia and increased pain. Anti-hyperalgesic and antiallodynic properties of pregabalin improve postoperative pain by preventing the development of central sensitization. This study was designed to compare the efficacy of two different doses of Pregabalin with that of placebo in reducing post-operative pain, analgesic requirement, prolongation of analgesia and side effects.

Method: Ninety female patients of ASA grade I & II undergoing gynaecological surgeries were randomly divided in three groups of thirty each. Patients received Pregabalin 150 mg (P_1), Pregabalin 300 mg (P_2) and placebo (P_0) one hour before surgery. Post-operatively parameters observed were visual analogue score (VAS) and sedation score, time to first analgesic requirement, total analgesic consumption and side effects for first 24 hours.

Result: VAS score were lower in the Pregabalin group as compared to placebo group. Sedation score was highest with Pregabalin 300 mg as compared to other two groups. Time to first rescue analgesia was 6.97±1.351 hours in group P_1, 8.47±1.408 hours in group P_2 as compared to 3.1±1.604 in placebo group. Mean number of total doses of rescue analgesics in first 24 was 1.67±0.711 hours in group P_1, 1.2±0.407 in group P_2 as compared to 2.97±0.668 in group P_0. Side effects like visual disturbance and dizziness were higher in group P_2 as compared to other two groups.

Conclusion: Pre-emptive pregabalin provide batter analgesia post operatively than placebo group. While 300mg pregabalin produces longer analgesia and require less number of doses of rescue analgesics than 150 mg Pregabalin, this dose produces more side effects like dizziness, sedation, visual disturbance and headache post operatively.

Keywords: Pre-emptive analgesia, Pregabalin, Gynaecological surgeries, Postoperative pain

Introduction

Post-operative pain is the most common clinical problem in hospitals among surgical patients and is the main reason for overnight hospital stay in 17-41% of surgical day care patients.[1] Post-operative pain, especially when poorly controlled, results in harmful acute effects (adverse physiological responses) and chronic effects (delayed long term recovery and chronic pain).[2,3]

With the emerging concepts of pre-emptive analgesia, a drug that has analgesic properties, opioid sparing effects, possibly reduces opioid tolerance, relieves anxiety, and is not associated with adverse effects typical for the traditional analgesic would be an attractive adjuvant for post-operative pain management.[4] The most effective pre-emptive analgesic regimens are those that are capable of limiting sensitization of the nervous system throughout the entire peri-operative period.[5]

The sensitization of dorsal horn neurons possibly play a role in the development of chronic pain after surgery.[6,7] Pregabalin appears to reduce the hyperexcitability of dorsal horn neurons that is induced by tissue damage and thus may have role in postoperative pain management.[8] Pregabalin is 2-4 times more potent analgesic than gabapentin.[9]

Aims & Objective

The study was undertaken to evaluate the efficacy of the two different doses of Pregabalin administered orally one hour before surgery for post-operative pain relief in patients undergoing gynaecological surgery.

Objectives of this study were:

1. To compare the clinical efficacy and quality of analgesia provided by two different doses (150mg & 300mg) of Pregabalin and a placebo group.
2. To observe the side effect profile of both the doses.

Material & Method

This study was a prospective, randomized placebo controlled one conducted with the permission of **Institute Research Committee (IRC)** for guided research of hospital and after written informed consent of 90 adult female patients of ASA grade I and II, diagnosed of gynaecological malignancies like carcinoma cervix, ovarian tumour and carcinoma endometrium posted for abdominal hysterectomy and bilateral salphyngo - oopherectomy. Detailed explanation about procedure, anesthesia technique and complications were given to all patients and their relatives.

Inclusion criteria:

- Age: 18-60 years

- ASA status: I and II
- Body mass index < 35
- Willingness to take part in the study

Exclusion criteria:

- Diabetes
- Uncontrolled Hypertension
- Surgical duration more than 3 hours
- Hypersensitivity reaction to drug
- Patients with acute or chronic renal disease
- Patients taking antidepressant, sedative, hypnotics, drugs with effects on Central Nervous System.

Pre anaesthetic assessment: All patients were examined pre operatively and history noted.

Group allocation: Ninety patients were randomly allocated in 3 Groups (n=30). Study drugs were administered orally one hour before surgery.

Group P_1: Tab. Pregabalin 150mg

Group P_2: Tab. Pregabalin 300mg

Group P_0: Placebo drug

Pre-operative baseline blood pressure and heart rate were recorded.

Patients were familiarized with the use of a 10-cm linear visual analogue scale (VAS) for pain, where 0 denotes "no pain" and 10 denotes "worst imaginable pain", the evening before surgery.

Procedure: All the surgeries were done under routine general anaesthesia. Induction of anaesthesia was done with Glycopyrrolate 0.01 mg/kg intravenously (IV), Fentanyl 1-2 mcg/kg IV, Thiopentone Sodium 5-7 mg/kg and vecuronium bromide 0.1-0.2 mg/kg. Anaesthesia was maintained with O2 + N2O and inhalational anaesthetics sevoflurane. Intermittent positive pressure ventilation was used for ventilation and vecuronium bromide as a muscle relaxant intra-operatively. After completion of surgery reversal of anaesthesia was done with Glycopyrrolate 0.02 mg/kg and Neostigmine 0.05 mg/kg IV and after full muscle tone and power, trachea was extubated.

Post-operative assessments: Vital parameters, VAS at rest and on movement/cough, sedation by Ramsay Sedation Score were assessed at 0, 30, 60 and 90 minutes, 2, 6, 12 and 24 hours post-operatively.

- If VAS ≥ 4 rescue analgesia will be given. First choice – Diclofenac sodium 75 mg Intramuscular (IM) Second choice – Tramadol hydrochloride 50 mg intravenous (IV) will be given if VAS ≥ 4 persists after first rescue analgesic.
- Time for requirement of first rescue analgesia and need of total number of doses of rescue analgesia on post-operative day zero will be assessed.
- Pregabalin adverse effects like dizziness/drowsiness, somnolence, nausea, vomiting, visual disturbances, itching, confusion and fatigue.
- Ondansetron 4 mg IV was administered if patient experienced severe nausea or an episode of vomiting.

The parameters recorded were entered on a computer and compared between the three groups using one way ANOVA test for continuous variables and $P \leq 0.05$ is deemed significant. And statistical software from below mentioned site was used.

http://www.graphpad.com/quickcalcs/ttest1/?Format=SD.

Results

The numbers of patients screened were 96, out of whom 90 were enrolled in the study and posted for total abdominal hysterectomy and bilateral salphyngo-oopherectomy.

The groups were comparable with respect to age, weight, ASA grade I/II, and duration of surgery. Mean age (year) and wt (kg) in both the groups were comparable and statistically not significant (p value >0.05). Mean surgical duration in both groups is statistically not significant (p>0.05). (Table 1)

Table 1: Demographic data

Variables	Group P_1	Group P_2	Group P_0	P value	Significance
Age (yrs)	44.8±9.242	44.87±7.956	45.63±9.529	0.5984	NS
Weight (kgs)	54.2±7.581	54.93±8.851	53.5±7.065	0.4603	NS
ASA Status (I/II)	24/6	26/4	25/5	--	--
Duration of Surgery (mins)	210.83±41.834	219.33±47.320	224.33±41.835	0.7434	NS

The post-operative VAS within the first 2 hours recorded increased values for both at rest and at movement in the control group with mean range score of 2 to 5 cms and 3 to 6 cms respectively. However, the two pregabalin groups recorded comparably insignificant lower VAS with mean range score of 0 to 2 cms and 2 to 4 cms at rest and at movement respectively. (Table 2, 3)

Table 2: Visual Analogue Score (VAS) at rest

Time	Group P_1	Group P_2	Group P_0	P value	Significance
0 min	0.33±0.479	0.27±0.450	0.37±0.490	0.8961	NS
30 mins	0.9±0.845	0.13±0.346	2.4±1.248	P < 0.01	HS
60 mins	1.1±1.125	0.2±0.407	3.27±1.412	P < 0.01	HS
90 mins	1.5±1.167	0.53±0.629	4.3±1.264	P < 0.01	HS
2 hrs	2.03±1.791	0.9±1.029	4.87±0.973	P < 0.01	HS
6 hrs	3.2±1.031	2.3±0.877	5.4±1.221	P < 0.01	HS
12 hrs	4.47±0.776	3.7±1.055	4.97±0.928	P < 0.01	HS
24 hrs	2.6±0.855	2.17±0.648	3.2±1.126	P > 0.05	NS

Table 3: Visual Analogue Score (VAS) at movement/coughing

Time	Group P_1	Group P_2	Group P_0	P value	Significance
0 min	2.90±0.803	2.47±1.042	3.17±0.791	0.2370	NS
30 mins	3.00±0.909	2.23±0.774	3.83±0.949	P < 0.01	HS
60 mins	3.10±0.845	2.33±0.758	4.67±1.093	P < 0.01	HS
90 mins	3.43±1.072	2.77±0.817	5.47±1.106	P < 0.05	HS
2 hrs	4.00±1.313	3.10±1.213	6.07±0.828	P < 0.01	HS
6 hrs	4.83±0.834	4.30±0.749	5.97±0.765	P < 0.05	HS
12 hrs	6.03±0.719	5.23±0.898	6.33±0.661	P < 0.01	HS
24 hrs	4.17±0.747	4.10±0.759	4.7±0.702	0.9086	NS

Mean pulse and blood pressure is statistically not significant among all three groups. So all patients remain vitally stable in both pregabalin and group P_0 and two different doses of pregabalin does not make any statistically significant difference in pulse and blood pressure. (Table 4, 5)

Table 4: Pulse measurements

Time	Group P_1	Group P_2	Group P_0	P value	Significance
0 min	82.6±14.801	87.8±14.416	88.7±15.717	0.8930	NS
30 mins	84.0±15.122	87.7±14.378	87.9±15.094	0.5222	NS
60 mins	81.9±13.457	88.3±11.721	85.3±14.588	0.1821	NS
90 mins	81.9±12.212	89.1±10.552	86.3±13.555	0.0750	NS
2 hrs	82.9±11.163	87.2±10.962	87.5±13.513	0.2534	NS
6 hrs	81.2±10.848	84.9±11.938	84.9±14.031	0.4109	NS
12 hrs	81.7±10.866	83.8±10.626	85.8±13.102	0.3947	NS
24 hrs	81.7±12.430	82.5±9.737	84.4±12.805	0.6591	NS

Table 5: Blood pressure measurements

Time		Group P_1	Group P_2	Group P_0	P value	Significance
0 min	S	111.47±21.437	114.47±21.410	111.27±19.528	0.8009	NS
	D	76.33±13.504	78.07±13.861	76.27±13.521	0.8420	
30 mins	S	111.13±19.516	115±19.311	112.4±16.900	0.7148	NS
	D	73.8±13.435	77.8±13.608	76±12.227	0.4988	
60 mins	S	114.4±18.772	111.87±18.702	112.73±15.611	0.8545	NS
	D	77.47±12.648	75.93±13.731	76.13±13.056	0.8857	
90 mins	S	112.13±15.615	115.53±16.697	110.2±18.401	0.4703	NS
	D	79.13±12.936	77.4±11.460	75.53±13.273	0.5433	
2 hrs	S	112±14.687	111.2±22.416	108.67±23.549	0.8080	NS
	D	76.6±11.781	78.67±10.819	76.4±10.921	0.6857	
6 hrs	S	119.67±11.792	122.00±14.259	123.27±11.608	0.6199	NS
	D	82.07±10.137	81.60±9.846	84.53±8.788	0.6814	
12 hrs	S	126.80±12.268	129.47±17.212	120.93±11.395	0.8093	NS
	D	88.13±7.371	89.47±10.712	81.67±9.022	0.2299	
24 hrs	S	110.87±12.612	111.53±14.862	109.87±13.255	0.8932	NS
	D	75.93±10.925	76.73±11.368	75.27±10.693	0.8760	

The sedation score as measured by Ramsay sedation score (RSS) at different time points recorded least (mean score range of 0 to 1.835) in the group P_0 followed by group P_1 (mean score range of 0 to 2) whereas it is highest in the group P_2 (mean score range of 0 to 3) which decrease gradually in due course of time ($P < 0.05$). However, as the groups P_0 and P_1 have lower RS score, pregabalin 150mg does not produce any significant clinical sedation. (Table 6)

Table 6: Sedation score

Time	Group P_1	Group P_2	Group P_0	P value	Significance
0 min	1.79±0.466	2.83±0.379	0.07±0.250	P < 0.001	HS
30 mins	1.53±0.507	2.6±0.563	0.17±0.370	P < 0.001	HS
60 mins	1.53±0.571	2.33±0.547	0.10±0.305	P < 0.001	HS
90 mins	1.17±0.592	2.03±0.490	0.03±0.183	P < 0.001	HS
2 hrs	0.77±0.679	1.4±0.621	0±0	P < 0.001	HS
6 hrs	0.43±0.504	1.23±0.626	0±0	P <0.001	HS
12 hrs	0.27±0.450	0.7±0.651	0±0	P < 0.01	HS
24 hrs	0±0	0±0	0±0	-----	----

The groups P_0 recorded significant number of patients with nausea and vomiting than the two pregabalin groups which recorded comparably lower number of patients. Group P_2 recorded more number of patients (5/30) with postoperative dizziness followed by group P_1 (1/30) and nil in the group P_0. Also the group P_0 did not have any patients with postoperative visual disturbances whereas the two Pregabalin groups P1 and P2 had got 0/30 and 3/30 patients respectively with such adverse effect. (Table 7)

The mean postoperative rescue analgesic free time interval in the group P_0 was 3.1±1.604 hours as compared with groups P_1 and P_2 which recorded analgesic free time interval of 6.97±1.351 hours and 8.47±1.408 hours respectively. The group P_0 also recorded significant maximum number of postoperative rescue analgesic (2.97±0.668) as compared with the two pregabalin groups which recorded least number of rescue analgesics with 1.67±0.711 and 1.2±0.407 respectively. (Table 8)

Table 7: Side effects

Side effects	Group P_1	Group P_2	Group P_0
Nausea/vomiting	4	3	9
Drowsiness/dizziness	1	5	0
Somnolence	0	1	0
Headache	1	3	1
Visual disturbance	0	3	0

Table 8: Rescue analgesia

Rescue analgesia	Group P_1	Group P_2	Group P_0	P value	Significance
Time to 1st dose of rescue analgesia (hrs)	6.97±1.351	8.47±1.408	3.1±1.604	P < 0.001	HS
Total number of doses of rescue analgesics in 24 hrs	1.67±0.711	1.2±0.407	2.97±0.668	P < 0.001	HS

Discussion

Pre-emptive analgesia, an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain.[5] Dahl et al described the use of anti-hyperalgesic drugs, such as gabapentin and pregabalin, as protective premedications prior to many different types of surgery. Protective medication is based on the principle that drugs given before an injury will reduce pain after the injury.[8]

This study was designed with aim of comparing the post operative analgesic efficacy of two different doses of Pregabalin and their side effects in patients undergoing gynaecological surgeries under general anaesthesia.

Elina M et al in their study concluded that Gabapentinoids effectively reduce postoperative pain, opioid consumption, and opioid related adverse effects after surgery. Pregabalin and gabapentin have very few adverse effects of their own.[10]

We had given tab pregabalin 1 hour before surgery to achieve maximal plasma concentration of the drug at the time of surgical stimulus as peak plasma level of the drugs is achieved within 30 minutes to 2 hour.

Pregabalin has been employed orally in various doses for the management of postoperative pain. Oral Pregabalin is used in the range of 75mg-600mg in both single and multiple doses. Several studies suggests that pregabalin dosage less than 150 mg has ineffective analgesia[11,12,13] effect and dose greater than 300mg causes more sedation.[14,15] The dose we choose (150mg and 300mg) are commonly used single dosage for control of pain for better analgesia with less sedation.

In two studies involving preoperative Pregabalin 150 mg for laparoscopic sleeve gastrectomy[16] and for lower limb orthopedic surgery[17] concluded that this dose is the recommended effective dose to start with and it reduces opioid consumption and provide safe analgesia with fewer side effects.

Various studies using Pregabalin 300 mg single dose recorded its effectiveness as multimodal analgesia as an alternative to opioid combination and that it is the commonly used highest effective and safe dose for control of pain.[18,19,20]

In our study Pregabalin groups had significantly lower pain scores in the initial hours of recovery both at rest and at movement as compared to placebo group however two Pregabalin groups had comparable VAS in the first 12 hours and there was no statically significant difference in pain scores after 12 hours of recovery. This findings correlates with the pharmacokinetic profile of the drug as they have short elimination life of 6 to 8 hours after a single dose.

T. Hemjit Singh et al in their study of 120 patients to receive oral pregabalin 150 mg and 300 mg or placebo 1 hour before the cholecystectomy reported increased VAS of 3 to 6 cms and 4 to 7 cms at rest and at movement in the control group and the two Pregabalin 150 and 300 mg groups recorded lower VAS of 0 to 1 and 0 to 3 cms for rest and at movement respectively.[21] Anand T Talikoti et al found in their study that time to VAS >3 was significantly increased with Pregabalin 225 mg and 150 mg than the placebo group.[22] Fatih Balaban et al also found significantly lower VAS with Pregabalin 150 and 300 mg then control group at 30 and 60 minutes postoperatively after laparoscopic cholecystectomy.[23]

In contrast to above trials Chang et al, Mathiesen O et al & Paul FW et al concluded that there were no improvement in pain score and analgesic consumption in Pregabalin groups and sedation increased with increasing dose of the drug.[14,24,25]

In our study, we gave rescue analgesia when patients had VAS ≥ 4 by giving Inj. Diclofenac sodium 75mg IM as a first choice and if still VAS ≥ 4, then Inj. Tramadol 50mg IV was given as a second choice. Time to first rescue analgesia in the two pregabalin groups were significantly longer than the control group. Mean time for first rescue analgesia was significantly longer ($P < 0.001$) in group P_2 (8.47±1.408) than group P_1 (6.97±1.351) and group P_0 (3.1±1.604). And requirement of first dose of rescue analgesia is little bit earlier in Group P_1 than Group P_2 which was statistically significant (p value < 0.001).

V Saraswat et al in their study of Pre-emptive gabapentin 1200mg (group G) and pregabalin 300mg (group P) reported total postoperative analgesic time of 8.98h in Group G whereas 14.17h in Group P (P< 0.001).[26] Monika Kohli et al reported analgesic free time of 202.42±6.77 in group P(300), 176.38±4.80 in group P(150) and 131.38±5.15 in Group P(0).[27]

In our study the numbers of rescue analgesic were also comparable in the two pregabalin groups and significantly less than the control group. The total number of rescue analgesics at 24 hours postoperatively was 2.97±0.668 in the control group as compared with the two pregabalin groups which recorded least number of rescue analgesics with 1.2±0.407 in group P2 and 1.67±0.711 in group P1 which was statistically significant between two groups.

Several studies reported reduction in 24 hour postoperative morphine requirement with Pregabalin 300 mg.[18,19,23,28] A Agarwal et al and Anand T et al in their study with Pregabalin 150 mg concluded that this single preoperative dose is effective in reducing postoperative analgesic consumption then placebo group.[22,29]

The sedation score in our study, as measured with the Ramsay sedation score were maximum with the pregabalin 300 mg group compared with Pregabalin 150 mg and control group and statistically significant. Five studies provided data on more sedation with Pregabalin 300 mg.[14,18,24,29,30]

In our study the incidence of side effects such as nausea and vomiting were lower in the two pregabalin groups as compared with the control. However, comparable incidence of nausea and vomiting episodes were reported in the two pregabalin groups. Pregabalin 300 mg group was associated with significant increased incidence of dizziness, headache and blurred vision than the 150 mg group, and was negligible in the control group which is in accordance with the studies of Jokela et al, Kim et al and Peach et al.[11,15,30]

Conclusion

Pre-emptive pregabalin provide batter analgesia post operatively than placebo group. While 300mg pregabalin produces longer analgesia and require less number of doses of rescue analgesics than 150 mg Pregabalin, this dose produces more side effects like

dizziness, sedation, visual disturbance and headache post operatively.

Conflict of Interest: None

Source of Support: Nil

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