



## Evaluation of role of preoperative oral pregabalin on postoperative pain in patients undergoing total abdominal hysterectomy.

**Dr Archana Vaidya**

Assistant Professor, Department of Anaesthesiology, Government Medical College and Hospital, Nagpur.

**Dr Priya Ishwar Besekar**

Senior Resident, Practising Anaesthesiologist, Department of Anaesthesiology, Government Medical College and Hospital, Nagpur.

**Dr Amrisha Raipure**

Assistant, Professor, Department of Anaesthesiology, Government Medical, College and Hospital, Nagpur.

### ABSTRACT

"It is easier to find men who will volunteer to die, than to find those who are willing to endure pain." This quote by Julius Caesar precisely sums up the importance of relieving pain. This prospective, randomized, double blind placebo controlled study aims to study the effect of preoperative oral pregabalin on postoperative pain in patients undergoing total abdominal hysterectomy. 74 patients, posted for total abdominal hysterectomy under spinal anaesthesia, were divided into two groups, receiving Pregabalin 300mg or placebo one hour prior to surgery. Pregabalin group & placebo group had VAS score (4 until 7hrs & VAS score-4 after 3hrs postoperatively, required first rescue dose of Diclofenac at 450 mins & 129.71mins respectively. Quality of anaesthesia was also better in Pregabalin group than the placebo group.

### KEYWORDS

"Pain is a more terrible lord of mankind than even death itself" said nobel laureate Albert Schweitzer. Pain is perhaps the most feared symptom of disease, which man is always trying to alleviate and conquer since ages. The relief of pain has been the fundamental aspect of the practice of anaesthesiology.

Wolf CJ & Max MB et al<sup>3,4</sup> in 1993, observed that hyper sensitisation contributing to post-operative pain can be controlled by blocking the initial nociceptive input to the spinal cord. This is the main rationale behind pre-emptive analgesia.<sup>3</sup> Pre-emptive analgesia is more effective than similar analgesia initiated after surgery. As pre-emptive analgesia, local anaesthetics, opioids, NSAIDS, gabapentin, pregabalin, clonidine and dexmedetomidine drugs are used.

Pregabalin, a precursor of gabapentin<sup>6</sup>, is a structural analogue of inhibitory neurotransmitter alpha/gamma-aminobutyric acid. It binds to alpha-2-delta subunit of voltage gated calcium channels, reducing the release of several excitatory neurotransmitter & blocks the development of hyperalgesia & central sensitization. Pregabalin has anti-convulsant, anxiolytic, antiallodynic & anti-hyperalgesic properties.<sup>6,7,9,10,11,12</sup> It is more potent than gabapentin with fewer side effects and better pharmacokinetics. The aim of this research was to study the effect of preoperative oral pregabalin on postoperative pain in patients undergoing elective total abdominal hysterectomy, as compared with a placebo.

**Methodology:** This study is a prospective, randomized, double blind placebo controlled study, approved by the Hospital Ethical Committee. The Aims and Objectives of study were to study the effect of preoperative oral pregabalin on postoperative pain in patients undergoing total abdominal hysterectomy & to study the side effects of preoperative oral pregabalin. The study included 74 ASA Grade I & II patients, posted for elective total abdominal hysterectomy under spinal anaesthesia, lasting upto 2 hrs.

Patients having any contraindication to spinal anaesthesia, not willing to participate in the study & those on analgesics, sedatives & psychiatric drugs were excluded. 74 patients were randomly divided into 2 groups:

Group G1 : Received Cap.Pregabalin 300mg

Group G2 : Received Cap.Placebo

A detailed pre-anaesthetic evaluation was done & a written informed consent obtained. An hour before surgery, in pre anaesthetic room, vitals were recorded & assigned drugs were given. Preoperative sedation was determined by Ramsay sedation score. Inside the OT, patients were preloaded with ringer lactate solution 10ml/kg. Spinal anaesthesia was administered with 3.5ml of 0.5% bupivacaine(Heavy). Intraoperatively heart rate, blood pressure, respiratory rate & SpO2 were recorded. The time of completion of surgery was noted & was considered as zero hour for studying post-operative pain. The following were recorded:

1. Sedation Score
2. VAS Score
3. Time for requirement of first analgesic.
4. Comparison of dose of analgesic required (in 24hrs)
5. Patient satisfaction score (On a scale of 1 to 5)
6. Quality of analgesia as experienced by patients (good, satisfactory or poor).
7. Postoperative side effects

Patient was shifted to PACU post-operatively & observed for 24hrs. When patient first complained of pain, time was noted along with VAS score. At a VAS score >4, injection diclofenac im 75mg was given & if VAS score remained >4, injection tramadol 1mg/kg was given. After this, VAS monitoring was done at 2 hourly intervals, and doses repeated when VAS>4 and tramadol was used for rescue analgesia, if needed. Total number & doses of diclofenac & tramadol boluses within 24 hours was noted.

Following parameters were noted postoperatively:

- 1) Quality of anesthesia intraoperatively
- 2) Quality of postoperative analgesia from VAS score at 0 hr, then hrly till first 8 hours, then 2 hrly till 12 hrs & 4 hrly thereafter till 24 hrs.
- 3) Time of first analgesic required.
- 4) Total number of inj.diclofenac doses & injection tramadol boluses within 24 hours
- 5) Patient satisfaction score at 2,4,8,12 & 24hrs
- 6) Incidence of side effects

**Statistical analysis:** Continuous variable between two groups were compared by unpaired t test. VAS score, amount of analgesia required and patient satisfaction score were compared by performing Mann-Whitney test. Categorical variables were

compared by Chi-Square test. Statistical software STATA version 10.0 was used for statistical analysis.

**Observation & results:** The mean age was 44.4±6.01 years in G1, 42.8±6.51 years in G2. Mean weight in G1 was 48.66 ± 4.6 & 50.03 ± 5.76 in G2. The mean duration of surgery was 97.86±13.24mins in G1 & 100.29±14.9mins in G2.

Preoperative sedation score was significantly (p< 0.05) more in patients receiving 300 mg pregabalin than placebo. (Table 1)

**Table 1: Comparison of Sedation Score**

Preoperative sedation score	No of patient (%)		P value
	Group 1	Group 2	
1	0(0.00%)	19(54.28%)	0.0000(S)
2	20(57.14%)	16(45.71%)	
3	15(42.85%)	0(0.00%)	
4	0(0.00%)	0(0.00%)	
5	0(0.00%)	0(0.00%)	
Total	35(100%)	35(100%)	

Group 2 had VAS score 4 after 3hrs postoperatively where as in Group 1, it was less than 4 until 7 hrs, the difference being statistically significant.(Table 2)

**Table 2: Comparison of VAS Score**

Post-operative time(hrs)	VAS Score(mean±SD)		P value
	Group 1	Group 2	
0	0.00±0.00	0.00±0.00	-
1	1.00±0.00	1.41±0.55	0.000
2	1.06±0.23	3.11±0.92	0.000
3	1.89±0.32	4.30±0.79	0.000
4	2.06±0.33	-	-
5	2.49±0.50	-	-
6	2.91±0.28	-	-
7	3.06±0.23	-	-
8	4.00±0.89	-	-

Group 2 required first analgesic at mean time of 129.71mins compared to Group 1 who required at 450mins; the difference being statistically significant.

Total doses of injection diclofenac required in group 2 were 2 with or without injection tramadol. But in group 1 less doses of injection diclofenac were required.

**Table 3: Comparison of dose of analgesic required (in 24hrs) in group 1 & group 2**

No of analgesia doses	Number of patients (%)	
	Group 1	Group 2
1	29 (82.85%)	0 (00.00%)
2	06 (17.14%)	3 (08.57%)
3	00 (00.00%)	32 (91.42%)

Patients postoperative satisfaction score which was >1 but <2 in Group 2 up to 24 hrs postoperatively. The score was >3 in Group 1 up to 4 hours but <3 till 24 hrs

Initially 74 patients were included in study, but in 4 patients quality of anaesthesia was poor & had to be converted to general anaesthesia. Hence, only 70 patients were considered. When compared with quality of anaesthesia it was good in maximum number of patients, in Group1; whereas quality was satisfactory in maximum number of patient in Group 2. (Table 4)

**Table 4: Comparison of quality of analgesia**

Quality of anaesthesia	Group		P - value
	Group 1	Group2	
Good	20	06	0.001
Satisfactory	15	29	0.001
Poor	00	04	-

The side effects like somnolence and dizziness was not observed in any group.8.57% and 11.42% of patients amongst the control group had vomiting and nausea respectively.

**Discussion:** Most of the drugs, used for the treatment of postoperative pain have side effects, which limits their use in clinical practice; demanding a new drug which significantly prevents central sensitization, improves the quality of opioid analgesia, reduces opioids requirement, prevents or reduces opioids tolerance, relieves anxiety, does not depress respiration & has no effect on the gastric mucosa, platelets and renal function

Several studies in the recent past found that pregabalin may fit in this profile. Pregabalin was first launched in 2004, gained US FDA approval for use in neuropathic pain associated with diabetic neuropathy & post herpetic neuralgia. Various studies have shown that Pregabalin has both antiallodynic<sup>11</sup> and antihyperalgesic<sup>12</sup> effects.

A. Agarwal et al<sup>31</sup> first used Pregabalin in the dose of 150 mg in patients undergoing laparoscopic cholecystectomy. Ritva Jokela et al in 2008<sup>29</sup> used Pregabalin as adjuvant to postoperative pain management.

Jong Cham Kim et al in 2011<sup>41</sup> found that pregabalin 150mg before & 12hrs post-operatively but not 75mg significantly reduced opioid consumption for 48 hours post-operatively without significant side effects in patients undergoing spinal fusion surgery.

Ghai et al in 2011<sup>37</sup> concluded that single dose of 300mg pregabalin given 1-2 hours prior to abdominal hysterectomy is superior to 900mg Gabapentin & placebo for post-operative analgesia.

In the present study we selected 300mg pregabalin to evaluate its role as preemptive analgesic in patients undergoing abdominal Hysterectomy.

Ramsay sedation score used in various studies(Hyong Rae JO et al<sup>51</sup>, F. Aubrun et al<sup>52</sup>) was followed in our study.

In our study 54.28% patients receiving placebo had sedation score-1 & 45.71% patients had sedation score of 2 (Mild sedation, eyes closed, responding to oral commands) with the mean sedation score of 1.46 ±0.50

In patients receiving 300 mg of preoperative oral pregabalin 54.28% patients had sedation score of 2 & 45.71% patients had a score of 3 with mean score 2.43±0.49, which correlates with the study of Godrat Akhavanakbari<sup>49</sup>, Dalim Kumar Baidya<sup>43</sup>.

In our study, it was observed that patients in G1 were more sedated than in G2. Anju Ghai et al<sup>37</sup> had similar observations with 300mg oral pregabalin.

White PF et al in 2009<sup>35</sup> noted preoperative pregabalin administration in doses of 75mg,150mg,300mg increased peri-operative sedation in dose related fashion.

In our study, overall VAS scores were less in G1 than G2. Ashraf M et al<sup>50</sup> also found that the VAS score was less in group receiving 300mg pregabalin preemptively than control group. Spreng UJ et al<sup>40</sup>, Cabrera Schulmeyer et al<sup>36</sup> also had similar results.

In our study, G2 & G1 patients required first analgesic after minimum time of 75mins & 300mins, with the mean time of 129.71mins & 400mins, respectively. Thus, the requirement was significantly delayed in G1 than G2. These findings are comparable to the observations of Anju Ghai et al,2011<sup>37</sup>. Monica Kohli et al,2011<sup>42</sup> also observed that the use of 300mg oral pregabalin preoperatively delays the requirement of first analgesic postoperatively.

In our study, in G2 & G1, the minimum amount of analgesic required in first 24 hours postoperatively was 150mg & 75mg, with mean of 218.57mg & 87.85mg, respectively, the difference being statistically significant. E Engelman et al,2011<sup>20</sup> V Saraswat et al,2008<sup>30</sup> found that the total requirement of analgesics postoperatively was much less in pregabalin group when they used oral pregabalin for preemptive analgesia for various surgeries. Pradeep Jain et al,2011<sup>40</sup>, A Agarwal et al,2008<sup>31</sup> while studying the role of oral pregabalin in reducing postoperative pain also had comparable observations.

In our study, patient satisfaction score was >1 but <2 upto 24hrs postoperatively in G2. However, the patient satisfaction score in G1 was >2 throughout postoperative period upto 24 hours, showing that the patients receiving oral pregabalin were more satisfied. Monica Kohli et al,2011<sup>42</sup> support our findings, who also found patient satisfaction was better in pregabalin 300 mg group.

It was observed that quality of anaesthesia was significantly better in G1 than G2. No studies in literature have commented about quality of anaesthesia intraoperatively.

The side effects like somnolence and dizziness were not observed in any of the patients in the study.

In our study, 8.57% and 11.42% of patients in G2 had vomiting & nausea respectively. Engelman E et al,2011<sup>20</sup> found that pregabalin 300mg when given preoperatively had a role in reducing the incidence of postoperative nausea and vomiting. This finding in their study supports the finding of our study. Godrat Akhavanakbari et al,2013<sup>49</sup> also had similar observations.

**Conclusion.** To conclude, the present study suggests that 300mg preoperative oral Pregabalin can be used effectively for reducing postoperative pain with minimal side effects in patients undergoing total abdominal hysterectomy.

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