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Original Research Article

Comparison of premedication with 75 mg and 150 mg pregabalin for postoperative analgesia in total hysterectomy patients - A randomised control trial

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ABSTRACT

Background: Pregabalin is an anticonvulsant, structural analogue of Gamma Amino Butyric Acid (GABA) and is very much efficient in the management of neuropathic pain and incisional injury.
Objectives: The aim of this research is to evaluate the efficacy of preoperative administration of pregabalin on postoperative analgesic requirement in subjects undergoing total abdominal hysterectomy under spinal anaesthesia.
Materials and Methods: A randomized, placebo-controlled trial was conducted in 129 patients undergoing total abdominal hysterectomy under spinal anaesthesia, divided in three groups (placebo group, 75 mg of pregabalin and 150 mg of pregabalin) of 43 patients each. Pre-operative Ramsay sedation scale was noted and post-operative VAS score for pain at rest and on cough at 30 minutes, 1hr, 2 hrs, 6 hrs, 12 hrs and 24 hrs post operatively was noted. Time for requirement of rescue analgesics on post-operative day one was assessed.
Results: The post operative pain scores reduced with the dose of pregabalin. Sleep score also was significantly better as the dose of pregabalin increases. The need for rescue analgesia decreased with the dose of pregabalin. As the dose increases, the side effects Dizziness, Nausea and vomiting also increases.
Conclusion: Pregabalin has been found to reduce the post operative pain effectively, reduces the need and dose for rescue analgesia and improves the post operative sleep pattern. The side effects are high for a dose of 300 mg. Therefore 150 mg of pregabalin is advocated for better pain management and sleep pattern.

1. Introduction

Pain is one of the three most prevalent medical reasons for delayed discharge following surgery, with drowsiness and nausea/vomiting being the other two. International Association for the study of pain defines it as an unpleasant sensory and emotional experience linked to existing or potential tissue injury or explained in terms of tissue damage.[1]

Acute pain after surgery that starts with the surgical lesion and ends with tissue recovery is known as postoperative pain. Modern anaesthesia is concerned not

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only with intraoperative analgesia but also with pain management after surgery which helps with a better post operative comfort, decreased risk of complications, a quicker recovery and hence lowers medical costs. Postoperative pain is being managed using a variety of techniques. The current post operative pain management includes the following: Opioids, small dose of ketamine, Non-steroidal anti-inflammatory drugs (NSAID), and local anaesthetic. The side effects of opioids, NSAIDs, psychotogenic effect of ketamine and the additional care and work for epidural anaesthesia potentiates the need for a better drug that has a better analgesic property, opioid-sparing effect, possibly reduces opioid tolerance and relieves anxiety and not associated with the adverse effects.[2]

Pregabalin (S-[+]-3 isobutylgaba) was created as a lipophilic GABA (-aminobutyric acid) analogue with a '3' position substitution to aid in blood-brain barrier diffusion. It's been proven to help with incisional injury, formalin-induced injury, neuropathic pain, inflammatory injury and in a variety of animals. Though the underlying mechanism for action of pregabalin is unknown, it does interact with the same binding site as gabapentin and has a comparable pharmacologic profile but a better pharmacokinetic profile. Its primary mechanism of action appears to be on the (2 —) subunit, and its efficacy is six times that of gabapentin.[3]

It's been utilised in laparoscopic operations as a prophylactic and postoperative analgesic with mixed success. Pregabalin at low doses has just a minor analgesic effect. Although high doses of pregabalin produce effective analgesia, they are linked to an increased risk of adverse effects.[4–7]

Since there is a limited evidence on the post operative effects of pregabalin, this research was designed to compare the efficacy of 75mg with 150mg pregabalin in terms of post operative analgesia, sleep and side effects, while given as a premedication for postoperative pain relief in patients undergoing total abdominal hysterectomy under spinal anaesthesia.

2. Materials and Methods

This comparative cross-sectional study was conducted among 129 patients enrolled conveniently (43 in each groups) within the age group of 30-65 years, who were scheduled for abdominal hysterectomy under spinal anaesthesia after getting institutional ethical committee clearance in a tertiary care setup in south India. Those patients who were posted for total abdominal hysterectomy (after detailed pre-anaesthetic evaluation) within the age group of 30-65 years, with ASA physical status of I and II, BMI within the range of 1835 kg/cm^2 were included in the study. Patients with known history of headache, dizziness, epilepsy, drug/alcohol abuse, taking anti-anxiety drugs, analgesic drugs were not included in the study. The patients were contacted by the principal investigator during pre-anaesthetic evaluation and was be explained about the objectives and need for the study, the rights of the participants and the ethical issues that needs concern. Those who accepted to participate were requested to sign a written informed consent. The selected patients were allotted to any one of the three groups- Placebo, 75 mg pregabalin and 150 mg pregabalin by computer generated randomization method (Figure 1). All the patients were kept nil per oral overnight. All patients were given oral Pantoprazole 40 mg on the morning of surgery. No anxiolytic premedication was given. Multivitamin, 75 mg capsule of pregabalin, 150 mg capsule of pregabalin to placebo group, 75mg pregabalin group and 150mg pregabalin group respectively along with a sip of water one hour before surgery and were shifted to operation theatre. The anaesthetist conducting the study and the patient were blinded about the drug given to them. Hemodynamic parameters (blood pressure and Heart rate were recorded before premedication, 30 min and 60 min after premedication. Ramsay sedation score (1 to 6) was assessed one hour after administering the drug. Score of three or four were considered adequate.

All patients were given spinal anaesthesia with 0.5% hyperbaric bupivacaine intrathecally which was adjusted for height and weight of the patients. Spinal anaesthesia was administered with patient in the sitting position, at Lumbar 2nd or 3rd intervertebral space with a 25-gauge Quincke 's needle.

All patients received injection paracetamol 1g intravenous,8th hourly, starting 30 mins on arrival to recovery room. VAS was utilized for categorizing pain in the patient at rest and on cough at 30 minutes, 1hr, 2 hrs, 6 hrs, 12 hrs and 24 hrs in the post operative period in the recovery room. Rescue analgesic was given if VAS score was more than 4. Injection tramadol 50 mg i.v was given if VAS score was more than 4, as first choice. If pain still persisted injection diclofenac 75mg i.v was considered as second choice.

Sleep quality in post operative session was evaluated on 1 to 5 grade scale. A grade of 4 or 5 was taken as adequate post operative sleep. Requirement of rescue analgesics and the time at which first and second rescue analgesic given was noted on the first post-operative day. Adverse effects like dizziness, nausea and vomiting were also noted.

2.1. Statistical methods

The statistical analysis was performed by STATA11.1 (College station TX USA). Analysis of variance was used for the assessment of difference between the duration of rescue analgesia, age, weight height, BMI, blood pressure, heart rate, visual analogue score in different time intervals. Chi square or fisher exact test was utilized to measure the association between the treatment groups with ASA grade, sedation scale, post operative sleep quality and adverse effects and it is expressed as frequency and percentage.

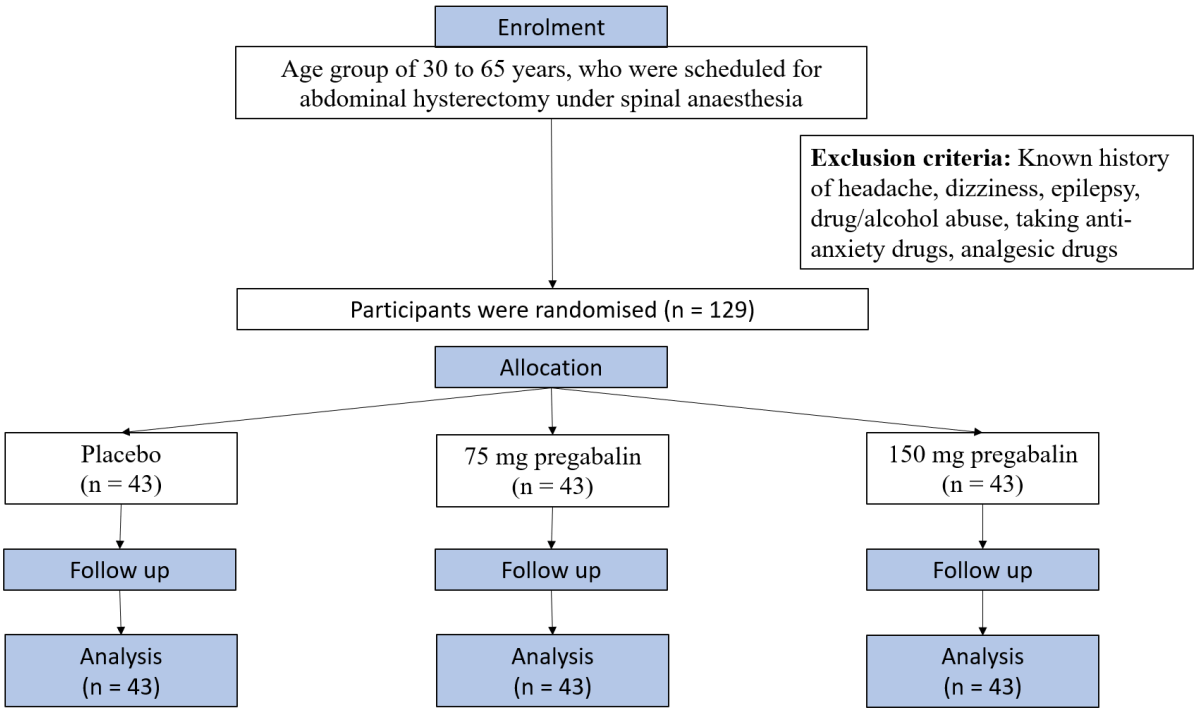

Fig. 1: CONSORT flow diagram

P<0.05 was considered for statistical significance.

3. Results

A total of 129 patients with 43 in each group were enrolled in the study. The mean age, BMI, HR/ MAP at all the times and ASA Grade distribution were more or less similar in all the three groups making them comparable with each other. The Ramsay Sedation Score increases as we move from Placebo to 150 mg of Pregabalin and the results are statistically significant (Table 1).

The VAS scores for 150 mg of Pregabalin was the least at all the times compared to other groups. Similarly, the VAS score for 75 mg of Pregabalin was lower than Placebo at all the times except at 12 hours. At 24 hours the VAS score was more or less similar in all the groups.(Table 2) The VAS scores for patients who had cough were analyzed separately and the results obtained were similar to the results obtained for all the study population.

More than 62% had sleep scores less or equal to three in Placebo, while 25% had a sleep score less than 3 in 75 mg of Pregabalin and only 2.3% had sleep score less than 3. As the dose of pregabalin increases, the sleep pattern increases and the results are statistically significant. (Table 3)

Almost all the participants in the control group required rescue analgesia while 58% in 75 mg of pregabalin group needed rescue analgesia and only 25% needed rescue analgesia in 150mg pregabalin group. And the results are statistically significant. (Table 4) The average time for first rescue analgesic was 125 minutes in Placebo, 165 minutes in 75 mg of Pregabalin and 181 minutes in 150 mg of Pregabalin group. Inter group comparison showed significance difference between them.

As the dose increases, nausea, vomiting and dizziness prevalence also increases. The difference is slightly high for nausea and vomiting while it was too high for dizziness in pregabalin group compared to placebo. Even among the two doses, it is too high for 150mg of pregabalin. The results are statistically significant. (Table 5)

4. Discussion

There is a greater need to assess the direct rational drug choices with minimal side effects to alleviate the post-operative nociceptive pain. It requires a lot of meticulous planning and multimodal techniques.

A neuroendocrine stress response is usually initiated by the pain which is characterized by the release of combination of local and systemic inflammatory substances. As a result, there is a secretion of catecholamine and catabolic hormone secretion that mediates sodium and water reabsorption and increased levels of ketone bodies, lactate, blood glucose and free fatty acids. The magnitude of stress response is proportional to the degree of surgical trauma. The resulting hyperglycemia may lead to immunosuppression and delayed wound healing.[8]

Table 1: Comparison of socio demographic and hemodynamic parameters between the three groups

	Placebo	75 mg of Pregabalin	150 mg of Pregabalin	P Value
Age	45.63±7.52	46.23±7.43	44.19±7.23	0.422
BMI	25.96±3.16	24.43±3.89	25.08±4.32	0.178
HR				
At premedication	78.88±7.97	76.84±6.75	78.81±7.42	0.349
After 30 min	78.63±6.58	76.42±8.12	78.70±7.87	0.285
After 1 hr	81.30±7.33	79.40±8.99	77.81±6.07	0.105
MAP				
At premedication	95.49±10.05	94.50±9.11	98.56±10.18	0.139
After 30 min	95.49±8.95	95.17±8.98	96.26±9.92	0.857
After 1 hr	99.93±13.46	96.47±9.15	97.93±11.02	0.369
ASA Grade				
Grade 1	20(46.5%)	21(48.8%)	22(51.2%)	
Grade 2	23(53.5%)	20(46.5%)	21(48.8%)	0.591
Grade 3	0(0%)	2(4.7%)	0(0%)	
RSS				
RSS (1+2)	38(88.4%)	32(74.4%)	21(48.8%)	
RSS(3+4)	5(11.6%)	11(25.6%)	20(46.5%)	<0.001
RSS(5+6)	0(0%)	0(0%)	2(4.65%)	

Table 2: Comparison of VAS scores of patients at rest in three groups

VAS at Rest	Placebo	75 mg of Pregabalin	150 mg of Pregabalin	Total	P value (between three gps)	Posthoc significance
30 min	2.53±0.93	1.53±0.77	1.05±0.21	1.71±0.94	<0.001	Within all three
1 hr	3.05±0.69	1.74±0.66	1.14±0.35	1.98±0.99	<0.001	Within all three
2 hrs	3.37±0.82	2.44±0.77	1.77±0.43	2.53±0.95	<0.001	Within all three
6 hrs	2.79±1.08	2.60±0.69	2.07±0.26	2.49±0.81	<0.001	2 Vs 0,1
12 hrs	2.93±0.91	3.30±1.01	2.79±0.71	3.01±0.91	0.024	1 Vs 2
24 hrs	3.53±0.67	3.35±0.81	3.14±0.60	3.34±0.71	0.35	None

Table 3: Post op sleep: Acomparison in three groups

Post op Sleep	Placebo	75 mg of Pregabalin	150 mg of Pregabalin	Total	CSV	P value (between three gps)
1	0(0%)	0(0%)	0(0%)	0(0%)		
2	7(16.3%)	3(7%)	0(0%)	10(7.8%)		
3	20(46.5%)	8(18.6%)	1(2.3%)	29(22.5%)	58.171	<0.001
4	16(37.2%)	23(53.5%)	16(37.2%)	55(42.6%)		
5	0(0%)	9(20.9%)	26(60.5%)	35(27.1%)		
Total	43(100%)	43(100%)	43(100%)	129(100%)		

Table 4: Rescue analgesics consumption – number of doses

No. of Doses	Placebo	75 mg of Pregabalin	150 mg of Pregabalin	CSV	P-value
0	0(0%)	18(41.9%)	32(74.4%)		
1	25(58.1%)	16(37.2%)	11(25.6%)	54.688	<0.001
2	18(41.9%)	9(20.9%)	0(0%)		
Total	43(100%)	43(100%)	43(100%)		

Table 5: Adverse effects in three groups

Adverse Effects	Placebo (n=43)	75 mg of Pregabalin (n=43)	150 mg of Pregabalin (n=43)	Total (n=129)	P-value
Nausea	34(79.1%)	38(88.4%)	40(93%)	112(86.8%)	0.175
Vomiting	13(30.2%)	14(32.6%)	22(51.2%)	49(38%)	0.068
Dizziness	2(4.7%)	26(60.5%)	40(93%)	68(52.7%)	<0.001

Hypercoagulability by inhibiting fibrinolysis leading to deep venous thrombosis, the vascular graft failure and myocardial ischemia are some of the detrimental effects of stress response.[9] Reduction in gastrointestinal motility causing paralytic ileus and the reduction in postoperative pulmonary function leading to pulmonary complications are the other adverse effects.

The nociception process includes the Transduction, transmission, perception and modulation.[10,11] An approach for balanced analgesia, i.e., Multimodal analgesic technique aims in reducing the postoperative pain by blocking one or more of these nociceptive pathways in the PACU expand setting. This in turn may improve the patient satisfaction and lessen the duration of PACU stays.[11]

The present research shows that, as the dose of pregabalin increases, Visual analogue scale VAS score, the RSS expand score, and the sleep score increases/improves towards positive spectrum, there is reduction in the need for rescue analgesia but the side effects especially dizziness was present in almost all the patients who were given150 mg of pregabalin.

Pregabalin has been considered as part of multimodal regimens for reducing pain. Pregabalin binds to calcium channels and then modulates the calcium influx and several excitatory neurotransmitters.[12] This mechanism can offer anxiolytic, antiepileptic and analgesic effects. After oral administration, the rapid absorption and the linear pharmacokinetics of pregabalin allow it to be a pre-emptive adjuvant as well and acute postoperative analgesic during the perioperative period.[13] Recent studies have analysed the effect of pregabalin in post-operative pain. Agarwal et al. found that the preoperative pregabalin have lessen the post-operative pain and the need for fentanyl in patients undergoing laparoscopic cholecystectomy.[14] In a study by Rajappa et al., preoperative administration of 150mg of pregabalin was optimal for alleviating acute post-mastectomy morphine consumption.[6] The analgesia effect of Pregabalin was observed in studies done nationally and internationally.[4,5,7,15,16] But, few studies have failed to demonstrate the analgesic effects of pregabalin during the perioperative period. Jokera et al. reported that preoperative use of pregabalin was not so proper after laparoscopic hysterectomy.[17] Furthermore, Paech et al. did not report any pain relief in the patients administered pregabalin preoperatively.[18] In a study done by park et al,[19] no effect of 150mg of pregabalin on post-surgical pain or attenuation of fentanyl consumption in patients undergoing gastrectomy. These conflicting results concerning the utility of pregabalin could be due to differences in type of surgery, the dosage of the drug and its regimen and the severity of pain.

As per the norms of pregabalin medication, 150mg of pregabalin is suggested as the stat dose for treating neuropathic pain.[12] The research done by Esmat et al., shows that both 150 mg and 300mg of pregabalin had exerted the similar analgesic effects on postoperative pain after laparoscopic cholecystectomy, but 300mg of pregabalin had resulted in more adverse effects.[20] Park et al did not find any analgesic effects of 150mg of pregabalin on post-gastrectomy pain. They attribute that the subtherapeutic doses of pregabalin used in this case.[20]

The time for first rescue analgesic was significantly increased ($P < 0.001$) in the pregabalin group and also post-operative rescue analgesic requirements was also significantly decreased in the pregabalin groups (group 2 < group 1 < group 0). There are other studies which showed the similar results.(21-23) These results signify that pregabalin premedication provides significant postoperative analgesia. The sedation has been ascertained as additional effect in the usage of pregabalin as well.[3] The participants who were on pregabalin were sedated adequately (RSS > 3) one hour after administration. Their sleep score was better than the placebo group post operatively. Akdogan et al[15] and Wang et al[16] also observed that the sleep profile was better with pregabalin

In our study, though nausea and vomiting was high in pregabalin group, the occurrence of dizziness significantly increases with dose of pregabalin. Ghai et al[21] also described dizziness as the most common adverse effect in their study. Similar results was obtained in other studies done by kohli et al,[22] Agarwal et al,[14] Alimian et al[23] in their studies. Contrary to our result, Agarwal et al[14] reported a significant nausea and vomiting in the pregabalin group.

5. Conclusion

Pregabalin has been found to reduce the post-operative pain effectively, reduces the need and dose for rescue analgesia and improves the post-operative sleep pattern. The side effects are high for a dose of 300 mg. Therefore, 150 mg of pregabalin is advocated for better pain management and sleep pattern.

6. Source of Funding

None.

7. Conflict of Interest

None.

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