Original Article

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Effect of use of oral Pregabalin as an adjunct in Spinal Anaesthesia

Amrita Panda*, Jagadish Chandra Mishra**

Abstract

Background: Pain relief with minimal side effect in post operative surgical patients is essential for early mobility and recovery.

Objective: This study was conducted to find out whether preoperatively oral pregabalin used as an adjunct in spinal anaesthesia has any effect in the prolongation of duration of dose of first rescue analgesic requirements, effect on anxiety, sedation scores and patient satisfaction level in the post operative period.

Patients and Methods: This is a randomized double blind placebo controlled study conducted in 60 ASA 1&2 patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. The patients are divided randomly into two groups. Group -1 patients the control group where placebo drug is given one hour prior to surgery as an adjunct in spinal anaesthesia and Group-2 patients 75mg oral pregabalin is given similarly. VAS Scale was used for anxiety score and Ramsay Sedation Scale was used for sedation score, patient satisfaction level, duration of dose of first rescue analgesic requirements were measured.

Results: Demographically there was no significant difference between both the groups. Comparison of time of first rescue analgesia there was statistically significant difference between Group-1 and Group-2 patients(p value >0.95) Sedation scores and anxiety scores are just significant between both the groups. No significant difference was found in the haemodynamic parameters between the groups.Patient satisfaction was better in the treated group as compared to the control group.

Conclusion: From this study we concluded that oral pregabalin reduced the anxiety level and also prolonged the time period for the need of first dose of rescue analgesia. No side-effects of Pregabalin were noted and patient's satisfaction was better in the treated group thanin the control group.

Keywords: Postoperative Pain; Calcium Channel Modulators; Spinal Anaesthesia; Rescue Analgesia; Sedation; Anxiety.

Introduction

Eighty percent of patients undergoing surgical procedures experience postoperative pain and require adequate pain relief for which many drugs are available nowadays [1]. Postoperative pain following orthopaedic surgeries has been shown to be a significant factor that delays patient recovery and contributes to serious complications. It may also result in larger use of healthcare resources and ultimately leads to poor outcomes. Spinal adjuvant drugs have been used in the subarachnoid anaesthesia. Clonidine is the most commonly used as an adjuvant in neuroaxial anaesthesia and analgesia[2].

Also calcium channel modulators like pregabalin and gabapentin are being increasingly used for postoperative pain management effectively. This has the advantage of avoiding the sideeffects of opioids. Pregabalin and Gabapentin are structural analogues of GABA-Gamma-aminobutyric acid. Pregabalin selectively binds to alpha-2 subunit of voltage dependent calcium channels which results in reduction of neurotransmitter release and hence decrease in neuronal hyper excitability [4,5]. Pregabalin is several times more potent than gabapentin. It is rapidly absorbed orally, achieves peak plasma levels within 30 minutes to 2 hours [6]. Pregabalin

Author's Affiliation:
*Assistant Professor, **Associate Professor, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India.

Corresponding Author:
Amrita Panda, Assistant Professor, Kalinga institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India Pin-751024.
E-mail: amritapanda1323@gmail.com

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has fewer side-effects with the most common adverse events being dizziness and somnolence.Any visceral irritation causes release of excitatory neurotransmitters which causes pain[7] and spinal anaesthesia is commonly given for orthopaedic procedures. So,the main objective of our study is to find out whether preoperative pregabalin has any effect in the postoperative analgesic requirement, anxiety, sedation scoreand satisfaction in patients undergoing lower limb surgery under spinal anaesthesia.

Patients & Methods

After obtaining clearance from ethics committee of our institution and informed consent from the patients, a randomized double blind placebo controlled study was conducted.60 patients ASA-1and 2 aged 20-60 years undergoing lower limb orthopaedic surgical procedures were chosen.

The exclusion criteria were patient refusal for spinal anaesthesia,local sepsis,spinal deformity, coagulopathy and bleeding disorders and patients on anticoagulant therapy.

Using computer derived random number sequence patients were allocated into two groups by means of sealed opaque envelopes, Group-1(control) and Group-2(study). Group-1 patients received the placebo drug given one hour prior to surgery in patients undergoing spinal anaesthesia. Group-2 patients received preoperative pregabalin 75mg one hour prior to surgery in patients undergoing spinal anaesthesia. All the patients received 0.5% hyperbaric bupivacaine 0.3mg/kg with 30 microgram clonidine intrathecallyusing 25 gauge Quincke needle in sitting posture.Preoperatively patients were nil per orally for 8 hours prior to the procedure.They were shifted to the preoperative room where baseline parameters and scales were assessed before the drug was given and transfer to the operation theatre. The scales of assessment chosen were Visual AnalogueScale(VAS) for anxiety[15].

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VAS score for anxiety

Baseline score was assessed in the preoperative room and one hour after premedication.Scoring of sedation was done using the Ramsay Sedation Score[15].

Score		Response
1	-	Anxious, agitated or restless or both
2	-	Co-operative,oriented,tranquil
3	-	Responding to commands only
4	-	Brisk response to light glabellar tap
5	-	Sluggish response to light glabellar tap
6	-	No response to light glabellar tap

Then the patients were transferred inside the operation theatre room and monitors placed like pulseoximetry,non-invasive blood pressure and electrocardiogram.Infusion was started using 18 gauge intravenous cannula with Ringer's lactate@15ml/kg and subarachnoid block was administered under aseptic measures with 25 gauge Quincke needle at L2-L3 or L3-L4 in sitting posture with 0.5% hyperbaric bupivacaine 0.3mg/kg with 30 microgram clonidine.Baseline parameters noted prior to start of anaesthesia were heart rate and blood pressure.

The following parameters were also measured:-

1-Demographic details like age,weight and height of the patients.

2-Blood pressure,heart rate of patients every 10 minutes intraoperatively and postoperatively every 30 minutes for first 4 hours.

3- The time of requirement of first rescue analgesic drug was noted and rescue analgesia intravenous diclofenac 75mg was administered when patient complained of pain on Visual Analogue Scale>5 in both the groups.Pain was measured using the Visual Analogue Scale 0 ————10(no pain——worst pain)where patients complaining of pain on VAS>5 were treated with first dose rescue analgesia.

4-Sedation and anxiety score,any adverse effect and patient satisfaction level were measured in the postoperative room.The patient's satisfaction for pain relief was recorded as-

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(Not satisfied) (highly satisfied).

Follow up & Results

Table 1:

N	Group 1 30	Group 2 30	P Value	Remark
Age (Years)	41.30+_10.02	40.80+_11.13	0.938	>0.05
Median	45	32		NO SIGNIFICANCE

(Inter Quartile Range)	(32-49)	(28-45)		
Height (cms)	159.5+_7.95	158.10+_8.04	0.891	>0.05
Median	160.4	159.6		NO SIGNIFICANCE
(Inter Quartile Range)	(157-162)	(157-164)		
Body weight (kgs)	52.20+_2.45	51+_2.91	0.861	>0.05
Median	50	48		NO SIGNIFICANCE
(Inter Quartile Range)	(48-54)	(47-55)		
Sex				
Male (%)	16 (53%)	17 (57%)		
Female (%)	14 (47%)	13 (43%)		

Table 2: Comparison of VAS Score for anxiety

	Preoperative [$Mean \pm SD$]	Postoperative [$Mean \pm SD$]
Group I (Control)	70.30 ± 11.96	71.20 ± 8.56
Group II (Treated)	76.30 ± 10.25	58.58 ± 9.87

Table 3: Probability value (Anxiety)

Difference between	Mann Whitney U Value	Standard Error of U	P value	REMARK
Placebo and Pregabalin	18.36	38.632	0.95	SIGNIFICANT

Table 4: Comparison of Sedation Score (Ramsay)

Score	Placebo (Control)	Pregabalin	Total
1	15	5	20
2	8	13	21
3	4	5	9
4	2	3	5
5	1	3	4
6	0	1	1
Total	30	30	60

Table 5: Probability value (Sedation)

Difference between	Mann Whiteny U Value	Standard Error of U	P value	Remark
Placebo and Pregabalin	19.28	43.982	0.95	Significant

Table 6: Time required for first rescue analgesia

	Placebo(Control) [$Mean \pm SD$]	Pregabalin [$Mean \pm SD$]	t-Value (degrees of freedom=58)	P Value	REMARK
N	30	30			
Time (Minutes)	232.45 ± 4.12	360.80 ± 2.58	8.98	> 95%	SIGNIFICANT

Table 7: Comparison of mean Blood Pressure (MBP)

	Placebo(Control) [$Mean \pm SD$]	Pregabalin [$Mean \pm SD$]
N	30	30
Preoperative	96.95 ± 6.92	99.25 ± 9.02
Postoperative	92.39 ± 7.25	88.36 ± 4.85
t-Value (degrees of freedom=29)	0.062	11.235
P Value	< 0.05	> 0.95
Remark	No Significance	Significant

Table 8: Comparison of Patient Satisfaction(VAS)

	Placebo(Control)	Pregabalin
N	30	30
$Mean \pm SD$	36.67 ± 11.52	78.32 ± 9.83

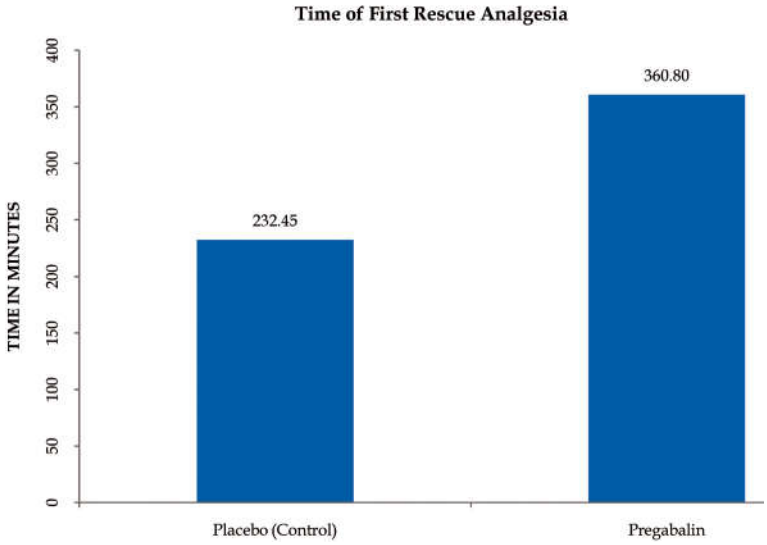

Fig. 1: Time of first rescue analgesia

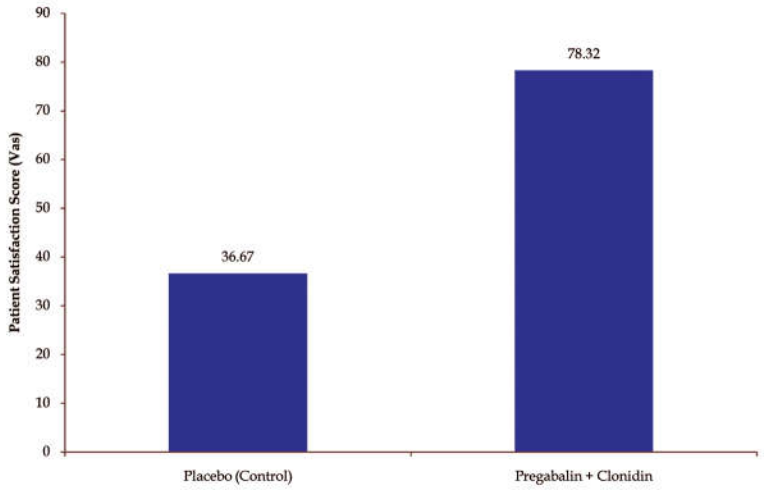

Fig. 2: Patient satisfaction score

Discussion

Postoperative pain is a model of mixed pain with nociceptive as well as neuropathic components. Postoperative pain leads to local inflammatory response, stimulation of nociceptors and nociceptive pain. Surgical stimulus also leads to sensitization of dorsal horn neurons,which is associated with augmentation of pain. This is referred to as central sensitization and represents the neuropathic component. Recent evidence suggests that alpha 2-D subunit calcium channel ligands like gabapentin and pregabalin,may aid in providing effective postsurgical analgesia[12].They mitigate central sensitization by calming down hyper excited dorsal horn neurones. This discovery has opened up the possibilities of using such drugs in the perioperative setting to counter the neuropathic component of postsurgical pain. These drugs were introduced as anticonvulsants presumably due to their ability to reduce neurotransmitter release from activated epileptic neurons[12]. Similarly their ability to reduce

neurotransmitter release from activated neurons in pain pathways and fear circuits may contribute to their role as an adjuvant in pain management and as anxiolytics.

Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that gaba-aminobutyric acid analogues such as gabapentin and pregabalin have antinociceptiveand antihyperalgesic properties[8]. Central neuronal sensitization may result in an amplification of postoperative pain [9]and that preoperative administration of these drugs may reduce the degree of central sensitization[10]. Due to its absence of hepatic metabolism, it has good pharmacokinetic properties and fewer drug interactions which make it a better drug than Gabapentin [11].

Pregabalin targets the alpha2-D subunit of voltage gated channels.The reduction in calcium flow through the channels decreases neuronal transmission in activated neuronal circuits, which may lead to decreased pain perception and analgesia [3].

The use of pregabalin in acute postoperative pain management has been evaluated in recent studies.In the first trial investigating the postoperative analgesic effect of pregabalin, a dose of 300mg pregabalin administered after dental operation was more effective in attenuating acute postoperative pain than placebo. It also had a longer duration of analgesia than ibuprofen [17].

Tippana and co-workers analysed 22 randomized, controlled trials examining the analgesic efficacy, adverse effects and clinical value of gabapentinoids(pregabalin, gabapentin) in postoperative pain. They concluded that gabapentinoids effectively reduce postoperative pain, opiod consumption and opiod related side effects after surgery [13].

In another study, Jokela and colleagues observed that preoperative administration of 300mg pregabalin, followed by the same dose repeated after 12 hours in patients undergoing laproscopic hysterectomy decreases oxycodone consumption. They also noted that the improved analgesia is associated with an increased incidence of adverse effects such as dizziness and blurred vision[14].

In a subsequent study by Jokela and colleagues [14] premedication with pregabalin 150 mg in patients undergoing daycase gynaecological surgery resulted in an improved quality of analgesia, but there was no difference in the amount of postoperative analgesics required or the degree of drowsiness.

In our study (Table 1) there was no significant difference as regards to age,weight and height of patients between the two groups(p-values-0.838 and 0.862 respectively), which is similar to other studies.

Anxiety scores (Table 2 and 3) were appreciably less in the treated group than placebo (Mann Whitney U=18.36, p value>0.95). R. Jokela et al [14] showed no reduction in anxiety scores with 75mg or 150mg Pregabalin. Also in the study by Kohli et al [16] no difference in anxiety scores were noted with higher doses of pregabalin like 150mg or 300mg,but the scores were better than the placebo group.

In our study similarly also the number of patients with various sedation scores (Table 4 and 5) increased in the treated group than the control group for which the Mann Whitney U value=19.28;p>0.95.No sideeffects like nausea, vomiting, dizziness,blurred vision were noted and patients were more satisfied in the treatment group than the control group.

The incidence of sedation is more with higher doses of pregabalin(150mg, 300mg) as in the same study by Kohli et al[15].

In a study conducted by R. Jokela et al[14] they found that 300mg pregabalin was more effective than pregabalin 150mg. The incidence of dizziness, headache, blurred vision were higher in the 300mg pregabalingroup. Also other studies showed that pregabalin has somnolence and dizziness as the most common side effects.

In our study of the time required for the first rescue analgesic drug(Table 6 and Figure 1) is more in the treated group than placebo(for 58 degree of freedom tc=8.98 with p value>0.95)

In the study conducted by Kohli et al[15]pregabalin 300 mg showed more effective prolongation of analgesia than pregabalin 150mg or placebo after spinal anaesthesia and this was correlating with the half life of pregabalin which is 4.6-6.8 hours.The advantage was that along with prolongation of analgesia there was no haemodynamic instability.

Agarwal et al [16] showed that single dose of pregabalin(150mg) was effective in reducing postoperative pain after laparoscopic cholecystectomy.

Hill et al [17] compared pregabalin(50mg, 300mg) to placebo in patients undergoing elective surgery for molar extraction and found that pain relief was better in the 300mg pregabalin group.

In a study conducted by Wichari et al [18] 300 mg pregabalin administered one hour preoperatively before abdominal hysterectomy significantly reduced pain score and improved satisfaction score at 24 hour postoperatively.

In our study conducted in our instituition significant difference in lowest mean blood pressure(Table 7) was observed between preoperative and postoperative periods in the treatment group(calculated value of tc=11.235; p0.95)No sideeffects like nausea, vomiting, dizziness, blurred vision were noted in our study and also patients were more satisfied in the treatment group than the control group(Table 8 and Figure 2). There was reduction in the haemodynamic parameters both blood pressure and heart rate due to the effect of anaesthesia and adjuvants used, but not much significant difference was found between both the treated and the control group.

Similarly in the study conducted by R. Jokela et al[14] they found that 300mg pregabalin was more effective than pregabalin 150mg. The incidence of dizziness, headache and blurred vision were higher in the 300mg pregabalingroup.Also other studies showed that pregabalin has somnolence and dizziness as the most common sideeffects. Also many other studies show reduction in blood pressure and heart rate in all the groups which is significant between pregabalin and placebo group.

Similarly the study by Kohli et al[15]patient satisfaction showed good results with pregabalin 300mg group than 150mg group than placebo. We did not use pregablin at higher doses as mentioned in various literatures, so we do not know whether this is the ideal dose which could be used alone with adjuvants in spinal anaesthesia.The limitation of our study was that the study period was restricted upto the time limit when the first dose of rescue analgesic drug was administered.

Declaration: The authors there is no conflict of interest regarding the publication of the paper.

Conclusion

From this study we conclude that oral pregabalin at the dose of 75mg does reduce the anxiety level and also prolongs the time period for the need of the first dose of rescue analgesic requirement,patients were more satisfied than the placebo group and no sideeffects were noted.

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