A Comparative Study of Oral Preemptive Gabapentin Versus Pregabalin for Acute post Operative Pain After Lower Limb Orthopaedic Surgeries Under Spinal Anaesthesia

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Abstract

Introduction: High-quality analgesia after surgery is still a major challenge. A multimodal analgesia approach has been suggested to improve postoperative pain control.

Preemptive administration of adjuvant drugs like pregabalin and gabapentin helps in better post operative pain relief, decreases opioid requirement and its side effect. Gabapentin and pregabalin have been used as a part of multimodal analgesia in neuropathic as well as post operative pain. Although pregabalin and gabapentin are effective in treating chronic neuropathic pain, there is limited evidence regarding their effectiveness in post operative pain.

Our study was designed to compare the analgesic efficacy of pregabalin and gabapentin with respect to reduction in post operative pain scores, total post operative requirement of analgesics and their side effects in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia .

Methods : After approval from institutional ethical committee, written informed consentwere taken from patients.About 60 patients, aged 18-60 yrs, belonging to ASA status 1 and 2 scheduled for lower limb orthopaedicsurgeries under spinal anaesthesia were randomized into 2 groups. Group G (gabapentin) received 600mg of gabapentin gropu p pragablin received 150mg of pregablin one hour before the asministration of spinal anaesthesia using 3ml of 0.5% hyperbaric bupivacaine Pain was assessed by visual analogue scale post operatively and every 2 hourly thereafter, which was explained to the patient during preoperative visit. Any patient with vas scale of more than 5 were administered diclofenac 1mg/Kg injection intramuscularly. Time since spinal anaesthesia to first dose of analgesic and total dose of analgesic in first 24 hours was recorded. Side effects like dizziness, somnolence, diplopia, vomiting, confusion and urinary retension was recorded in first 24 hour of post operative period.

Results: The total postoperative analgesic time was 9.20hin Group G whereas 13.03hin Group P (HS, $P < 0.009$). Total dose of analgesics in first 24h was 48.42mgin Group P and

63.33mgin Group G and was highly significant (*P*=0.007). Dizziness and somnolence were the only side effects noticed in both groups.

Conclusion: Oral preemptive use of pregabalin is more effective in prolongation of post-spinal analgesia than gabapentin and decreases the requirement of analgesic in first 24hours in lower limb orthopaedic surgeries under spinal anaesthesia,Pregabalin is moreeffective than Gabapentin for acute postoperative pain and can be used as part of multimodal therapy if not as sole analgesic.

Keywords: Pregabalingabapentin ,preemptive analgesia, postoperative pain .

INTRODUCTION

Pain is the common complaint during post operative period. Many a times post operative pain is under estimated and managed less intensively. Better pain control during post operative period is still a major challenge .

Post operative pain has got negative psychological and physiological effect on the patient, Effective post operative analgesia results in improvement of respiration, decreased stress on cardiovascular system , early return of gastrointestinal motility, early ambulation and discharge from hospital.

Surgical injury causes secondary changes in the central nervous system which may lead to post operativehyperalgesia and reduction in pain threshold and causes central sensitization .

Oral therapy to treat post operative pain include opioids, NSAID's or cox-2 inhibitors. Still there is no single ideal drug to control acute pain, as opioids are associated with vomiting , risk of respiratory depression and addiction.

The use of NSAID's and cox -2 inhibitor is associated with gastric intolerance, gastrointestinal bleed and renal injury. To minimize the side effects of opioids and NSAID's adjuvant drugs are being used preemptively to treat post operative pain which improves the quality of opioid analgesia and decreases opioid requirement and its side effects .

Our study was designed to compare the analgesic efficacy of pregabalin and gabapentin with respect to reduction in post operative pain scores, total post operative requirement of analgesics and side effects in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia .

MATERIALS AND METHODS

Source of data:

The data for the study was collected from patients admitted to S S Institute of Medical Sciences and Research Centre, Davangere for lower limb orthopaedic surgeries over a period of two years.

Inclusion criteria:

Patients with

- Age group of 18- 60 years.
- American Society of Anaesthesiologist's Physical status class I and II
- Undergoing elective lower limborthopaedic surgeries under spinal anaesthesia were included.

Exclusion criteria:

Patients with

- Known drug allergy to pregabalin or gabapentin

- Uncontrolled hypertension, Diabetes mellitus, ischemic heart disease, Cerebrovascular disease, renal and hepatic disease.
- History of alcohol and drug abuse.
- Patient with any general contraindications for spinal anaesthesia.
- Patient with chronic pain, neurological disorders and patients on NSAID's and other analgesics were excluded.

Sample Size:

- Sample size was calculated in consultation with the statistician Thirty was the smallest number in each group where any result could be statistically significant hence sample size was taken as 30 patients per group (total 60 patients)

Method of collection of data:

This study was conducted in S S Institute of Medical Sciences and Research Centre, Davangere. In a prospective non randomized comparative study in 60 patients posted for elective orthopaedic lower limb surgeries under spinal anaesthesia with American Society of Anaesthesiologist's class I and II aged 18 - 60years old were allocated in two equal groups of 30 patients and the data was analysed after clearance from the ethical committee.

Patients were subjected to preanaesthestic assessment and informed consent was taken from all patients. All patients were kept nil orally for 6 hours. 1 hour before the administration of spinal anaesthesia in patients undergoing electivelower limborthopaedic surgeries. Group G patients were given an oral single dose of 600mg gabapentin, whereas 150mg of pregabalin was given in group P. Routine monitoring in the form of NIBP, Pulse oximetry and ECG were instituted on arrival in operation theatre. Patients were preloaded with 10ml/Kg ringer lactate solution before administration of spinal anaesthesia with 3ml of 0.5% bupivacane (15mg). Fluid administration was continued intraoperatively and hypotension if any was treated with fluid replacement and ivmephenteramine.

Pain was assessed by visual analogue scale post operatively and every 2 hourly thereafter, which was explained to the patient during preoperative visit. Any patient with vas scale of more than 5 were administered diclofenac1mg\Kg injection intramuscularly. Time since spinal anaesthesia to first dose of analgesic and total dose of analgesic in first 24 hours were recorded. Side effects like dizziness, somnolence, diplopia, vomiting, confusion and urinary retension was recorded in first 24 hour of post operative period.

Statistical Analysis:

Statistical Analyses was performed with IBM SPSS program for Windows Version 22. Categorical variables were presented as frequency and percentages. To study the association between categorical variables Chi Square test and if the cell values were small Fisher's Exact Test was used .

Continuous variables represented as mean and Standard Deviation. Inter group comparison was done with Unpaired t test.

A P value of <0.05 is considered as significant.

Results

Sixty patients, thirty in each group, were included in the study and analyzed. The groups were comparable with respect to demographic characteristics like age, gender, ASA physical status and duration & type of surgery (Table 1 to 5)

Table 1: Age Distribution

Age	Group-G	Group-P	Total
< 50	14	16	30
> 50	16	14	30
Total	30	30	60
Chi Square test = 0.267, P<0.398, NS			

Age	N	Mean	Std. Deviation	Unpaired t Test	
				t Value	P Value
Group-G	30	48.83	5.33		
Group-P	30	49.53	2.05	0.671	P<0.505

Table 2: Gender Distribution

Gender	Group-G	Group-P	Total
Male	15	15	30
Female	15	15	30
Total	30	30	60
Chi Square test = 00.00,			

Table 3: ASA Grade

ASA Grade	Group-G	Group-P	Total
I	23	22	45
II	7	8	15
Total	30	30	60
Chi Square test = 0.089, P<0.766, NS			

Table 4: Duration of Surgery in Min

DURATION OF SURGERY IN MIN	N	Mean	Std. Deviation	Unpaired t Test	
				t Value	P Value
Group-G	30	100.84	8.09		
Group-P	30	98.17	8.30	1.26	P<0.213

The type of surgery conducted in two groups were also similar (Table 5).

Table 5: Distribution of patients according to type of surgery

Type of surgery	**Group G**	**Group P**
Tibial implant removal	2	2
Diagnostic arthroscopy	1	1
ORIF with IMIL Nailing for Tibia	10	10
Patellectomy	2	2

Retrocalcaneal bursitis for excision	2	2
ORIF with IMIL Nailing for femur	8	7
Fracture neck of femur for PFN	5	6
Total	**30**	**30**

Table 6: TIME FROM SPINAL TO RESCUE ANALGESIC

TIME FROM SPINAL TO RESCUE ANALGESIC						
Group-G		Group-P		Unpaired t Test		
Mean	Std. Deviation	Mean	Std. Deviation	t Value	P Value	Inference
9.20	4.05	13.03	6.67	2.692	P<0.009	HS

Table 7: POST OPERATIVE PAIN SCORE ASSESMENT BY VISUAL ANALOGUE SCALE

POST OPERATIVE PAIN SCORE ASSESMENT BY VISUAL ANALOGUE SCALE							
Time (In Hrs)	Group-G		Group-P		Unpaired t Test		
	Mean	Std. Deviation	Mean	Std. Deviation	t Value	P Value	Inference
0 Hrs	0		0				
2 Hrs	1.00	0.26	0.93	0.25	1	0.321	NS
4 Hrs	1.97	0.32	1.77	0.43	2.04	0.046	S
6 Hrs	2.93	0.58	2.27	0.74	3.876	0.000	HS
8 Hrs	3.87	0.63	2.77	0.82	5.843	0.000	HS
10 hrs	4.53	1.22	2.93	0.78	6.026	0.000	HS
12 Hrs	0.20	0.55	3.50	0.82	-18.297	0.000	HS
14 Hrs	1.03	0.41	4.53	1.11	-16.235	0.000	HS
16 Hrs	1.87	0.43	0.43	1.01	7.163	0.000	HS
18 Hrs	2.03	0.41	1.33	0.80	4.247	0.000	HS
20 Hrs	2.20	0.48	2.23	0.68	-0.219	0.827	NS
22 Hrs	3.03	0.32	3.10	0.48	-0.632	0.53	NS
24 Hrs	3.93	0.45	3.87	0.43	0.584	0.561	NS
NS = NOT SIGNIFICANT, S = SIGNIFICANT, HS = HIGHLY SIGNIFICANT							

Table 8: NO OF ANALGESIC DOSES IN FIRST 24 HOUR

NO OF ANALGESIC DOSES IN FIRST 24 HOUR						
Group-G		Group-P		Unpaired t Test		
Mean	Std. Deviation	Mean	Std. Deviation	t Value	P Value	Inference
1.00	0.37	0.90	0.40	1	0.321	NS

NO OF ANALGESIC DOSES IN FIRST 24 HOUR			
Number	Group-G	Group-P	Total
Zero	2	4	6
One	26	25	51
Two	2	1	3
Total	30	30	60
Chi Square test = 1.02, P<0.601, NS			

Table 9: TOTAL ANALGESIC DOSES REQUIREMENT IN FIRST 24 HOUR

TOTAL ANALGESIC DOSES REQUIREMENT IN FIRST 24 HOUR						
Group-G		Group-P		Unpaired t Test		
Mean	Std. Deviation	Mean	Std. Deviation	t Value	P Value	Inference
63.33	22.36	48.42	19.00	2.783	0.007	HS

Table 10: Side Effects

Side effects	Group-G	Group-P
Dizziness	7	5
Somnolence	4	4
Urinary Incontinence	1	0
Total	12	9
Chi Square test = 1.564, P<0.668, NS		

The total postoperative analgesic duration (time from spinal analgesia to first dose of analgesic) was 9.20hin Group G whereas 13.03hin Group P, which was highly significant (*P* < 0.009) (Table 6) .

In Group G, two patients did not require any analgesic as compared to four in Group P. A single dose was required in first 24 hours in 26 patients in Group G as compared to 25 patients in Group P and only two patients in Group G and one in Group P required two doses in first 24 hours. Total number of analgesic doses given in first 24h was lower in Group P (mean 0.9 as against 1.0 in Group G) but not statistically significant.(Table -8)

The mean total dose of analgesic in first 24h was 63.33mg in Group G, whereas 48.42mg in Group P and it was not statistically significant (P<0.05).(Table-9)

Dizziness and somnolence were the only side effects noticed in both groups. four patients in group G and three patients in group P experienced somnolence and hence was not significant.

Dizziness was experienced in seven patients (23%) in Group G as compared to six patients (20%) in Group P, which was again not significant (P<0.05).

One patient in the Group G required bladder catheterization following urinary retention. No other side effects such as nausea, vomiting, ataxia, vertigo, visual disturbances and headache were observed in either group.

DISCUSSION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or expressed in terms of such damage is the definition given by international Association for the study of pain [1]

Postoperative pain is a common consequence of surgery with an incidence ofaround 80%. In one US survey of 250 patients, 39% of patients withpostoperative pain experienced severe or extreme pain [2].

Pain is cited as one of the main concerns of patients undergoing surgical procedures[2] (59%)

The consequences of postoperative pain are not limited to negativepsychological effects for the patient. Detrimental physiological sequelae canresult from postoperative pain, which may lead to negative postoperativeoutcomes. Postoperative pain is associated with increase in postoperativedelirium [3],pulmonary complications[4] and increase in the stress response to surgery [5]. Furthermore, postoperative pain can negatively affect the patient experience.Pain can interfere with general activities such as walking and sleeping while also negatively affecting mood[6].

The effects of postoperative pain are not limited to the immediate postoperativeperiod. Indeed, acute postoperative pain is associated with the development of chronic pain in 10-50% of patients, with incidence dependent on the type ofsurgery[7]

Various authors have studied the pain pathways and the pathophysilogy of nociception after surgical stimulus. Surgical stimulus releases various catabolic neurohumoral substances like bradykinin, prostaglandins and substance p which stimulate peripheral nerve endings. The nerve impulses in turn are transmitted through the A delta and C fibers of the spinal cord to the central nervous system. Repeated stimulation of peripheral nerves can decrease the threshold for the stimulation of the nerves leading to augmentation of stimuli and ultimately leading to central sensitization of pain. Thus the brain starts perceiving even mild pain as severe as a result of this phenomenon.[8,9,10]

Allodynia and hyperalgesia are cardinal signs and symptoms of neuropathic pain but they are also often present after trauma and surgery.Sensitization of neurons in the dorsal horns, a mechanism in neuropathic pain, has been demonstrated in acute pain model.[11,12] The persistence of this mechanism may be responsible for the increasingly recognized problem of chronic pain after surgery.[13,14]

Earlier it was considered that the pathophysiology and management of postoperative pain and neuropathic pain were different anddistinct entity but now they are regarded as same as far management is concerned.

A new concept of pain control has recently been increasingly used in the form of preventive or preemptive analgesia. This is nothing but administration of analgesic drugs prior to surgical incision so as to reduce the transmission of impulses from periphery to CNS. This technique has also shown to reduce central sensitization and hence reduce the intensity of postoperative pain.[15,16,17,18]

High quality pain control after surgery is still a major challenge. Oral therapy may include Opioids, NSAIDS or COX-2 inhibitors. Though none of the drug therapy is ideal for controlling acute pain, as opioids are inevitably associatedwith emesis, risk of respiratory depression and addiction. The use of NSAIDs and COX-2 inhibitors is limited by complications like dyspepsia, GI bleed, renal failure, etc.

A multimodal approach has been suggested to improve postoperative analgesia and to reduce opioid related side effects.

Opioids, NSAIDs and local anaesthetics were the toolsfor dealing with acute pain; while anticonvulsants and tricyclicantidepressants were given to the chronic pain patients. However, recent investigations and trials indicated that these drugs also have a role in acute pain management especially postoperative pain. Anticonvulsants, gabapentin and pregabalin which are being used for chronic pain are also being used currently for acute pain.[15]

Preemptive analgesia has been shown to be more effective in control of postoperative pain by protecting the central nervous system from deleteriouseffects of noxious stimuli and resulting allodynia, and increased pain.Gabapentinoids(Gabapentin and pregabalin) have antiallodynic and antihyperalgesic properties useful for treating neuropathic pain and may also be beneficial in acute postoperative pain. Several studies have reported the useful-ness of Gabapentin and pregabalin in perioperative settings resulting in reduced postoperative pain, postoperative analgesic requirement, side effects, prolongation of analgesia, and higher patient satisfaction. [31-34]

Recent studies[30,33]suggest that gabapentinoids may be useful in the perioperative setting, as an adjuvant to parenteral opioids.

Gabapentin is a structural analogue of gamma-aminobutyricacid (GABA) which was initially introduced as an antiepileptic drug. It binds to α2-δ protein subunit of voltage-gated calcium channels widely distributed in the central and peripheral system. This inhibits calcium influx and reduces excitatory neurotransmitter release in pain pathways.[2]Pregabalin has an amino acid substitution at third position, which allows increased lipid solubility and diffusion across blood brain barrier, better pharmacokinetic profile and fewer drug interactions due to the absence of hepatic metabolism.[3] It is a potent and more effective analogue of gabapentin and acts as a better ligand for α2-δ protein subunit than gabapentin.[4] It has shown superior analgesic potency than gabapentin in rodent models of neuropathic pain.[5]Pregabalin has been found to be equally effective to gabapentin, however, at much lower doses. It is due to much higher bioavailability (90% vs. 33–66%) with low intersubjectvariability [6]Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins.[7,8] It does not induce or inhibit liver enzymes such as the cytochrome P450 system. Therefore, pregabalin is unlikely to cause, or be subject to, pharmacokinetic drug–drug interactions studies. It is excreted virtually unchanged (<2% metabolism) by the kidneys and the elimination half-life ranges from 5.5 to 6.7 hours. This is not true with gabapentin as plasma concentrations have been found to have a non-linear relationship to increasing doses. The elimination half-life is 5–9 hours.[9]

Anand T Talikoti et al, in a study concluded that pregabalin in doses of 150mg and 225mg used preemptivelyoffers good postoperative pain control and decreases the requirement of analgesics in the first 24 hrs after spinal anaesthesia. Higher doses of pregabalin 225mg was associated with increased incidence of adverse effects. Hence single highest safe dose of pregabalin (150mg) was selected for this study.[30] The antihyperalgesic effects of pregabalin have been observed at dosages twofold to fourfold lower than that of gabapentin in rodent models of neuropathic pain.[28] Our purpose of choosing gabapentin 600 mg was also to find whether a dose below the already tested dose of 1200 mg could be equally efficacious at the cost of less side effects as the absorption of gabapentin is limited by saturable, active, dose-

dependent transport in the gastrointestinal tract. So the doses for two drugs was selected that is 150mg for pregabalin and 600mg for gabapentin.

Saraswat et al. in their study observed that preemptive oral pregabalin and gabapentin prolong the analgesic effects of spinal analgesia, which far exceeds the normal duration of spinal analgesia. The analgesic effect is longer lasting followingpregabalin as compared to gabapentin (8.98h in Gabapentin group Vs 14.17h in Pregabalin group). The difference in two groups was highly significant. ($P < 0.009$) Although total number of analgesic doses and total dose of analgesic in first 24h were lower in Pregabalin group, the difference was not statistically significant.($P > 0.05$)

Our present study shows that in lower limb othopaedic surgeries under spinal anaesthesia , in the absence of opioid or non opioid analgesics,preemptive oral pregabalin and gabapentin prolong the analgesic effects of spinal analgesia, which far exceeds the normal duration of spinal analgesia. The analgesic effect is longer lasting following pregabalin as compared to gabapentin (9.20hin Gabapentin group Vs13.03hin Pregabalin group). The difference in two groups was highly significant. ($P < 0.001$)

Although total number of analgesic doses in first 24h were lower in Pregabalin group, the difference was not statistically significant. Total dose of analgesic in first 24h where lower in pregabalin group than gabapentin and was statistically highly significant. hence it can reasonably be presumed that dose of perioperative analgesics could be reduced. The observations of our study were almost similar to that of study by saraswat et al. [29]

Somnolence and dizziness are the two most common side effects associated with gabapentin and pregabalin. The incidence reported in present study is similar to earlier studies.[27] This is usually not disabling and antianxiety effect has been found to be beneficial in some studies.

CONCLUSION:

Oral preemptive use of pregabalin is more effective in prolongation of post-spinal analgesia than gabapentin and decreases the requirement of analgesic in first 24hours in lower limb orthopaedic surgeries under spinal anaesthesia,Pregabalin is moreeffective than Gabapentin for acute postoperative pain and can be used as part of multimodal therapy if not as sole analgesic.

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