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A study on side effects oral gabapentin versus oral pregabalin for orthopedic surgery under spinal anesthesia

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Abstract

Pregabalin is a structural analogue of gamma aminobutyric acid, substituted at the 3-position; this facilitates diffusion across the blood-brain barrier. Efficacy of pregabalin has been proven in neuropathic pain, incisional injury, inflammatory injury. Its mechanism of action is probably the same as gabapentin but it is more lipid soluble and has superior pharmacokinetic profile. Due to its sleep modulating effects, it has been used as an anxiolytic. Pregabalin increases stages III-IV sleep phases and also decreases awakening at night. Patients were counselled regarding the tablet used in preemptive analgesia its advantages and disadvantages, the purpose of its use, they were also explained regarding the follow up till 24hr and spinal anaesthesia procedure to be used in the study and consent was taken for the same. Ramsey sedation score of all the patients was score = 2. None of patients complained of dizziness in group A. Ramsey sedation score of all the patients was score = 2.2.85% (1 patient) complained of dizziness in group B.

Keywords: Side effects, oral gabapentin versus, oral pregabalin

Introduction

Gabapentin [1-(amino-methyl)-cyclohexane acetic acid], structural analogue of gamma aminobutyric acid, which was introduced in 1994 is a novel antiepileptic agent used basically to refractory partial seizures and has proved to be especially effective at relieving allodynia and hyperalgesia.

Gabapentin has been clearly demonstrated to be effective for the treatment of neuropathic pain in diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, painful neuropathy from HIV infection, cancer and complex regional pain syndromes.

Gabapentin's mechanism of action is not quite clear, but most likely involves inhibition of neuronal α2δ subunit voltage-gated calcium currents (VGCC) and suppression of excitatory neurotransmitter release (glutamate), leading to decreased postsynaptic excitatory responses [1].

The molecular weight is 171.34 and at physiological pH it is highly charged, existing as a zwitterion with two pKa values of 3.68 and 10.70. Gabapentin, available only as oral

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preparations, is absorbed in the small intestine by a combination of diffusion and facilitated transport. Its transport from the gut is facilitated by its binding to a receptor linked to a saturable l-amino acid transport mechanism. Brain tissue concentrations are 80% the plasma level. Gabapentin is not metabolized in humans and is eliminated unchanged in the urine. It undergoes first-order kinetic elimination and renal impairment decreases gabapentin elimination in a linear fashion with a good correlation with creatinine clearance. Unlike other anticonvulsant drugs, it does not induce or inhibit hepatic microsomal enzymes [2].

Gabapentin has its limited use because of its side effects like nausea, vomiting, dizziness, visual disturbance and sedation.

Pregabalin is a structural analogue of gamma aminobutyric acid, substituted at the 3- position; this facilitates diffusion across the blood-brain barrier. Efficacy of pregabalin has been proven in neuropathic pain, incisional injury, inflammatory injury. Its mechanism of action is probably the same as gabapentin but it is more lipid soluble and has superior pharmacokinetic profile. Due to its sleep modulating effects, it has been used as an anxiolytic. Pregabalin increases stages III-IV sleep phases and also decreases awakening at night [3].

Binding affinity for the α2-δ subunit, and potency, is six times more than that of gabapentin. Up regulation of α2-δ subunit may play an important role in hypersensitization processes. Pregabalin inhibits modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections such as the neocortex, amygdala, and hippocampus [4].

Pregabalin is rapidly absorbed with peak blood concentrations within 1 h. Average bioavailability exceeds 90% and is independent of dose, which may produce a more predictable patient response. The elimination half-life of pregabalin ranges from 5.5 to 6.7 h, and is independent of dose & repeated dose administration. Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins. It is renally excreted and 98% of the absorbed dose is excreted unchanged in the urine. Pregabalin elimination is nearly proportional to creatinine clearance. Pregabalin clearance is reduced in subjects with impaired renal function. No pharmacokinetic drug-drug interactions have been identified [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 inter subject variability. As with gabapentin, pregabalin is inactive at GABAA and GABAB receptors, is not metabolically converted into GABA, and does not alter the GABA uptake or degradation and thus increasing GABA at the presynaptic receptors.

Pregabalin is well tolerated and associated with dose dependent adverse effects that are mild-to moderate and are usually nausea, vomiting, transient, dizziness, somnolence, myoclonus, asterixis [6].

Methodology

The study population was randomly divided into two groups of 35 patients each with the help of a computer-generated table of random numbers into

Group A: Oral Gabapentin 600 mg.

Group B: Oral Pregabalin 75 mg.

Pre-anesthetic evaluation was done on the day before surgery assessing:

- General condition of the patient.
- Airway assessment.
- Examination of the Cardiovascular system.
- Examination of the Respiratory system.
- Examination of Central nervous system

Patients were counselled regarding the tablet used in preemptive analgesia its advantages and

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disadvantages, the purpose of its use, they were also explained regarding the follow up till 24hr and spinal anaesthesia procedure to be used in the study and consent was taken for the same.

The necessary basic investigations depending on patient were advised that included:
1. Complete blood count.
2. Urine routine.
3. Standard 12-lead electrocardiogram.
4. X-ray chest.
5. Blood sugar.
6. Blood urea, serum creatinine.
7. Bleeding time/clotting time.
8. Serum electrolytes.
9. LFT/RFT/PT-INR were indicated

All patients included in the study were kept nil per oral for a minimum period of 6 hours before the surgical procedure. (20).
On the arrival of patient in the waiting room tablet assigned according to randomization number was given 1.5 hr before the procedure with sips of water.

Blinding: The identical looking study medications were packed and sealed in opaque covers labelled with investigators name, project title and randomization number. Each patient received appropriate randomization number and allocated to their group according to the number. No anaesthetist or assessor were aware of the group assignment until the entire 70 patients included in the assessment were completed.

Double Blinding: was done by keeping both patient and the investigator blinded to the contents of the packet.
Anaesthesia was standardized in all patients, all cases were preloaded with 10 ml/kg ringer lactate before giving spinal anaesthesia for various surgical procedures.15 mg of 0.5% bupivacaine heavy was used as sole anaesthetic agent for spinal anaesthesia. After surgery all patients were transferred to post-operative ward.

Side effects

Nausea, vomiting, dizziness, sedation were observed and recorded both intra-operatively and post-operatively for 24 hour at 2, 4, 6, 8, 10, 12, 16, 20, 24hr.
The severity of PONV was graded on a four-point ordinal scale (4).

0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea with vomiting.

Results

In Group A, minimum and maximum age was 20 years and 60 years respectively with a mean age of 40.40 ± 12.90 years. In Group B, minimum and maximum age was 18 years and 60 years respectively with a mean age of 38.89 ± 13.41 years. There was no statistically significant difference between two groups (P= 0.2857).

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Table 1: Age distribution

Age (in years)	Group A (n=35)		Group B (n=35)		
	No. of patients	Percent	No. of patients	Percent	
18-30	9	25.71	16	45.71	
31-40	11	31.43	9	25.71	
41-50	5	14.29	6	17.14	*P* value 0.2857
51-60	10	28.57	4	11.43	
Mean ±SD	40.40 ± 12.90 years		38.89 ± 13.41 years		
Minimum	20 years		18 years		
Maximum	60 years		60 years		
Unpaired t test was used for statistical analysis					

In Group A the percentage of male and female patients was 74.29% and 25.71% respectively. In Group B the percentage of male and female patients was 77.14% and 22.86% respectively. There was no statistically significant difference between two groups ($P = 0.7805$).

Table 2: Sex distribution

Sex	Group A (n=35)		Group B (n=35)		
	No. of patients	Percent	No. of patients	Percent	
Male	26	74.29	27	77.14	*P* value 0.7805
Females	9	25.71	8	22.86	
Chi-square test was used for statistical analysis					

In Group A percentage of patients with ASA physical status 1 and 2 were 88.57% and 11.43% respectively, while in Group B percentage of patients with ASA physical status 1 and 2 were 91.43% and 8.57% respectively. There was no statistical significant difference between the two groups ($P = 0.6903$).

Table 3: ASA Physical Status

Status	Group A (n=35)		Group B (n=35)		
	No. of patients	Percent	No. of patients	Percent	
1.	31	88.57	32	91.43	*P* value 0.6903
2.	4	11.43	3	8.57	
Chi-square test was used for statistical analysis					

Side effects were noted intraoperatively and postoperatively for first 24 hr, In Group A, 8.57% (3 patients), 5.71% (2 patients) were hypotensive and complained of nausea respectively. None of patient complained of vomiting. Ramsey sedation score of all the patients was score = 2. None of patients complained of dizziness.

In Group B, 11.42% (4 patients), 2.85% (1 patients) were hypotensive and complained of nausea respectively. None of patient complained of vomiting. Ramsey sedation score of all the patients was score =2. 2.85% (1 patient) complained of dizziness. There was no statistical difference between either groups.

Table 4: Side effects

Side effects	Group A(n=35)		Group B(n=35)		*P* value
	No. of patients	Percent	No. of patients	Percent	
Hypotension	3	8.57	4	11.42	0.6903
Nausea	2	5.71	1	2.85	0.5551
Vomiting	0	0	0	0	-
Ramsey Sedation Score = 2	35	100	35	100	-
Dizziness	0	0	1	2.85	0.3138

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Discussion

Side effects like hypotension, nausea, vomiting, sedation, dizziness were noted both intra op and post operatively for first 24 hr.

The side effects like nausea and dizziness were comparable with both the groups. When we compared our study with previous studies who used much higher doses of Gabapentin or Pregabalin like Bon Sebastian *et al*., [7] Kim *et al*., [8] Peach *et al*., [9] Godrat *et al*., [10] Induja Rajendran *et al*., [11] V Saraswati *et al*., the intergroup side effects were comparable which was in consistent with our study, but the incidence of vomiting was higher in comparison to our study. Geetha Chamanalli *et al*., who compared Pregabalin 75mg, 150mg with placebo found lower incidence of nausea and vomiting with Pregabalin 75 mg group as observed in our study [13]. None of the patient of either groups complained of vomiting which was similarly seen by Usha Bafna *et al*., who used Gabapentin 600mg, dose same as used in the present study [14]. All the patients in the study remained calm and tranquil with Ramsey sedation score 2 which was same as seen by Usha Bafna *et al*., Godrat *et al*., and Geetha Chamanalli *et al*., Induja Rajendran *et al*., with higher doses showed higher Ramsey sedation scores. So with optimal analgesic doses of Gabapentin and Pregabalin an attempt was made through our study to provide patient anxiolysis that provides good patient satisfaction by augmenting rapid post op recovery.

Post op patient are over lot of drugs like pain killers, nutritional supplements, antibiotics and also patient are asked to stay nil by oral for hours after surgery. This along with anxiety causes nausea and vomiting. By decreasing the dosages, incidence of nausea and vomiting was reduced and patient remained calm and conscious throughout the perioperative period. Due to the fewer number of studies with these drug dosages in patient undergoing lower limb surgeries, we designed this clinical trial. More studies are to be conducted to compare the intra and post-operative side effects of Gabapentin 600mg and Pregabalin75mg without compromising analgesic efficacy.

Conclusion

Side effects were noted intraoperatively and postoperatively for first 24hr, In Group A, 8.57% (3 patients), 5.71% (2 patients) were hypotensive and complained of nausea respectively. None of patient complained of vomiting. Ramsey sedation score of all the patients was score = 2. None of patients complained of dizziness.

In Group B, 11.42% (4 patients), 2.85% (1 patients) were hypotensive and complained of nausea respectively. None of patient complained of vomiting. Ramsey sedation score of all the patients was score = 2. 2.85% (1 patient) complained of dizziness. There was no statistical difference between either groups.

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