Original Research Article

Efficacy of Gabapentin on combined spinal epidural anesthesia for lower limb orthopedic surgeries

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Abstract

Background: Orthopedic patients can be particularly challenging for anesthesiologists. Many orthopedic procedures are well suited for regional anesthetic techniques. Epidural analgesia is the one method which can be performed easily, can provide intra-operative and postoperative analgesia better than other methods with better patient comfort.

Aim: To study the efficacy of Gabapentin on combined spinal epidural anesthesia for lower limb orthopedic surgeries with respect to postoperative epidural analgesic requirements.

Materials and methods: This study involved, using Gabapentin and the effects of it on combined spinal epidural anesthesia in respective of postoperative epidural analgesic requirements. 60 patients of ASA I, II undergoing lower limb surgeries were randomly assigned into two groups Group G, and Group P. Surgery was done under combined spinal epidural anesthesia. The patients' in-group G received three Gabapentin capsules (1200 mg). In-group P, three placebo capsules were given. Subarachnoid block was performed with 0.5% Bupivacaine 3 ml (Hyper baric). Epidural analgesia was given by 0.125%bupivacaine with Fentanyl 2 µg/ml (8 ml volume).

Results: The parameters observed were the mean time to regress by two segments from higher level of blockade (90.7 ± 4.7 minutes (G) VS 85.8 ± 3.5 minutes (P), $p < 0.05$), the time to require first epidural analgesic supplementation (228.5 ± 19.96 minutes (G) VS 195.5 ±13.3minutes (P), $p < 0.05$), the time interval between the epidural analgesic supplementations (8.25 ±1.5 hours (G) VS 4.8± 0.5 hours (P), $p < 0.05$), the total number of epidural requirements in first 24 hours (2 ± 0.2 (G) VS 2.93 ± 0.2(P), $p<0.05$) , and in the next 24 hours (3 (G) VS 4 (P) , $p<0.05$).

Conclusion: This provides an evidence of the Gabapentin before surgery significantly prolongs two-segment regression time and duration of analgesia in subarachnoid blockade and it significantly reduces the postoperative epidural analgesia requirements.

Key words

Gabapentin, Epidural analgesia, Bupivacaine.

Introduction

Pain is a fundamental biological phenomenon. The relief of pain during surgery as well as in the post operative period is the main part of anesthesia. Orthopedic patients can be particularly challenging for anesthesiologists. Many orthopedic procedures are well suited for regional anesthetic techniques. Regional anesthesia may reduce the incidence of major perioperative complications like, deep vein thrombosis (DVT), pulmonary embolism (PE), and blood loss. In addition, regional anesthesia provides superior postoperative pain relief. Even though there are various methods of providing post operative pain relief, like intravenous opioids, NSAIDS, patient controlled analgesia, continuous peripheral nerve blocks, epidural analgesia etc, Epidural analgesia is the one method which can be performed easily, can provide intraoperative and postoperative analgesia better than other methods with better patient comfort. But in epidural analgesia, it needs higher volume or higher dosage and sometimes it may exceed toxic dosage. So as to reduce the requirement of post operative epidural analgesic supplementation there are drugs that can be used as preemptive analgesia like opioids, NSAIDS etc. This study involves, using Gabapentin, (An atypical anticonvulsant which was originally used for chronic pain) and the effects of Gabapentin on combined spinal epidural anesthesia in respective of postoperative epidural analgesic requirements. Gabapentin, specifically a GABA analogue was first synthesized in 1977.It was originally developed for the treatment of epilepsy and First introduced as an anticonvulsant in 1994, and currently Gabapentin is widely used to relieve pain, especially neuropathic pain, chronic pain and more recently for acute pain relief also.Gabapentin is available in oral preparation (capsules, tablets).It is orally absorbed in small intestine. Oral bioavailability varies inversely with dose. The bioavailability for the dose of 900 mg is about 60%, where as that of 1200 mg is about 47% only. Volume of distribution is about 0.6-0.8 liter/kg. Cerebrospinal fluid and brain tissue concentrations are 20%, 80% respectively that of plasma levels. Gabapentin is not metabolized in humans and excreted unchanged in urine. Elimination half-life is 5-7 hours. Peak effect will last for 2-4 hours and duration of action is around 8 hours. Various mechanisms of actions are proposed regarding pain relief in acute as well as in chronic pain. Among them antagonism of NMDA receptors and calcium channel blocking actions are the most supporting evidences.

Materials and methods

After Institute ethical committee approval and written consent from the patients, A randomized double blind control study was conducted at Government Rajaji Hospital attached to Madurai Medical College, Madurai. 60 patients who were posted for lower limb orthopedic surgeries

Inclusion criteria

Age Group of 18 – 60 years in the ASA I and II grade were included.

Exclusion criteria

Patients who were contraindicated to central neuraxial blockade (patient refusal, local site infections, bleeding disorders), Age > 60 years, Known allergic patients to local anesthetics, and Gabapentin.

Patients were divided into two groups. 30 patients in each group.

Group G– Patients received cap. Gabapentin 1200 gram (3 capsules of 400 mg)
Group P – Patients received three placebo capsules.

Preoperatively, patients were given three capsules of 400 mg Gabapentin (1200 mg) or three placebo capsules according to their group one hour before surgery. Under strict aseptic precautions patient in sitting position, epidural space identified by using 18G Tuohy needle with loss of resistance technique at L2-L3 inter vertebral space. After the epidural space was identified, epidural catheter was inserted and 4 cm length of catheter kept inside the space. A test dose of 3 ml of 1.5% lignocaine with 15µg adrenaline was given. After excluding inadvertent subarachnoid or intravascular placement of catheter, Subarachnoid block was performed at L3- L4 Inter space by using 25G Quincke type spinal needle. 3ml of Inj. Bupivacaine 0.5% (heavy) was injected into the subarachnoid space. Patient positioned supine gently. When the sensory blockade reached T10 level, surgery was commenced. Intra operatively pulse rate, respiratory rate, blood pressure, saturation of Hb (SpO_2), urine output were monitored. After the surgery, patient was shifted to ICU for postoperative pain management. In the ICU, postoperative epidural analgesia was given in the dose of Inj. Bupivacaine 0.125% 8 ml with Fentanyl 2 µg / ml and time of epidural analgesic supplementation was noted. On next day morning at 8.30am, three Gabapentin capsules (or) Placebo capsules were given respectively according to their groups. If side effects were present they were treated accordingly. Parameters observed were Time to reach T10 segment sensory block - since the time of subarachnoid block to loss of pin prick sensation at T10. Two segment regression time in subarachnoid block (in minutes) - time to regress sensation to pin prick two segments from the highest level of blockade. Time to require first epidural top up since the time of subarachnoid block performed (when VAS score > 5).

Visual analogue pain score: Patients were asked to mark a point on the 10 point visual analogue scale of Pain according to the intensity of pain. It was observed every hour. The pain relief is graded according to VAPS as per **Table - 1** (Elbaz. 1984).

Table – 1: VAPS score and the quality of analgesia.

VAPS	Quality of analgesia
0-1	Excellent
1-4	Fair
4-6	Good
6-8	Slight
8-10	No releif

Results

Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008). Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 was taken to denote significant relationship.

Age distribution in the Gabapentin (group G) mean value of 41.9 years ± 10.9(S.D.) The Observed difference between the two groups in age is statistically not significant (‘p’= 0.08243,>0.05). Sex distribution is not statistically significant **(‘p’= 0.398 >0.05)** between the two groups (**Table – 2**). The height **(‘p’ =0.2243)** and weight **(‘p’ =0.3381)** distribution between the two groups are statistically not significant **(‘p’>0.05)** as per **Table - 2.**

Duration of surgery is statistically not significant **(‘p’ =0.5346, >0.005).** It also shows the pulse rate, blood pressure, respiratory rate, saturation monitored in every 15 minutes intra operatively in both groups. The changes in intra-operative pulse rate in both group statistically not significant **(‘p’= 0.2287, > 0.05).** The changes in

systolic blood pressure during intra-operative period between the two groups is statistically not significant **('p' = 0.859,> 0.05).** Changes in diastolic Blood pressure between the two groups is statistically not significant **('p' = 0.8941, >0.05)** as per **Table - 3**.

The changes in respiratory rate and saturation are statistically not significant **('p' >0.05).** Ramsay sedation score was monitored every 4 hours since the oral capsules given up to 48 hours and compared in both groups. The observed difference between the two groups in sedation score is statistically significant **('p'<0.05)** as per **Table - 4.**

Table - 2: Demographic distribution.

Group	Age	Sex		Height (cm)	Weight (kg)
	Mean ±SD	**Male**	**Female**	**Mean ±SD**	**Mean ± SD**
Group G	41.5±15.8	19 (63.3%)	11 (36.7%)	160.8±3.8	56.1± 3.3
Group P	41.9±10.9	23 (76.7%)	7 (23.3%)	162.1±3.4	56.7±2.8
'p'	**0.08243**	**0.398**		**0.2243**	**0.3381**

Table – 3: Duration of surgery and hemodynamic properties.

Duration of surgery (minutes)			**Group G**		**Group P**	
Range			90 -180		105 -180	
Mean± S.D			134.5±19.9		138±18.6	
'p'			**0.5346 (Not significant)**			
Group	**Pulse rate/min**		**Systolic BP (mmHg)**		**Diastolic BP (mmHg)**	
	Mean ±SD	**Percentage Changes Mean ±SD**	**Mean ±SD**	**Percentage changes Mean ±SD**	**Mean ±SD**	**Percentage Changes Mean ±SD**
Group G	86.5±2.8	5.4±5.9	116.5±3.1	1.9±7.4	74.0±2.8	3.4±8.7
Group P	83.9±6.0	6.2±6.6	116.3±3.2	1.2±7.8	73.1±2.6	2.9±8.9
'p'	**0.2287**	**0.6711**	**0.8359**	**0.6623**	**0.8941**	**0.8881**

Table - 4: Respiratory rate and saturation of HB (SpO2) and sedation score.

Group	**Respiratory rate/min**		**Saturation of Hb**
	Mean ±SD	**Percentage Changes Mean ±SD**	**Mean ±SD**
Group G	14.9±05	-3.7±13.2	97.6±1.4
Group P	15.3±1.9	-1.3±10.0	98.3±1.5
'p'	**0.6133**	**0.7079**	**0.0514**
Day	**Group G**	**Group P**	**'P'**
	Mean± SD	**Mean± SD**	
Day 1	2.33±0.48	1.83±0.38	**0.0401**
Day2	2.17±0.38	1.4±0.5	**0.0001**

Most commonly noted side effects in this study were dizziness, and headache. On comparison of the incidence of side effects between the two groups are statistically not significant **('p'= 0.7763, >0.05)** as per **Table - 5.**

Time to reach T10 segmental block between the two groups is statistically not significant **('p'= 0.2499, >0.05).** Two segment regression time is statistically significant **('p'=0.0001, <0.05).** Time to require first epidural analgesic supplementation is statistically significant **('p'=0.0001, <0.05).** Time interval between the epidural analgesic supplements is statistically significant **('p'=0.0001, <0.05)** as per **Table - 6.**

The observed difference between the two groups in total number of epidural analgesic requirements for two days is statistically significant **('p'=0.0001, <0.05)** as per **Table - 7.**

Table - 5: Side effects in present study.

Side effects	**Group G**		**Group P**	
	No	**%**	**No**	**%**
Dizziness	7	23.3	-	-
Head ache	5	16.7	8	26.7
Nausea	-	-		
Vomiting	-			
Pruritus	-			
Ataxia	-			
Side effects present Side effects absent	9 21	30 70	8 22	26.7 73.3
'p'	0.7763			

Table - 6: Time required to reach T10 segment sensory block, two segment regression time, time to require first epidural analgesic supplementation, time interval between the epidural analgesic supplementation in present study.

Group	**Time to reach T10 segment sensory block Mean (minutes)**	**P- Value**
Group G	4.77±0.97	0.2499
Group P	4.53±0.9	
Two segment regression (minutes)		
Group G	90.7±4.7	0.0001
Group P	85.8±3.5	
Time to require first epidural analgesic supplementation		
Group G	228.5 ± 19.96	0.0001
Group P	195.5 ± 13.3	
Time interval between epidural analgesic supplementation		
Group G	8.254 ±1.5276	0.0001
Group P	4.83 ± 0.529	

Table – 7: Total number of the epidural analgesic requirements.

Day	**Group G**		**Group P**		**'P'**
	Mean	**SD**	**Mean**	**SD**	
Day 1	2.07	0.25	2.93	0.25	0.0001
Day2	3	-	4	-	

Discussion

From the present study, it was observed that Gabapentin has high sedative property by acting on central nervous system, and that is the main side effect. Patient may have dizziness and sedation. Various studies proved that it alters sleep pattern also. The mean sedation score in gabapentin group (group G) on day 1 is 2.33, on day 2 is 2.17 and that in placebo group on day 1 is 1.83, and on day 2 is 1.4. Ramsay sedation score is significantly higher in Gabapentin group on day1 **('p'=0.0401, <0.05)** and on day 2 **('p'=0.0001, <0.05)** when compared to placebo group. The effect on subarachnoid block was that mean time to regress by two segments from the highest level of blockade in group G is 90.7minutes and that in group P is 85.8 minutes Two segment regression time prolonged in Gabapentin group than placebo group which is statistically significant **('p'=0.0001, <0.05).** The mean time duration to require first epidural analgesic supplementation (When the patient's VAS score >5), in Gabapentin group (group G) is 228.5 minutes and that in placebo group is 195.5 minutes .The time to require first Epidural analgesic requirement is prolonged in Gabapentin group than placebo group which is statistically significant **('p'=0.0001,<0.05).** These two parameter showed that Gabapentin has effect on subarachnoid block which prolongs the two segment regression time and duration of Analgesia of subarachnoid block. The total number of epidural analgesic requirements on day 1, varied from 1-2 supplements in Gabapentin group, in placebo group varied from 2-3 supplements. Total number of epidural analgesic requirements on day 2, varied from 2-3 supplements in Gabapentin group ,in placebo group varied from 3-4 supplements .Totally in Gabapentin group only one patient received 6 supplmentations (others received 5 supplementations) and in placebo group two patients received 6 supplementations (others received 7 supplementations). The total number of epidural analgesic requirements are significantly less in Gabapentin group than that in placebo group **('p' = 0.0001, < 0.05).** The mean time interval in Gabapentin group (group G) is 8.254hrs ±1.5276 (SD) and the same in placebo group is 4.8 hours ± 0.529 (SD). The time interval between each epidural supplements is significantly prolonged in Gabapentin group (group G) than in placebo group (group P) and which is statistically significant **('p'=0.0001, <0.05)**.In this study cap. Gabapentin which was given 1 hr before surgery had no effect on time to reach T10 segment sensory blockade. The two segment regression time and time to require first epidural analgesic supplementation are significantly prolonged in Gabapentin group than placebo group. The total number of epidural analgesic requirements is significantly lower in Gabapentin group than placebo group. The time intervals between the epidural supplements are significantly prolonged in Gabapentin group than in placebo group. Patients in Gabapentin group have better sedation score but with side effect of dizziness. The study was done by A. Turan, et al. [1] showed, up to 72 hours by using PCA pump for epidural top up , the total usage was only 38 hours in Gabapentin (1200mg) group while comparing 57 hours in placebo group. The post operative VRS pain score was also lower in Gabapentin group than in placebo. The study of Alparslan Tauran, et al. [1], gabapentin for intravenous regional anaesthesia, the study of Sen H, et al. [2], The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy showed that 1200 mg of gabapentin which was given orally , significantly reduced rescue analgesic requirements or opioids consumption in the postoperative period. From the study done by ChandraKanth Pandey, et al. [3], 459 ASA I and II patients were randomly assigned to receive 300 mg Gabapentin, 100 mg tramadol or placebo two hours before laparoscopic cholecystectomy under general anesthesia. Postoperatively, patients' pain scores were recorded on a visual analogue scale for the next 12 hr. Patients received Fentanyl 2 μg/kg intravenously on demand. The total Fentanyl consumption for each patient was recorded. Patients in the Gabapentin group had significantly lower pain scores at all time intervals (2.65 ± 3.00, 1.99 ±

1.48, 1.40 ± 0.95, 0.65 ± 0.61) in comparison to tramadol (2.97 ± 2.35, 2.37 ± 1.45, 1.89 ± 1.16, 0.87 ± 0.50) and placebo (5.53 ± 2.22, 3.33 ± 1.37, 2.41 ± 1.19, 1.19 ± 0.56). Significantly less Fentanyl was consumed in the Gabapentin group (221.16 ± 52.39 μg) than the tramadol (269.60 ± 44.17 μg) and placebo groups (355.86 ± 42.04 μg; $P < 0.05$). From the study done by Montazeri K, et al. [4], 70 ASA I and II patients were assigned to receive 300 mg Gabapentin or placebo two hours before surgery under general anesthesia. Postoperatively, the pain was assessed on a VAS score at 2, 4, 12, and 24 hours at rest. Morphine 0.05 mg/kg intravenously was used to treat postoperative pain on patients' demand. Total morphine consumption in the first 24 hours after surgery was also recorded. Patients in the Gabapentin group had significantly lower Visual Analogue Scale scores at all time intervals of 2, 4, 12, and 24 hours, than those in the placebo group respectively, 55.50 [mean] ±15.80[standard deviation], 57.30 ±19.30, 45.74±16.00, 44.60 ± 17.64, versus 72.30 ±14.00, 70.50 ± 18.13, 62.00 ± 23.32, 66.50± 25.70,($p < 0.05$). The total morphine consumed after surgery in the first 24 hours in the Gabapentin group (15.43 ± 2.54) was significantly less than in the placebo group (17.94 ± 3.00; $p< 0.05$). In study done by Prabhakar H, et al. [5], 20 adult patients undergoing surgery for brachial plexus injury under general anesthesia were enrolled for the study. Patients randomly received either oral Gabapentin 800 mg or placebo capsules 2 hours before surgery. Intra operative Fentanyl and propofol requirements were noted. Postoperatively, all patients were alert and pain was assessed using Visual Analogue Scale for 24 hours, both during rest and movement. Whenever VAS score was more than 50 or on patients' demand, ketorolac 30 mg was given as rescue analgesic. Significant difference was noted in intraoperative Fentanyl consumption ($p=0.03$), total dose of rescue analgesic ($p=0.004$), and VAS score was less in Gabapentin group as compared with placebo group ($p=0.01$ and 0.04, at rest and movement, respectively). From work done by Anil Verma, et al. [6], 50 patients with ASA grade I and II were assigned to receive 300mg Gabapentin or placebo 2hr before surgery. Surgeries were conducted under combined spinal epidural anesthesia. Post operatively pain was assessed by visual analogue score (VAS). Patients were given epidural boluses of bupivacaine (0.125%) on demand. Patients in Gabapentin group have significantly lower VAS score 2, 4,8,12 and 24hrs postoperatively as compared to the placebo (1.3 ± 1.3, 2.3±1.4, 3.2 ± 2.1, 1.8 ± 1.7, 1.2 ± 1.3 vs. 2.1 ± 1.7, 3.2±1.6, 4.4 ± 1.2, 3.3 ± 1.1, 2.1 ± 1.2 respectively; $P <0.05$). Total numbers of epidural boluses were significantly less in Gabapentin group (3.4±1.6 vs. 5.6±2.1, $P<0.05$). They concluded that preemptive use of Gabapentin 300mg orally significantly reduces the number of postoperative epidural bolus requirements and postoperative pain in patients undergoing total abdominal hysterectomy under combined spinal epidural anaesthesia. From study done by Sussan Soltani Mohammadi, et al. [7], 120 ASA I and II patients were scheduled for elective abdominal surgery were randomly assigned to receive either 0.2mg oral clonidine (n=40) or 300mg gabapentin (n=40) or placebo (n=40) 1hr before surgery. They were anesthetized using the same technique. Demographic data, post operative visual analogue scale (VAS), PONV and total morphine consumption by PCA pump were recorded in the recovery room and during first 6 hr after surgery. Two patients in gabapentin compared with 13 patients in clonidine group ($p<0.05$) and 29 patients in placebo group ($p<0.05$) had VAS >3 in recovery room. The mean morphine consumptions were 4.75±7.5, 1.95±5.51 and 1.56±1.5mg in placebo, clonidine and gabapentin group with significant differences ($p<0.05$). These measurements were 18±15.8, 13.1±12.6 and 12.1±12.9 mg respectively during first 6 hr after surgery with significant differences ($p<0.05$). PONV was not statistically different between the study groups in the recovery room and during first 6 hr after the surgery. From Harshel G. Parikh, et al. [8] study, 60 patients were divided into two groups. Group A received 600mg gabapentin and group B oral received placebo 1 h prior to surgery. Surgery

was done under general anaesthesia. Assessment of post-operative pain was made with the visual analog score (VAS) at extubation (0 h), 2, 4, 6, 12, and 24 h post-operatively. Post-operative analgesia was provided with intravenous Tramadol. The first dose was given in the post anesthesia Care Unit as 2mg/kg, and repeated at 8 and 16 h. Rescue analgesia was given with diclofenac 1.5mg/kg, slow intravenous. The number of doses of rescue analgesia in both the groups was noted. The VAS scores at 0, 2, 4, 6, 12, and 24 h were 1.9 *vs.* 2.4 (p=0.002), 2.3 *vs.* 3.0 (*p*=0.000), 3.2 *vs.* 3.7 (p=0.006), 2.9 *vs*. 4.4 (*p*=0.000), 3.6 *vs.* 4.6 (*p*=0.000), and 3.7 *vs.*4.6 (p=0.000), respectively. Numbers of patients requiring rescue analgesia with diclofenac were 3 *vs.* 14 (*P*=0.004). Above studies reported 300 to 800 mg of gabapentin is effective in reducing supplemental analgesia. The studies done by Anil Verma, et al. [6] used 300 mg of Gabapentin 2 hr before surgery for abdominal hysterectomy showed that reduction number of 2 supplementations of epidural analgesia than in placebo group. Christophe Menigaux, Frederic Adam, Bruno Guignard, Daniel I. Sessler, et al. [9] showed that 1200mg of gabapentin not only reducing postoperative opioid consumption, but also reducing anxiety score significantly. As various studies showed that using 1200mg of Gabapentin is effective in reducing opioid demand and pain score, 1200mg of Gabapentin was choosen for this study. In this study, 1200 mg Gabapentin significantly reduced number of post operative epidural analgesic supplementations; it prolonged the two segment regression time and produced better sedation also than the placebo group.

Conclusion

Gabapentin before surgery significantly prolongs two segment regression time and duration of analgesia in subarachnoid blockade and it significantly reduces the post operative epidural analgesia requirements.

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