

# The effects of gabapentin on severity of post spinal anesthesia headache

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**Abstract:** Spinal anesthesia is a common anesthesia method and post dural puncture headache (PDPH) is one of its most common adverse effects. Gabapentin is a popular anticonvulsant drug that has been used as an oral nonopioid analgesic in recent years. In this placebo-controlled double-blind study, 120 patients were randomized in two equal groups (Placebo or gabapentin). The patients in the gabapentin group received gabapentin 300 mg orally one hour before the surgery and then every 12 hours for the first 24 hours after the surgery while the placebo group received placebos in the same way. Severity of headache and postoperative pain assessed by verbal rating score for pain (VRSP), morphine consumption, nausea, vomiting, somnolence, pruritus, dizziness in the first 48 hours, hypertension, hypotension, bradycardia and tachycardia in the first 24 hours after the surgery were recorded. In first 48 hour after surgery the mean of severity of headache in the gabapentin group was  $0.20 \pm 0.05$ , and in the placebo group it was  $0.93 \pm 0.01$ . The mean of postoperative pain in the gabapentin group was  $2.25 \pm 0.793$ , and in the placebo group it was  $3.77 \pm 0.813$ . In the first 24 hours post operative the mean of morphine consumptions were  $0.20 \pm 0.030$  and  $0.32 \pm 0.030$  mg in gabapentin and placebo groups. No significant differences were found between the two groups regarding incidence rate of the adverse effects. In this study, administration of gabapentin decreased the incidence and severity of post spinal anesthesia headache, postoperative pain and morphine consumption, without any significant differences in serious adverse effects.

**Keywords:** post spinal anesthesia headache, gabapentin, spinal anesthesia.

## INTRODUCTION

Spinal anesthesia (SA) is a common method of anesthesia with predictable and acceptable associated complications and its benefits are assessed individually (Ahmed *et al.* 2006; Stoelting *et al.*, 2002).

Hypotension, bradycardia, post SA headache, high spinal anesthesia, nausea, urinary retention, back pain, neurological damage (rare) and decreased ventilation are some of its complications (Stoelting *et al.* 2002).

Post dural puncture headache (PDPH) is one of the commonest complications after surgery. This headache does not occur only after SA, it may occur due to myelography and diagnostic lumbar puncture (Ronald, 2005).

This headache involve anterior frontal or occipital regions, become severer with sitting, improved by sleeping and sometimes is associated with diplopia due to the extension of the 6<sup>th</sup> cranial nerve. Tinnitus and acute hearing loss may be accompanied with post SA headache. Headache without positional feature cannot be PDPH (Stoelting *et al.* 2002).

Young ages, female gender, using larger needles,

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pregnancy, and frequent perforating of dura are some factors which may increase possibility of PDPH. This headache is apparently more common in pregnant women and postpartum period in comparison to general population. Using appropriate needle for spinal block and anesthesiologist with adequate skill will result in lower incidence of PDPH after cesarean section with SA (Ronald, 2005; Lubusky *et al.* 2006).

PDPH is a complication that should not treated carelessly and potentially can lead to considerable disability and even death. In a remarkable percentage of cases it will be solved spontaneously and in some it will last for months and even years. In outpatients service PDPH may affect the choosing of SA (Stoelting *et al.* 2002; Turnbull and Shpherd, 2003).

Treatment of PDPH is initiated with bed rest, administration of analgesics and oral or intravenous solutions (3 Lit or more daily). Whenever PDPH exists in spite of conservative treatments, it is suggested to block epidural foramen with blood in epidural space by using 10-20 ml of patient's blood (usually from antecubital veins). The most common complications of administration of blood into the epidural space are back pain and referral pains (Stoelting *et al.* 2002).

Gabapentin is one of the recent anticonvulsant drugs which were approved by FDA in 1993 (Azar and Nuhi,

2007). Gabapentin is absorbed in intestinal tracks and colon and its absorption is dose-dependent due to the saturable mechanism of L-amino acids transferring. After a single dose of oral gabapentin 300 mg, its peak plasma concentration is achieved in 2-3 hours. Bioavailability of a single dose of oral gabapentin 300 mg is 60% and it decreases with increase in dosage. It easily passes blood brain barrier and its half life is about 5 to 10 hours (Azar and Nuhi, 2007; Kong and Irwin, 2007; Goa and Sorokin, 1993).

Gabapentin had been efficient in treatment of inflammatory and neuropathic pains in studies on animals and human and there is an excellent efficacy in association of gabapentin and morphine in treatment of neuropathic pains (diabetic neuropathy and post-herpes neuralgia) (Gilron *et al.* 2005; Hurley *et al.* 2006). In recent years gabapentin has been used as an oral non-opioids analgesic for treatment of postoperative pains (Turan *et al.* 2004a; Turan *et al.* 2004b; Turan *et al.*, 2006a; Turan *et al.*, 2006b).

Administration of oral gabapentin in patients with PDPH after SA is a safe treatment (Dogan Eral, 2006). Two cases of resistant PDPH to usual treatment have been reported that had an acceptable response to gabapentin (Lin *et al.*, 2007).

Considering PDPH is associated with apparent disability after SA and increase duration of hospitalization and restrict usual activity, this study is designed to assess the effects of gabapentin on severity of headache after spinal anesthesia.

## **MATERIALS AND METHODS**

In this double-blinded randomized clinical trial study, all the patients who were candidate for urologic or lower abdominal surgery and underwent spinal anesthesia in ASA class I and II were enrolled the study. The study protocol was approved by ethics committee of Lorestan University of Medical Sciences. An informed consent was obtained from the patient's prior entrance to the study.

Inclusion criteria of the study were: Age  $\geq 20$  years, patients with ASA class I and II, without a history of tension headache or migraine, without chronic pain syndromes, without chronic or recent use of opioid anesthetic, without a history of use of gabapentin, without a history of sensitivity to the drugs used in this study and not being pregnant.

Patients were categorized in intervention and placebo groups using classified blocking method. Age, gender and kind of surgery were classification factors in this study. Sample size was calculated using below formula:  $S = (Max-Min)/6$ ;  $D=1$ ,  $\alpha=0.05$  and  $\beta=0.1$ ;  $N = [(Z1 - \alpha/2 + Z1 - \beta)^2 (2s^2)]/d^2 = [(1.96+1.28)^2 (2 \times 1.67)^2]/(1)^2 \approx 60$ .

One hour before transfer to the operation room patients received oral gabapentin 300 mg or placebo (exactly similar to gabapentin) in intervention (n=60) or Control (n=60) group. The selected dosage of 300 mg was based on previous premedical studies. Subsequent taking IV line using angiocath no. 25 and infusion of 30CC/Kg ringer's lactated solution in the operation room, all the patients underwent spinal anesthesia using needle no.25 and 2cc lidocaine 5% through L4-L5 or L5-S1 spaces to achieve an anesthesia level equal to T10. During surgery monitoring of blood pressure each 3 minutes, arterial O2 saturation and electrocardiography were performed. Midazolam 0.03 mg/kg/IV was used for sedation during the surgery.

In the cases of decreased blood pressure less than 100 mm Hg, ephedrine 5-10 mg were used to raise blood pressure higher than 100 mm Hg. Patients were transferred to recovery room and then to the ward after operation. Patients in each group received their related capsule twice a day in the first 24 hour after the operation.

An interviewer who was not aware of patients' groups registered a questionnaire for all the patients 12 and 24 hours after the operation which consisted variables including severity of headache based on Verbal Rating Score For Pain (VRSP), site of headache and being positional or not, back pain, drug adverse effects such as nausea, vomiting, hypotension and hypertension (described as mean arterial pressure  $<60$  mm Hg and  $>120$  mm Hg respectively), bradycardia (heart rate  $<50$  beat/min), tachycardia (heart rate  $>100$  beat/min), drowsiness, vertigo, pruritus, severity of postoperative pain based on VRSP and need for further treatment. In the second day, 36 and 48 hours after the operation a similar questionnaire was recorded using a constant interviewer. Patients who were discharged in the second day were asked by telephone to fill the questionnaire indirectly.

Hospitalized patients with headache or postoperative pain with VRSP  $< 4$  only underwent hydration and bed rest but in those with VRSP  $\geq 4$  besides hydration and bed rest, Morphine 0.1 mg/kg/IM was administrated and registered in the questionnaire.

In the cases of discharge in the first 24 hours after the surgery, inadequate spinal anesthesia that need narcotics or other drugs or more than one time attempt for spinal anesthesia patients were excluded from the study.

## **STATISTICAL ANALYSIS**

Results were reported as mean  $\pm$  standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t- test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. P values of 0.05 or less were considered statistically

significant. All the statistical analyses were performed using SPSS version 13 (SPSS Inc, Chicago, IL, USA) for Windows.

## RESULTS

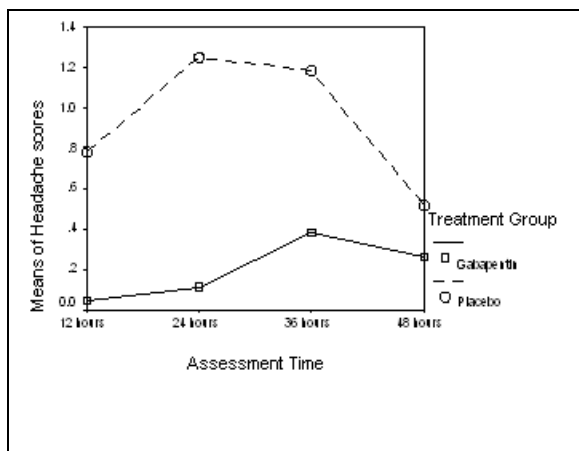
Of the total number of 120 patients (28 females and 92 males) 15 women were categorized in gabapentin group (53.6%) while 13 others were in placebo group (46.4%). Forty-Five (48.9%) and 47 (51.1%) of males were in gabapentin and placebo groups. There was not a significant association between groups and gender based on Fisher exact test ( $P=0.415$ ).

Regarding types of surgery patients' distribution were as below: 40 patients inguinal hernia repair surgery, 26 ones hemorrhoidectomy surgery, 24 ones pilonidal sinus surgery, 26 ones TUL (trans urethral lithotripsy) and 4 other ones underwent varicocele surgery and based on the K2 test no significant relation was seen between types of surgery and group types ( $P>0.999$ ).

The mean age of all participants was  $40.97\pm 17.052$  and the mean age of patients in two studied groups did not show a significant difference (Gabapentin:  $40.80\pm 16.953$ , placebo:  $40.78\pm 17.292$ ,  $P=0.996$ ).

The repeated measuring test showed that in general time of measurement has a significant effect on severity of headache and this relation was a second-degree type ( $P<0.001$ ). Meanwhile, in two studied groups severity of headache was not similar in different times means in different times the severity of headache was not the same in gabapentin and placebo groups ( $P=0.005$ ).

The peak mean of post SA headache in gabapentin group registered at 36 hours after surgery ( $1.151\pm 0.38$ ) and its least value recorded 12 hours after the operation ( $0.387\pm 0.05$ ). In placebo groups these values were registered 24 hours ( $1.781\pm 1.25$ ) and 48 hours ( $1.228\pm 0.52$ ) after surgery, respectively (fig. 1).

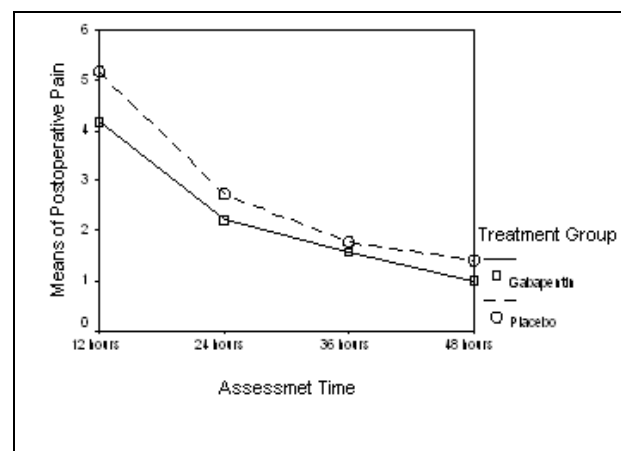


**Fig. 1:** Mean headache score in treatment group

The incidence rate of headache in each group was different in various times and this difference was significant ( $P<0.001$ ). These differences were significant at 12, 24 and 36 hours ( $P<0.001$ ) but not at 48 hours ( $P=0.148$ ) after surgery.

Student's t-test showed that administration of gabapentin is generally effective on severity of post SA headache (VRSP in gabapentin group:  $0.565\pm 0.02$ , in placebo group:  $1.250\pm 0.093$ ,  $P<0.001$ ).

Time of measurement showed a linear relation with severity of postoperative pain based on the repeated measuring test ( $P<0.001$ ). There was not a significant difference between gabapentin and placebo groups toward severity of postoperative pain in various times ( $p=0.024$ ). The maximum mean of pain in the operation site in gabapentin ( $4.18\pm 1.864$ ) and placebo ( $5.17\pm 1.806$ ) groups were registered at 12 hours after surgery while its minimum mean were recorded 48 hours after surgery in both gabapentin ( $1.02\pm 0.676$ ) and placebo ( $1.42\pm 0.766$ ) groups (fig. 2).



**Fig. 2:** Mean postoperative pain score in treatment group

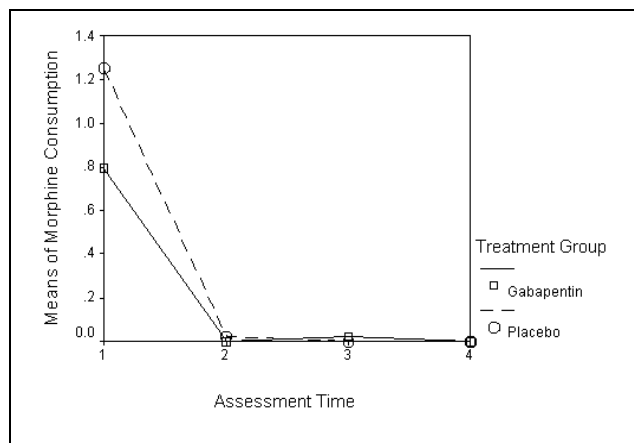
The mean of postoperative pain scores in the first 48 hours after surgery was  $2.25\pm 0.793$  and  $3.77\pm 0.813$  in gabapentin and placebo groups and based on student's T test, administration of gabapentin had a significant effect on severity of postoperative pain ( $p=0.001$ ).

The mean use of Morphine varied significantly in different times after surgery ( $p<0.001$ ).

The maximum consumption of Morphine in two groups was recorded 12 hours after surgery (Gabapentin:  $1.226\pm 0.79$ , placebo:  $1.271\pm 0.25$ ) and its minimum use (0.0 mg) in gabapentin group was registered at 24 and 48 hours after surgery and in placebo group at 36 and 48 hours after surgery minimum administration of Morphine was recorded (0.0 mg) (fig. 3).

Administration of gabapentin had a considerable effect on quantity of Morphine consumption after surgery; the

mean value of needed Morphine was significantly lower in gabapentin group compared with placebo (0.306±0.020 mg vs. 0.330±0.032 mg, P=0.051).



**Fig. 3:** Mean dose of Morphine consumption in treatment group.

Post-operation Complications in placebo groups in the first 48 hours were: back pain (31.94%), nausea (16.91%), vomiting (5.49%), hypertension (9.68%), drowsiness (7.17%) and vertigo (8.85%). Other complications like tachycardia, bradycardia and hypotension were not seen in the first 24 hours postoperatively and pruritus was not found in the first 48 hours in placebo groups.

There was not a significant difference between two groups for incidence of back pain, nausea, vomiting, hypertension, drowsiness and vertigo (P>0.05).

## DISCUSSION

This study is conducted to assess the effects of gabapentin on severity of post SA headache. This study showed that administration of gabapentin 300 mg before surgery and then twice a day in the first 24 hours after surgery significantly decrease severity of PDPH (P<0.0010). Meanwhile, gabapentin decreased the need for Morphine after surgery (0.051) and had favorable effects on decreasing the severity of postoperative pain (0.001).

Sirvastava U *et al* in a study in 2010 on 120 patients who underwent cholecystectomy with restricted laparotomy and received a single dose of gabapentin 600 mg preoperatively or tramadol after the surgery found that administration of gabapentin similar to Tramadol can lead to an apparent decrease in pain score in both resting and activity (p<0.01) (Sirvastava *et al.*, 2010).

In this study the use of tramadol has been evaluated after surgery while we compared values of Morphine in our two groups, but in both studies gabapentin lead to decrease in use of mentioned analgesics after surgery. Number of patients in both studies are 120 with this

difference that Sirvastava U *et al* assessed the analgesic effects of gabapentin in open cholecystectomy with mini-laparotomy while we studied patients underwent urology or lower region of the abdominal surgeries. They assessed pain using verbal analogue pain scores (VAS) at 0, 2, 4, 8, 12 and 48 hours after surgery while we used VRSP at 12, 24, 36 and 48 hours after surgery.

In this assessment by Sirvastava U *et al* drowsiness had been common while nausea and vomiting had been considerably less prevalent in gabapentin group. In our study the most common complication was back pain, followed by nausea which might be due to spinal anesthesia and finally there was not a significant difference between two groups about prevalence of complications.

In other study by Grover VK *et al* in India it has been illustrated that administration of a single dose gabapentin 600 mg one hour before surgery had a remarkable analgesic effect without important complications after total mastectomy and auxiliary dissection surgery (Grover *et al.*, 2009). In this study the dosage and administration schedule of drug were not similar to our study. In their study the required dose of Morphine was considerably lower in gabapentin group (P=0.001), the mean time for receiving the first analgesic was longer in gabapentin group (p=0.001) and incidence of complications was the same in two groups, also in our study the needed doses of Morphine were partially lower in gabapentin group (0.051) and there was not a significant difference between two groups toward complications.

Eral DD *et al* in a study in 2006 confirmed that oral administration of gabapentin in patients with PDPH after SA is a safe treatment (Dogan Eral, 2006). Meanwhile, two cases of PDPH in Taiwan have been reported which were resistant to usual anesthetic but showed a favorable response to treatment with gabapentin 400 mg/3 times a day and their headache excellently improved (Lin *et al.*, 2007). The administration schedule of drug in these two studies was not similar to our study and although we applied gabapentin as prophylaxis it lead to decrease in severity of headache after SA (p<0.001).

In an assessment for tolerance and safety of gabapentin on 2216 patients under anticonvulsant treatment, drowsiness (15.2%) was the most common side effect of the drug, followed by vertigo (10.9%) (Kong and Irwin, 2007). In our study the commonest side effects of the drug was nausea (7.9%) followed by vertigo 2.50%) and drowsiness (1.25%).

## CONCLUSION

Administration of gabapentin can lead to decrease in severity of post spinal anesthesia headache and

postoperative pain and lessen the need for Morphine in the first 48 hours postoperatively without a remarkable difference in incidence of complications. Administration of gabapentin is suggested as a treatment and a safe prophylaxis for post SA headache and postoperative pain and decreasing the need for Morphine after surgery.

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