Single Dose of Gabapentin for Prophylaxis Intrathecal Morphine-Induced Pruritus in Orthopedic Surgery: A Randomized Controlled Trial

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Objective: *Gabapentin has an antipruritus effect, which its efficacy in reducing pruritus induced by intrathecal morphine has not been well documented. The purpose of the present study was to know if a single smaller dose of gabapentin could decrease the intrathecal morphine-induced pruritus.*

Material and Method: *One hundred sixty eight patients from the 180 recruited patients fulfilled the trial requirement and were scheduled for orthopedic surgery under spinal anesthesia using 0.5% isobaric bupivacaine and 0.2 mg preservative-free morphine. The patients were divided into two groups, each of 84 subjects and received either gabapentin 600 mg or a placebo, two hours preoperatively, in a prospective, randomized, double-blind, placebo-controlled trial. The pruritus was evaluated at 1, 2, 3, 4, 6, 9, 12 and 24 hours after intrathecal morphine administration. Adverse events were noted.*

Results: *The overall incidence of pruritus was not significantly different between the two groups while the incidence and severity of pruritus was significantly decreased in the gabapentin group at four hours after intrathecal morphine injection (18 of 84 subjects, 21.4% vs. 35 of 84 subjects, 41.7%; p = 0.008 and 0.045 respectively). The urinary retention was significantly higher in the study group compared to the placebo group (50.0% (42 of 84 subjects) vs. 33.3% (28 of 84 subjects) p = 0.042).*

Conclusion: *Preoperative gabapentin 600 mg did not significantly reduce the postoperative intrathecal morphine-induced pruritus.*

Keywords: *Gabapentin, Prophylaxis, Intrathecal morphine-induced pruritus, Orthopedic surgery*

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Gabapentin is an antiepileptic agent. It is a structural analog of gamma-aminobutyric acid (GABA). The US. Food and Drug Administration currently approve gabapentin for management of partial seizures, postherpetic neuralgia[1] and neuropathic pain[2]. Gabapentin administration has shown to be effective for treatment in cases of neuropathic itch[1,2], chronic itch[3-8] and itch of unknown origin[9]. However, the antipruritic effect in reducing pruritus induced by neuraxial opioid has not been well documented.

The incidence of pruritus induced by intrathecal morphine has been reported as 20 to 100%[10]. In the present study hospital, Songklanagarind Hospital, the incidence of pruritus is 63%. The pathophysiology of opioid-induced pruritus remains unclear and more than one mechanism may be involved in the development of opioid-induced pruritus. Many medications that have been used to treat pruritus include antihistamines, serotonin 5-HT_3 receptor antagonists, nonsteroidal anti-inflammatory drugs, opioid agonist-antagonists, opioid antagonists and propofol[10-12]. Sheen et al has shown the effectiveness of gabapentin 1,200 mg in prevention of intrathecal morphine-induced pruritus in orthopedic surgery, which could reduce the incidence of pruritus from 77.5 to 47.5%, 38.7% reduction[13]. However, the minimum effective dose of gabapentin has never been investigated. The rationale of the present study was to determine the minimum effective dose of gabapentin that can prevent pruritus induced by intrathecal morphine and minimize the side effects of gabapentin, which will be useful in clinical practice.

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Material and Method

The present study was registered with ClinicalTrials.gov (identifier: NCT01236859). A prospective, randomized, double-blind, placebo-controlled trial study was designed and approved by the ethic committee of Songklanagarind Hospital in Songkla, Thailand. A written informed consent was given by each participant after receiving information of the present study. The participants were enrolled between September 2009 and August 2010. The inclusion criteria were defined as patients aged between 15 to 70 years, ASA physical status I-III, and scheduled for lower extremity orthopedic surgery under spinal anesthesia. The exclusion criteria were defined as patients who had a contraindication for spinal anesthesia, known history of gabapentin, morphine and bupivacaine allergy, history of pruritus preoperatively, morbid obesity (BMI > 35 kg/m^2), concomitant skin illness, pruritus related with systemic disease, currently using antiepileptic agents or antihistamines, known history of convulsion, mental disorder or neuropathic pain.

Patients were allocated randomly into the gabapentin and the placebo groups under a computer-generated randomization list. The assessment investigators were blinded and separated from the investigators who kept the treatment code. Patients in the gabapentin group were given two capsules of gabapentin 300 mg (Neurontin®, Pfizer) and two capsules of an assembly identical- placebo were given to the patients in the placebo group at 2 hours before spinal anesthesia.

Ringer's lactate or normal saline solution 7 to 10 mL/kg was administered to the patients for prehydration. Spinal anesthesia was achieved at the L_{2-3} or L_{3-4} interspace with a 27-gauge Quincke-type needle using 0.5% isobaric bupivacaine plus 0.2 mg of preservative-free morphine. Intraoperatively, midazolam, morphine, fentanyl and propofol were administered intravenously (IV) for sedation under the anesthesiologist's discretion.

The pruritus, the primary outcome, was evaluated at 1, 2, 3, 4, 6, 9, 12 and 24 hours after intrathecal morphine administration by a blinded investigator. The degree of pruritus, the secondary outcome, was assessed and classified as 0 = absent, 1 = mild (restricted to one area such as the face or arms, not troubling the patient and often reported only after prompting), 2 = moderate (affecting a larger area such as the face and arms or face and anterior surface of the thorax, not disturbing the patient and therefore not requiring treatment), or 3 = severe (extensive or generalized, often disturbing the patient to the point of necessitating treatment)[14]. Chlorpheniramine 10 mg IV was administered to treat severe pruritus condition.

Postoperative nausea and vomiting (PONV) were assessed and graded on a four point scale as 0 = no nausea or vomiting, 1 = mild nausea only, 2 = nausea or vomiting responding to initial treatment and 3 = nausea or vomiting requiring repeat treatment[15]. Ondansetron 4 mg IV or metoclopramide 10 mg IV was administered if the PONV scale was ≥ 2. Other side effects including urinary retention and drug treatment side effects were also recorded. The Ramsay Sedation Scale was evaluated intraoperatively.

Statistical analysis

The sample size was calculated using the power analysis with a probability of 0.2 for a type II error and type I error of 0.05. A sample size of 80 patients in each group was calculated to detect a 35% reduction based on the incidence of pruritus in the present study hospital. A 10% patient dropout for protocol violations was accommodated by assigning 88 patients into each group. The R 2.11.1 software program with the Epicalc package was used for statistical analysis. The onset time of pruritus was analyzed by means of Kaplan-Meier probability curves. Continuous data were analyzed using unpaired Student's t-test for normal distribution data such as BMI and by the Mann-Whitney U test for non-normal distribution data such as age and dose of intraoperative sedative agent used. The categorical data were analyzed using the Chi-squared test such as the incidence and severity of pruritus and by Fisher's exact test if the expected value was < 5. The results were expressed as mean $\pm$ standard deviation (SD) for normal distribution data and median (interquartile range, IQR) for non-normal distribution. The p-values of < 0.05 were considered statistically significant.

Results

One hundred eighty patients were initially recruited. Twelve patients were excluded because of protocol violations (n = 10: prolonged operative time which needed further general anesthesia in eight cases and no intrathecal morphine added in two cases) and failure of spinal anesthesia (n = 2). Thus, 168 patients fulfilled the trial requirement, with 84 patients in each group. There were no statistical differences in the patients' characteristics; age, BMI, gender and ASA classification, as well as intraoperative data;

intraoperative Ramsay Sedation Scales, dose of isobaric bupivacaine, intraoperative agents (midazolam, fentanyl, morphine and propofol), duration of surgery, and type of surgery among both groups, as major variables shown in Table 1. The proportion of the gabapentin/placebo groups of ASA class II were 70.2/65.5% and 15/15.75 mg of median bubivacaine dose, as well as intraoperative sedative agents; 2/1.5 mg of median midazolam dose (n = 23/31), 50/80 mcg of median fentanyl dose (n = 5/5), 7/10 mg of median morphine dose (n = 4/3) and 175/422 mg of median propofol dose. The common surgical procedures were open reduction with internal fixation 23.8/32.1%, total hip replacement 16.7/14.3% and the remains were total knee replacement, anterior cruciate ligament reconstruction, irrigation and debridement, removal of implant, iliac bone grafting, and miscellaneous procedures.

The overall incidence of pruritus was not significant between the two groups: 49 of 84 (58.3%) in the gabapentin group, and 55 of 84 (65.5%) in the placebo group, with 11% reduction (p = 0.427). The onset time of pruritus was earlier in the placebo group (6 ± 0.8 h) compared to the gabapentin group (9 ± 2.8 h), without statistical significance (p = 0.206).

The incidence and severity of pruritus was significantly decreased in gabapentin group at 4 hours after intrathecal morphine injection (18 in 84 subjects, 21.4% vs. 35 in 84 subjects, 41.7%; p = 0.008 and 0.045 respectively) as demonstrated in Table 2. In addition, the number of patients and total dose of Chlorpheniramine (IV) needed 24 hours postoperatively was not statistically different in the gabapentin/ placebo group (number of 32 of 84/30 of 84; median (IQR) of 10 (10 to 20)/10 (10 to 20) mg, p = 0.65).

The proportions of adverse events had no statistical significance in the gabapentin/placebo groups: nausea and vomiting of 22.6/13.1%, bradycardia of 3.6/3.6%, hypotension of 28.6/22.6% and shivering of 11.9/16.7%, as well as the severity of PONV. Whereas the urinary retention had statistically

Table 1. Demographic characteristics and intraoperative data

Variable	Gabapentin (n = 84)	Placebo (n = 84)	p-value
Age (yr) *	40.5 (25, 55.2)	42.5 (29.5, 54.2)	0.86
BMI (kg/cm^2)$^+$	23.5 (4)	23.5 (3.5)	0.95
Gender (M/F)	53/31	50/34	0.75
Duration of surgery (min)*	112.5 (65,145)	120 (80,180)	0.14

BMI = body mass index; M = male; F = female
* Median (IQR) compared by Mann-Whitney U test
$^+$ Mean (SD) compared by unpaired student's t test

Table 2. Assessment of severity of pruritus at different interval after intrathecal morphine administration

	1 h	2 h	3 h	4 h*	6 h	9 h	12 h	24 h
Gabapentin								
No pruritus	76 (90.5)	67 (79.8)	64 (76.2)	66 (78.6)	57 (67.9)	55 (65.5)	50 (59.5)	56 (66.7)
Mild pruritus	8 (9.5)	14 (16.7)	13 (15.5)	12 (14.3)	5 (6.0)	15 (17.9)	21 (25.0)	15 (17.9)
Moderate pruritus	0	2 (2.4)	2 (2.4)	4 (4.8)	8 (9.5)	6 (7.1)	9 (10.7)	6 (7.1)
Severe pruritus	0	1 (1.2)	5 (6.0)	2 (2.4)	14 (16.7)	8 (9.5)	4 (4.8)	7 (8.3)
Placebo								
No pruritus	75 (89.3)	61 (72.6)	52 (61.9)	49 (58.3)	54 (64.3)	52 (61.9)	52 (61.9)	57 (67.9)
Mild pruritus	7 (8.3)	15 (17.9)	21 (25.0)	22 (26.2)	15 (17.9)	17 (20.2)	20 (23.8)	19 (22.6)
Moderate pruritus	1 (1.2)	4 (4.8)	6 (7.1)	8 (9.5)	5 (6.0)	8 (9.5)	11 (13.1)	5 (6.0)
Severe pruritus	1 (1.2)	4 (4.8)	5 (6.0)	5 (6.0)	10 (11.9)	7 (8.3)	1 (1.2)	3 (3.6)

Values are number of patients (%)
* p = 0.045 compared by Fisher's exact

higher significance of 42 in 84 subjects (50.0%) in the present study gabapentin group than 28 in 84 subjects (33.3%) in the placebo group, p = 0.042.

Discussion

The present study did not show that preoperative gabapentin 600 mg decreased the incidence of intrathecal morphine-induced pruritus, compared with placebo. The rationale of the ineffective gabapentin probably is inadequate single dose and the short half life of 2 to 3 hours[16]. Secondly, oral gabapentin has inherent pharmacokinetic deficiencies, which are highly variable and unpredictable absorption that may limit its effectiveness[17]. As a result, it is often difficult to predict the dose of gabapentin necessary to achieve an optimal therapeutic effect in a given patient, and the desired treatment response may not be achieved.

Thirdly, a different pathophysiology between neuropathic itch induced by a chronic condition and neuropathic itch induced by a neuraxial opioid might be existed because gabapentin has antipruritic effect for the treatment of chronic itching with or without neuropathy in origin but could not reduce pruritus induced by neuraxial opioids which is believed to be a neurogenic itch[18].

Thus, the effective of antipruritic dose and the other pharmacological mechanisms of gabapentin need further study. Beside, the pruritus assessment should be cautious due to its subjective sensation, and involve with a complex interaction with neuropathic pain that might be misdiagnosed as allodynia or hyperalgesia causing a false negative result[19-22].

Postoperative urinary retention can be caused by either regional anesthesia or the drug induced entity. Toward higher proportion of urinary retention in the gabapentin group, there is no previous evidence and no clear mechanism of gabapentin used as a co-analgesic agent with an intrathecal opioid where and why gabapentin can increase the incidence of urinary retention. A possible explanation could be that gabapentin enhances the analgesic effect and other side effects of intrathecal morphine such as urinary retention and nausea and vomiting.

In conclusion, preoperative gabapentin 600 mg did not significantly reduce the postoperative intrathecal morphine-induced pruritus.

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Potential conflicts of interest

None.

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ยากาบาเพนตินขนาดเดียวเพื่อป้องกันอาการคันกระตุ้นเหนี่ยวนำโดยยามอร์ฟีนในช่องเยื่อหุ้มไขสันหลังในการผ่าตัดศัลยศาสตร์ออร์โธปิดิกส์: การศึกษาแบบสุ่มที่มีตัวควบคุม

วิรินทร์ดา ชิรวานิช, มลิวัลย์ ออฟูวงศ์, นลินี โกวิทวนาวงศ์

วัตถุประสงค์: *ยากาบาเพนตินมีฤทธิ์ต้านอาการคัน มีประสิทธิผลในการลดอาการคันเหนี่ยวนำโดยยามอร์ฟีนในช่องเยื่อหุ้มไขสันหลังยังไม่เป็นที่ทราบชัด วัตถุประสงค์การศึกษาเพื่อทราบว่ายากาบาเพนตินขนาดเดียวสามารถลดอาการคันเหนี่ยวนำโดยยามอร์ฟีนในช่องเยื่อหุ้มไขสันหลังได้หรือไม่*

วัสดุและวิธีการ: *ผู้ป่วย 168 ราย ใน 180 ราย ที่คัดเข้าสู่การศึกษามีเกณฑ์ครบถ้วนในการศึกษาและได้รับการผ่าตัดศัลยศาสตร์ออร์โธปิดิกส์ ภายใต้การระงับความรู้สึกทางไขสันหลัง ด้วยยาบิวพิวาเคนแบบ isobaric ความเข้มข้นร้อยละ 0.5 ร่วมกับมอร์ฟีนที่ปราศจากสารถนอมยาขนาด 0.2 มิลลิกรัม ผู้ป่วยถูกแบ่งเป็น 2 กลุ่ม กลุ่มละ 84 คน ได้รับยากาบาเพนตินขนาด 600 มิลลิกรัม หรือได้รับสารไร้ตัวยาก่อนผ่าตัด 2 ชั่วโมง เป็นการศึกษาแบบสุ่มที่มีตัวเปรียบเทียบแบบไปข้างหน้า อาการคันและผลข้างเคียงได้รับการประเมินที่ 1, 2, 3, 4, 6, 9, 12 และ 24 ชั่วโมงหลังฉีดมอร์ฟีนในช่องเยื่อหุ้มไขสันหลัง*

ผลการศึกษา: *อุบัติการณ์รวมของอาการคันไม่แตกต่างอย่างมีนัยสำคัญระหว่างสองกลุ่ม ขณะที่อุบัติการณ์และความรุนแรงลดลงอย่างมีนัยสำคัญในกลุ่มยากาบาเพนตินที่ 4 ชั่วโมง หลังฉีดมอร์ฟีนในช่องเยื่อหุ้มไขสันหลัง 18 ใน 84 ราย (ร้อยละ 21.4) กับ 35 ใน 84 ราย (ร้อยละ 41.6) ในกลุ่มสารไร้ตัวยา ค่า p = 0.008 และ 0.045 ตามลำดับ ภาวะปัสสาวะกักคั่งในกลุ่มศึกษาสูงกว่ากลุ่มสารไร้ตัวยาอย่างมีนัยสำคัญ 42 ใน 84 ราย (ร้อยละ 50) เทียบกับ 28 ใน 84 ราย (ร้อยละ 33.3) ค่า p = 0.042*

สรุป: *ยากาบาเพนตินขนาด 600 มิลลิกรัม ก่อนการผ่าตัดไม่สามารถลดอาการคันหลังผ่าตัดเหนี่ยวนำโดยยามอร์ฟีนในช่องเยื่อหุ้มไขสันหลังอย่างมีนัยสำคัญ*