Preoperative Gabapentin Prevents Intrathecal Morphine-Induced Pruritus After Orthopedic Surgery

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BACKGROUND: Pruritus is the most common side effect of intrathecal morphine. Gabapentin is an anticonvulsant and had been reported to be effective in some chronic pruritus conditions. Its effect in intrathecal morphine-induced pruritus has not yet undergone an evaluation.

METHODS: We randomly allocated 86 patients scheduled for lower limb surgery under spinal anesthesia into two equal groups that received either gabapentin 1200 mg or placebo 2 h before operation in a prospective, double-blind manner. All patients received an intrathecal injection of 15 mg of 0.5% isobaric bupivacaine and 0.2 mg preservative-free morphine. Pruritus was evaluated at 3, 6, 9, 12, and 24 h after intrathecal morphine administration.

RESULTS: The incidence of pruritus was significantly more frequent in the placebo group compared with the gabapentin group (77.5% vs 47.5%; $P = 0.01$). The onset time of pruritus in the gabapentin group (6.2 ± 1.8 h) was significantly delayed compared with that in the placebo group (3.1 ± 0.8 h) ($P < 0.0001$). The severity of pruritus was significantly more in the placebo group compared with the gabapentin group at 3 and 6 h after intrathecal morphine injection.

CONCLUSION: Preoperative gabapentin prevents pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anesthesia.

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A single dose of intrathecal morphine provides excellent postoperative analgesia for up to 18–24 hour after administration.[1] Pruritus is the most common side effect of intrathecal morphine, with a reported incidence of 62%–94%.[2] Pharmacological strategies to tackle this difficult-to-manage side effect have included antihistamines, 5-HT3 (serotonin) receptor antagonists, opioid antagonists, opioid agonist-antagonists, propofol, and nonsteroidal antiinflammatory drugs.[1,3] Gabapentin is an anticonvulsant, a structural analog of γ-aminobutyric acid, and currently approved by the Food and Drug Administration for the treatment of partial seizures and postherpetic neuralgia. Several studies have shown gabapentin to be effective in the case of brachioradial pruritus,[4] uremic pruritus,[5–7] multiple sclerosis-induced pruritus,[8] and pruritus of unknown origin.[9] However, its antipruritic activity in opioid-induced pruritus has not been evaluated. We thus tested the hypothesis that preventive gabapentin would decrease the incidence and severity of intrathecal morphine-induced pruritus in patients undergoing orthopedic surgery.

METHODS

The study was approved by the IRB of Tri-Service General Hospital in Taipei, Taiwan, and was designed as a randomized, double-blind, placebo-controlled trial. All patients gave their informed consent after receiving written information about the study, which was performed in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines. Between July 2006 and June 2007, patients from our orthopedic department were invited to participate. Patients were considered eligible if they were aged 20–40 yr, ASA physical status I, and were scheduled for lower limb surgery under spinal anesthesia. Patients were excluded for any of the following reasons: contraindication for spinal anesthesia, known allergy history to gabapentin, complaint of pruritus before surgery, morbid obesity, coexisting skin disorder, and any systemic disease associated with pruritus. Patients who had history of seizure attacks, mental illness, chronic headache, or neuropathic pain and were concomitantly using of anticonvulsants, antidepressants, or antipsychotics were also excluded. Patients were randomized to treatment groups according to a computer-generated randomization list with blocks of

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four and patients were allocated consecutively. Sealed code envelopes were kept by the principal investigator and were returned to the monitor after study termination. The blinding was maintained by keeping the treatment code with one of the investigators, separating them from the investigator performing the assessments until the database was closed. Patients in the gabapentin group received three capsules of gabapentin 400 mg at 2 h before operation. Patients in the placebo group received equal numbers of identical-looking placebo capsules in which the active ingredients had been removed and replaced by glucose powder, according to the same schedule. Drug compliance was monitored by one of our residents. After standard monitoring (electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry) was set-up in the operating room, each patient was prehydrated with Ringer's lactate solution 5–10 mL/kg, spinal anesthesia was performed at the L2–3 or L3–4 interspace with a 25-gauge Quincke-type needle using 15 mg of 0.5% isobaric bupivacaine plus 0.2 mg of preservative-free morphine. Fentanyl 50 μg was given for each patient before the procedure. Midazolam, in 0.5 mg increments, was administered IV for intraoperative sedation at the discretion of the anesthesiologist. The sedation level was evaluated by the Ramsay Sedation Scale during the operation. The patients were followed for 24 h after intrathecal administration of morphine. Postoperative wound pain at rest and during activity was assessed with a 10-cm visual analog scale. Rescue treatment for postoperative pain was provided with meperidine IM injection. Pruritus was evaluated at 3, 6, 9, 12, and 24 h after intrathecal administration of morphine by a blinded investigator. Pruritus was defined as the sensation that provokes the desire to scratch. The patients were questioned about the presence, location, and degree of pruritus. The degree of pruritus was classified as no pruritus, mild pruritus, moderate pruritus, and severe pruritus that needed rescue treatment.[10,11] Severe pruritus was treated with 5 mg IV nalbuphine. Patients were also evaluated the severity of postoperative nausea and vomiting, the presence of urinary retention and the side effects of drug treatment. Patients who reported vomiting received 0.625 mg IV droperidol and 10 mg IV metoclopramide. The primary outcome measure of the study was the incidence of pruritus during the 24 h follow-up period. The difference of onset time of pruritus in the gabapentin and placebo groups served as the secondary outcome measure. Additional secondary outcome measures were degree of severity of pruritus, duration of pruritus, and percentage of patients in both groups who needed rescue treatment. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 11, SPSS, Inc., Chicago, IL). We considered a 50% reduction in the incidence of pruritus to be clinically important. Power analysis was performed to determine the sample size with a probability for a type II error of 0.1 and type I error of 0.05. To detect a 50% reduction in the incidence of pruritus, using the results of a pilot study, in which pruritus was present in 15 (75%) of 20 patients, a sample size of 35 patients in each group was estimated to be required. To accommodate for patient dropouts and failure of spinal anesthesia, 40 patients were enrolled in each group. Continuous data were analyzed using repeated measures ANOVA and *post hoc* analysis with the unpaired test or the Friedman statistic and *post hoc* analysis with the Mann-Whitney *U*-test where appropriate. The normal distribution of the data was assessed according to the Kolmogorov-Smirnov test. The onset time of pruritus was analyzed by means of Kaplan–Meier probability curves and the log-rank test. Comparison of the categorical data was performed using χ^2 analysis or the Fisher's exact test with Yates correction if appropriate. Results are expressed as median (range) unless the data were normally distributed. For all determinations, P values of <0.05 were considered to be statistically significant.

Table 1. Demographic Characteristics and Intraoperative Data

Variable	Placebo (n = 40)	Gabapentin (n = 40)
Age (yr)	27 (21–33)	28 (23–33)
Height (cm)	173 (169–177)	175 (168–181)
Weight (kg)	68 (63–72)	70 (65–75)
Gender (M/F)	38/2	39/1
Intraoperative midazolam (mg)	2.5 (1.5–3.5)	0 (0–1)*
Ramsay sedation score	3 (2–4)	3 (2–4)
Duration of surgery (min)	105 (50–130)	110 (55–145)
Type of surgery		
Cruciate ligament reconstruction	18 (45)	22 (55)
Open reduction	10 (25)	7 (17.5)
Removal of implant	7 (17.5)	5 (12.5)
Arthroscopy	5 (12.5)	6 (15)

Values are median (range) or number of patients (%).

* $P < 0.0001$ when compared with Mann–Whitney *U* test.

RESULTS

From July 2006 to June 2007, we recruited 86 patients in our study, 6 of whom were excluded for the following reasons: failure of spinal anesthesia (n = 3), incomplete collection of postoperative data (n = 2), and protocol violations (n = 1). Therefore, 80 patients completed the trial, 40 in each group. The demographic and surgical data of patients who completed the study are listed in Table 1. The incidence of pruritus in the 24 h follow-up period was significantly more frequent in the placebo group (31 of 40, 77.5%) compared with the gabapentin group (19 of 40, 47.5%) (P = 0.01) (Table 2). The overall reduction rate of pruritus by gabapentin was 38.7%. The onset time of pruritus between groups was also significantly different in the gabapentin group (6.2 ± 1.8 h) compared with placebo (3.1 ± 0.8 h) ($P < 0.0001$) (Fig. 1). The severity of pruritus was significantly more in the

Table 2. Incidence and Onset of Pruritus After Intrathecal Morphine

	Placebo ($n = 40$)	Gabapentin ($n = 40$)
No. of patients with pruritus (%)	31 (77.5)	19 (47.5)*
Onset of pruritus (h)	3.1 ± 0.8	6.2 ± 1.8†

* $P < 0.05$ when compared with placebo with χ^2 test.

† $P < 0.0001$ when compared with placebo with unpaired t test.

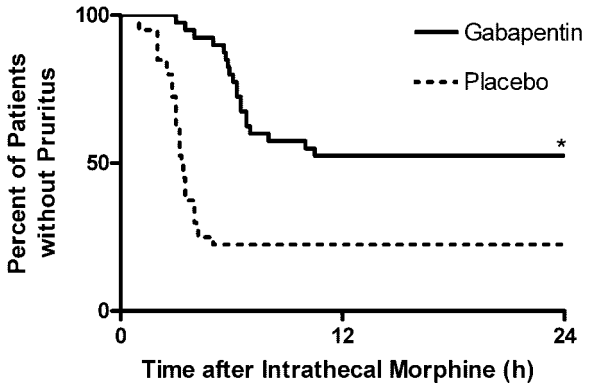

Figure 1. Onset time of pruritus in the first 24 h after intrathecal morphine administration, shown as Kaplan–Meier curves. *$P < 0.0001$ when compared to placebo with log-rank test.

placebo group compared with gabapentin group at 3 and 6 h after intrathecal morphine injection and was not statistically different at 9, 12, and at 24 h (Table 3). The degree was most severe at 3 h in the placebo group, and at 6 h in the gabapentin group. When we compared the severity of pruritus at the two time points, there was also a significant difference between groups ($P = 0.0001$). Although we did not measure the exact time course of pruritus, the duration of pruritus in the placebo group was longer (from 3 to 9 h) than that in the gabapentin group (from 6 to 9 h). Even at 9 h, the proportion of pruritus in the placebo group was still larger than in the gabapentin group (35% vs 17.5%). The patients requiring rescue treatment was higher in the placebo (8 of 40) than that in the gabapentin group (1 of 40) ($P = 0.033$). When pruritus occurred, the areas most involved were the trigeminal region (68%) and the anterior chest region (23%). Side effects included somnolence (38%) and dizziness (26%). The sedation score was the same between the two groups but the total dose of midazolam given during operation was significantly more in the placebo group (Table 1). Patients remained awake during the follow-up period, and no patients in the study period suffered from respiratory depression.

DISCUSSION

The most important finding of the current study was that gabapentin had a significant effect in the prophylactic treatment of intrathecal morphine-induced pruritus. Our results showed that preoperative gabapentin 1200 mg decreased the incidence of intrathecal morphine-induced pruritus by 38.7% ($P = 0.01$) compared with placebo. Gabapentin also significantly reduced most of the secondary outcomes. The patients in the gabapentin group who had symptoms of pruritus showed delayed onset time of pruritus, decreased severity of pruritus, and fewer patients needed antipruritic treatment compared with those in the placebo group.

The rationale of this study design is based on the fact that there are complex interactions between pain and itching.[12–15] Recent data show that the pattern of central neuron sensitization between pain and itching is astonishingly similar: painful stimulation in the periphery can generate central sensitization, including allodynia and punctuate hyperalgesia. Similarly, alloknesis and punctuate hyperkinesis have also been observed in itch processing.[15] Based on these findings, gabapentin used to treat neuropathic pain has also been used to treat chronic itching conditions. The antipruritic effects of gabapentin have been reported in the treatment of brachioradial pruritus, uremic pruritus, multiple sclerosis-induced pruritus, and pruritus of unknown origin. Intrathecal morphine-induced pruritus is a neurogenic itch[16] and its pathophysiology probably is not exactly the same as the ones in chronic itch conditions. It is also not clear if central neuron sensitization plays a role in intrathecal morphine- induced pruritus. However, from our data, we did demonstrate an antipruritic effect of gabapentin in intrathecal morphine-induced pruritus. Preoperative gabapentin 1200 mg decreased the incidence of pruritus by 38.7% and half of our patients who took gabapentin were symptom-free during the follow-up period. A single dose of gabapentin, however, cannot completely prevent the occurrence of pruritis. Whether this is due to inadequate dosage or to other mechanisms not covered by the pharmacological actions of gabapentin needs further study.

From our data, the onset time of pruritus was delayed from 3.1 h in the placebo group to 6.2 h in the gabapentin group. The average onset time in intrathecal morphine-induced pruritus was 2–3 h after intrathecal injection. Our data were compatible with others.[17,18] It is curious that the onset time was delayed in the gabapentin group, since the rate of bulk flow of cerebrospinal fluid containing morphine should have been the same in both groups. One plausible explanation for this is that gabapentin may delay the neuronal transmission during itch processing. Several studies have demonstrated that itch has its own primary afferent histamine-sensitive C-fibers[19] and has its distinct "itch-selective" secondary neurons in the lamina I spinothalamic tract neurons of the dorsal horn.[20] These histamine-sensitive neurons did not show spontaneous activity and were tonically inhibited by spontaneously active wide dynamic range (WDR) or nociception-specific (NS) neurons. Intrathecal morphine decreased the activity of WDR and NS neurons, leading to reduced tonic inhibition, and therefore

Table 3. Assessment of Severity of Pruritus at 3, 6, 9, 12 and 24 Hours After Intrathecal Morphine Administration

	3 h*	6 h†	9 h	12 h	24 h
Placebo					
No pruritus	9 (22.5)	16 (40)	26 (65)	38 (95)	40 (100)
Mild pruritus	12 (30)	18 (45)	12 (30)	2 (5)	0
Moderate pruritus	11 (27.5)	6 (15)	2 (5)	0	0
Severe pruritus	8 (20)	0	0	0	0
Gabapentin					
No pruritus	39 (97.5)	27 (67.5)	33 (82.5)	39 (97.5)	40 (100)
Mild pruritus	1 (2.5)	10 (25)	6 (15)	1 (2.5)	0
Moderate pruritus	0	2 (5)	1 (2.5)	0	0
Severe pruritus	0	1 (2.5)	0	0	0

Values are no. of patient (%).

* $P < 0.0001$ compared by χ^2 test.

† $P = 0.044$ compared by χ^2 test.

allowed spontaneous activity of central itch neurons. Although systemically administered gabapentin can markedly reduce C-fiber-evoked responses after inflammation,[21] it may not have a similar effect on "itch-specific" C-fibers in that the intrathecal morphine-induced pruritus is of central origin and does not involved the stimulation of afferent pruriceptors. Gabapentin, however, might target against the excitation of the central "itch neurons" as well as WDR and NS neurons and inhibit such selective neural networks that were activated by intrathecal morphine.[22]

Our data showed that gabapentin reduced the severity of pruritus. The duration of pruritus was also shorter in the gabapentin group. The reason for this was not clear. However, one of the reasons was the central reduction of itch perception by gabapentin.[23] Using functional positron emission tomography, the supraspinal processing of pruritus have been assessed and showed that the pattern of activation is very similar for pain sensation.[24] A broad overlap of activated brain areas is evident for pain and pruritus. Iannetti et al. also showed, by using functional magnetic resonance imaging, that gabapentin can modulate pain-related brain activity in humans.[25] The main effect of gabapentin was demonstrated in insular cortex, anterior cingulated cortex, primary somatosensory cortex and thalamus, the areas that were also involved in itch processing.[15] Therefore, we can speculate that gabapentin might have similar effects in itch processing in the brain and can reduce itch perception during central processing. Another explanation was that gabapentin can modulate the release of neurotransmitters and thus can reduce the excitability of spinal and supraspinal neurons during itch transmission. Gabapentin can inhibit the substance P-facilitated K^+-evoked release of glutamate from rat caudal trigeminal nucleus slices.[26] It can also have a modulatory action on other transmitter systems. Gabapentin can activate the descending noradrenergic system and suppress the activity of spinal nociceptive neurons.[27] Furthermore, it can activate spinal cholinergic circuits in rats after peripheral nerve injury.[28] The role of such pathways in mediating intrathecal morphine-induced pruritus needs to be established.

The serotonergic system is implicated in the development of the pruritus associated with administration of neuraxial opioids. A high density of 5-HT3 receptors was found in the superficial layers of the dorsal horn and in the nucleus of the spinal tract of the trigeminal nerve in the medulla. The spinal trigeminal nucleus located superficially in the medulla is an integrative center for sensory input from the face and an area known as the "itch center." Activation of 5-HT3 receptors by morphine appears to be one of the mechanisms of intrathecal morphine-induced pruritus. Gabapentin can inhibit spinal-supraspinal serotonergic circuits when spinal 5-HT3 receptors are activated.[29] Although gabapentin in our study reduced the incidence and severity of pruritus, this side effect still occurred in 21 (52.5%) of the 40 patients during the 24 h follow-up period, showing the complexity of the pathogenesis of pruritus. More studies are needed to investigate the effects of multimodal antipruritic therapy in these patients.

Our study had two limitations. First, we only studied the antipruritic effect of gabapentin in a specific group of patients using a single large dose. Although most patients responded well, more than half of them still experienced side effects. More studies are required to evaluate optimal dose-related efficacy. Second, pruritus is a subjective sensation and data from our study might be misinterpreted by the fact that each patient perceives pruritus differently. Scratching behavior, on the other hand, can be measured. A monitoring system that records scratching activity will help overcome this limitation.

In summary, preoperative gabapentin 1200 mg decreased the incidence, delayed the onset time, decreased the severity, and shortened the duration of pruritus in patients undergoing lower limb surgery under spinal anesthesia with 15 mg of 0.5% isobaric bupivacaine and 0.2 mg of preservative-free morphine.

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