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Prophylactic mirtazapine reduces intrathecal morphine-induced pruritus†

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Background. Activation of the serotonergic system is an important factor in the pathogenesis of intrathecal morphine-induced pruritus. Mirtazapine is a new antidepressant that selectively blocks 5-HT_2 and 5-HT_3 receptors. We therefore tested the hypothesis that preoperative mirtazapine would reduce the incidence of intrathecal morphine-induced pruritus.

Methods. One hundred and ten ASA I patients undergoing lower limb surgery under spinal anaesthesia were randomly allocated into two equal groups and received either mirtazapine 30 mg or an orally disintegrating placebo tablet 1 h before operation in a prospective, double-blinded trial. All patients received an intrathecal injection of 15 mg of 0.5% isobaric bupivacaine and 0.2 mg preservative-free morphine. The occurrence and the severity of pruritus were assessed at 3, 6, 9, 12, and 24 h after intrathecal morphine.

Results. Pruritus was significantly more frequent in the placebo group compared with the mirtazapine group (75% *vs* 52%, respectively; $P=0.0245$). The time to onset of pruritus in the two groups was also significantly different. The patients who experienced pruritus in the placebo group had a faster onset time than that in the mirtazapine group [mean (SD): 3.2 (0.8) *vs* 7.2 (4.1) h, $P<0.0001$].

Conclusions. Mirtazapine premedication prevents pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anaesthesia.

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A single dose of intrathecal morphine provides excellent postoperative analgesia, but its use is often associated with side-effects. Pruritus occurs most frequently[1] and activation of serotonergic pathways has been implicated in the pathogenesis of this pruritus.[2] The current management of intrathecal morphine-induced pruritus includes: 5-HT_3 (serotonin) receptor antagonists, opioid antagonists, opioid agonist–antagonists, antihistamines, propofol, droperidol, and non-steroidal anti-inflammatory drugs (NSAIDs).[3 4] Mirtazapine is a noradrenergic and specific serotonergic antidepressant that acts by blocking presynaptic α_2-autoreceptors and α_2-heteroreceptors, in addition to antagonizing postsynaptic 5-HT_2 and 5-HT_3 receptors.[5] It therefore enhances noradrenergic transmission and selectively increases 5-HT_1-mediated serotonin transmission.[6] Mirtazapine also has H_1-antihistamine activities. Because it blocks most of the known major receptors associated with pruritus (H_1, 5-HT_2, and 5-HT_3), the use of mirtazapine to treat pruritis induced by malignancy[7] and inflammatory skin disorders has been reported.[8] Its effects in intrathecal morphine-induced pruritus have not yet undergone an evaluation. We tested the hypothesis that preoperative mirtazapine would decrease the incidence and severity of intrathecal morphine-induced pruritus in patients undergoing orthopaedic surgery.

Methods

After obtaining the approval of the Institutional Review Board of Tri-Service General Hospital and signed informed consent from each patient, 110 patients with ASA physical

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status I and aged 20–40 yr undergoing lower limb surgery under spinal anaesthesia were recruited in this randomized, double-blinded, placebo-controlled study. Patients were excluded for any of the following reasons: known drug allergy history, the presence of pruritus before surgery, coexisting skin disorders, and any systemic disease associated with pruritus. Patients who had history of mental illness and concomitant use of antidepressants or antipsychotics were also excluded. Patients were randomized to treatment according to a computer-generated randomization list. An oral disintegrating mirtazapine 30 mg tablet or a placebo tablet was given 1 h before surgery in the waiting area by one of our residents, who was blinded to the treatment. After entering the operating theatre, standard monitoring was applied (ECG, non-invasive arterial pressure, and pulse oximetry) and patients received 500–1000 ml of normal saline. Subarachnoid anaesthesia was performed at the L3–4 or L4–5 interspace with a 26-gauge Quincke-type needle using 15 mg of isobaric bupivacaine plus 0.2 mg of preservative-free morphine. Fentanyl 50 μg was given to each patient before surgery. The sedation level was assessed by the 6-point Ramsay sedation score during operation.[9] Midazolam, in 0.5 mg increments, was given i.v. to patients for intraoperative sedation at the discretion of the anaesthetists to achieve a Ramsay sedation score between 2 and 4. Pruritus was assessed 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 asked about the presence, location, and severity of pruritus. The severity of pruritus was defined as no pruritus, mild pruritus, moderate pruritus, and severe pruritus that needed rescue treatment.[10] Severe pruritus was treated with 5 mg i.v. nalbuphine. The side-effects of intrathecal morphine, including postoperative nausea and vomiting, urinary retention, and respiratory depression were also evaluated. The primary outcome measure of the study was the incidence of pruritus during the 24 h follow-up period. Secondary outcome measures included the onset time of pruritus, severity, duration, location of pruritus, and percentage of patients in both groups who needed rescue treatment. Statistical analysis was performed using SPSS software, version 11.5 (Chicago, IL, USA). We considered a 30% reduction in the incidence to be clinically important. Power analysis was performed to determine the sample size with a probability of a type II error of 0.1 and a type I error of 0.05. To detect a 30% 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 55 patients in each group was estimated to be required. Continuous data were analysed using repeated measures ANOVA and *post hoc* analysis with the unpaired *t*-test or using Friedman's test 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. Categorical data were analysed using the χ^2 test with the Yates correction if appropriate or Fisher's exact test. Correction for repeated testing at five time points was made by similar analysis 2×2 tables for intergroup differences. Comparison of the number of patients with adverse effects was done by Fisher's exact test. Results were expressed as median (range). *P*-values of <0.05 were considered to be statistically significant.

Results

Of the 110 patients recruited in the study, six of whom were excluded for the following reasons: inadequate spinal anaesthesia ($n=2$), incomplete data collection ($n=1$), and the use of NSAIDs for postoperative pain ($n=3$). Therefore, 104 patients completed the study, 52 in each group (Fig. 1). The groups were similar in age, gender, height, weight, type of surgery, and duration of surgery (Table 1). The overall incidence of pruritus in 24 h follow-up period was significantly less in the mirtazapine group (27 of 52, 52%) compared with the placebo group (39 of 52, 75%) ($P=0.024$). The overall reduction rate by mirtazapine was 30.6%. The onset time of pruritus was significantly delayed in the mirtazapine group [mean (SD): 7.2 (4.1) h] compared with that in the placebo group [3.2 (0.8) h] ($P<0.0001$). The severity of pruritus was significantly less in the mirtazapine group

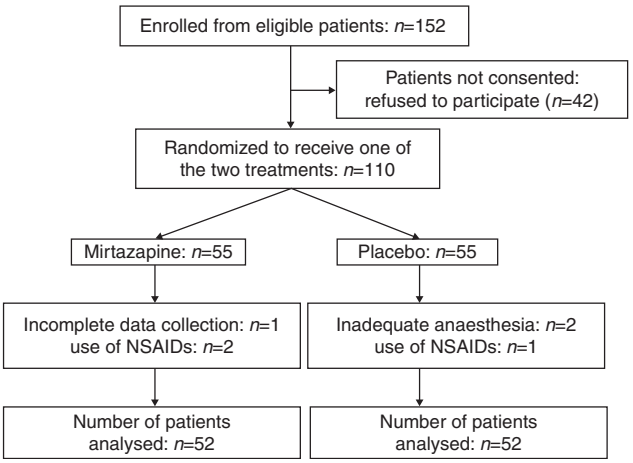

Fig 1 CONSORT diagram for the study.

Table 1 Patients characteristics and surgical data. Values are median (range), mean (SD), or number of patients (%). There were no significant differences between the groups

	Mirtazapine ($n = 52$)	Placebo ($n = 52$)
Age (yr)	27 (20–34)	25 (22–36)
Height (cm)	172.2 (2.3)	173.1 (3.1)
Weight (kg)	69.6 (3.2)	70.5 (3.7)
Gender (M/F)	48/4	50/2
Duration of surgery (min)	115 (65–130)	100 (50–150)
Ramsay score during operation	3 (2–4)	3 (2–4)
Type of operation		
Cruciate ligament reconstruction	31 (60%)	27 (52%)
Open reduction	11 (21%)	14 (27%)
Removal of implant	6 (11%)	7 (13%)
Arthroscopy	4 (8%)	4 (8%)

compared with that in the placebo group at 3, 6, and 9 h after intrathecal morphine administration and it was not statistically different at 12 and 24 h (Table 2). At 9 h, the proportion of pruritus in the placebo group (38%) was still higher than that in the mirtazapine group (17%). The number of patients requiring antipruritic treatment was higher in the placebo group (10 of 52, 19%) than that in the mirtazapine group (2 of 52, 4%) (P=0.028). The distribution of pruritus between two groups was statistically different (P=0.0013). The typical facial scratching induced by intrathecal morphine was commonly seen in the placebo group (72%). On the other hand, the occurrence of pruritus in the mirtazapine group was more located over the trunk area (57%) than in the facial area (33%) (Table 3). Adverse effects of treatment were more frequent in the mirtazapine group. More patients who took mirtazapine had sedation (Ramsay score=3) or somnolence (Ramsay score=4) during the perioperative period (Table 4). The sedation level was not significantly different, however, between the two groups (P=0.27). The patients in the placebo group received more doses of midazolam to achieve the similar level of sedation during the operation [3 (2–4) *vs* 0 (0–1) mg, P<0.0001]. No patients were over-sedated (Ramsay score $\geq$5) and no patient had respiratory depression during the 24 h follow-up period.

Discussion

Activation of 5-HT_3 receptors in the superficial layers of the dorsal horn and in the trigeminal nucleus by morphine appears to be one of the mechanisms of pruritus. Mirtazapine selectively blocks 5-HT_2 and 5-HT_3 receptors. In our study, preoperative mirtazapine reduced the incidence of pruritus from 75% to 52%. The rationale of use of antidepressants to treat pruritus is that they can reduce pruritus signalling presumably through alteration in neurotransmitter concentrations within the central nervous system.[11] Mirtazapine has a unique pharmacological profile unrelated to selective serotonin reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors.[12] Apart from increasing noradrenergic and serotonergic neurotransmission, mirtazapine can exert its antidepressant[13] and antinociception action[14] through κ-opioid system. Its antipruritic activity was first reported by Davis and colleagues[8] who found that mirtazapine was effective in treating pruritus induced by cholestasis, Hodgkin's disease, and chronic renal insufficiency. Yosipovitch and colleagues[11 15] extended the use of mirtazapine in the treatment of psoriatic itch, the itch of prurigo nodularis, and other types of pruritus associated with inflammatory skin disease. In this clinical trial, we examined the antipruritic efficacy of mirtazapine in intrathecal morphine-induced pruritus. Mirtazapine reduced the incidence of pruritus by 30.6%. Mirtazapine cannot completely abrogate the occurrence of pruritus. Nearly half of patients who took mirtazapine still had symptoms of pruritis. This could be due to inadequate dosage of mirtazapine or it is possible that other neurotransmitters not affected by the action of mirtazapine participate in the pathogenesis of pruritus. For instance, the involvement of prostaglandins,[16] the inhibitory neurotransmitters glycine and GABA,[17] or activation of the *N*-methyl-D-aspartate (NMDA) receptors[18] may also be important in the aetiology of pruritus.

From our data, the onset time of pruritus was delayed from 3.2 to 7.2 h after premedication with mirtazapine. We also observed that the distribution of pruritus was different between the two groups. The distribution of pruritus in the mirtazapine group was located more over the trunk region, lower than that typical facial pruritus observed in the placebo group. A plausible explanation for this is that

Table 2 Severity of pruritus assessed at 3, 6, 9, 12, and 24 h after intrathecal morphine administration. Values are number of patients (%). *P<0.0001 compared by χ^2 test. †P=0.004 compared by χ^2 test

	3 h*	6 h*	9 h†	12 h	24 h
Mirtazapine					
No	49 (94%)	40 (77%)	43 (83%)	47 (90%)	50 (96%)
Mild	3 (6%)	8 (15%)	7 (13%)	5 (10%)	2 (4%)
Moderate	0	2 (4%)	2 (4%)	0	0
Severe	0	2 (4%)	0	0	0
Placebo					
No	21 (40%)	22 (42%)	32 (62%)	47 (90%)	52 (100%)
Mild	9 (17%)	17 (33%)	15 (28%)	5 (10%)	0
Moderate	12 (24%)	13 (25%)	5 (10%)	0	0
Severe	10 (19%)	0	0	0	0

Table 3 Distribution of pruritus after intrathecal morphine. Values are number of patients. There was a significant difference in the frequency of distribution of pruritus over the facial region (P=0.0005) between two groups compared by Fisher's exact test

	Mirtazapine (n = 52)	Placebo (n = 52)
Number of patients with one or more sites of pruritus		
Face	10	28
Trunk	17	10
Low extremities	3	1
Number of patients with no pruritus	25	13

Table 4 Adverse events. Data are expressed as number of patients. There were significant differences in the occurrence of sedation (P<0.0001) and somnolence (P=0.028) between two groups (Fisher's exact test). The other listed adverse events reached no differences. There was a significant difference (P<0.0001) in the number of patients reporting one or more adverse events between two groups (Fisher's exact test)

	Mirtazapine (n = 52)	Placebo (n = 52)
Sedation	28	1
Somnolence	10	2
Dizziness	1	2
Dry mouth	12	10
Nausea	1	1
Vertigo	1	0
Blurred vision	0	1
Number of patients with one or more AEs	40	13
Number of patients with no AEs	12	39

mirtazapine may inhibit the neuronal transmission during itch processing. The descending facilitatory pathways releasing serotonin from the rostral ventromedial medulla can facilitate spinal itch processing by the activation of the excitatory 5-HT_3 receptors localized in the superficial dorsal horn.[19] Mirtazapine could work on the spinal level and antagonize the excitatory 5-HT_3 receptors to decrease neurotransmitter release. On the other hand, mirtazapine could work on descending inhibitory pathways to potentiate the noradrenergic transmission.[20] Furthermore, there is cross-talk between voltage-gated Ca^{2+} channels and 5-HT_3 receptors.[21] Mirtazapine might therefore target directly on spinal neurones to inhibit the neuronal excitability by modulating the openings of these channels. One of the above three mechanisms might account for the delayed onset and lower frequency of facial pruritus in patients who took mirtazapine before operation.

Our data indicate that mirtazapine can reduce the severity and shorten the duration of pruritus. Such effects may not be due to 5-HT_3 antagonism alone but also due to the other actions of mirtazapine. First, mirtazapine could exert its antipruritic effect through activating the κ-opioid system. Secondly, mirtazapine can work on the cerebral cortex to reduce the perception of pruritus. Thirdly, mirtazapine had strong antihistamine effect. From the pharmacokinetic viewpoint, mirtazapine has another advantage over the first-generation 5-HT_3 receptor antagonists. The peak concentration of mirtazapine is reached 2 h after single dose and the elimination half-life ranges from 20 to 40 h,[22] allowing the drug to cover the onset and duration of pruritus.

Mirtazapine decreased the incidence of pruritus, but on the other hand it increased sedation. In addition, most of the patients experienced mild pruritus and would have probably not noticed this side-effect if not asked about it. Thus, to assess the clinical value of giving mirtazapine to patients, it could be more interesting to focus on moderate to severe pruritus. From the data, we calculated the number-needed-to-treat (NNT) to prevent pruritus equal or greater than moderate severity, the relative risk (RR) of developing pruritus of moderate or greater severity when receiving mirtazapine compared with placebo and the absolute risk reduction. The NNT is 2.9, the RR is 4 (95% CI: 1.59, 10.02), and the absolute risk reduction is 34.6%. Such favourable results are comparable with that of μ-opioid receptor antagonists, naloxone, or naltrexone.[4] These result favour mirtazapine in comparison with other drugs used to prevent intrathecal morphine-induced pruritus. The NNT and RR for 4 mg i.v. for ondansetron calculated to be 8 (95% CI: 3.0, −12) and 1.22 (95% CI: 0.87, 1.70); for 2.5 mg i.v. of droperidol values of 4.9 (95% CI: 3.2, 10) and 1.71 (95% CI: 1.28, 2.29)[4] have been reported.

Around 70% of our patients who took mirtazapine displayed sedation and somnolence which raised concern as to whether this adverse effect was clinically important. This percentage is higher than in previously published data and is probably due to interaction of mirtazapine with midazolam.[12] Mirtazapine alone may be useful for perioperative sedation. Furthermore, all of our patients were easily roused during operation and none was over-sedated during follow-up.

Our study had several limitations. First, pruritus is a subjective sensation and individual variation in pruritus perception is wide. We did not record the scratching. The dose we chose was arbitrary. Additional studies are required to determine the optimal dose. Our results can only be applied in a group of young and mostly male patients. The safety of mirtazapine in older or debilitating patients needs further evaluation. We chose morphine because it has a longer duration of analgesia (18–24 h) than that of lipophilic opioids (fentanyl and sufentanil). Although the incidence of pruritus among the three opioids is similar (65–95%),[3] the antipruritic efficacy of mirtazapine in intrathecal fentanyl or sufentanil-induced pruritus is unknown.

In summary, preoperative mirtazapine 30 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 anaesthesia with 15 mg of 0.5% isobaric bupivacaine and 0.2 mg of preservative-free morphine.

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