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ORIGINAL ARTICLE

Nalbuphine added to intrathecal morphine in total knee arthroplasty; effect on postoperative analgesic requirements and morphine related side effects

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KEYWORDS

Nalbuphine;
Intrathecal anaesthesia;
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Abstract *Introduction:* Intrathecal morphine is widely used for postoperative pain control in major orthopaedic surgery. However, its use is associated with frequent side effects.
Aim of the work: Aim of the work was to investigate the effects of intrathecal coadministration of nalbuphine with intrathecal morphine on morphine related side effects and postoperative analgesic requirements.
Methods: In this study, the intrathecal addition of 1 mg nalbuphine hydrochloride to a combination of 3 ml hyperbaric bupivacaine 0.5% and 0.2 mg morphine sulfate was tried in patients undergoing total knee arthroplasty.
Results: Patients who received intrathecal nalbuphine suffered significantly less than the control group from vomiting and pruritus meanwhile there was no effect on the postoperative analgesic requirements or the incidence of urinary retention. Intrathecal addition of nalbuphine to morphine decreased the opioid related side effects without affection of postoperative analgesia.

Abbreviations: ASA, American Society of Anesthesiologists; Mg, milligram; G, gauge; VAS, visual analogue scale; 1st, first; $PaCO_2$, arterial carbon dioxide tension; mmHg, millimeter mercury; SPSS, statistical package for social sciences; Hr, hour; SD, standard deviation; PCA, patient controlled analgesia.

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Conclusions: The addition of nalbuphine to morphine intrathecally decreases the opioid related side effects without affection of postoperative analgesia. This combination can improve postoperative pain management in patients undergoing knee surgery under spinal anaesthesia.

1. Introduction

Prolonged postoperative pain control following major orthopaedic procedures may be achieved by the administration of a single dose of intrathecal morphine.[1] However, the use of intrathecal (IT) morphine may result in serious side effects e.g. pruritus, urinary retention, nausea and vomiting[2] and delayed respiratory depression.[3] These side effects may lead to patient discomfort and prolonged hospital stay thus limiting the usefulness of IT morphine.[4] Morphine binds most readily to the mu-opioid receptor and less well to the kappa-opioid receptor. So, the undesirable adverse events of morphine are thought to result from agonism at the mu-opioid receptor.[5]

Many drugs have been tried with morphine to potentiate its analgesic effects or to reduce the adverse events.[6] Nalbuphine is a mixed opioid agonist–antagonist that acts mainly through kappa-opioid receptors, and it may attenuate mu-opioid-receptor related side effects.[3] Moreover, recent studies suggested that the analgesic effects of morphine and nalbuphine may be additive.[7]

2. Aim of the work

Aim of the work was to investigate the effects of adding nalbuphine to intrathecal morphine on postoperative analgesic requirements and morphine related side effects.

3. Methods

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University. A written consent was obtained from the patients for participation in the study. Sixty patients scheduled for total knee arthroplasty were selected and the following were the criteria of patients to be included in the study:

Age 50–70 years.
ASA class I–II.

Exclusion criteria included:

Patient's refusal to participate in the study.
Uncooperative patients.
Any contraindication to spinal anaesthesia such as coagulopathy or low fixed cardiac output states.
Any patient with a history of allergy to any of the study drugs.

Complete history was taken from the patients and all patients were subjected to thorough examination and routine laboratory investigations including base line arterial blood gas analysis. All patients were premedicated with oral midazolam 7.5 mg two hours before admission to the operative theatre. On admission, an intravenous line was inserted to all patients and 1litre of Ringer lactate solution was transmitted as a preload. Standard monitoring in the form of 3 leads electrocardiograph, pulse oximetry and non-invasive arterial blood pressure were attached. All patients were then subjected to spinal anaesthesia with 25G spinal needle. They were divided randomly into two equal groups of 30 patients each as follows:

Group A: Thirty patients received intrathecal injection of 3 ml hyperbaric bupivacaine 0.5% + 0.2 mg morphine sulfate in a total volume of 4 ml.

Group B: Thirty patients received intrathecal injection of 3 ml hyperbaric bupivacaine 0.5% + 0.2 mg morphine sulfate + 1 mg nalbuphine hydrochloride in a total volume of 4 ml.

All patients received spinal anaesthesia in the sitting position at the L_{2-3} intervertebral space with a 25G spinal needle without barbotage after proper disinfection and local anaesthesia at the site of injection.

At the end of the operation, patients were discharged to the post anaesthesia care unit where they were monitored for 24 h for the following:

Pulse rate using 3 leads electrocardiograph.
Oxygen saturation using pulse oximetry.
Non-invasive arterial blood pressure every 2 h.
Respiratory rate every 2 h.
$PaCO_2$ via arterial blood gas analysis every 4 h.
Pain was assessed using Visual analogue scale (VAS)[8] every 2 h. Patients were given boluses of 30 mg ketorolac intravenously if VAS score > 4.
Incidence of complications.
Vomiting: was managed with 4 mg ondansetron.
Pruritus: was treated with 8 mg dexamethazone.
Urinary retention: was managed with warm compresses and urinary catheterization if needed.

3.1. Measurements

Pain assessment:

Visual analogue scale.
Time to first analgesic requirement.
Total dose of intravenous ketorolac given postoperatively.
Evidence of complications:
Respiratory depression evidenced by respiratory rate < 8 breaths / minute or $PaCO_2$ > 10 mm Hg of the base line value.
Nausea and vomiting: was assessed using a 3-point scale[9] (0 = no nausea and vomiting, 1 = mild to moderate nausea or vomiting not needing treatment, and 2 = severe nausea or vomiting needing treatment).
Itching: incidence.
Urinary retention requiring urinary catheterization.

3.2. Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 17) software. The statistical test used was as follows: Arythematic mean and standard deviation. For categorized parameters, Chi square test was used, while for two groups, *t*-test was used for parametric data. The level of significance was 0.05.

4. Results

All patients completed the study thirty in each group. Patients' characteristics and surgical data of the two groups were not significantly different (Table 1). There was no significant difference between the groups with respect to the time of the first postoperative requirement of analgesia as well as the total dose of postoperative ketorolac consumed for pain relief (Table 2).

No evidence of respiratory depression was detected in any patient during the study period. Vomiting occurred significantly more frequently among patients in group A (16 out of 30) compared with patients in group B (8 out of 30); $p = 0.018$) (Table 3).

The incidence of itching was significantly reduced in group B (7 out of 30, 23.3%) relative to group A (15 out of 30, 50%; $p = 0.032$). No significant difference was detected as regards the incidence of urinary retention between the two groups (Table 3).

5. Discussion

In this study, the intrathecal combination of morphine and nalbuphine did not affect the postoperative analgesia or the total postoperative analgesic requirements. Otherwise, the incidence of morphine related side effects was reduced regarding postoperative vomiting and itching. Intrathecal morphine resulted in a moderate and clinically relevant increase in the incidence of nausea, vomiting, pruritus and urinary retention in the meta-analysis done by Gehling et al.[10] Since morphine binds most readily to the mu-opioid receptor, and less well to the kappa-receptor, this implies that the undesirable side effects of morphine are likely related to the mu-opioid receptor.[7] In a study of 5969 patients who received between 0.2 and 0.8 mg morphine intrathecally, Gwirtz and coworkers[11] described the side-effects and complications of intrathecal morphine. Without a control group they found nausea or vomiting in 25%, pruritus in 37% and respiratory depression in 3% of their patients. Nortcliffe et al.[12] used 0.1 or 0.2 mg of spinal morphine for analgesia in caesarean delivery and observed 67% and 60% incidence rates of nausea and vomiting, respectively which is slightly higher than the incidence in the current study (53.3%). They also demonstrated that pruritus was the most frequent side effect of intrathecal morphine and the incidence (87%) was consistent with previous research.[11] Neuraxial opioid-induced pruritus is likely due to cephalad migration of neuraxial opioids to the medulla where the ''itch center'' is suggested to be located and where they interact with the trigeminal nucleus.[13] In the study carried out by Hein et al.,[14] the most common side effect of intrathecal morphine for labour analgesia was pruritus which was equally common in all groups including controls (58–61%). Pruritus is known to occur due to activation of mu-opioid and 5-hydroxytryptamine 3 receptors and non-nociceptive neurons in the medulla and dorsal horn of the spinal cord, particularly in trigeminal nerve distribution.[15]

For nalbuphine, in 1997, Parker and coworkers[16] demonstrated that the combination of morphine and nalbuphine in patient-controlled epidural analgesia (PCA) resulted in a dose-dependent decrease in epidural morphine related side effects. The analgesic effects of nalbuphine are due to activation

Table 1 Demographic data of the studied sample.

	Group A	Group B	*P*
Age (years)			
Range	59–72	60–74	
Mean ± S.D.	61.9 ± 10.3	62.1 ± 12.9	0.428
Gender			
Male	9 (30.0%)	11 (36.7%)	0.25
Female	21 (70.0%)	19 (63.3%)	
Duration of operation (h)	2.0–3.5	2.0–3.25	
Range	2.95	2.58	0.366
Mean ± S.D.	0.82	0.76	

Table 2 Comparison between the two studied groups regarding time to 1st analgesia (hr) and total consumption of ketorolac (mg).

	Group A	Group B	*P*
	N = 30	*N* = 30	
Time to 1st analgesia (hr)			
Range	13.5–19	13.5–18.2	
Mean ± S.D.	16.17 ± 1.66	16.39 ± 1.37	0.286
Total ketorolac (mg)			
Range	0–60	0–60	0.122
Mean ± S.D.	19.00 ± 24.26	12.00 ± 21.72	

Table 3 Comparison between the two studied groups regarding complications.

	Group A		Group B		*P*
	N = 30		*N* = 30		
	No.	%	No.	%	
Nausea & vomiting					
0	14	46.7	22	73.3	0.018*
1	10	33.3	8	26.7	
2	6	20.0	0	0.0	
Itching					
Yes	15	50.0	7	23.3	
No	15	50.0	23	76.7	0.032*
Urinary retention					
Yes	9	30.0	5	16.7	0.22
No	21	70.0	25	83.3	

Nausea and vomiting: 0 = no nausea and vomiting, 1 = mild to moderate nausea or vomiting not needing treatment, 2 = severe nausea or vomiting needing treatment.
* *P* is significant.

of the kappa-opioid receptor, and nalbuphine also has the potential to attenuate the mu-opioid receptor related effects. When combining morphine and nalbuphine together, the analgesic effect from mu-opioid receptor decreases, but the analgesic effect from kappa opioid receptor increases. The reduction in the incidence of pruritus is the major benefit of combining morphine and nalbuphine in PCA. Opioid-related pruritus derives from agonism at the mu opioid receptor.[17] Nalbuphine does not lead to pruritus and it can suppress morphine-related pruritus.[7]

Although nalbuphine antagonizes the effect of mu-opioid receptor, Yeh et al.[18] did not find that the severity and incidence of nausea, vomiting, or requirement of antiemetics were less in patients receiving this drug. They explained that nausea and vomiting may result by other mechanisms such as the effect of pain on the vomiting centre, the residual effect of anaesthetics on the chemoreceptor trigger zone or the effect of surgery. Secondly, the types of surgery, the methods of anaesthesia and the population in their study were different from the studies which reported that nalbuphine can reduce the incidence of morphine-induced nausea and vomiting.

6. Conclusions

Intrathecal addition of nalbuphine to morphine decreases the opioid related side effects without affection of postoperative analgesia. This combination can improve postoperative pain management in patients undergoing knee surgery under spinal anaesthesia.

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