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Ketorolac and spinal morphine for postcesarean analgesia

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SUMMARY. This study was designed to compare spinal morphine (SM), ketorolac (K), and a combination of the two drugs with respect to analgesic efficacy and side effects in postcesarean patients. Forty-eight parturients having bupivacaine spinal anesthesia for cesarean delivery randomly received in a double-blind manner either: SM: 0.1 mg or SM: 0.2 mg (but no K); SM: 0.1 mg plus K 60 mg intravenously (i.v.) one hour after spinal injection, and 30 mg i.v. every 6 h for three doses; or i.v. K dosed as previously described (but no SM). Analgesia and side effects were evaluated during the first 20 h. Forty-eight women were studied. There were no significant differences in analgesia among the groups, although patients receiving SM: 0.1 mg tended to have less satisfactory intraoperative analgesia. Pruritus was common in all patients receiving SM whereas patients who received K had the lowest overall scores for severity of side effects. No serious complications occurred and all groups expressed similarly high satisfaction at the 24 h visit. We conclude that there is no advantage to combining SM and K, and that K provides satisfactory postcesarean analgesia with few side effects.

INTRODUCTION

Spinal morphine (SM) provides excellent postcesarean analgesia but results in frequent nausea and pruritus, a risk of delayed respiratory depression, and the need for supplemental analgesia in some patients.[1-3] Ketorolac (K), a non-steroidal anti-inflammatory drug (NSAID) might be an attractive alternative for postoperative analgesia in view of its lack of sedation, respiratory depression and other minor side effects. A prostaglandin synthetase inhibitor, it has proved effective both when given alone and in combination with systemic or epidural opioids.[4] Because K and opioids act at different sites and via different mechanisms, an additive or even synergistic effect might be expected.[5,6] Thus, combined therapy potentially offers improved analgesia with fewer opioid side effects. This study of postcesarean patients was designed to compare the analgesia and side effects resulting from SM or K alone with those resulting from a combination of the two drugs. SM was given as both our routine dose (0.2 mg) and a reduced dose (0.1 mg).

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METHODS

This study was approved by the Stanford Human Subjects Committee and all subjects gave written informed consent. The study population consisted of 48 healthy parturients who had selected spinal anesthesia for non-urgent cesarean section. Patients with a positive or suspicious history of bleeding tendencies, sleep apnea, morbid obesity, renal disease, peptic ulcer symptoms, asthma, nasal polyps, or allergy to aspirin, NSAIDs or opioids were excluded from the study. After the rapid intravenous (i.v.) infusion of 1500–2000 ml of Ringer's Lactate solution, we performed spinal anesthesia with the patient in the sitting position at the L2–3 or L3–4 interspace using a 24 gauge Sprotte needle. All patients received 12 mg (1.6 ml) 0.75% hyperbaric bupivacaine. Subjects were randomly assigned to receive, in addition, one of four treatments in a double-blind manner. Group SM: 0.2 received preservative-free SM (Astramorph™) 0.2 mg (0.4 ml), and Group SM: 0.1 received SM 0.1 mg (0.2 ml) + 0.2 ml preservative-free saline with the spinal bupivacaine; Group spinal morphine/ketorolac (SM/K) received SM 0.1 mg with saline as in the previous group, as well as K 60 mg i.v. one hour after spinal injection and 30 mg i.v. every 6 h for three doses; Group K received saline 0.4 ml spinally, and i.v. K dosed as in Group SM/K. Group assignments were designated in sealed consecutively numbered

envelopes and all study solutions were prepared in unlabelled numbered syringes by an anesthesiologist not involved in data collection. A saline placebo was added to the spinal injection so that all patients received a total of 2 ml (1.6 ml bupivacaine and 0.4 ml study solution). Patients in Groups SM: 0.2 and SM: 0.1 received i.v. saline placebo at the same times that those in Groups SM/K and K received K. The anesthesiologist injected the initial i.v. K or saline, as a bolus, usually in the operating room. The postpartum nursing staff infused subsequent doses i.v. over a 20 min period.

Patients complaining of pain received i.v. fentanyl (50–100 μg) intraoperatively, and i.v. meperidine (12.5–25 mg q 30 min to a maximum of 50 mg per hour) postoperatively. We recorded the time at which patients requested supplemental meperidine, and the total dose administered during the study period. Nausea and vomiting were treated with i.v. metoclopramide 10 mg, and pruritus with diphenhydramine 25–50 mg IM. Nursing staff monitored patients hourly recording respiratory rate and checking level of sedation. Patients who received more than 50 mg meperidine or who appeared sedated were monitored with a pulse oximeter. Naloxone was only ordered for treatment of respiratory depression.

Visual analog scales (VAPS) (0–10 cm, where 0 = no symptom and 10 = worst possible symptom) were used to assess pain, pruritus, nausea, and sedation at the following times: before spinal anesthesia; intraoperatively 15 min after delivery; and 2, 8, 14 and 20 h after injection of the i.v. study drug. The frequency of vomiting and the incidence of treatment for side effects were noted. At 24 h we assessed overall satisfaction and severity of side effects using 10 cm visual analog scales where 0 = completely dissatisfied, or very mild, respectively, and 10 = completely satisfied, or extremely severe side effects. The nurse rated the degree of bleeding or oozing on the abdominal wound dressing and noted the heaviness of the lochia.

Data were analysed using ANOVA and χ^2 analysis, with Fisher's exact test where indicated. A P value ≤ 0.05 was considered significant. Values are stated as mean ± SEM unless otherwise indicated.

RESULTS

The groups were similar with respect to age, height, and weight (Table 1). Surgical anesthesia was satisfactory in all patients with statistically similar numbers of patients receiving intraoperative fentanyl (Group SM: 0.2 – 14%, Group SM: 0.1 – 42%, Group SM/K – 28%, and Group K – 14%). There was a trend towards higher intraoperative VAPS (P = 0.1) with SM: 0.1. Postoperatively, there were no differences among the groups in mean VAPS at any time (Fig. 1), maximum VAPS reported during the study period, time to first request for additional analgesics, number of patients requiring postoperative meperidine, and total dose of meperidine given during the 20 h study period (Table 2).

Table 1. Patient demographics

	Group SM: 0.2 (n = 11)	Group SM: 0.1 (n = 12)	Group SM/K (n = 13)	Group K (n = 12)
Age (yr)	30 ± 2	32 ± 2	34 ± 1	34 ± 2
Height (cm)	150 ± 15	158 ± 3	160 ± 3	160 ± 3
Weight (kg)	86 ± 4	85 ± 7	80 ± 5	75 ± 4

SM = spinal morphine; K = ketorolac.
Values are mean ± SEM. No significant differences.

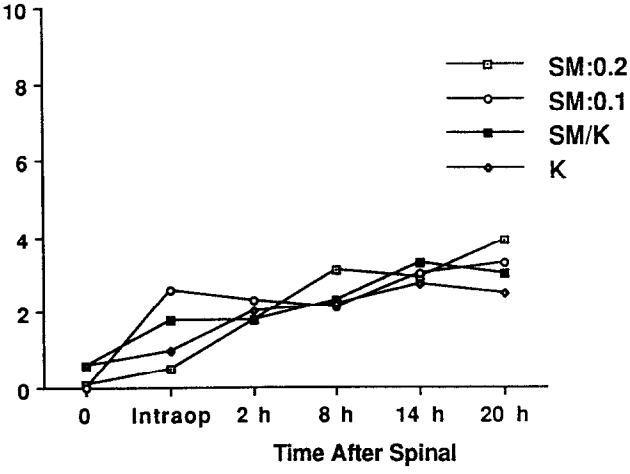

Fig. 1 Mean visual analog pain scores (0–10 cm) during the first 20 h after spinal morphine (SM): 0.2, SM: 0.1, SM/Ketorolac (K) and K.

The incidence of pruritus (Table 3) and the maximum pruritus score (Fig. 2) were significantly lower with K alone compared with all other groups. Pruritus was equally troublesome in all groups receiving spinal morphine. Two patients in the SM: 0.2 group refused to continue with the study because of severe pruritus. The incidence of nausea (Table 3) did not differ statistically among the groups (Fig. 2). Although vomiting was less frequent with K vs all morphine-containing groups (Table 3) the difference was not significant (P = 0.08, Fisher's exact test). Sedation was similar among the groups. The overall score for severity of side effects was lowest with ketorolac (Fig. 3); however at the 24 h postoperative visit, patients in all groups reported similarly high satisfaction scores (Fig. 3). Overt respiratory depression or slow respiratory rate was not observed in any patient, although one patient in the SM: 0.1 group who received 250 mg meperidine had a transient decrease in oxygen saturation. No patient experienced excessive bleeding.

Table 2. Postoperative analgesic efficacy

	Group SM: 0.2 ($n = 11$)	Group SM: 0.1 ($n = 12$)	Group SM/K ($n = 13$)	Group K ($n = 12$)
Maximum visual analog pain score*	4.4 ± 0.7	5.4 ± 0.9	4.8 ± 0.7	3.8 ± 0.7
Time to first analgesic (min)*	828 ± 169	603 ± 182	697 ± 143	693 ± 165
Patients given meperidine (%)	72	75	77	67
Total meperidine dosage (mg)*	46 ± 21	72 ± 22	39 ± 11	49 ± 15

SM = spinal morphine; K = ketorolac.
*Values are mean ± SEM.
No significant differences.

Table 3. Percentages of patients with side effects

	Group SM: 0.2 ($n = 11$)	Group SM: 0.1 ($n = 12$)	Group SM/K ($n = 13$)	Group K ($n = 12$)
Pruritus	100	83	85	17*
Nausea	45	50	31	33
Vomiting	36	17	15	0

SM = spinal morphine; K = ketorolac.
*$P = 0.0001$ vs all other groups.

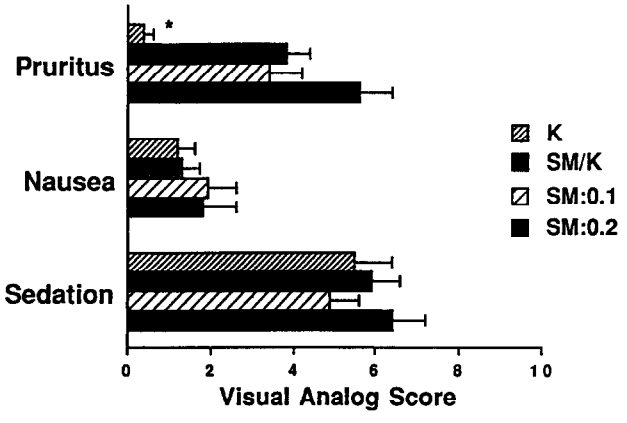

Fig. 2 Mean maximum visual analog scores (0–10 cm, where 0 = no symptom and 10 = worst possible symptom) for pruritus, nausea and sedation after each treatment during the first 20 h. Bars represent standard errors.

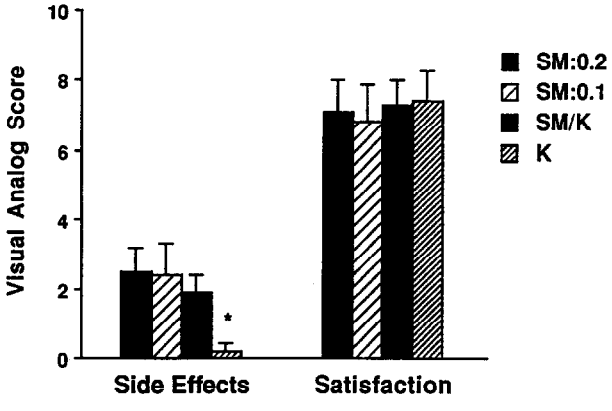

Fig. 3 Patients' overall evaluation of the severity of side effects and overall rating of their satisfaction with their postoperative analgesia (visual analog scores of 0–10 cm, assessed 24 h after delivery). Mean with standard error.

DISCUSSION

Dahl and Kehlet[6] have suggested that inclusion of NSAIDs in the 'multimodal' treatment of postoperative pain may be valuable because of additive or synergistic effects. After cesarean delivery, prostaglandin synthetase inhibitation from NSAIDs should exert an anti-inflammatory effect at the incision site, as well as reducing uterine cramping pain via a depressant effect on uterine contractility.[7] A recent in vitro study also demonstrated naloxone-reversible antinociceptive synergy between i.v. K and morphine and suggested that K may exert a central modulatory effect on the opioid receptor or opioid pharmacokinetics separate from its peripheral anti-inflammatory action.[5] The primary goal of this study was to determine whether combining K with a reduced dose of SM resulted in better analgesia than with either drug given alone, with fewer side effects than with a larger dose of SM. We found no advantages to the combination versus either drug alone with respect to analgesia, and side effects occurred with similar frequency with both SM doses.

Our findings differ from those in two previous studies[7,8] in which a NSAID was administered with a subanalgesic dose of epidural morphine. In one study,[8]

a combination of IM K 30 mg with epidural morphine 2 mg provided better postcesarean analgesia than either drug alone, and in another,[7] IM diclofenac (also a NSAID) enhanced low-dose epidural morphine analgesia. These low doses of epidural morphine may provide less effective analgesia than either of our SM doses, leaving more room for improvement with addition of the NSAID. However, in contrast to these findings, Waters et al[9] found no improvement in analgesia when IM K was given with epidural morphine 2 mg. In all these studies IM K alone produced inadequate analgesia, whereas i.v. K in the current study provided satisfactory analgesia which was similar to that obtained with SM. The i.v. route may have advantages over the IM route, perhaps by more rapidly producing higher plasma concentrations.[10]

Our failure to show better postoperative analgesia with the SM/K combination versus 0.1 mg SM might be a consequence of the latter producing adequate analgesia by itself. The minimum effective dose of SM in this circumstance has not yet been established. Although doses of 0.2–0.3 mg are commonly used,[1,2] some have suggested that 0.1 mg or less is adequate.[11] Our data suggest that none of the study treatments provided perfect analgesia, as most patients received supplemental meperidine. The cumulative meperidine dose was modest in all groups except the SM: 0.1 group, in which the mean dose was 72 ± 22 mg and one patient required a very large dose which caused a transient oxyhemoglobin desaturation. Administering larger doses of SM in an attempt to provide longer or more complete analgesia is probably unwise, as larger doses pose a greater hazard of respiratory depression.[3]

Another reason for the lack of differences in analgesia among the groups might relate to the size of our study population. We believe that we did not miss major differences among the groups because sufficient subjects were studied to have an 80% probability of detecting a statistically significant difference in VAPS of two points, with 95% confidence (Type 1 error = 0.05). The longest time to first request for analgesia occurred with SM: 0.2 and the shortest with SM: 0.1 mg, a statistically insignificant difference of 225 min. Approximately 50 patients would have been necessary in each group to have an 80% probability of detecting a statistically significant difference of 200 min with 95% confidence. It is possible that, with larger numbers, analgesic efficacy in Group SM: 0.1 might have proved significantly inferior to the other groups. However, the minimal differences in analgesia among the other groups are unlikely to be of any clinical importance.

Although analgesia was similar among the groups, side effects were less frequent and less severe with K compared with all the morphine-containing groups. Pruritus was rare with K, but occurred in the majority (83–100%) of patients receiving SM, with no difference between the two doses. Because our data suggest that 0.1 mg SM might provide slightly less effective analgesia than the higher dose, we would not expect an even lower dose to be satisfactory. Thus, pruritus may inevitably accompany effective analgesia with SM. As in studies of IM K after cesarean section,[12,13] the number of patients studied in the current investigation was insufficient to compare the incidence of infrequent side effects such as delayed respiratory depression.

K does not cause respiratory depression, but can cause increased postoperative bleeding, gastric irritation, renal insufficiency, and allergic reactions.[14–17] It can inhibit platelet aggregation by the reversible block of prostaglandin synthetase, and while it prolongs the bleeding time slightly, values remain within the normal range in patients with otherwise normal hemostatic function.[18,19] Several studies discussed in two reviews[4,14] did not report excessive bleeding, and data from the drug manufacturer suggest that increased perioperative hemorrhage does not occur with daily doses up to 120 mg. However, two reports comment on an increased incidence of significant postoperative hematoma after K in patients undergoing plastic surgery[20] and those receiving i.v. regional anesthesia.[4] A myometrial depressant effect of K is also possible as a result of its inhibitory effect on prostaglandin synthesis.[21] Therefore, it is preferable to wait until sustained uterine tone has been confirmed and intraoperative hemostasis secured before administering K.

Other rare side effects of NSAIDs include renal insufficiency (particularly in the presence of hypovolemia) and gastric irritation and bleeding.[22] K should be avoided in obstetric patients with hemorrhage, hypovolemia, or pregnancy-induced hypertension. When this study was performed, the high doses we used were commonplace. Recently, revised guidelines from the drug's manufacturers suggest using lower doses of K (i.e. a 30 mg i.v. or IM loading dose and 15 mg doses thereafter) and restricting treatment to less than 5 days.[22]

An additional concern when providing analgesia to postpartum patients is the risk of neonatal exposure via the milk to maternally administered drugs. An advantage of SM is that the very small doses of opioid should not pose a hazard to the neonate. The concentration of K in breast milk after parenteral postpartum administration has not been studied. Wischnik et al[23] studied 10 women between 2 and 6 days postpartum who received four 10 mg doses of oral K daily. Drug concentrations were below the limit of detection (5 ng/ml) in the breast milk of four

women; in the others, measurable concentrations (5.2–7.9 ng/ml) were reported. The ratio of breast milk: plasma concentrations of K ranged from 0.015 to 0.037.[23] Thus, although small amounts of K are excreted in the milk, we think it unlikely that the healthy neonate would be at risk from maternal K therapy restricted to the first postoperative day. Greer et al[24] studied the effects on platelet aggregation in neonates after administration of 10 mg K to six women during labor; 12 women received meperidine as controls. Tests of platelet aggregation in umbilical vein blood sampled at delivery demonstrated no effect of K on ADP-induced platelet aggregation, but statistically significant inhibition of aggregation in response to arachidonic acid and collagen. The authors suggest that K should be used with caution before delivery in mothers of infants with particular susceptibility to hemorrhagic problems.[24] The drug's manufacturers in the USA have recently relabelled K to state that it is 'contraindicated in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.'[22] Ibuprofen and other NSAIDs with similar anti-prostaglandin effects are widely used as postpartum analgesics. We believe that further studies are needed to determine whether maternal K therapy poses a risk to healthy neonates via the milk.

In summary, we found no better pain relief with a combination of i.v. K and SM than with either drug given alone. Although patients receiving SM had a high incidence of pruritus, overall satisfaction was high and similar in all groups.

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