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Preoperative oral administration of fast-release morphine sulfate reduces postoperative piritramide consumption

Ana Reiter, Ernest Zulus, Thomas Hartmann, and **Klaus Hoerauf**

Department of Anesthesiology and General Intensive Care, University of Vienna, Vienna, Austria

Prämedikation mit nicht-retardiertem Morphinsulfat reduziert den postoperativen Schmerzmittelbedarf

Zusammenfassung. Ziel dieser prospektiven, randomisierten Plazebo-kontrollierten Studie war es, den Einfluss einer Prämedikation mit einem nicht-retardierten Morphinsulfat auf den postoperativen Schmerz zu untersuchen.

Achtundneunzig Patienten, die sich einer Operation für einen totalen Knieersatz oder eine totale Hüftendoprothese unterzogen, wurden randomisiert zwei Gruppen zugeordnet. Gruppe 1 erhielt 20 mg Morphinsulfat p.o. etwa 1 Stunde präoperativ, Gruppe 2 erhielt zum selben Zeitpunkt ein Placebo. Die postoperative Schmerztherapie erfolgte mittels einer Piritramid PCA-Pumpe. Zielgrößen waren postoperativer Schmerzmittelbedarf und Schmerzscore.

Die Dauer der chirurgischen Eingriffe war vergleichbar in beiden Gruppen (Gruppe 1: 145 ± 42 min, Gruppe 2: 131 ± 35 min). Der postoperative Schmerzmittelbedarf in Gruppe 1 unterschied sich signifikant (37,5 ± 12,5 mg versus 46,8 ± 22,1 mg, t-test, $p < 0{,}05$) von der Gruppe 2, wobei beide Gruppen eine vergleichbare Schmerzkontrolle aufwiesen (VAS Gruppe 1: 4,8 ± 1,8 und 3,6 ± 1,7, Gruppe 2: 4,8 ± 1,6 und 3,4 ± 2,0, jeweils eine und 24 Stunden postoperativ.

Die vorliegenden Daten zeigen, dass eine präoperative orale Gabe eines nicht-retardierten Morphins unabhängig von seiner kurzen Halbwertszeit zu einer signifikanten Reduktion des postoperativen Schmerzmittelbedarfs führen kann.

Schlüsselwörter: Schmerz, postoperativ, Anästhesie, Prämedikation.

Summary. The aim of this prospective randomized placebo-controlled double-blind study was to investigate the effect of premedication with morphine sulfate on postoperative pain.

Ninety-eight ASA I–III patients undergoing total replacement of the knee or hip joint were randomly assigned to one of two groups. Group 1 received 20 mg morphine sulfate p.o. approximately one hour before the start of surgery; group 2 received placebo. After surgery, piritramide was administered via patient-controlled analgesia over 24 hours. Piritramide consumption and pain scores (visual analog scale) were recorded.

The duration of surgery (mean ± SD) was comparable in the two groups (group 1: 145 ± 42 min, group 2: 131 ± 35 min). In group 1 the cumulative piritramide consumption during 24 hours postoperation was significantly less than in the placebo group (37.5 ± 12.5 mg versus 46.8 ± 22.1, t-test, $p < 0.05$), although similar pain scores were recorded (group 1: 4.8 ± 1.8 and 3.6 ± 1.7, group 2: 4.8 ± 1.6 and 3.4 ± 2.0, at 1 and 24 hours, respectively).

These data show that the preoperative oral administration of morphine sulfate, regardless of its short half-life, can reduce postoperative consumption of opioids at similar pain levels.

Key words: Pain, morphine, anaesthesia, premedication.

Introduction

In addition to the broad value of morphine derivatives in clinical practice [1, 2], their use for premedication before general anaesthesia has aroused increasing interest [3]. Several clinical studies in which morphine derivatives were administered by intramuscular, intravenous or epidural routes have proved the beneficial effect of preoperative administration of these drugs on postoperative pain [4–8].

Preemptive analgesia is the administration of a drug before the onset of a painful stimulus. This reduces pain to a much greater extent than when the drug is administered after the painful stimulus [9]. The theory of preemptive analgesia is based on neurophysiologic studies suggesting that a nociceptive input may induce prolonged hyperexcitability of the central nervous system [10–12].

It has been shown in two studies that oral and intramuscular premedication with morphine derivatives is able to reduce postoperative pain [13, 14]. In contrast, other investigators observed no significant benefit of preoperative administration of sublingual buprenorphine or oral controlled-release morphine derivatives with regard to postoperative pain relief [15–17]. In another study, 10 mg of morphine sulfate was administered orally one hour before ambulatory gynecological laparoscopy, but when compared with a placebo there was no significant reduction in postoperative pain assessed using a visual analog

scale and by measurement of postoperative opioid consumption [18]. However, in all those studies the morphine derivatives tested, showing no preemptive analgesic effect, achieved maximum plasma concentrations of morphine more slowly than morphine sulfate pentahydrate.

Morphine sulfate pentahydrate is a fast-release capsule that disintegrates in the duodenum within 30 minutes; maximum plasma concentrations of morphine are achieved after one hour [19].

Premedication with morphine derivatives has a long tradition in anaesthesia. It was common clinical practice to administer intramuscular morphine derivatives and neuroleptics as premedication. The disadvantages of the method were the painful injection procedure and occasional hematoma or infection at the puncture site. Oral premedication is easier to apply and more comfortable for patients than the intravenous, intramuscular, or epidural routes.

In the present study we hypothesized that oral morphine sulfate pentahydrate one hour before surgery could reduce the need for postoperative opioids, with comparable postoperative pain control.

Methods

After approval by the institute's ethics committee, 98 patients (ASA I–III, age range, 18 to 75 years) undergoing total replacement of the knee or hip joint were studied prospectively. Patients with bronchial asthma, pancreatitis, porphyria, stenosis of the gastrointestinal tract or bile duct, hepatic or renal malfunction and cardiac insufficiency were not included in the study (Fig. 1).

Morphine sulfate pentahydrate was used in a randomized, placebo-controlled, double-blind fashion. The randomization, blinding and drug/placebo preparation were performed by the in-house pharmacy. Verum and lactose placebo were placed in size 0 gelatine capsules of the same color (the capsules had no influence on the pharmacokinetics of the substances being studied). The filled capsules were placed in small bags and numbered from 1 to 100. Neither the testing physician nor the patient could distinguish between verum and placebo. The randomization codes were placed in an envelope and stored in the pharmacy, and a second copy was placed in a separate registered drug box for the study medication.

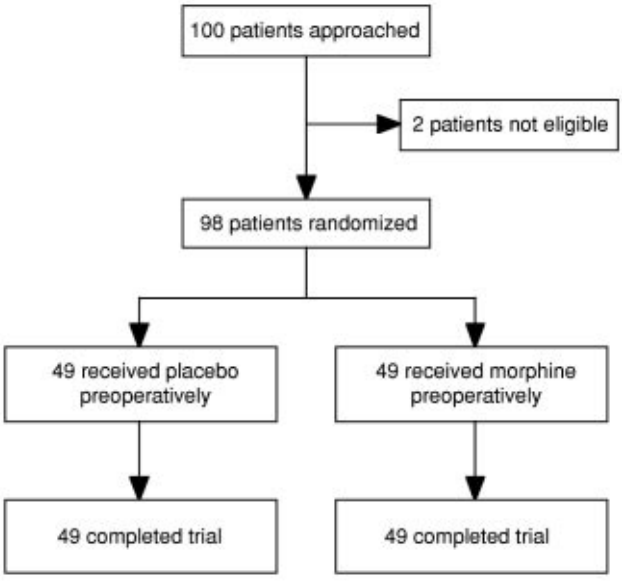

Fig. 1. Trial profile

Table 1. Demographic and procedural characteristics of patients

	Group 1	Group 2
n	49	49
Sex (m/f)	19/31	21/29
Age (yrs)	64 ± 12	61 ± 14
Weight (kg)	77 ± 18	78 ± 15
Height (cm)	164 ± 8	162 ± 9
Hip joint replacement	23	29
Knee joint replacement	26	20

All patients received midazolam 7.5 mg p.o. as premedication. Blood pressure, ECG and oxygen saturation were monitored until the start of anaesthesia. Approximately one hour before the operation the patients were admitted to the recovery room and received either 20 mg morphine sulfate pentahydrate (group 1: n = 49) or placebo (group 2: n = 49). One anaesthesiologist recorded potential side effects.

Anaesthesia was induced with fentanyl 3 µg kg^{-1} i.v., thiopental 3–5 mg kg^{-1} i.v., and vecuronium 0.1 mg kg^{-1} i.v. Anaesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen.

After surgery, analgesia was provided via a patient-controlled pump, preset with a bolus of piritramide 0.04 mg/kg i.v. and a lock-out of 20 minutes.

The pain scores were assessed at 1 and 24 hours after surgery, using a visual analog scale (VAS, 0 = no pain, 10 = maximum pain). Twenty-four hours after surgery the cumulative piritramide consumption was recorded.

The study plan was based on the assumption that preoperative morphine 20 mg p.o. is equipotent to 10.5 mg piritramide i.v. and, if there were no preemptive effect of morphine, we should detect a difference in postoperative piritramide consumption with a common standard deviation of 15 mg. With 49 patients in each group, the minimum power reached would be 90%.

Unpaired t-tests were used to compare pain scores on the visual analog scale and piritramide consumption in the two groups. Differences between groups were considered statistically significant at a two-tailed p value < 0.05. Data are presented as means ± standard deviations.

Results

There were no demographic differences among the patients in the two groups (Table 1). The type and duration of surgery had no impact on outcome. Morphine sulfate and placebo were given 57 ± 17 minutes (group 1) and 59 ± 17 minutes (group 2) before the start of anaesthesia. The duration of anaesthesia was comparable: 148 ± 42 minutes in group 1 and 134 ± 30 minutes in group 2.

Visual analog scale scores for pain were 4.8 ± 1.8 after 1 hour and 3.6 ± 1.7 after 24 hours in group 1, and 4.8 ± 1.6 after 1 hour and 3.4 ± 2.0 after 24 hours in group 2 (NS). There were no side effects that were related to the

oral morphine sulfate pentahydrate, such as vertigo or sickness. No harmful effects on blood pressure, oxygen saturation, or respiratory rate were observed.

Piritramide consumption was highest during the first two hours and decreased steadily over the postoperative period.

There was a significant difference between the two groups in the cumulative consumption of piritramide. During the 24 hours after surgery patients who received placebo (group 2) needed a significantly higher dose of piritramide than patients in group 1 (Fig. 2).

Discussion

Two groups of patients who received either morphine sulfate pentahydrate or placebo as premedication before orthopedic surgery were compared for postoperative consumption of piritramide. Pain scores were not significantly different between the two groups, therefore the postoperative consumption of piritramide in the verum and placebo groups was equianalgesic. However, during the 24 hours after surgery, the verum group needed approximately 20% less piritramide than the placebo group.

Morphine sulfate pentahydrate is a fast-release capsule that disintegrates in the duodenum within 30 minutes and, in contrast to retard tablets [20], maximum plasma concentrations of morphine are achieved within one hour after administration. As early as 4 hours later, plasma concentrations are below the therapeutic analgesic level.

In contrast to our results, previous investigators observed no particular benefit in postoperative pain relief in patients receiving oral morphine or buprenorphine as premedication [15–18], although the positive effects of intravenous morphine derivatives on postoperative analgesia were demonstrated [7, 8]. The use of morphine preparations with different pharmacokinetic properties in those studies may explain the apparently contradictory findings. For controlled-release oral tablets, maximum plasma concentrations of morphine were recorded after 2.5 hours and for buccal tablets after 6 hours [21]. It is noteworthy that all the authors who found no positive effect on postoperative analgesia used morphine derivatives that do not provide therapeutic plasma levels before the beginning of surgery.

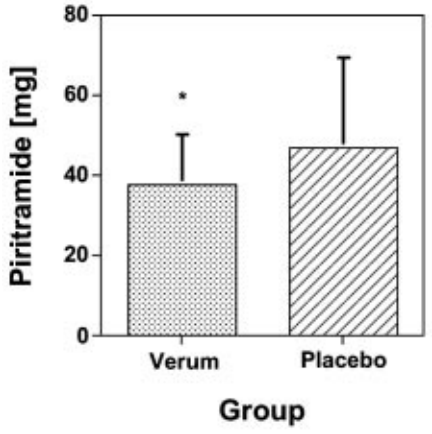

Fig. 2. Means ± standard deviations of piritramide consumption during 24 hours postoperation in the two groups (group 1: morphine sulfate pentahydrate, n = 49; group 2: placebo, n = 49); * $p < 0.05$, unpaired t-test

Preemptive analgesia is the administration of an analgesic before the onset of a painful stimulus. This approach is more effective in reducing the intensity of pain than the administration of the drug after the stimulus [9]. The theory of preemptive analgesia is based on neurophysiologic studies suggesting that a nociceptive input may induce prolonged hyperexcitability of the central nervous system [10].

Thus, prevention of pain, rather than symptomatic treatment, appears to be a better approach for achieving sufficient postoperative analgesia. Surgical damage of tissue leads to peripheral and central sensitization. The result is a state of neuronal hyperexcitability or a "wind-up" phenomenon, which could partly explain painful postoperative states and hyperalgesia [22]. The neurophysiologic mechanisms responsible for this phenomenon involve the action of peripheral prostaglandins and central excitatory amino acids such as glutamic acid, which act as N-methyl-D-aspartate receptors at the spinal level. Our study shows that preoperative administration of oral morphine sulfate pentahydrate significantly reduces the need for postoperative piritramide. Given the fast onset of action of morphine sulfate pentahydrate compared with the morphine derivatives used in previous studies, it may be assumed that therapeutically relevant plasma levels, and therefore early occupation of pain receptors, had been achieved before the exposure to nociceptive stimuli. Furthermore, it has been proposed that preemptive preoperative analgesia may have prolonged effects that last significantly longer than the presence of the drug in the organism [23]. Other researchers have shown that the preemptive administration of fentanyl or ketamine markedly reduces wound hyperalgesia [23], and the effect was sustained significantly longer than when the same drugs were used to treat existing pain [24]. Whether higher preoperative doses of fentanyl result in a similar postoperative analgesic effect must remain unclear.

Our study, which concludes that the preoperative oral administration of morphine sulfate pentahydrate reduces postoperative consumption of piritramide in orthopedic patients, further supports the recent discussion on the value of preemptive analgesia [25]. The advantages of this particular morphine derivative are: a) oral administration, b) no obvious side effects such as nausea or depression of breathing in most patients without major underlying illness, and c) the fast onset of action that possibly has a preemptive analgesic effect.

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Correspondence: Klaus Hoerauf, MD, Department of Anesthesiology and General Intensive Care, Vienna General Hospital, University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria, E-mail: klaus.hoerauf@univie.ac.at

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