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Anesthesiology
66:819–822, 1987

Epidural Ketamine or Morphine for Postoperative Analgesia

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Intrathecal and epidural narcotics have been widely used since 1979 to relieve pain and provide postoperative analgesia.[1,2] However, their use has been tempered by the potential of respiratory depression.[1,2] Thus, other substances have been tried that have the advantages of opioids but not their drawbacks. Ketamine has analgesic properties which apparently are mediated by various pathways and, especially, opiate receptors.[3–7] Yet, Fratta *et al.*[8] have disproven fixation to opiate receptors. Still, Ketamine analgesia is antagonised by naloxone, an opioid antagonist.[9] Ahuja[10] showed that intrathecally administered ketamine could produce analgesia, but its effect is of short duration and inconsistent. As iv ketamine administered at the usual doses does not produce respiratory depression, Ahuja[10] thought it would be the same by intrathecal route. Animal experiments[11] showed that ketamine with preservative had probably no neurotoxic effect, despite what had been presented in two studies.[10,12] However, the neurotoxic effect observed are questionable (*i.e.*, very high doses in one case[10] and difficulties for lumbar puncture in the other case[12]). Moreover, according to five clinical observations,[13–17] ketamine should, therefore, be a good choice for epidural analgesia. In the above mentioned studies, epidural ketamine seemed to be a potent and safe method for postoperative analgesia. However, this method had never been compared to a technique using epidural opioids. This is, therefore, the purpose of this work where morphine was chosen as the reference opiate.

PATIENTS AND METHODS

This study was conducted with the informed consent of 20 patients and with the approval of the Hospital Ethic Committee. Patients had undergone orthopedic surgery (table 1). The operative anesthesia was provided by a lumbar epidural anesthesia (catheter inserted at the L_{3-4} interspace) with or without supplementation by inhalation of enflurane. The patients were allocated by computerized randomisation into two groups of ten: one "ketamine" group, and one "morphine" group. This study was a single blind study.

Pain was assessed according to a five-step scale (equivalent to a visual analog scale[18]), as follows: 0 = no pain; 1 = very slight pain, simple bother; 2 = slight pain that can be temporarily forgotten; 3 = permanent and tolerable pain that cannot be forgotten; 4 = marked pain that leads the patient to request an analgesia; and 5 = intolerable pain with screams and restlessness.

This five-step scale was explained preoperatively to the patient, and pain was measured by asking the patient (when the patient was asleep, pain was estimated at the "0" level).

Monitoring was under the direct responsibility of an anesthesiologist in an intensive care unit. Analgesia was

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Key words: Analgesia: postoperative. Anesthetics, intravenous: ketamine; morphine. Anesthetic techniques: epidural.

TABLE 1. Patients

Patients	Age	Sex	Type of Surgery	Duration of Surgery (Min)
1	57	M	Total hip replacement	410
2	54	F	Tibial osteotomy	90
3	22	M	Knee ligamentoplasty	195
4	64	M	Lithocystostomy	105
5	52	M	Tibial osteotomy and inguinal herniorraphy	240
6	83	F	Total knee replacement	165
7	19	M	Knee ligamentoplasty	210
8	26	M	Knee ligamentoplasty	80
9	51	F	Abdominal hysterectomy and ganglial curage	240
10	33	M	Knee ligamentoplasty	130
11	19	M	Knee ligamentoplasty	288
12	72	M	Abdominal prostatectomy	10
13	21	M	Knee ligamentoplasty	10
14	20	M	Knee ligamentoplasty	10
15	36	M	Knee ligamentoplasty	10
16	19	M	Knee ligamentoplasty	10
17	52	M	Tibial osteotomy	10
18	19	M	Knee ligamentoplasty	10
19	18	M	Knee ligamentoplasty	10
20	61	F	Tibial osteotomy	10

M = male; F = female.

defined by measurement of pain at time = 0 min. (Pto) and pain at specific time (Pt). It was formulated as $\frac{Pto - Pt}{Pto}$.

Injection of morphine was made as soon as step 3 pain appeared. The dose level used was 0.05 mg/kg for peripheral orthopedic surgery (excluding hip surgery) and 0.1 mg/kg for abdominal and hip surgery. Morphine hydrochloride was diluted in 10 ml 0.9% saline. Patients were monitored every 15 min during the first hour and every hour during the first 24 h. Pain, respiratory rate, heart rate, arterial blood pressure, and potential side effects (pruritus, nausea, vomiting, urinary retention, and respiratory depression) were recorded. After that time, the catheter was removed. The patient was examined at 48 h and the duration of analgesia recorded by asking the patient. A neurologic examination was performed once during the first 24 h.

TABLE 2. Epidural Doses of Ketamine and Morphine Employed

Patients	Epidural Drug	Total Dose/24 H
1	Morphine	6 mg
2	Morphine	3 mg
3	Morphine	4 mg
4	Morphine	9 mg
5	Morphine	8 mg
6	Morphine	4 mg
7	Morphine	4 mg
8	Morphine	4 mg
9	Morphine	6 mg
10	Morphine	4 mg
11	Ketamine	10 mg
12	Ketamine	288 mg*
13	Ketamine	10 mg
14	Ketamine	10 mg
15	Ketamine	10 mg
16	Ketamine	10 mg
17	Ketamine	10 mg
18	Ketamine	10 mg
19	Ketamine	10 mg
20	Ketamine	10 mg

* Continuous infusion (12 mg per hour).

Epidural injection of ketamine was also made as soon as step 3 pain occurred. The dose used was 4 mg for orthopedic surgery (excluding hip) and 6 mg for abdominal or hip surgery. The substance used was 1% ketamine hydrochloride. Each dose was diluted in 10 ml 0.9% saline. Patients were monitored every 5 min until pain decreased below step 3. If hypoalgesia had not been obtained within 20 min (twice the maximum onset time reported by Saissy[14,15]), an epidural dose of 6 mg was given. If pain decreased within 25 min after second dose, analgesia was then performed with continuous epidural infusion of ketamine. Continuous dose was calculated with duration of best analgesic bolus dose. For example, if 30 min duration analgesia—*i.e.*, pain above step 3—is provided with 6 mg ketamine hydrochloride, continuous dose is 12 mg per hour. If analgesia was not obtained with epidural ketamine, pain relief was performed with epidural morphine, and the patient was excluded from the study. When patients had been given ketamine, and analgesia had occurred, monitoring was performed as with morphine group (the same variables were recorded). All patients from both groups were connected to an apnea detector.

Statistical analysis was carried out by the "Département Statistique du Centre de Recherche du Service de Santé des Armées" (Dr. Picard). Kruskal-Wallis test was used (equivalent to Wilcoxon test).

RESULTS

Statistical analysis showed that these two series of patients were comparable as far as age, sex, and type and duration of surgery were concerned. Epidural doses of ketamine and morphine administered are reported in table 2.

Pain score is reported in both groups on figure 1 (at times 0, 15, 30, and 45 min after administration). It diminished in the morphine group, whereas, in the ketamine group, it did not. Differences were significant at 30 min ($P < 0.05$) and at 45 min ($P < 0.01$) after epidural administration.

Analgesia at 0, 15, 30, and 45 min, and at the time of maximal analgesia, are reported on figure 2 for both groups. The maximal value for analgesia was reached in

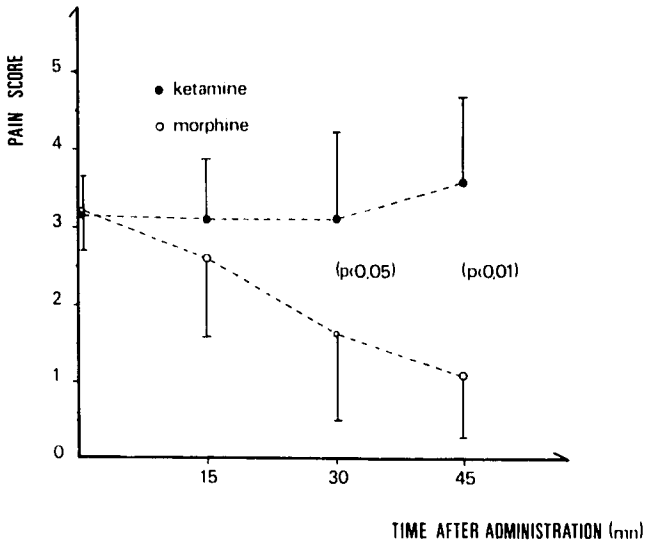

FIG. 1. Pain scores after epidural administration of morphine or ketamine.

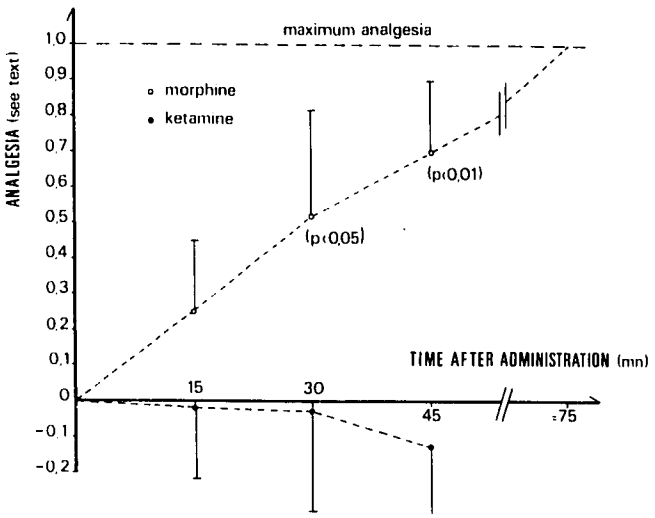

FIG. 2. Analgesia after epidural administration of morphine or ketamine.

the morphine group. This was never the case in the ketamine group. Difference became statistically significant at 30 min ($P < 0.05$) and 45 min ($P < 0.01$) after epidural administration. Only one patient in the ketamine group underwent the complete procedure with two bolus doses of 6 mg and a 12 mg infusion per hour. In this patient (No. 12), pain never returned when the continuous infusion of ketamine was stopped. The other patients had to be given epidural morphine, and analgesia was obtained with this method.

Kinetics of analgesia in the morphine group is reported in table 3. Minimum pain score was 0 in all cases, and maximal analgesia was 1. Mean onset time was 78 ± 31 min (range 30–120 min), and mean duration was 28 ± 7.6 h (range 18–42 h).

Side effects in the morphine group are reported on table 4. No respiratory depression was observed. Neurologic examination showed no sensitive or motor deficits in either group, apart from a decrease in pain sensitivity in the morphine group. The treatment provided was: droperidol for nausea and vomiting; naloxone or bladder catheterization for urinary retention; and naloxone for pruritus. No side effects were observed following epidural ketamine.

DISCUSSION

In all patients of this study, except one (No. 12), ketamine was unable to relieve postoperative pain, whereas maximal analgesia was obtained in all cases with epidural morphine (fig. 1, 2). In the case of patient No. 12, no pain was felt under epidural ketamine infusion; however, pain never returned when the administration of ketamine was terminated. It is possible, in fact, that ketamine's efficacy corresponded to a spontaneous disappearance of the pain. Failure of analgesia with epidural ketamine is not a technical problem related to improper catheter because analgesia was ultimately provided with epidural morphine. The doses administered (bolus of 4 or 6 mg) were those used by other authors[14–16] which resulted in analgesia. In two pilot cases, we injected a larger dose, 30 mg, of ketamine epidurally and observed analgesia as others with such doses;[17] however, a sedative effect also occurred that could be explained by vascular uptake from epidural space and systemic action. Bolus doses ranging from 6–30 mg were not used in this study, and that could explain the failure of analgesia with epidural ketamine. Volume of injectate in the present study was similar to that used by other authors.[14,17] The solvents used in various studies were different: Islas *et al.*[16] used 5% dextrose in water; Saissy *et al.*,[14,15] Naguib *et al.*,[17] and we used 0.9% saline in water. However, analgesia was provided either with 5% dextrose or with 0.9 saline solvent for ketamine injectate.[14–17]

TABLE 3. Characteristics of Analgesia in Patients Administered Epidural Morphine

Patients	Minimum Pain Score (0–5)	Maximum Analgesia (0–1)	Onset of Analgesia (Min)	Duration of Analgesia (H)
1	0	1	30	42
2	0	1	75	40
3	0	1	30	25
4	0	1	60	30
5	0	1	90	25
6	0	1	105	30
7	0	1	90	30
8	0	1	60	20
9	0	1	120	18
10	0	1	120	21
Mean			78 ± 31	28 ± 7.6

TABLE 4. Side Effects in Morphine Group

Side Effects	Number	Percent
Retention of urine	6 (7)*	85%
Nausea and vomiting	5 (10)	50%
Pruritus	2 (10)	20%
Respiratory depression	0 (10)	0%
Others	0 (10)	0%

* Number of patients with no bladder catheterization before epidural injection.

Solution of ketamine hydrochloride contains two different isomers. Two studies showed that (+) isomer was more potent than (−) isomer for analgesic properties.[19,20] This does not appear to be due to marked differences in biodisposition, but it seems to be related to the stereoselective metabolism of the ketamine isomers.[19,20] Binding to opiate receptors could be more powerful with ketamine's (+) isomer,[6,7] but the commercial product is a 50:50 racemic mixture.[19] Therefore, there is no possibility for suspecting that a predominance of the (−) ketamine isomer was responsible for the lack of analgesia after epidural ketamine. Analgesia with ketamine is mediated by various pathways including opiate receptors which is controversial.[8] Analgesia with intrathecal ketamine is inconsistent,[10] which may also be the case with the epidural route, although our results are contrary to similar studies.[14-16]

Analgesia with epidural morphine in our study had longer duration than what has been described in the literature (28 ± 7.6 h). Side effects were more dominant than those observed in larger series of patients,[21-24] but less than those observed by Bromage *et al.*, in a study on ten volunteers.[25] There were probably not enough subjects in our study to allow any conclusion on the duration of analgesia and the side effects with epidural morphine in comparison to the data from the literature.

In summary, we compared ketamine and morphine administered epidurally for postoperative analgesia. The data show that epidural ketamine was unable to relieve postoperative pain at the dose levels used (*i.e.*, 4–6 mg), whereas morphine was effective in all cases. The patients given ketamine had to be given epidural morphine to be free of pain.

The authors thank Nathalie Rollin and Dr. Yves Bouffard for their help in writing up this clinical report, and Dr. Picard for statistical analysis.

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