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Intrathecal Injection of Morphine for Obstetric Analgesia

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Intrathecal injection of morphine was used to provide obstetric analgesia in 20 primiparous women in labor. When the cervix was at least 3 cm dilated, morphine, 1 or 2 mg, was injected intrathecally. In all parturients, labor pains were completely relieved after 15–60 min and analgesia lasted as long as eight to 11 hours. The analgesia was not associated with any alteration of pin-prick sensation or motor power, and there was no change in the arterial blood pressure or heart rate. All infants were delivered vaginally by use of episiotomy and a low forceps, except two infants of mothers in the 2 mg morphine group who needed cesarean section. During the second stage of labor, analgesia was supplemented by lidocaine, 2 per cent, using local perineal infiltration in 14 parturients and pudendal block in two parturients, and by epidural block in four parturients. Nineteen of the 20 newborns cried immediately at birth, and had Apgar scores of 7–9 at 1 min and 8–10 at 5 min. During the first 24 hours of life, the neurobehavioral responses of all newborns were scored as normal. Systemic maternal side effects such as somnolence, nausea, vomiting, and itching occurred in a high proportion of the parturients. However, in the majority of cases, these side effects were mild. Only two parturients of the 2 mg morphine group complained of marked somnolence, itching, and vomiting, which persisted post partum; these were effectively reversed by the specific antagonist naloxone.

The analgesic effect of intrathecal morphine can be attributed to its action on the opiate receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. However, supraspinal effects of morphine cannot be excluded. The low lipid solubility of morphine can explain its slow onset and prolonged duration of action. Also, this will result in minimal systemic absorption of morphine, which protects the fetus and results in selective maternal analgesia. (Key words: Analgesics, narcotic: morphine. Anesthesia, obstetric. Anesthetic techniques: spinal.)

THE DEMONSTRATION of opiate receptors and the discovery of naturally occurring opiate substances (enkephalins) in the central nervous system[1,2] have started a new era of pain control. Cell bodies containing enkephalins have been demonstrated in various sites, which include the substantia gelatinosa of the dorsal horn of the spinal cord.[3]

Recent experiments have demonstrated that opiates injected into the spinal subarachnoid space produce a prolonged increase in the pain threshold.[4] Such an effect has been clinically applied in man for the relief of intractable pain.[5] Intrathecal injection of morphine has been also experimentally used in the parturient rat and rabbit without any detectable effect on the initiation of labor and the viability of the newborn.[6] These results suggest that intrathecal morphine may provide selective obstetric analgesia without other sensory, motor, or autonomic side-effects.[7]

In the present clinical trial we have investigated the analgesic effect of intrathecally injected morphine in parturient women. We also report its side effects on both the mother and the newborn.

Materials and Methods

This investigation was approved by the Human Studies Committee. The protocol was explained to each participating parturient and her informed consent was obtained. Observations were carried out on 20 full-term primiparous women whose ages ranged from 15 to 34 years (mean = 22.3 years, SD = 4.0). All parturients were admitted to the delivery suite in active labor, and all had cephalic presentations. An intravenous infusion of lactated Ringer's solution was started. When the cervix was fully effaced and at least 3 cm dilated, morphine was administered intrathecally. Parturients were positioned in the left lateral position and a lumbar puncture was done in the third lumbar interspace using a 22-gauge spinal needle. In 13 parturients, 2 mg morphine hydrochloride in 2 ml saline solution, 0.9 per cent (isobaric solution, specific gravity = 1.007) was intrathecally injected, while in the other seven parturients only 1 mg morphine was used. The morphine solution was freshly prepared by our pharmacy without adding any preservative. Following the intrathecal injection of morphine, an epidural catheter was placed in the same space using a 16-gauge Tuohy needle. The parturient was then allowed to lie in the supine position until analgesia was achieved, but afterwards was encouraged to lie on the left side. Continuous recording of uterine contractions and fetal heart rate was obtained throughout labor, using a Hewlett-Packard cardiotocograph.

The following were observed and recorded.

THE ONSET AND DURATION OF ANALGESIA

Pain was scored according to the visual linear analog, which has been suggested to be a reliable method of evaluating severe pain such as that of labor.[8] The technique involved the use of a 10-cm line on a piece of white paper, and represented the continuum of the patient's opinion of the severity of

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pain. One of the investigators explained to the parturient that the top extremity of the line (10) represented "as much pain as she could possibly imagine," while the zero point represented "no pain at all." The parturient rated pain by making a mark on the line. Scale values were then obtained by measuring the distance from zero to that mark.[8] A previous painful experience, such as toothache or dysmenorrhea, was used as an example for explaining the pain scale to the parturient, and checking her reliability. The baseline labor pain intensity was then determined before the intrathecal injection of morphine. After administration of morphine, decrements in the pain scale were assessed with every contraction until the pain was completely relieved. The onset time of analgesia was considered to be the time from intrathecal injection of morphine until complete relief of labor pain. The parturients were then told to record, at 30-min intervals, whether pain relief was still present.

Progress of Labor and Need for Oxytocin Augmentation

Progress of labor was monitored by continuous external cardiotocography, and by repetitive (hourly) vaginal determination of cervical dilatation. Oxytocin augmentation was indicated whenever uterine activity was inadequate to achieve effective and progressive cervical dilatation. A Harvard infusion pump was routinely used to infuse a standard oxytocin solution (10 mU/ml). Augmentation was begun, whenever indicated, by infusion of oxytocin at a rate of 2 mU/min; the dose was doubled every 20 min till effective uterine contractions were achieved. The maximum doses used ranged from 8 to 20 mU/min.

Fetal and Neonatal Side Effects

Fetal heart rate was continuously monitored externally by the Hewlett-Packard cardiotocograph. At birth, the neonates were assessed by use of the Apgar score. In the nursery, a neurobehavioral assessment[9] was made within 24 hours by a neonatologist who was unaware of the anesthetic management. The following variables were scored: resistance against passive motion, rooting, sucking, Moro's response, habituation to light, placing, and altertness. The neurobehavioral response was scored as absent, weak or normal.

Maternal Side Effects

Maternal sensory (pin-prick sensation), motor (reflexes and motor power), and autonomic (blood pressure and pulse rate changes) side effects were recorded by one of the investigators at 5-min intervals during the first 60 min following the intrathecal injection of morphine, and then at 30-min intervals. Systemic side effects attributable to morphine, such as itching, nausea, somnolence, and respiratory depression, were also observed, and were rated absent, mild, or severe by one of the investigators during the first 60 min, then by the obstetrical resident, who was blind to the dose of morphine administered.

Student's t test was applied to compare data related to the analgesia and the progress of labor. The incidence of maternal side-effects and the incidence of oxytocin augmentation were compared by the test for significance between two proportions (Z test). $P < 0.05$ was considered significant.

Results

Obstetric Analgesia

All parturients reported complete relief of labor pain 15 to 60 min following the intrathecal injection of morphine. The mean times to onset of analgesia (*i.e.*, the times elapsing between the intrathecal injection of morphine and complete relief of pain) were 32.1 min (SD 19.5) in parturients receiving 1 mg morphine and was 35.8 min (SD 17.8) in those receiving 2 mg morphine. There was no statistically significant difference between the two groups ($P > 0.05$). The analgesia was not associated with numbness or heaviness of the lower limbs, and there was no alteration of pin-prick sensation or motor power. Also, there was no change in the arterial blood pressure or heart rate.

Times from intrathecal injection of morphine to delivery ranged from 2.0 to 10.5 hours in the 1 mg morphine group, and from 3.0 to 14.5 hours in the 2 mg morphine group. All parturients except three were completely relieved of labor pain throughout these periods; these three, in the 2 mg morphine group, started to feel pain after eight hours.

Progress of Labor

In parturients given 1 mg morphine, the progress of labor was normal without oxytocin augmentation. The mean time elapsed between the intrathecal injection of morphine and full cervical dilatation was 4.8 hours (SD = 2.7). In all cases, vaginal delivery was achieved at a mean time of 35.6 min (SD = 14.4) after full cervical dilatation, using episiotomy and low forceps. Analgesia was complete throughout the first and second stages of labor except at the final stage of

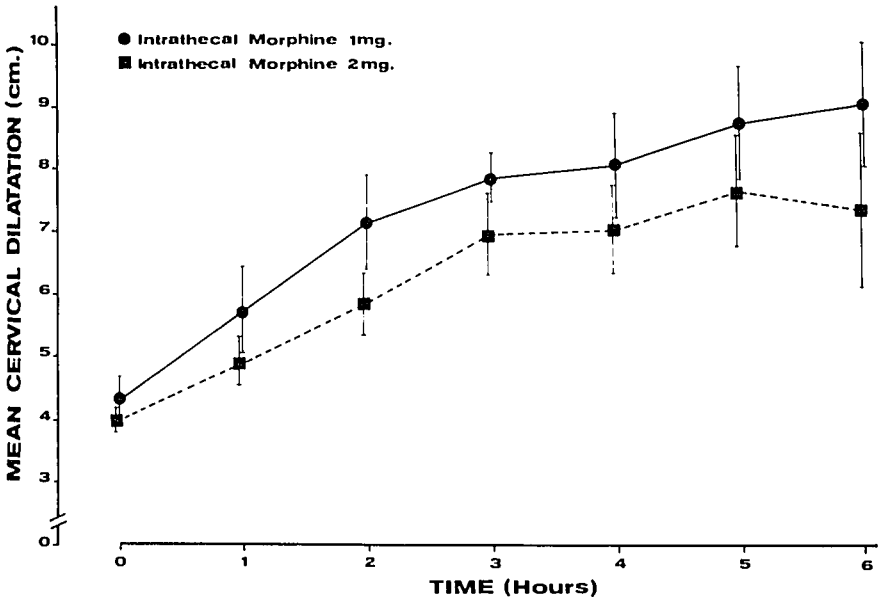

FIG. 1. Mean (±SE) cervical dilatation versus time in the two groups of parturients. Zero time denotes the time of intrathecal injection of morphine. There was no significant difference between the means at any time.

episiotomy and low forceps extraction, when it was supplemented by lidocaine, 2 per cent, using local perineal infiltration in five parturients and pudendal block in one parturient, and by one dose for epidural in the remaining parturient.

Unlike the parturients in the 1 mg morphine group, in eight of the 13 parturients given 2 mg morphine (61.5 per cent) labor was augmented by infusion of oxytocin; the difference between the two groups was statistically significant ($Z = 2.82$, $P < 0.01$). Also, labor failed to progress for 12 hours, despite augmentation, in two parturients in this group, and delivery was carried out by cesarean section. For the other 11 parturients, the mean time elapsed between the intrathecal injection of morphine and full cervical dilatation was 5.2 hours (SD = 2.6). There was no significant difference between the two groups ($P > 0.05$). Vaginal delivery occurred at a mean time of 30.9 min (SD = 10.2) after full cervical dilatation. As in the 1 mg morphine group, episiotomy and low forceps were used. Analgesia was supplemented by lidocaine, 2 per cent, using local perineal infiltration in nine parturients and pudendal block in one parturient, and by epidural block in three parturients.

Mean cervical dilatation as a function of time after the intrathecal injection of morphine is shown in figure 1. Morphine was injected at a mean cervical dilatation of 4.3 cm (SE 0.4) in the 1 mg morphine group, and at a mean cervical dilatation of 4.0 cm (SE 0.2) in the 2 mg morphine group. There was no significant difference between the means versus time in the two groups of parturients.

Fetus and Newborn

External monitoring of fetal heart rate by continuous cardiotocography, showed a normal pattern with no loss of beat-to-beat variability in 19 of the 20 cases. The 19 newborns cried immediately at birth and had Apgar scores of 7–9 at 1 min and 8–10 at 5 min. In one case of prolonged labor, in the 2 mg morphine group, the fetal heart rate showed bradycardia, and on delivery, the newborn was depressed, had meconium aspiration, and scored 5 at 1 min and 7 at 5 min. In the nursery, the neurobehavioral responses of the newborns were assessed during the first 24 hours of life; all modalities assessed were considered normal.

Systemic Maternal Side Effects

Systemic maternal side effects attributable to morphine, such as feeling sleepy, nausea, and itching, were observed, without asking leading questions, in the two groups of parturients (table 1). In the majority of parturients these systemic side effects were mild, and in no instance was decreased respiratory rate, bradycardia, or hypotension evident. Marked somnolence was limited to 10 per cent of the patients. Itching was usually localized to the nose and face, and was generalized in only 20 per cent of the patients. Nausea was slight but was associated with occasional vomiting in 25 per cent of the parturients. Mild postpartum headache attributable to lumbar puncture was observed in three patients, but none needed treatment.

The onset of systemic side effects coincided with the onset of maternal analgesia; these were observed to different extents for as long as 24 hours. Eighteen of the 20 parturients considered their anesthetic and labor experiences to have been pleasant. They were relaxed, sleepy, and felt no numbness or heaviness in their lower limbs at a time labor was progressing without pain. Only two parturients of the 2 mg

TABLE 1. Maternal Side Effects Following the Intrathecal Injection of 1 mg and 2 mg Morphine

	Morphine, 2 mg (n = 13)		Morphine, 1 mg (n = 7)			
	Number	Per Cent	Number	Per Cent	Z Value	P
Itching	12	92	7	100	0.68	>0.05
Nausea and vomiting	8	62	7	100	1.87	>0.05
Somnolence	12	92	6	85	−0.49	>0.05

morphine group complained of the systemic side effects of morphine. One of these two parturients had marked somnolence associated with dizziness and miosis, and the second parturient had vomiting and generalized itching, which persisted post partum. These side effects were readily antagonized by intravenous injection of naloxone, 0.4 mg. In both cases, naloxone also antagonized the residual analgesic effects of intrathecally injected morphine, and the two parturients started to complain of pain at the episiotomy sites.

Discussion

The mechanism of pain during the various stages of childbirth is complex.[10] It is attributed to progressive uterine contractions associated with dilatation of the cervix and the lower uterine segment. During the second stage, additional pain is produced by dilatation, stretching and distention of the vagina and perineum. The pain originating from the first mechanism reaches the spinal cord via the eleventh and twelfth thoracic nerves; it is typical of visceral pain and is referred to the dermatomes supplied by spinal cord segments; severe pain can spread above to the T10 neurotome and below to the L1 and L2 neurotomes. Unlike the experienced pain initially, the pain produced by distention of the lower birth canal, vulva and perineum is largely due to stretching of fascia, skin, subcutaneous tissues, and other somatic structures, and is conveyed by sensory components of the pudendal nerve, which enters the spinal cord via the posterior roots of the second, third and fourth sacral nerves.[10]

The present study has shown, in the parturient primipara, that the intrathecal injection of morphine, 1 or 2 mg, can completely relieve the visceral type of labor pain for periods lasting eight to 11 hours. This was a selective analgesic effect without any motor or autonomic side effect. The intrathecally injected morphine, however, did not block pin-prick sensation and similar somatic sharp localized pain, such as that induced by episiotomy or by stretching of the vulva and perineum. Morphine and its analogs are powerful suppressors of visceral pain, and have virtually no effect on pricking sensation.[11]

The intrathecal analgesic effect of morphine can be attributed to its action on the opiate receptors located in the substantia gelatinosa of the dorsal horn of the spinal cord.[4,6] Painful impulses are transmitted to the spinal cord via the small myelinated A delta fibers and the umyelinated C fibers, and will release substance P in the substantia gelatinosa, which is blocked by morphine or enkephalin.[12] This may result in selective analgesia with no action on other sensory, somatic or autonomic functions.

Yaksh and colleagues have suggested that the analgesic effect of intrathecal morphine in the rat can be entirely attributed to a spinal action.[4,6] However, clinical observations have suggested that intrathecal morphine can spread cephalad to the brain stem and higher centers.[13–15] Also, in our parturients, a cephalad diffusion of morphine to supraspinal opiate receptors must be considered, in view of the high incidences of maternal somnolence, nausea and itching. These side effects cannot be attributed to systemic absorption because of the small dose of morphine injected intrathecally, and its limited release into the blood stream. It is possible that intrathecally injected morphine can readily spread cephalad via the cerebrospinal fluid, and that a supraspinal effect of morphine may contribute to the analgesic effect and produce maternal side effects. In the parturient, the volume of cerebrospinal fluid in the spinal canal is probably decreased due to a reduction of the subarachnoid space by engorged epidural veins. Also, CSF pressure is continuously fluctuating during uterine contractions with bearing down and movements in response to pain.[16] The possible diminution of CSF volume associated with pressure fluctuations may increase the spread of intrathecally administered drugs in the parturient.[10]

The onset of the maternal side effects following intrathecal injection of morphine coincides with the onset of analgesia, and the two continue for similar durations. Also, both the analgesic action of morphine and its side effects can be reversed by intravenous injection of the specific antagonist, naloxone, suggesting that such effects are mediated by an opiate synapse and are not likely to be due to a nonspecific effect of the intrathecal injection.

Yaksh and colleagues have shown that analgesia produced by intrathecal injection of morphine has no detectable effect on the initiation and progress of labor in rats.[6] In our parturients, there was no significant difference between the rates of cervical dilatation in the two groups. However, in the 1 mg

morphine group, labor progressed in all cases without any oxytocin augmentation, while with 2 mg morphine, labor necessitated augmentation in 61.5 per cent of the cases. Interpretation of these data should be guarded in view of the small number of parturients observed.

The onset of analgesia in our parturients following intrathecal injection of morphine was slow, and its duration was prolonged. Morphine, a hydrophilic substance, has a low lipid partition coefficient, hence passes with difficulty across the blood–brain barrier. Thus, following systemic administration, large amounts of the drug are needed to produce a central pharmacologic effect.[17] When morphine is directly injected intrathecally[4,6] or in the ventricular system,[17] a much smaller dose is needed to produce an analgesic effect. The delay in the onset of analgesia following intrathecal injection of morphine may be attributed to its poor lipid solubility and its slow access to the receptor sites. The hydrophilic character of morphine may also explain its retention in the CNS and its slow release into the systemic circulation, resulting in a prolonged effect.[17] The small effective dose of intrathecally injected morphine and its slow release into the systemic circulation[4,6] may spare the fetus and result in selective maternal analgesia.

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