

Intrathecal Morphine Does Not Reduce Minimum Alveolar Concentration of Halothane in Humans: Results of a Double-blind Study

Michael G. Licina, M.D.,* Armin Schubert, M.D.,* James E. Tobin, M.D.,†
Honorato F. Nicodemus, M.D.,‡ Loren Spitzer, C.R.N.A., M.S.§

The effect of intrathecal morphine on the minimum alveolar concentration (MAC) of halothane was investigated in 22 patients undergoing elective abdominal surgery. The patients were randomly assigned to the control (CTRL) or intrathecal morphine sulfate (ITMS)-treated groups. Approximately 2.5 h before induction of anesthesia with halothane, the ITMS-treated group received 15 µg/kg preservative-free ITMS (Duramorph®; Elkins-Sinn, Cherry Hill, NJ) while in the right lateral decubitus position. The CTRL group was treated in an identical fashion except that, after placement of the introducer needle, actual dural puncture was omitted. After inhalational induction with halothane as the sole anesthetic agent, the patients' responses to surgical incision were recorded. MAC was determined with the modified up-down method of Dixon and verified with probit analysis. MAC (±SE) after ITMS was 0.76 ± 0.06 , compared with a CTRL MAC of 0.78 ± 0.15 (not significant). Under the conditions of this study, the MAC of halothane in humans was not significantly affected by ITMS. (Key words: Analgesics, intrathecal: morphine. Anesthetic techniques, spinal: morphine. Anesthetics, volatile: halothane. Potency: MAC.)

A PRIOR REPORT and clinical observations suggest that anesthetic requirements are reduced when intrathecal opioids are given preoperatively.¹ Similarly, recent evidence suggests that intrathecal morphine sulfate (ITMS) will reduce the minimum alveolar concentration (MAC) of isoflurane in rats² and halothane in humans.³ We conducted a randomized, placebo-controlled, double-blind clinical trial to evaluate the effect of preoperative ITMS on halothane MAC and were unable to confirm these prior findings. Several possible explanations are discussed.

* Staff Anesthesiologist, Cleveland Clinic Foundation.

† Staff Anesthesiologist, Portsmouth Naval Hospital, Portsmouth, Virginia.

‡ Associate Professor, Georgetown University, Washington, D. C.

§ Head, School of Nurse Anesthesia, Bethesda Naval Hospital.

Received from the Departments of Anesthesiology, Cleveland Clinic Foundation, Cleveland, Ohio; Portsmouth Naval Hospital, Portsmouth, Virginia; Georgetown University, Washington, D. C.; and Bethesda Naval Hospital, Bethesda, Maryland. Accepted for publication December 12, 1990. Presented in part at the 1988 Annual Meeting of the American Society of Anesthesiologists, San Francisco, California.

The opinions expressed herein are those of the authors and are not to be construed as reflecting the views of the Navy Department, the Naval Service at large, or the Department of Defense.

Address reprint requests to Dr. Licina: Department of Cardiothoracic Anesthesia, The Cleveland Clinic Foundation, One Clinic Center, Cleveland, Ohio 44195-216.

Materials and Methods

After institutional approval and informed consent were obtained, we studied 25 adult ASA Physical Status 1 or 2 patients scheduled for lower abdominal surgery that included midline and transverse incisions. None was taking medication known to affect MAC, and no preanesthetic medication was given. They were randomly assigned to control (CTRL) or ITMS-treated groups. ITMS-treated patients received 15 µg/kg preservative-free undiluted ITMS (Duramorph®; Elkins-Sinn, Cherry Hill, NJ) (concentration 1 mg/ml). Lumbar puncture was performed at L4-5 (after infiltration with 2-3 ml 1% lidocaine) in the right lateral decubitus position at least 2.5 h before surgical incision to ensure onset of clinical effect.⁴ Subarachnoid needle placement was confirmed by cerebrospinal fluid aspiration in all cases. With the exception of subarachnoid puncture, CTRL patients underwent an identical procedure, including initial skin infiltration and placement of the introducer needle. Care was taken to blind all patients to the administration of ITMS. Approximately 2 h thereafter, anesthesia was induced with halothane and oxygen. Tracheal intubation was facilitated by intravenous succinylcholine. After tracheal intubation, age-adjusted⁵ end-tidal halothane (ET_{hal}) was selected according to the modified up-down method of Dixon.⁵⁻⁸ Ventilation was controlled to maintain end-tidal carbon dioxide tension (ET_{CO₂}) between 27 and 34 mmHg. ET_{HAL} and ET_{CO₂} were measured with a Puritan-Bennett model 254 airway gas monitor. The instrument was calibrated immediately before each study according to the manufacturer's recommendations, with the use of a standardized calibration gas mixture. The preselected ET_{HAL} was maintained constant for a minimum of 20 min before skin incision to allow for adequate equilibration between alveolar and brain anesthetic partial pressures.⁹ Neuromuscular blockade, mean blood pressure (MBP), heart rate (HR), ET_{CO₂}, oxyhemoglobin saturation measured by pulse oximeter (SpO₂), and pharyngeal temperature were monitored at 5-min intervals throughout the study period. An observer blinded to the patient's assignment (ITMS vs. CTRL) determined whether movement occurred with skin incision. The surgeon was asked only to

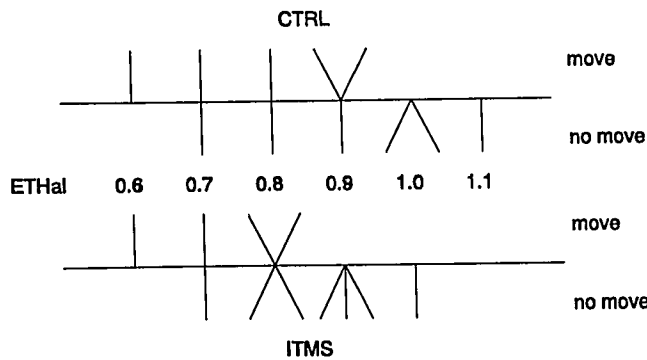


FIG. 1. Response to surgical incision in the control (CTRL) and intrathecal morphine sulfate (ITMS) groups.

perform skin incision and refrain from using electrocautery until the patient's response was determined. Purposeful extremity or head motion—but not coughing, chewing, or swallowing—was considered movement. The data were analyzed with a modification of Dixon's method for sequential sampling of quantal response data. These results were also verified with probit analysis. Student's *t* test was used where appropriate.⁶⁻⁸

Results

Twenty-five patients consented to participate in the study. One patient was eliminated because of premature surgical incision, which prevented adequate time for equilibrium between alveolar and brain anesthetic partial pressures. Because of a procedural error in applying the up-down method of Dixon, one patient from each group was eliminated. The procedural error consisted of the selection of an ET_{HAL} level for the second patient in each group that was higher than that called for by the Dixon method. Thereafter, the Dixon method was scrupulously adhered to, causing the exclusion of only the first patient in each group. The elimination of these two patients did not alter the results as determined by probit analysis. All patients tolerated induction of anesthesia and tracheal intubation without incident. Complete return of neuromuscular transmission was present before skin incision in all cases. The responses to incision are shown in figure 1.

MAC (\pm SE) after ITMS was 0.76 ± 0.06 compared with a CTRL MAC of 0.78 ± 0.15 (not significant [NS]). There were no significant differences among the groups with respect to age, gender, preincision temperature, MBP, HR, SpO_2 , or ET_{CO_2} . Likewise, times from anesthetic partial pressure equilibrium, from injection, and from induction to incision did not differ between the groups (table 1). Probit analysis CTRL MAC (\pm SE) was 0.80 ± 0.06 and ITMS MAC was 0.76 ± 0.05 (NS).

The dose of ITMS used ranged from 0.75 to 1.4 mg. Eleven of the 12 patients in the ITMS-treated group required a postoperative naloxone infusion for respiratory depression, perioral pruritus, nausea, or vomiting. All the ITMS-treated patients were pain free for at least 14 h postoperatively.

Discussion

Various studies in animals and humans have shown that systemic administration of opioids reduces MAC.^{9-11,¶} The magnitude of this MAC reduction ranges from 20 to 67%, depending on the dose and method of administration. Our clinical experience, as well as a case report,¹ suggested that preoperative administration of ITMS may reduce the anesthetic requirement. The current study was performed to address this question. While our work was in progress, preliminary studies in animals and humans reported MAC to be reduced by ITMS.^{2,3} However, our results fail to show a significant effect of preoperative ITMS on the MAC of halothane in humans.

Failure to obtain a clinical effect could have resulted in our inability to demonstrate the effect of ITMS on MAC. Gray *et al.* used $10 \mu\text{g}/\text{kg}$ of lumbar-administered ITMS in patients after thoracotomy, which was very effective and provided analgesia within 30 min.⁴ Our patients received $15 \mu\text{g}/\text{kg}$ of ITMS at least 2 h before incision to ensure a clinical effect. Postoperatively, all patients were pain free, and all but one required a naloxone

¶ Murphy MR, Hug CC: Efficacy of fentanyl in reducing isoflurane MAC: Antagonism by naloxone and nalbuphine (abstract). ANESTHESIOLOGY 59:A338, 1983

TABLE 1. Physiologic Variables and Time Intervals

	Age (yr)	BP* (mmHg)	HR* (beats per min)	ET_{CO_2} * (mmHg)	Temperature* ($^{\circ}$ C)	T_A (min)	T_B (min)	T_C (min)
CTRL	31.2 ± 8.9	77.5 ± 9.6	74.4 ± 15.9	31.0 ± 3.4	36.1 ± 0.2	22 ± 3	41 ± 6	203 ± 65
ITMS	31.4 ± 7.9	73.2 ± 8.8	66.4 ± 9.5	29.8 ± 2.6	35.7 ± 0.6	22 ± 4	37 ± 8	189 ± 56

Data are means \pm SD.
BP = mean arterial pressure; T_A = Time from stable ET_{HAL} to incision; T_B = time from induction to incision; T_C = time from injection

of ITMS to incision.
CTRL = control; ITMS = intrathecal morphine sulfate.
* At incision.

infusion. It is reasonable to assume that our ITMS-treated group had clinically effective subarachnoid injections of ITMS.

Differences in study design could have accounted for the discrepancy between our results and those of other investigators. The study by Drasner *et al.*³ included only female patients and incorporated the use of nitrous oxide and intratracheal lidocaine into the anesthetic technique. Furthermore, it lacked double-blinding and used dextrose as a diluent for ITMS.

We induced anesthesia with halothane-oxygen, whereas Drasner *et al.*³ used oxygen, nitrous oxide, 160 mg intratracheal lidocaine, and halothane. Himes *et al.* studied the effect of intravenous lidocaine on MAC and found a 10–28% reduction.¹² The use of intratracheal lidocaine should have equally affected both the experimental and CTRL groups. The CTRL MAC for the patients of Drasner *et al.*³ was 0.81%, which is close to previously reported values.^{8,9} This indicates that lidocaine did little to affect MAC in the CTRL group of Drasner *et al.*³ It is still possible, although unlikely, that ITMS and intratracheal lidocaine may have acted synergistically to reduce MAC.

We used undiluted morphine sulfate, whereas Drasner *et al.* used morphine sulfate at a concentration of 0.5 mg/ml diluted 1:1 with 10% dextrose solution.³ The effect of baricity on the narcotic effect of intrathecal opioids has not been studied. Gray *et al.* used 10 µg/kg morphine sulfate in either normal saline or 10% dextrose in patients after thoracic surgery and found that all patients had excellent postoperative analgesia, but the group that did not receive dextrose had the same onset time but a longer duration of action.⁴ Our failure to show a reduction in MAC with ITMS cannot be explained easily by the difference in the baricity of the ITMS administered. However, it is conceivable that the addition of dextrose may dilute the local sodium concentration in the subarachnoid space in two ways and thus decrease MAC.¹³ First, the injection of a solution devoid of sodium may cause an immediate dilution of the local subarachnoid sodium concentration. Second, if the resulting subarachnoid solution after injection of the ITMS and dextrose were hyperosmotic, water could be drawn from the perfusing blood to cause additional dilution of the sodium concentration. If these effects did occur in the patients of Drasner *et al.*, the MAC reduction can be explained.

The patients in the current study all had abdominal operations that included midline incisions, whereas the patients of Drasner *et al.* underwent low (T12–L1) horizontal abdominal incisions.³ Because a vertical incision could stimulate more dermatomes, our study may have been biased against MAC reduction with ITMS. However, MAC has been shown to be unaffected by the type of

stimulation, provided a supramaximal stimulus is applied.¹⁴ Many previous clinical investigations of MAC have used skin incision as the supramaximal stimulus.^{8–10,12} Our patient population included male and female patients, unlike the patient population of Drasner *et al.*, which included only female patients.³ Our groups were similar with respect to gender distribution. Gender has not been shown to affect MAC, and we believe our results were not caused by differences in the patient population.¹⁵

Patients in the current study were unaware of their randomization to receive either ITMS or placebo. In contrast, the CTRL patients in the study by Drasner *et al.* received an intramuscular injection.³ Hospital nurses frequently inform patients of the advantages of ITMS, and many patients request ITMS even before we begin our preoperative interview. There is evidence in the literature indicating that suggestion or hypnosis may decrease anesthetic requirements and the need for postoperative opioids.^{16–19} The lack of double-blinding in the study by Drasner *et al.* may have introduced bias in favor of MAC reduction.³ In their study, the patients' knowledge that they were receiving a potentially beneficial treatment modality with the expectation of a pain-free postoperative course may have resulted in a quieter induction with less catecholamine release; thus, it may have acted like a hypnotic suggestion, influencing the results.

Although there were differences in methods, none fully explains the different results between the two human studies. In conclusion, our randomized placebo-controlled, double-blinded study failed to demonstrate that ITMS reduces MAC of halothane in humans. The issue of MAC reduction by intrathecally administered opioids remains unresolved.

References

1. Tung A, Maliniak K, Tenicela R, Winter P: Intrathecal morphine for intraoperative and postoperative analgesia. *JAMA* 244: 2637–2638, 1980
2. Drasner K, Bernards C, Ciriales R: Intrathecal morphine reduces the minimum alveolar concentration of isoflurane in the rat (abstract). *ANESTHESIOLOGY* 67:A668, 1987
3. Drasner K, Bernards CM, Ozanne GM: Intrathecal morphine reduces the minimum alveolar concentration of halothane in humans. *ANESTHESIOLOGY* 69:310–312, 1988
4. Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstrup DM: Intrathecal morphine for post-thoracotomy pain. *Anesth Analg* 65:873–876, 1986
5. Gregory GA, Eger EJ, Munson ES: The relationship between age and halothane requirement in man. *ANESTHESIOLOGY* 30:488–491, 1969
6. Dixon WJ: The up and down method for small samples. *J Am Statist Assoc* 60:967–973, 1965
7. Dixon WJ: *Introduction to Statistical Analysis*. New York, McGraw-Hill, 1969, pp 377–393
8. Dixon WJ: Quantal response variable experimentation: The up-and-down method, *Statistics in Endocrinology*, Proceedings.

Edited by McArthur JW, Colton T. Cambridge, MIT Press, 1970, pp 251-267

9. Saidman LJ, Eger EI: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *ANESTHESIOLOGY* 25:302-306, 1964
10. Munson ES, Saidman LJ, Eger EI: Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. *ANESTHESIOLOGY* 26:134-139, 1965
11. Murphy MR, Hug CC: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. *ANESTHESIOLOGY* 57:485-488, 1982
12. Himes RS, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *ANESTHESIOLOGY* 47:437-440, 1977
13. Tanifuji Y, Eger EI: Brain sodium, potassium, and osmolality: Effects on anesthetic requirement. *Anesth Analg* 57:404-410, 1978
14. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. *ANESTHESIOLOGY* 26:756-763, 1965
15. Eger EI II: *Anesthetic Uptake and Action*. Baltimore, Williams and Wilkins, 1974, p 5
16. Marmer MJ: Hypoanalgesia and hypoanesthesia for cardiac surgery. *JAMA* 171:512-517, 1959
17. Dobernick RC: Hypnosis as an adjunct to surgical therapy. *Surgery* 46:299-304, 1959
18. Bowen WF: Hypnosis: Useful adjunct in surgery. *Surg Bull* 46: 8-10, 1966
19. Ruiz ORG, Fernandez A: Hypnosis as an anesthetic in ophthalmology. *Am J Ophthalmol* 50:163, 1960