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Efficacy and Safety of Epidural Opioids for Postoperative Analgesia

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Epidural narcotics for postoperative analgesia. By Bromage PR, Camporesi E, Chestnut D. Anesth Analg 1980; 59:473–80. Reprinted with permission.

Epidural narcotic analgesia was assessed in 66 patients after surgery under epidural and light general anesthesia. Changes of forced expiratory volume in 1 s (FEV_1) were measured after upper abdominal or thoracic surgery in 41 patients, and comparisons were made with results in an additional 17 upper abdominal surgery patients who received general anesthesia and muscle relaxants followed by intravenous morphine for postoperative pain relief. Methadone, 1.0 mg, hydromorphone, 1.0 mg, or morphine sulfate, 5 mg, was administered epidurally and increments were repeated as necessary until satisfactory analgesia was reported, with the following results (mean ± SD): intravenous morphine: latency 3 to 10 min, duration 3.1 ± 1.6 h; epidural methadone: latency 17.2 ± 4 min, duration 5.6 ± 2.7 h; epidural hydromorphone: latency 22.5 ± 6 min, duration 9.8 ± 5.5 h; epidural morphine: latency 36 ± 6 min, duration 16.4 ± 7 h. Duration of action was slightly longer after lower abdominal surgery. Addition of epinephrine 1/200,000 to the epidural narcotic solutions did not prolong duration. Narcotic requirements for satisfactory analgesia were approximately the same by the intravenous route as by the epidural route and equivalent to 8.5 to 9 mg of morphine. FEV_1 was reduced to 36.8 ± 13.2% of preoperative control values after general anesthesia and muscle relaxants and to 46 ± 12% of control after epidural and general anesthesia. Intravenous morphine improved FEV_1 to 45.3 ± 12% of control, whereas epidural narcotics and local anesthetics produced a greater increase of FEV_1 in the following amounts: epidural local anesthetic to 68.7 ± 9.1% of control and epidural narcotics to 67.1 ± 14.7% of control. Epidural narcotics did not cause sympathetic depression or bladder dysfunction, and analgesia was segmental. We conclude that epidural narcotics in adequate dosage are an effective means for production of prolonged and segmental postoperative analgesia.

ALMOST 25 yr have elapsed since Philip Bromage, M.B., B.S., Enrico Camporesi, M.D., and I published our study of epidural opioids administered for postoperative analgesia.[1] Dr. Bromage, who was Professor of Anesthesiology at Duke University Medical Center (Durham, North Carolina) and who subsequently served as Chair of Anesthesiology at the University of Colorado Health Sciences Center (Denver, Colorado), was the principal investigator. Both he and his Duke faculty colleague, Dr. Camporesi, who was subsequently appointed as Chair of Anesthesiology at the State University of New York Upstate Medical Center (Syracuse, New York), provided the intellectual firepower. As a young resident in anesthesiology, I was the gofer. This study was my introduction to academic medicine and clinical research, for which I remain grateful.

It is instructive to consider the practice climate that existed in 1980. Few anesthesiologists consistently played an active role in the provision of postoperative analgesia. Surgeons typically prescribed intramuscular opioids when writing the general postoperative orders. Pain relief typically was poor, and adverse effects occurred frequently. In 1973, one study noted that 73% of postoperative patients experienced distressing pain despite the use of intramuscular opioids. The authors concluded that most physicians prescribed inadequate doses of analgesics at infrequent intervals.[2] In 1980, another study found that the duration of the minimum effective analgesic concentration of meperidine was only 35% of the prescribed 4-h dosing interval.[3] Accordingly, patients uniformly feared surgery, in part because of the high risk of severe postoperative pain.

In 1979, Wang *et al.*[4] published the first report of intraspinal opioid administration in humans. These in-

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vestigators, who were consultants in the Departments of Anesthesiology and Neurology at the Mayo Clinic (Rochester, Minnesota), observed prolonged, profound analgesia after intrathecal administration of morphine (0.5–1.0 mg) in six of eight patients with intractable cancer pain. Behar *et al.*[5] made similar observations of the efficacy of epidural administration of morphine (2 mg) in 10 heterogeneous patients with severe acute or chronic pain. Subsequent letters reported the administration of either intrathecal or epidural opioids for postoperative analgesia, with impressive claims of success.[6–8]

To my knowledge, our study, published in 1980, was the first controlled study of epidural opioids for postoperative analgesia. We enrolled 84 patients undergoing thoracic, abdominal, or perineal surgery. The number of study subjects was relatively large when compared with other prospective, controlled studies of that era.

We sought to answer five questions: (1) How good is the analgesia produced by epidural opioids? (2) How well does epidural opioid analgesia improve postoperative respiratory function compared with other methods of analgesia? (3) Is one opioid (*i.e.*, morphine, hydromorphone, methadone) better than another when injected epidurally? (4) Does the addition of epinephrine increase the duration of epidural opioid analgesia? (5) Are epidural opioids safe and practical for providing effective postoperative analgesia?

Contemporary readers may argue that we did not answer some of these questions very well. The patient population and the surgical procedures were heterogeneous, the study subjects were not randomized, the investigators were not blinded to the group assignment, and the method of statistical analysis was not stated. However, the study's tripartite emphasis on quality of analgesia, restoration of respiratory function, and patient safety was somewhat unusual for that era. Also, subsequent studies have largely confirmed most of our observations.

The final, summary paragraph of the article included an acknowledgment that we had obtained only "partial answers" to those five questions: (1) The quality of postoperative epidural opioid analgesia was typically satisfactory but was more variable and less intense than the profound analgesia provided by local anesthetic agents administered epidurally. However, we observed that epidural opioid analgesia had a greater duration than that provided by local anesthetics and was devoid of adverse effects attributable to sympathetic and proprioceptive blockade. Further, the analgesia seemed to be segmental in distribution, which suggested an intraspinal selectivity. (2) Epidural opioids provided more effective restoration of respiratory function (as measured by forced expiratory volume in 1 s) than did intravenous opioids. (3) Of the three opioids tested, epidural methadone had the fastest onset but provided analgesia of a relatively short duration. In contrast, epidural morphine had a delayed onset but also had a prolonged duration of action. (4) We observed no evidence that epinephrine either shortened the latency or prolonged the duration of epidural opioid analgesia. (5) We observed no cases of central respiratory depression. However, shortly before the publication of our study, correspondence described cases of unexpected and delayed respiratory depression after intraspinal opioid administration.[9–11] Likewise, we called attention to the consequences of transdural migration and possible cephalad subarachnoid spread of the opioid, and we urged both caution and vigilance with the use of this technique.

Today, we recognize that epidural opioids are not the "magic bullet" for which we had hoped. In a recent conversation, Dr. Bromage commented, "They don't go the whole distance, do they, David?" Nonetheless, epidural opioid administration is a significant component of the contemporary prevention and treatment of postoperative pain in both obstetric and nonobstetric patients. Most major medical centers provide epidural analgesia through an Acute Pain Service, which includes anesthesiologists and nurses who manage postoperative analgesia on a 24/7 basis until the patient is ready to make the transition to alternative forms of analgesia. While cost-*versus*-benefit analysis and debate continue, epidural opioids are administered to provide postoperative analgesia in patients who have undergone cesarean delivery, upper abdominal or thoracic surgery, and selected orthopedic surgical procedures.

Intraspinal (*i.e.*, epidural and/or intrathecal) opioids, typically coadministered with local anesthetic agents, are also a staple of intrapartum pain management. The administration of epidural and intrathecal opioids undoubtedly has facilitated the epidural administration of more dilute solutions of local anesthetic during labor, which has likely improved patient safety and perhaps has had a favorable influence on obstetric outcome (*e.g.*, decreased risk of operative delivery). Further, the investigation and use of intraspinal opioid analgesia spawned the identification and investigation of both multiagent and multimodal analgesic regimens, with the hope that the resulting synergy might improve the efficacy of analgesia while reducing the incidence of troublesome adverse effects and significant complications (*e.g.*, respiratory depression). I should emphasize that today's standards require the performance of laboratory toxicity testing before the epidural or intrathecal injection of a new drug (or drugs) in humans.

A Personal Note

Dr. Bromage gave me the privilege of presenting the results of our study at the March 1979 Annual Meeting of the American Society of Regional Anesthesia in San Francisco, California. This was my first scientific presentation, and I had a high level of anxiety. Dr. Bromage assured me that his wife and astute editor and literary

critic, Meg Bromage, would help me get it right. And she did. At first I resisted some of her suggestions, but I soon concluded that it would be best that I accept her advice. After two Saturday afternoons of rehearsals in the Bromage living room, I seemed to be ready. The American Society of Regional Anesthesia presentation went well, except that I stumbled badly in my response to a question from Dr. Rudolph de Jong, who (correctly) observed that our study had not clearly established the spinal selectivity of opioids administered either epidurally or intrathecally.

Sadly, Mrs. Bromage recently passed away. Through the years, Dr. Bromage and I collaborated on other projects, and in every case, Mrs. Bromage was an active participant, always asking me pointed questions and insisting on the proper use of language and clarity of expression. As was true for many of the great clinician–scientists of that era, Dr. Bromage was blessed with a devoted, intellectually brilliant spouse who received little public acclaim but who worked behind the scenes, supporting his career.

Speaking of proper language, I should note that Dr. Bromage preferred, as do I, the word *opioids* or *opiates*, rather than *narcotics*. The title of the original manuscript referred to epidural *opiates* rather than epidural *narcotics*. Apparently someone considered this to be somewhat radical, and the word *narcotics* was substituted for *opiates* during the editorial review process.

Through the years, Philip and Meg Bromage have been very supportive of me, both professionally and personally. I do not think that we ever had a conversation when they failed to ask me about my family. I am grateful for this opportunity to acknowledge their contributions to my career development.

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