LUMBAR EPIDURAL MORPHINE AS AN EFFECTIVE ANALGESIC FOLLOWING CHOLECYSTECTOMY*

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ABSTRACT

Relief of pain with epidural morphine was evaluated in five patient subjects during two consecutive twenty-four hour periods after cholecystectomy. In one period, each subject received lumbar epidural morphine, first 4–6 mg, and twelve hours later, 2–3 mg; in the other period, epidural placebo at the same times. Except for four hours before each injection and twenty minutes thereafter, intramuscular morphine was administered as required throughout. The experiments were double-blind. Epidural morphine, unlike epidural placebo, reduced both a visual pain analogue score ($p < 0.05$) and a pain questionnaire score ($p < 0.01$) twenty minutes after injection. Epidural morphine compared to placebo reduced by one-half the total amount of narcotic (epidural plus intramuscular) administered over the twenty-four hour period ($p < 0.05$). Four of five subjects clearly preferred analgesia with epidural morphine over the effect of placebo plus therapeutic doses of intramuscular morphine. We conclude that epidural morphine, administered in this manner, is effective in relieving pain after cholecystectomy and that it may be preferred by patients over conventional intramuscular morphine.

KEY WORDS: EPIDURAL MORPHINE; POSTOPERATIVE ANALGESIA

CLINICAL TRIALS suggest that small doses of opiates in the epidural space produce good to excellent pain relief after thoracic, abdominal and orthopaedic surgery.^{1–5} The analgesia is said to be “selective” in that other sensory, motor and sympathetic modalities are not obviously impaired. The duration of effect appears to be prolonged (6–24 hours) and the requirement for only a small dose of narcotic (e.g. morphine 2–5 mg) is believed to reduce the risk of adverse systemic effects. Thus, epidural opiate for postoperative pain relief might have a more favourable therapeutic to side effect ratio than either systemic narcotic or regional local anaesthetic blocks.⁶

In spite of the initial enthusiasm for epidural narcotic in the treatment of postoperative and other types of pain, there have been to our knowledge only two studies comparing epidural

narcotic to placebo in a double-blind fashion.^{7,8} Both were conducted in patients after abdominal surgery; one found epidural morphine to be effective,⁷ but the other failed to detect a difference from placebo.⁸ Unfortunately the former study employed only an indirect estimate of pain relief (observer estimate of quality of deep breathing) and neither study “crossed subjects over” from treatment to placebo. To determine the efficacy of an analgesic in the clinical setting, one must pay scrupulous attention to the possibility of interference from added variables, employ sensitive methods for estimating pain relief, and guard carefully against the potential for subject and/or observer bias.^{9,10}

With these objectives in mind, we have attempted to determine if one method of administering epidural morphine relieves pain following cholecystectomy. Our study employed a double-blind cross-over technique and several methods of assessing pain relief.

METHODS

Potential subjects were selected from adults booked for elective cholecystectomy at University Hospital, London, Ontario. Exclusion criteria were age greater than 55 years, cardiovascular, pulmonary or neurological disease; the regular taking of medication; a history suggestive of allergy or unusual reaction to narcotic; evi-

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dence of a potential anaesthetic problem. During an interview, potential subjects were informed of the details and known risks of the proposed study and those agreeing to participate gave written consent. Five subjects were studied, three males and two females, whose mean ages, weights and heights were respectively 39 ± 12 years, 80 ± 12 kg and 171 ± 10 cm (means $\pm$ S.D.). This study was approved by the University of Western Ontario Committee on Human Research.

Each subject was premedicated with diazepam 10 mg orally two hours before operation and received a nitrous oxide, halothane and muscle relaxant (d-tubocurarine or pancuronium) anaesthetic. No narcotics were administered during operation. During the course of the anaesthetic, an epidural catheter was inserted through the L2-L3 or L3-L4 interspace.

The study commenced in the recovery room when the subject was awake, stable and indicating the first need for analgesia. There were two consecutive twenty-four hour study periods, one for the assessment of epidural morphine – "treatment day" – and the other for epidural placebo – "placebo day". At the beginning and at the mid-point of each period the subject received either epidural morphine or placebo, according to one of the two sequences outlined in Figure 1. Assignment of subjects to one or other sequence was made randomly by the consulting pharmacist and was known only to her throughout the study periods.

Individual doses of epidural morphine were based upon body weight.* For subjects weighing less than 60 kg, the initial dose of morphine was 4 mg and the mid-period dose 2 mg, each diluted in saline 10 ml. For subjects 60–80 kg, the doses were respectively 5.0 and 2.5 mg, each in saline 12.5 ml. For subjects weighing more than 80 kg, doses were 6 and 3 mg in saline 15 ml. Individual volumes of placebo injected were the same. Morphine for epidural injection was prepared by the Pharmacy Department of the Hospital and consisted of the required dose of preservative-free morphine dissolved in sterile saline. Placebo was preservative-free saline alone.

To assure analgesia during the placebo period and in the event that epidural morphine was ineffective, morphine by intramuscular injection ($0.2 \text{ mg} \cdot \text{kg}^{-1}$) was available on a q4h p.r.n. basis. We suggested that recovery room and ward nurses administer intramuscular morphine ac-

FIGURE 1 Summary of protocol. The study began with the subject awake in the recovery room and indicating a need for analgesia. Individual subjects were assigned randomly to sequence #1 or #2.

cording to their usual indications in response to patient request and/or apparent need. The only special request was that intramuscular morphine be withheld for twenty minutes following any epidural injection so that the investigators could assess early subject response to the epidural injection alone. In addition, epidural injections were deferred for at least four hours following any intramuscular injection to minimize the possibility of interaction between the two.

One of us (I.A. or W.T.) evaluated each subject immediately before and twenty minutes after each epidural injection. We measured blood pressure, pulse and respiratory rate, and examined the upper and lower limbs for pin-prick, proprioceptive and vibration senses as well as motor power and tendon reflexes. We also estimated severity of pain, using a visual pain analogue scale¹¹ and a modified McGill pain questionnaire.¹² The visual analogue was a vertical straight line 10 cm in length, the extremities of which were defined as no pain at the bottom and maximal imaginable pain at the top. Subjects were requested to mark on the line a point representing the severity of their pain. The pain questionnaire consisted of four classes of words describing four dimensions of pain – sensory, affective, temporal and evaluative (Table). From each class, the subject was asked to select a word which best described his pain at the time. Individual words within each class had been assigned a score of one, two or three, based upon the relative pain intensity the word implied, as had been previously determined in volunteers.¹² The location of the point along the analogue scale (measured in centimeters) and the total score of words selected from the pain questionnaire provided two quantitative estimates of pain, each of which could be analyzed statistically.

*The decision to base dose upon body weight was arbitrary; the criteria for optimal doses of epidural morphine remain to be established.

TABLE
MODIFIED MCGILL PAIN QUESTIONNAIRE

Class	Word Description		
Sensory	pulsing	throbbing	pounding
	dull	aching	heavy
	pulling	cramping	wrenching
	pricking	boring	stabbing
Affective	nagging	sickening	agonizing
	slightly tiring	tiring	exhausting
Temporal	brief	every now and then	constant
Evaluative	annoying	miserable	unbearable
	mild	discomforting	excruciating
	slightly distressing	distressing	very distressing
Assigned Score:	1	2	3

After forty-eight hours we asked the subject to compare the two twenty-four hour periods retrospectively and, in particular, to indicate whether pain relief was approximately equal during each or superior during one or the other.

With the completion of all studies, the assisting pharmacist identified the sequence that had been assigned to each subject. We compared visual analogue and word scores before and after epidural placebo and morphine, as well as the total narcotic administered during placebo and treatment periods. For statistical analysis we employed a Student's *t*-test for paired data, accepting a *p* value of 0.05 or less as indicative of a significant difference.

RESULTS

Three subjects received morphine the first day, two subjects placebo. All completed both phases of the study. There were no complications except for minor itching experienced by two subjects during the treatment day.

Visual analogue scores before and twenty minutes after epidural placebo and morphine are depicted in Figure 2, word or pain questionnaire scores in Figure 3. Overall, changes in each of these scores were significantly correlated to changes in the other ($r = 0.68$, $p < 0.01$).

Placebo reduced the visual and word scores slightly (N.S.), due to an effect in one subject only. Epidural morphine reduced both scores significantly (visual, $p < 0.05$; word, $p < 0.01$), but only modestly. When the reduction produced by each dose of morphine was considered separately, the effect of the initial 4–6 mg dose alone did not achieve conventional statistical signifi-

FIGURE 2 Visual analogue scores (means $\pm$ S.E.M.) observed immediately before and twenty minutes after epidural placebo and epidural morphine. The reduction of scores after epidural morphine was statistically significant.

cance (both scores, $p < 0.10$), but the effect of the mid-period 2–3 mg dose alone did (both scores $p < 0.05$). There was no evidence of a difference between doses.

Total doses of intramuscular and epidural morphine administered to each subject on each day (i.e. the sum of individual doses described in Methods) are given in Figure 4. Doses for each experimental period or day were expressed on a mg per hour basis, because the duration of individual periods varied slightly (20–26 hours). During the placebo day the dose of intramuscular morphine was 2.32 ± 0.65 mg/hour; during treatment day, the intramuscular dose was reduced to 0.81 ± 0.78 mg/hour (means $\pm$ S.D., $p < 0.05$). The total dose of morphine on treatment day,

FIGURE 3 Word or pain questionnaire scores (means $\pm$ S.E.M.) observed immediately before and twenty minutes after epidural placebo and epidural morphine. The reduction of scores after epidural morphine was statistically significant.

which included both intramuscular and epidural doses, was 1.17 ± 0.78 mg/hour, a value which was less than the intramuscular dose on placebo day ($p < 0.05$).

In subjects 2, 3, 4 and 5, the amount of intramuscular morphine required throughout treatment day was very small (Figure 4); in three subjects, it consisted of only one intramuscular injection and in the fourth, only two. In these subjects, the request for intramuscular morphine was, with one exception, five hours or more after receiving epidural morphine. Subject 1, on the other hand, required four intramuscular injections of morphine on treatment day, the first at 30 minutes after epidural morphine; subject 1 was also the "placebo responder".

FIGURE 4 Intramuscular and epidural doses of morphine, expressed as mg per hour, administered to each patient subject during each experimental period or day. Left bars indicate intramuscular doses of morphine during placebo day; right bars indicate total doses of morphine during treatment day, as well as intramuscular and epidural dose components. Both total and intramuscular doses were significantly less on treatment day (p values < 0.05).

At the post-study interview, all subjects correctly identified the period or day during which they had received epidural morphine. Four of five subjects clearly preferred the epidural morphine period; the fifth, subject 1, was equivocal as to preference, although she could differentiate the two days clearly. Reasons offered for favouring the epidural morphine day were better pain relief, less nausea, fewer intramuscular injections and less drowsiness.

Vital signs remained virtually unchanged after epidural injections and there was no clinical evidence of autonomic, motor or sensory blockade other than analgesia.

DISCUSSION

This study demonstrates that lumbar epidural morphine 4–6 mg followed twelve hours later by epidural morphine 2–3 mg is effective in relieving pain after cholecystectomy. This analgesic technique was preferred over conventional intramuscular morphine therapy by four of five patient subjects who compared the two.

The effectiveness of new analgesic techniques should always be tested in the relevant circumstances, that is in the presence of clinical or pathological pain.^{9,10,13} However, studies evaluating pain relief in the clinical environment can be very difficult, especially in the postoperative period. The usual conditions after operation are not conducive to sensitive assessments of subjective pain relief. In addition, there are potentially many uncontrolled and unpredictable variables which can modify responses to analgesic therapy, related to the subject's psychological and physical status, the painful stimulus, overall patient management and the subject's expectations of pain relief. An indication of the importance of the latter is that approximately 40 per cent of subjects suffering postoperative pain will receive some relief from placebo.¹⁰ These variables assume particular importance when the analgesic being studied alters only the subject's pain experience and does not produce objective neurological signs, as is apparently the case with intrathecal and epidural narcotics, which impair only nociceptive pathways from deep and visceral structures¹⁴ and do not alter superficial sensations, motor or autonomic functions in an obvious way.¹⁻³

In an attempt to reduce the influence of added variables to a minimum we studied only healthy subjects undergoing the same operative proce-

dures through the same midline abdominal incision and with a standardized anaesthetic technique. We avoided the use of narcotics and epidural local anaesthetics during operation, either of which might have modified the effects of epidural narcotic administered subsequently. Since the requirement for systemic narcotic is nearly the same on the first and second postoperative day after cholecystectomy,¹⁵ we assumed a similar magnitude of pain severity on each day and used one to test epidural morphine and the other to test epidural placebo, "crossing-over" each subject in a double-blind fashion between the two, thereby greatly reducing the problem of added variables.

We chose the lower lumbar region for insertion of epidural catheters, as we felt this would be the safest and most practical technique for general use and, therefore, the one which would be of widest interest. Doses and timing of morphine injections were arbitrary. Clinical trials had suggested that small (2–3 mg) doses were frequently inadequate to establish analgesia postoperatively and that better results might be obtained with larger "loading" doses.^{4,8} Reports also suggested that duration of effect was variable, but on the average was about twelve hours.^{1–5} Accordingly, we studied an initial dose of 4–6 mg followed twelve hours later by a dose of 2–3 mg, the precise doses dependent upon subject weight. We assumed that all injections of narcotic were deposited in the epidural space and we did not verify localization of the catheter with local anaesthetic injections. If, in error, we had placed morphine outside the epidural space, this would have acted to underestimate our results. On the other hand, if we had deposited morphine directly into the sub-arachnoid space (unlikely we believe), this may have overestimated our results.

We employed three different approaches to evaluate analgesia. The first was to measure pain intensity before and twenty minutes after each epidural injection, to assess early analgesic effect. Pain was measured with a visual analogue scale¹¹ and the McGill pain questionnaire,¹² each of which yields a sensitive score of pain intensity. Epidural morphine reduced both scores of pain significantly (Figure 2 and Figure 3), although the overall magnitude of effect was only modest and, when each dose of morphine was considered separately, significant only after the mid-period (twelve hour) dose. Not unexpectedly, one subject responded to placebo.

We have subsequently observed in volunteers that the peak analgesic effect of epidural mor-

phine is about ninety minutes after injection.¹⁶ Therefore, what was observed in this study twenty minutes after injection probably represented only a fraction of the full analgesic effect. This may explain in part why McClure, *et al.*,⁸ were unable to detect an effect of epidural morphine (2 or 5 mg) different from placebo twenty minutes after injection in patients who had undergone abdominal hysterectomy.

As a second assessment of analgesia, we determined the total dose of morphine given to each subject over each twenty-four hour period (Figure 4). This total dose varied according to the amount of intramuscular morphine given each day by nurses who were unaware of the nature of epidural injections. The amount of morphine given intramuscularly presumably reflected a combination of overall pain experienced by the patient, his communication of this to the nurse, and the nurse's assessment of narcotic need. Assuming the last two of these factors to be constant during treatment and placebo periods, we interpret differences in the amount administered during each twenty-four hour period to reflect differences in overall pain experienced. The total dose of narcotic on the treatment day was markedly reduced and the occasional injection of intramuscular morphine required was, with one exception, given at least five hours after epidural morphine. These data indicate that epidural morphine was effective and that its duration of action usually exceeded five hours.

The third estimate of analgesia was the retrospective comparison of each twenty-four hour period by each subject while still unaware of the nature of injections. Like the requirement for intramuscular morphine, this assessment was taken to represent adequacy of overall analgesic effect.¹⁷ A preference of subjects for a treatment over placebo when they have experienced the two in sequence is probably the best evidence of efficacy of an analgesic technique. Four of five patient subjects clearly favoured the day in which epidural morphine was given, citing both much better analgesia and fewer side effects. The fifth subject, the placebo responder, was equivocal. We are unable to attribute this preference solely to epidural morphine, as each subject also received intramuscular morphine on treatment day and we cannot totally dissociate the effects of the two. However, in the cases of subjects 2, 3, 4 and 5, most of the twenty-four hour treatment period was probably free of the effects of intramuscular morphine (in three subjects only one intramuscular injection given, in the fourth only two), and

thus it is reasonable to conclude that the preference was at least in part due to the efficacy of epidural morphine.

The standard with which epidural morphine (plus one or two intramuscular supplements) was compared in these retrospective evaluations was not just placebo, but placebo plus regular intramuscular injections of morphine. As it turned out, intramuscular morphine on placebo day was administered in doses and at intervals very similar to those usually employed after cholecystectomy (i.e. morphine $0.2 \text{ mg} \cdot \text{kg}^{-1}$ q 4–6h). Thus the preference for the epidural morphine period over the placebo period could be interpreted to mean that epidural morphine was not only effective, but that it was more effective than conventional intramuscular morphine therapy. This possibility needs to be confirmed in a more rigorously controlled study.

It must be stressed that although the pain-relieving effect of epidural morphine was very good, it was usually not complete. Three subjects recalled having some discomfort during the epidural morphine period, even in the first hours following epidural injections.

In this standardized study, we made no attempt to define optimal doses or injection volumes, or the optimal vertebral column levels for injection. Evidence suggests that after upper abdominal operations the quality of analgesia may be improved when the injection site is close to the vertebral level corresponding to the mixed spinal nerves innervating the painful region⁷, even though the site of action of morphine is probably higher in the corresponding segments of the spinal cord.¹⁴ Our site of injections at the L2-L3 or L3-L4 lumbar interspace may have been too low for optimal analgesia and on that account we may have underestimated the potential efficacy of this technique.

We were unable to detect any sensory changes other than analgesia in our subjects, including the hypoalgesia to pin-scratch which has been observed by Bromage, *et al.*⁴ We detected no evidence of motor or autonomic effect. The only complication noted was minor itching in two subjects. There was no indication of ventilatory depression, either early or delayed, but we measured neither minute ventilation nor PCO_2 levels in these subjects.

We conclude that lumbar epidural morphine, administered in the manner described, provides effective analgesia after upper abdominal operations. It may be preferred by patients over conventional intramuscular morphine.

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RÉSUMÉ

Le soulagement de la douleur par injection épidurale de morphine a été évalué sur cinq patients pendant deux périodes consécutives de 24 heures après cholécystectomie. Pendant une période on a administré à chacun des sujets de la morphine par la voie épidurale, d'abord à la dose de 4 à 6 mg et 12 heures plus tard à la dose de 2 à 3 mg; pendant l'autre période on a administré un placebo épidural aux mêmes intervalles. A l'exception des 4 heures qui précédaient chacune des injections et 20 minutes par la suite, de la morphine a été administrée par la voie intra-musculaire lorsque requis. La méthode employée était à double insu. La morphine épidurale, contrairement au placebo épidural, a diminué le score de la représentation graphique de la douleur ($p < 0.05$) et ainsi que le score du questionnaire de la douleur ($p < 0.01$) 20 minutes après l'injection. La morphine épidurale lorsque comparée au placebo a diminué de moitié de la dose totale de narcotique (i.e. dose épidurale plus dose intra-musculaire) administrée pendant la période de 24 heures ($p < 0.05$). Quatre des cinq sujets ont préféré de façon nette l'analgesie épidurale à la morphine sur celle que procurait le placebo additionné de dose thérapeutique de morphine par la voie intra-musculaire. Nous en concluons que la morphine par la voie épidurale administrée comme nous l'avons fait est efficace pour procurer un soulagement de la douleur après cholécystectomie et qu'elle pourrait être préférée par les patients à la méthode conventionnelle d'administration intra-musculaire.