Post-Caesarean section analgesia: a comparison of epidural butorphanol and morphine

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Epidural butorphanol 1, 2 and 4 mg were compared with morphine, 5 mg, for postoperative analgesia in 92 consenting, healthy, term parturients who had undergone Caesarean section under epidural lidocaine anaesthesia in a randomized double-blind study. Postoperative pain was assessed using a visual analogue scale and recorded with heart rate, blood pressure and respiratory rate. The demographic characteristics, and the incidences of primary and repeat Caesarean sections, were not different among the four treatment groups. At 15, 30, 45 and 60 min after treatment the median pain scores following butorphanol were similar and lower than those following morphine (P < 0.05). Calculated median percentage pain relief values for butorphanol were higher than morphine at each of these times (P < 0.05). At 90 min and 2 hr the pain scores and pain relief values were similar. Beyond 45 min the number of patients requesting supplemental medication and dropping out of the study increased progressively in both the butorphanol and morphine treated patients. The attrition profiles for butorphanol were different from morphine (P < 0.01). The median time in the study was >24 hr for morphine, and 3, 2.5 and 4 hr for butorphanol, 1, 2 or 4 mg, respectively. No patient developed a clinically important change in heart rate or blood pressure, and none experienced a decrease in respiratory rate below 12 breaths · min⁻¹. One of 69 patients (1.4 per cent) who received butorphanol developed pruritus compared with ten (43 per cent) of 23 patients who received morphine. The global assessments of the adequacy of analgesia were indistinguishable between morphine and butorphanol. Epidural butorphanol provides safe, effective postoperative analgesia, has a prompt onset, and a limited duration.

Key words

ANALGESIA: epidural, obstetrics, postoperative;
ANALGESICS: butorphanol, morphine.

Dans une étude à double insu lors de césarienne chez 92 parturientes à terme, nous avons comparé l'efficacité de 1, 2 et 4 mg de butorphanol à celle de 5 mg de morphine injectés dans le cathéter employé pour l'anesthésie épidurale à la lidocaïne. Nous jaugions la douleur postopératoire sur une échelle visuelle analogue et mesurions le pouls, la tension artérielle et la fréquence respiratoire. Les variables démographiques et la proportion de césariennes itératives étaient semblables dans les quatre groupes. Les valeurs médianes d'intensité douloureuse 15, 30, 45 et 60 min après l'injection de butorphanol étaient les mêmes pour les trois doses et étaient inférieures à celle de la morphine (P < 0,05) ; en même temps, les pourcentages médians de soulagement étaient plus grands avec le butorphanol qu'avec la morphine (P < 0,05). Toutefois, à 90 min et 2 h post injection, ces variables étaient les mêmes pour les deux morphiniques. A partir de la 45ième minute, de plus en plus de patientes traitées à la morphine ou au butorphanol nécessitaient d'autres analgésiques, mettant ainsi un terme à leur participation à l'étude mais à une fréquence différente selon le morphinique (P < 0,01). La durée médiane de participation à l'étude était de plus de 24 h pour la morphine et de 3, 2,5 et 4 h pour les doses de 1, 2 et 4 mg de butorphanol respectivement. Il n'y eut pas de modification clinique du pouls ou de la tension artérielle non plus que de bradypnée à moins de 12 min⁻¹. Une seule des 69 patientes (1,4 pour cent) ayant reçu du butorphanol se plaint de prurit mais 10 des 23 patientes (43 pour cent) du groupe morphine firent de même. L'évaluation globale de l'efficacité analgésique était la même pour la morphine et le butorphanol. Le butorphanol épidural offre une analgésie postopératoire sûre et efficace ; il agit rapidement et pendant une période limitée.

The use of epidural morphine for the relief of postoperative pain after Caesarean section is associated with prolonged analgesia, a decreased requirement for supplemental narcotics, early ambulation and improved

maternal-infant bonding.[1-8] Morphine, a pure opioid agonist, primarily activates mu receptors and may induce the undesirable side-effects of respiratory depression, pruritus, nausea, vomiting, and sedation.[9-12] In addition, the poor lipid solubility of morphine results in a slow onset of action, and is believed to be the cause of respiratory depression by cephalad spread of the drug to the respiratory centres by migration in the cerebrospinal fluid.[13]

Butorphanol, a synthetic opioid, is a strong kappa receptor agonist, a weak mu receptor agonist/antagonist, and is relatively lipid soluble.[14-16] For these reasons, the use of epidural butorphanol for post-Caesarean section analgesia should produce less respiratory depression and a reduced incidence of pruritus, nausea, and vomiting. The present study, a triple-blind, randomized evaluation, was conducted to compare the responses to three doses of butorphanol with morphine for providing postoperative epidural analgesia, and to assess the side-effects of each drug following Caesarean section.

Methods

The study was approved by the Institutional Committees on Human Research and written informed consent was obtained from each patient. Ninety-two healthy parturients at term who had undergone a successful delivery by Caesarean section under epidural anaesthesia were enrolled. These were patients at a large urban county hospital affiliated with Baylor College of Medicine. Patients with evidence of major organ disease, a substance abuse history, or a major complication of pregnancy were excluded. The age, height, weight, ethnic background and Caesarean section history of each patient were recorded.

Anaesthesia for the Caesarean section (T_4 sensory level) was produced with lidocaine, two per cent with 1:200,000 epinephrine, injected through an epidural catheter inserted in the L_{2-3} or L_{3-4} interspace. The epidural catheter was left in place. During resolution of the epidural block, postoperative pain was evaluated at 15 min intervals using a 100 mm visual analogue scale where 0 = "no pain" and 100 = "worst pain ever." Each patient was instructed to mark the scale at the point which she felt was representative of her level of discomfort. When the patient indicated that her pain was "moderate" (5-6 scale units or more), a single dose of test drug was injected and the epidural catheter removed. Selection of the test drug was based on a computer-generated randomization schedule. Each dose of medication was prepared by the hospital pharmacy and supplied in identically appearing coded vials. The test medications were morphine, 5 mg, and butorphanol 1, 2, or 4 mg. Each was preservative-free, and diluted to a total volume of ten ml with sterile saline at

the time of injection. The anaesthetist, the research nurse and the patient were blinded as to which drug/dose was administered.

Each patient was instructed that she could request supplemental medication at any time. Following the test drug, repeated measurements of pain were made using the same visual analogue scale for 24 hr or until the patients requested supplemental analgesia. The measurement intervals were: 15, 30, 45, 60 and 90 min, and 2, 3, 4, 6, 8, 12, 16, and 24 hr. Measurements of respiratory rate, blood pressure and heart rate were recorded before the test drug was administered, and at intervals during the time the patient remained in the study. These measurement intervals were: 30, 60 and 90 min, and 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hr. The mean blood pressure ([systolic − diastolic/3] + [diastolic]) was calculated. Each patient was observed for the incidence of adverse side effects, including nausea and/or vomiting, pruritus and a decrease in the respiratory rate to less than 12 breaths·min⁻¹. Patients who developed clinically "mild" pruritus were given intravenous diphenhydramine 25 mg, while those developing clinically "moderate" pruritus were given intravenous naloxone in increments of 0.8 mg titrated to effect. The choice of treatment was left to the discretion of the responsible anaesthetist. When a patient requested supplemental medication, data from the time interval immediately preceding the request were used as the end of her participation in the study. The drug(s), dose(s) and route(s) of administration for the supplemental medication(s) were not standardized. These decisions were, again, made by the responsible anaesthetist on the basis of his/her assessment of the clinical situation. Each patient who received supplemental medication was observed for a minimum of 24 hr because of the late respiratory depression known to occur with one of the test medications, morphine.[9,11,12] At the end of the period of observation, each patient was asked to provide a global evaluation of the adequacy of her epidural analgesia using the following scale:

0 = no relief
1 = poor relief
2 = fair relief
3 = good relief
4 = very good relief
5 = excellent relief

After the study was completed, the code was broken and the patients sorted into four groups on the basis of the study drug/dose administered. The pain score measurements were rounded to the nearest 0.5 cm for analysis. The visual analogue scale (VAS) provided a continuous-valued numeric measure of pain with values from 0 to 10. However, pain assessment was necessarily subjective

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TABLE III   Subject pain score values, median (1st, 3rd quartile)

| Time min/hr | Subject group | | | |
| | Morphine 5 mg | Butorphanol | | |
		1 mg	2 mg	4 mg
Baseline	6(5,9)	5(4,7)	6(5,7.5)	7(5,9)
15	4(2,8)	2(0,4)	1(0,3)	1(0,2)
30	2.5(1,6.5)	0(0,2)	0(0,1)	0(0,1)
45	2(0,6)	0(0,1)	0(0,1.5)	0(0,1)
60	3(0,5)	0(0,0.5)	0(0,1)	0(0,1)
90	0(0,2)	0(0,1.75)	0(0,1)	0(0,1)
2	0(0,2)	1(0,5)	0(0,5)	1(0,4)
2.5	0(0,2)	1.5(0,4)	0(0,2)	0(0,2)
3	0(0,2)	3(0.5,4.5)	1(0,2)	0(0,1)
4	0(0,1)	3.5(0,7)*	2(0,5.5)*	1.5(0,4)
6	0(0,0.5)	6(3,6)*	0.5(0,5)*	5(2,9)
8	0(0,0)	0(0,3)†	5(0,10)*	3.5(1,7.5)†
12	0(0,1)	‡	‡	5.5(1,10)†
16	0(0,0)	‡	‡	5.5(1,10)†
24	0(0,1)	‡	‡	10(10,10)†

*Between five and ten subjects.
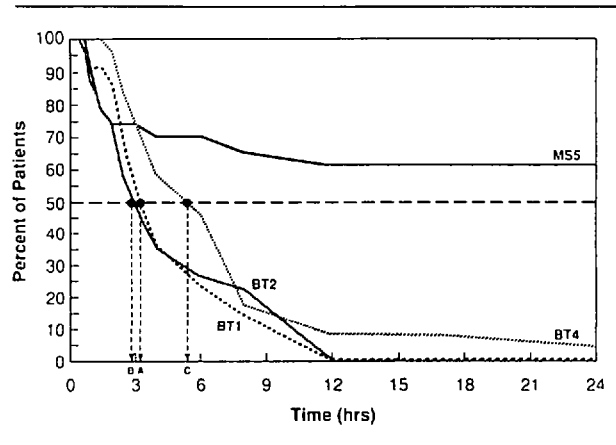†Less than five subjects.
‡No subjects.

FIGURE   Attrition profiles for the subjects. Median time (50 per cent of patients) in the study was >24 hr for morphine, and 3(A), 2.5(B) and 4(C) hr, respectively for butorphanol, 1, 2 or 4 mg. MS5 = morphine, 5 mg; BT1 = butorphanol, 1 mg; BT2 = butorphanol, 2 mg; BT4 = butorphanol, 4 mg.

As shown in Table III, the median baseline pain score differences among patients who received morphine and those who received each dose of butorphanol were not statistically significantly different. The median pain scores were statistically different in the four treatment groups at 15, 30, 45 and 60 min ($P < 0.05$). Although the scores were similar for the three butorphanol dosages these were consistently lower than those for morphine. At 90 min and two hours, the pain scores for butorphanol and morphine were almost equal. As shown in the Figure, the number of patients requesting supplemental medication, and dropping out of the study, increased progressively beyond 45 min in both the butorphanol- and morphine-

treated patients. The attrition profiles for butorphanol were different from morphine ($P < 0.01$, Kruskal-Wallis). Further, the Figure illustrates that the median time in the study was: >24 (1.5, >24) hr for morphine; and 3(2.0, 4.5), 2.5 (1.5, 6.0) and 4.0 (2.6, 6.0) hr, respectively for butorphanol, 1, 2 or 4 mg. Comparison of the pain score profiles over time (multivariate analysis of variance with repeated measures), suggested that the treatments were statistically nonparallel, i.e., that there was a significant treatment-time interaction ($P = 0.001$). Because of the potential bias introduced by the drop-out rate, statistical comparisons of the differences in pain scores beyond two hours were not performed.

The calculated median percentage pain relief values by treatment and time are shown in Table IV. Each dose of butorphanol produced greater pain relief than morphine at 15, 30, 45 and 60 min ($P < 0.05$). At 90 min and two

TABLE IV   Calculated percent pain relief, ([baseline – treatment]/[baseline]), median (1st, 3rd quartiles)

| Time, min | Subject group | | | | |
| | Morphine 5 mg | Butorphanol | | | |
		1 mg	1 mg	4 mg	P-value*
15	25.0(−14.3,75.0)	60.7(21.5,100.0)	80.0(40.0,100.0)	88.9(64.4,100.0)	<0.001
30	58.3(11.1,83.3)	100.0(68.6,100.0)	100.0(80.0,100.0)	100.0(80.8,100.0)	<0.01
45	71.4(11.1,100.0)	100.0(74.1,100.0)	100.0(61.9,100.0)	100.0(87.8,100.0)	<0.05
60	66.7(29.2,100.0)	100.0(90.6,100.0)	100.0(76.2,100.0)	100.0(84.4,100.0)	<0.05
90	100.0(75.0,100.0)	100.0(55.0,100.0)	100.0(76.7,100.0)	100.0(78.3,100.0)	NS
120	100.0(70.7,100.0)	75.0(11.1,100.0)	100.0(8.3,100.0)	88.9(50.0,100.0)	NS

*Kruskal-Wallis.

TABLE V   Heart rate (HR) and calculated mean blood pressure (BP) values, median (1st, 3rd quartiles), HR, (bpm⁻¹) is the upper number, and BP (mmHg) the lower number in each pair at each time

Time, min·hr⁻¹	Morphine 5 mg	Butorphanol 1 mg	2 mg	4 mg	P-value¶
Baseline	94.0(82.0,101.0) 93.3(87.3,101.7)	82.0(73.5,94.0) 92.3(82.9,101.4)	84.0(78.0,100.0) 86.7(76.7,94.7)	79.5(70.5,96.0) 85.5(80.0,93.5)	0.1 0.0223
30	94.0(81.0,105.0) 95.0(83.3,103.3)	87.0(71.8,101.2) 89.7(80.6,98.4)	82.0(77.0,90.0) 84.0(79.3,89.3)	88.0(78.0,102.0) 84.7(76.0.88.7)	0.2 0.0033
60	94.0(87.5,101.5) 92.7(86.7,100.3)	83.0(74.0,103.0) 89.7(78.0,95.7)	84.0(75.0,95.0) 81.7(77.4,85.8)	85.0(73.5,96.8) 83.3(78.5,89.6)	0.3 0.0014
90	93.0(87.0,107.0) 95.2(87.6,97.4)	82.5(69.0,104.0) 86.7(79.5,95.8)	81.0(76.8,94.5) 82.2(78.4,88.0)	91.0(75.2,98.0) 83.2(76.8,89.3)	0.2 0.0148
2	93.0(81.5,105.0) 90.7(87.8,95.7)	80.5(71.0,100.5) 84.3(77.8,94.5)	80.0(78.0,91.2) 84.8(80.9,88.8)	84.0(74.0,96.0) 84.3(77.3,89.7)	0.2 0.07
2.5	90.0(83.5,102.5) 92.3(82.7,95.3)	72.0(67.0,102.0) 85.7(77.3,93.3)	80.0(70.0,89.5) 85.3(79.8,88.0)	85.0(75.2,100.2) 85.3(79.5,92.5)	0.1 0.4
3	94.0(84.0,106.5) 86.3(78.8,96.5)	75.0(67.0,100.5) 88.7(78.7,94.3)	75.5(68.8,80.5) 82.5(80.8,89.5)	83.0(71.8,93.2) 89.0(83.3,92.0)	‖ ‖
4	88.5(81.2,115.2) 87.7(78.7,96.8)	64.5(61.2,96.5)* 85.2(77.8,97.5)*	73.0(63.8,82.0)* 84.2(79.2,85.8)*	83.0(73.2,89.0) 86.2(84.2,91.1)	‖ ‖
6	91.0(85.5,104.2) 89.2(83.7,95.3)	68.0(61.5,102.0)* 87.3(81.3,103.8)*	72.0(65.5,86.0)* 82.0(79.8,93.3)*	83.5(77.2,91.8) 90.3(87.6,92,8)	‖ ‖
8	91.0(84.0,110.0) 88.7(82.3,94.0)	73.0(68.0,100.0)† 95.7(90.7,100.0)†	74.0(68.0,87.5)† 91.3(78.7,98.0)†	91.0(85.5,95.0)† 88.3(84.7,100.5)†	‖ ‖
12	95.0(77.5,104.2) 90.5(81.6,92.9)	‡ ‡	‡ ‡	98.0(98.0,98.0)§ 96.7(96.7,96.7)§	‖ ‖
16	86.0(79.5,101.0) 93.3(88.7,97.3)	‡ ‡	‡ ‡	88.0(88.0,88.0)§ 97.3(97.3,97.3)§	‖ ‖
24	88.0(86.0,96.0) 90.0(85.8.97.5)	‡ ‡	‡ ‡	90.0(90.0,90.0) 94.0(94.0,94.0)§	‖ ‖

*Between five and ten subjects.
†Less than five subjects.
‡No subjects.
§One subject.
¶Analysis not performed due to possible bias from attrition.

hours each dose of butorphanol and morphine produced similar pain relief. To test whether the pain relief profiles over time were similar, a multivariate analysis of variance with repeated measures (BMDP5V) was performed. This analysis suggested that the profiles were statistically nonparallel (i.e., there was a treatment-time interaction; $P < 0.05$). Unfortunately, because of the very heavy negative skew in the data, none of the simple transformations (log, antilog, square root, inverse) yield anything close to approximately normal distributions. Thus, the results of this analysis which assumes normally distributed data are suspect. The authors are unaware of a satisfactory solution to this dilemma. The results of the analysis agree with visual inspection of the data, i.e., the morphine profile is clearly different from the butorphanol

profiles. The comparisons at each time point were carried out using the rank-based, non-parametric Kruskal-Wallis test which is not affected by the heavy skew.

The heart rate and blood pressure changes by treatment and time are shown in Table V. These profiles were compared over time using a multivariate analysis of variance with repeated measures (BMDP5V). The heart rate analysis indicated that the profiles were not significantly different (i.e., the treatment-time interaction was not significant, treatment-effect was not significant, and the time-effect was not significant). The blood pressure analysis indicates that the mean blood pressure trends were parallel (i.e., the treatment-time interaction was not significant, that there was a time-effect, $P < 0.001$, and a treatment-effect, $P < 0.001$). However, in each instance

the profiles may have been biased by attrition of patients from the study beyond 2.5 hr.

None of the patients experienced a decrease in respiratory rate below 12 breaths $\cdot$ min^{-1}, nausea, or vomiting. Although most patients readily drifted off to sleep at some time during the study, they were easily arousable. One patient (1.4 per cent) who received butorphanol developed pruritus compared with ten patients (43 per cent) who had received morphine ($P < 0.0001$). The presence of urinary retention was not evaluated since indwelling urinary catheters were used routinely for 24 hr postoperatively.

The median global pain assessment of the epidural analgesia following morphine was 4 (2, 5), compared with 3 (2, 4), 3 (2, 4) and 4 (3, 5), respectively following butorphanol 1, 2 or 4 mg. These differences were not statistically significant.

Discussion

The results of the present study demonstrate that epidural butorphanol or morphine provide effective postoperative analgesia following Caesarean section. The mean median pain scores 15, 30, 45 and 60 min following each dose of butorphanol were significantly lower than the corresponding values in the patients who received morphine. Thus the time to onset of epidural analgesia following butorphanol was more rapid than following morphine. Beyond 45 min after epidural administration of either drug, there was a progressive increase in the number of patients who requested supplemental medication. However, it may be of practical clinical interest that 14, 22 and 17 per cent of patients treated with butorphanol 1, 2 or 4 mg respectively, had not requested supplemental medication at eight hours, and that one in the latter group had adequate analgesia for 24 hr. In contrast, 65 per cent of the morphine patients had not been remedicated at eight hours and 61 per cent had adequate analgesia for 24 hr.

Pruritus occurred in only 1.4 per cent of the butorphanol patients compared with 43 per cent of the morphine patients. Importantly, pruritus following either drug responded promptly to either intravenous diphenhydramine or naloxone. The global assessments of the adequacy of epidural analgesia following butorphanol were essentially indistinguishable from those following morphine.

Abboud *et al.*[15] evaluated the respiratory effects of butorphanol using the ventilatory responses to progressive hypercapni. A decrease in the central sensitivity to CO_2 was observed as early as 1.5 hr after administration and lasted between 6–12 hr. Morphine produced persistent respiratory depression of 24 hr duration. In a recent letter, Lippman and Mok quoted unpublished data that 4 mg of epidural butorphanol produced elevations in $PaCO_2$

although clinically significant respiratory depression, i.e., a respiratory rate less than 10 breaths $\cdot$ min^{-1}, was not observed.[20] Since neither CO_2 responses nor $PaCO_2$ was measured in our patients, we can neither support nor refute these observations.

An acute abstinence syndrome has been reported following the epidural injection of butorphanol after Caesarean delivery.[21] This case report suggests that it is advisable to avoid the use of butorphanol in patients with a history of substance abuse.

The present data support the conclusion that epidural butorphanol is safe and effective in providing postoperative analgesia. Importantly, the calculated pain relief scores following each dose of butorphanol were significantly lower than morphine 15, 30 and 45 min following administration. The more rapid onset of analgesia following epidural butorphanol suggests that the drug may be particularly useful in clinical situations where: (1) a prompt onset and/or limited duration of analgesic action may be indicated, and (2) with epidural patient-controlled analgesia (PCA). Further, the present results suggest that a combination of epidural butorphanol and morphine might provide a more prompt onset and more stable level of analgesia for 24 hr or longer. However, to our knowledge, the use of such a combination has not been reported. Although none of the patients in the present study developed a respiratory rate below 12 breaths $\cdot$ min^{-1}, we concur with others[16] that observation for clinical respiratory depression is indicated during the period of analgesia following butorphanol as it is with other epidural opioids.

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