Original Article

Postoperative analgesia with epidural opioids after cesarean section: Comparison of sufentanil, morphine and sufentanil-morphine combination

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Abstract

Background: Epidural analgesia with opioid provides good control of postoperative pain in cesarean section, thereby improving the mother's ability to mobilize and interact with her newborn infant.
Aim: The aim of this study is to evaluate and compare the analgesic actions and side effects of epidural analgesia with sufentanil, morphine or combination of the two after cesarean section.
Materials and Methods: 60 women undergoing elective cesarean section were allocated into three groups of 20 each in a randomized blinded fashion. Epidural analgesia was administered with sufentanil 50 mcg in Group S; morphine 4 mg in Group M; and, a combination of sufentanil 25 mcg and morphine 2 mg was used in Group SM. Analgesic efficacy in terms of onset of action and duration of analgesia was assessed by using the Visual Analog Scale (0 to 10 cm) for 24 hours. Number of opioid doses needed in 24 hours was noted. Side effects like respiratory depression /excessive sedation, pruritus and nausea were recorded.
Results: Onset of action were at 7.6 ± 1.5 minutes in group S, 67.6 ± 1.5 minutes in group M and 12.2 ± 2.6 minutes in group SM. Duration of analgesia was longer in group M 17.5 ± 1.9 hours and SM 13.8 ± 1.6 hours than in group S 5.2 ± 1.2 hours. More doses of analgesia were required in group S compared to group M and SM. Side effects were comparable in the three groups.
Conclusion: Epidural administration of a combination of sufentanil and morphine offered the advantage of faster onset of action and longer duration of analgesia as compared to the two drugs administered alone.

Key words: Cesarean section, epidural, postoperative pain

Introduction

Neuraxial opioids provide superior postoperative pain relief compared to intravenous (IV) analgesia.[1,2] Epidural administration of opioids by continuous infusion or intermittent boluses via a catheter is being used increasingly for analgesia after cesarean section. Morphine remains the reference substance amongst the agents used in this situation.[1-4] It shifts the pain experienced by patient after cesarean delivery from the 1st postoperative day to the 2nd postoperative day[2] with maximum intensity of pain observed at around 36 hours post-cesarean delivery.[1,4] However, the major drawbacks of morphine are its hydrophilic nature, and its propensity to remain sequestered in cerebrospinal fluid (CSF).[5] Its delayed onset of analgesic effect[6,7] and late onset respiratory depression limits its widespread routine use.[8] In contrast, sufentanil is a lipid soluble drug with high receptor affinity and intense analgesia of rapid onset,[9] its only limitation being short duration of analgesia,[10] which necessitates continuous infusion.[11]

Considering the properties of hydrophilic and lipophilic opioids, we hypothesized that the combination of morphine and sufentanil would improve the overall quality of epidural analgesia, overcoming the limitation of each drug when used alone. We designed a study to compare the efficacy and safety of postoperative analgesia provided by a mixture of sufentanil-morphine with extradural injection of each drug used alone after cesarean section.

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Materials and Methods

60 American Society of Anesthesiologists (ASA) I-II patients aged between 21 - 35 years scheduled for elective lower segment cesarean section were enrolled in a prospective randomized double blind study after approval by the ethics committee. Patients were familiarized with visual analog scale (VAS), and their informed written consent obtained. Patients with a history of alcohol or opioid abuse, severe pregnancy induced hypertension, neurological disorder, coagulopathy, history of allergy to study drug or local anesthetics were excluded from the study. No anesthetic medication was administered to the parturient during the study, other than the two opioids investigated and local anesthetics by epidural route. Preoperatively, all the patients were hydrated with lactated Ringer's solution 10 ml/kg. An epidural catheter was introduced through the L2-3 or L3-4 interspace and advanced 5 cm cephalad. A T4 sensory level to pinprick was achieved using mixture of equal volumes of 0.5% bupivacaine and 2% lignocaine, and injected in incremental doses into the extradural space. The urinary bladder was catheterized. No fluid bolus was administered; however, ephedrine 15 mg was administered intravenously (IV) when there was a decrease in mean arterial pressure (> 25% of baseline).

After surgery, the patient was transferred to the post anesthesia care unit (PACU). She was asked to indicate her level of pain intensity on a 10 cm VAS anchored with 0 representing "no pain" and 10 cm as "worst pain". Baseline vital parameters like heart rate (HR), noninvasive blood pressure (NIBP), respiratory rate (RR) and oxygen saturation (SpO_2) were noted. On the first request for pain relief by the patient (VAS ≥3), an anesthetist, blinded to the drug, administered a 10 ml epidural bolus containing either 50 mcg sufentanil (Group S) or 4 mg morphine sulfate (Group M) or 25 mcg sufentanil plus 2 mg morphine sulfate (Group SM) as per the group allocated. These study solutions were prepared and delivered in unlabeled syringes by another anesthetist who took no further part in the study. After the extradural injection of opioid, the vitals, pain intensity by VAS and level of sedation were recorded initially every 5 minutes for 1 hour, and every 2 hourly till 24 hours. Side effects such as nausea, vomiting, itching, sedation or drowsiness and respiratory depression were recorded. Patients having pain after 20 minutes of receiving study drug were given a bolus of fentanyl 50 mcg IV as a rescue analgesic. When patient again complained of pain (VAS ≥ 3) the same drug, in the same dose, was repeated. The same data were collected thereafter.

The total number of doses administered in 24 hours was noted. Serial VAS was estimated to determine the following: (a) Onset of analgesia constituted the time until a reduction in VAS < 1 on two consecutive evaluations (b) Duration of analgesia was taken as time interval between onset of analgesia to VAS >3. (c) The level of sedation was assessed using a 5 point ordinal scale where 0 = alert; 1 = drowsy; 2 = frequently drowsy; 3 = very drowsy and disoriented; and 4 = stuporous and difficult to arouse.[12] Side effects like respiratory depression (RR < 10/minute), pruritus or nausea and vomiting were recorded. Severity of pruritus was graded as absent; mild – restricted to one area, not troubling the patient and reported only after prompting; moderate – affecting a large area, not disturbing the patient and not requiring treatment; severe – generalized, often disturbing the patient and needing treatment.[13] Side-effects were treated with promethazine 25 mg IV (pruritus), ondansetron 8 mg IV (nausea and vomiting) or naloxone 0.2 mg IV (respiratory depression). After 24 hours, the epidural catheter was removed and patient was sent to the ward.

All patients recruited were included for statistical analysis. Statistical analysis was done by using the Statistical Package for Social Sciences (SPSS) version 12 software. For calculating sample size of the study, standard deviation for VAS reduction was taken as 1.7 based on an earlier study[12] and a reduction of two points in the mean VAS score (50% of the baseline value in the study), for 0.05 level of significance, the calculated sample size was around 13 patients per group. Demographic variables and adverse effects within the three treatment groups were compared simultaneously via analysis of variance (continuous variable) and the chi square test (categorical variables). Baseline pain intensity was compared via one –way analysis of variance. P value ≤ 0.05 was considered to be statistically significant.

Results

All the 60 enrolled patients completed the study were without any significant complications [Figure 1]. Surgical anesthesia using epidural was acceptable to all patients. There were no significant differences among the three treatment groups with regard to patients' demographics [Table 1]. Time to the onset of pain relief [Figure 2] was faster in the sufentanil and sufentanil-morphine groups (7.6 ± 1.5 minutes and 12.2 ± 2.6 minutes respectively), compared to morphine group (67.6 ± 1.5 minutes) which was statistically significant (P< 0.0001). Figure 3 illustrates the VAS difference from 60 minutes after extradural drug injection to a 24 hour of study period. There was no significant difference in VAS between the patients in group M and group SM, whereas in group S patients, the VAS was less initially, and became significantly greater (between 6, 11, 16 and 22 hours) than the two other groups thereafter.

Analgesia lasted longer in group M and SM, respectively, (17.5 ± 1.9 and 13.8 ± 1.6 hours) than group S (5.2 ±

1.2 hours), which was statistically significant ($P < 0.0001$) [Table 2]. A total of 3 or 4 additional doses of the same drug were required in group S compared to only 1 additional dose required in group M and SM to keep VAS < 3 ($P < 0.0001$) [Figure 4]. Total drug requirement in group S was sufentanil 150 - 200 mcg; in group SM sufentanil 50 mcg and morphine 4 mg; and in group M was morphine 8 mg. Vital parameters did not change significantly in any group during the whole study; only one patient had respiratory rate (9/minute) at 5 hours in group M which did not require any treatment. 30% of the patients in group M had mild to moderate pruritus compared to 15% in group S and 10% in group SM. Sedation score ≤ 1 was noted in all the three groups; however, percentage of patients having sedation was higher in group S (15%) and M

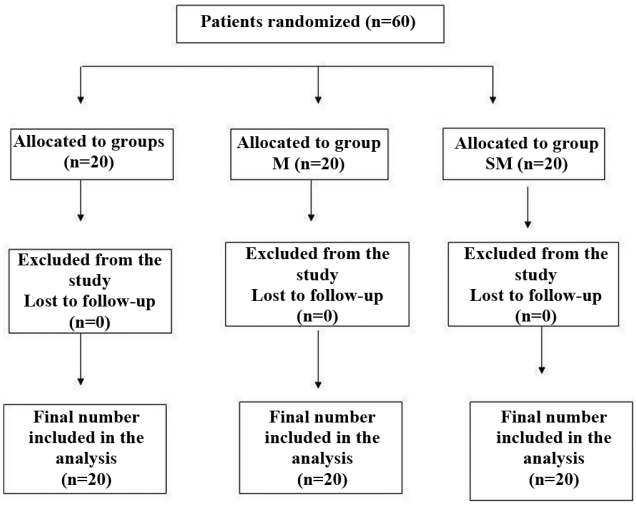

Figure 1: Consort chart

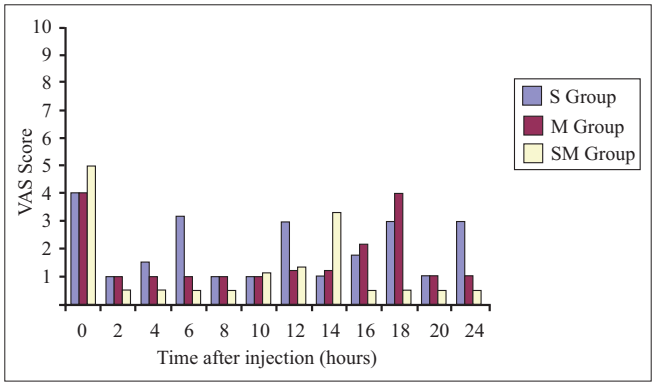

Figure 3: Duration of Analgesia: Visual Analog Score at 2 hours interval in three groups during 24 hours of the study period. Significant difference (*P < 0.0001) was seen in group S (sufentanil 50 mcg) as compared to groups SM (a combination of sufentanil 25 mcg and morphine 2 mg) and M (morphine 4 mg)

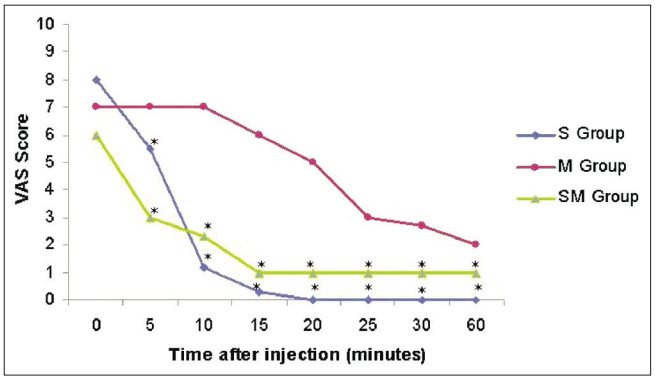

Figure 2: Onset of Analgesia: Visual Analog Score during 60 minutes after first dose of study drugs. Significant difference in onset time (*P < 0.0001) was seen in groups S (sufentanil 50 mcg) and SM (a combination of sufentanil 25 mcg and morphine 2 mg) as compared to group M (morphine 4 mg)

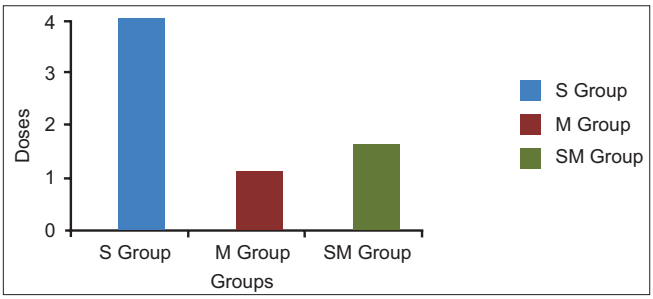

Figure 4: No of total doses in 24 hours: Total number of doses required in 24 hours in each group. Significant difference (*P < 0.0001) was seen in in group S (sufentanil 50 mcg) as compared with groups M (morphine 4 mg) and SM (a combination of sufentanil 25 mcg and morphine 2 mg)

Table 1: Demographic data (mean± Standard Deviation) of the patients included in the study

Data mean ± SD	Group S n = 20	Group M n = 20	Group SM n = 20	P value
Age (years)	26.9 ± 3.8	26.0 ± 4.6	28 ± 3.8	0.927
Weight (kg)	66 ± 6.2	63 ± 5.7	61 ± 5.5	0.081
Height (cm)	158 ± 3	156 ± 1.9	157 ± 4.2	0.053

No statistically significant difference between groups. Where, SD = Standard Deviation; Group S = Patients administered with sufentanil 50 mcg; Group M = Patients administered with morphine 4 mg; Group SM = a combination of sufentanil 25 mcg and morphine 2 mg.

Table 2: Time to onset and duration of analgesia in the patients in the study

Analgesia	Group S (sufentanil 50 μg)	Group M (morphine 4mg)	Group SM (combination)	P value
Onset (minutes)	7.6 ± 1.5	67.6 ± 1.5	12.2 ± 2.6	< 0.0001
Duration (hours)	5.2 ± 1.2	17.5 ± 1.9	13.8 ± 1.6	< 0.0001

Where, Group S = Patients administered with sufentanil 50 mcg; Group M = Patients administered with morphine 4 mg; Group SM = a combination of sufentanil 25 mcg and morphine 2 mg.

Table 3: Incidence of side effects in the patients in the study

Parameter	Group S (sufentanil 50 μg) n (20) (%)	Group M (morphine 4 mg) n (20) (%)	Group SM (sufentanil 25 μg + morphine 2 mg) n (20) (%)	*P* value
Sedation score ≤ 1	3 (15)	4 (20)	2 (10)	0.676
Respiratory depression	0 (0)	1 (5)	0 (0)	0.362
Nausea	3 (15)	6 (30)	2 (10)	0.235
Vomiting	2 (10)	4 (20)	1 (5)	0.322
Pruritus	3 (15)	6 (30)	2 (10)	0.235

Where, Group S = Patients administered with sufentanil 50 mcg; Group M = Patients administered with morphine 4 mg; Group SM = a combination of sufentanil 25 mcg and morphine 2 mg.

(20%), as compared to group SM (10%) without any statistical significance. Incidence of nausea and vomiting was higher in group M; however, was not statistically significant. Overall, the incidence of side effects was lower in the combination group [Table 3] as compared to use of each drug alone, and they were mild to moderate in nature not requiring any treatment.

Discussion

This study conducted specifically for postoperative pain relief in cesarean section suggests that patients who received epidural bolus injections of sufentanil, morphine, or a combination of sufentanil plus morphine achieved effective pain relief; however, significant differences were observed with respect to onset and duration of analgesia between the three groups. This can be attributed to differences in physicochemical, pharmacokinetic and pharmacodynamic characteristics of both the drugs. Sufentanil, a highly lipophilic opioid has a high affinity for spinal cord mu opioid receptors.[14] This results in a rapid and highly effective pain relief which was advantageous in the study, as patients experienced good pain relief before their local anesthetic level wore off. The disadvantage is its short duration (3-4 hours) and repeated boluses are required to achieve adequate pain relief,[15] unless continuous infusion is used. In contrast, onset of effective analgesia with morphine alone took 80-90 minutes; however, was associated with longer duration of analgesia (18 hours) due to hydrophilicity and its property to remain sequestrated in cerebro-spinal fluid.[16] Combining the two drugs provided rapid onset of action with identical analgesic efficacy like morphine alone, with mean duration of effective analgesia of 22.7 ±1.6 hours.[17] Onset of analgesia with epidural sufentanil is four times faster than morphine, however the analgesia of morphine lasts for 18 – 23 hours.[15]

2 to 5 mg of single epidural bolus dose of morphine, irrespective of bodyweight of the patients, are commonly used for postoperative analgesia after cesarean section.[3,18] A retrospective review of the use of epidural morphine found that 3 mg is an adequate dose for postoperative analgesia.[19] A study with three doses of epidural morphine (2, 5, and 7.5 mg) unfortunately focused only on the duration of analgesia.[18] A study comparing the effectiveness and duration of analgesia of epidural morphine 4 mg and 5 mg concluded that though 5 mg provided adequate and longer duration of analgesia, it was associated with a higher frequency of pruritus and vomiting.[20] Palmer *et al.* in a dose response study found that quality of analgesia increases as the dose of epidural morphine is increased up to 3.75 mg; however, increasing the dose further to 5 mg did not improve analgesia.[21] We used 4 mg morphine as patients undergoing cesarean section are young and anxious, although the Indian population is more prone to morphine induced respiratory depression.[22] In the combination group, at least 2 mg morphine was needed to keep the patient pain free for longer duration.

It is not clear whether combination of lipophilic opioid with small amount of hydrophilic opioid provides effective and long duration of analgesia due to sequential or additive action. One study has indicated sequential effect,[12] whereas other studies using combination of sufentanil,[11] fentanyl[23] or alfentanil[24] with morphine observed rapid onset and same or longer duration of analgesia than larger doses of morphine alone. Cohen *et al.* have reported shortened analgesic duration and increased requirement of supplemental systemic opioids when patients were given the combination of epidural morphine and fentanyl compared to morphine alone.[25] We did not observe an additive effect on using a combination of the two drugs; however, they supplemented each other as it offered the benefit of immediate onset as compared to morphine alone, and lesser requirement of the total number of additional doses needed in 24 hours.

The incidence and severity of side-effects were not statistically significant between the three groups in present study; however, they were higher in the S and M group compared to the combination group which is in agreement with previous studies.[11,17,25] This seems to be related to 50% reduction in the dose of each opioid, thus reducing the incidence of side effects caused by excess of either drug used alone. Drowsiness has been reported with repeated epidural bolus or continuous infusion of sufentanil,[26] limiting its acceptability for routine use in obstetric patients, whereas repeated IV doses cause increased sleepiness, difficulty in breast feeding, breathing difficulties or limpness in neonates.

[27] We did not observe these side effects in the sufentanil group possibly because a 25 mcg dose was only administered, and our study was limited to 24 hours. Hemodynamic and respiratory variables were comparable in the three groups except one patient in morphine group who developed RR < 10/minute. Our study could not totally exclude respiratory depression as the number of patients in our study was insufficient to evaluate this worrisome complication. It is likely that the risk of respiratory depression was attenuated with this mode of combined opioid administration. Although we did not aim to compare cost of therapy, we found that the cost was lower in the morphine group (INR 12-15) compared to sufentanil alone (INR 225-300) and the combination group (INR 156).

Limitation of this study was that we evaluated fixed doses of epidural sufentanil and morphine alone or in combination. The use of different doses to extend the duration of pain relief with acceptable side effects needs to be evaluated, and a large study needs to be conducted to evaluate the occurrence of respiratory depression and sedation.

Conclusion

In conclusion, the combination of sufentanil and morphine administered epidurally, for post-cesarean section analgesia, offers the advantage of a more rapid onset as well as longer duration of analgesia, with fewer side effects, than the two drugs used alone.

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