

A COMPARATIVE STUDY BETWEEN INTRATHECAL MORPHINE AND INTRATHECAL BUPRENORPHINE FOR POST-OPERATIVE ANALGESIA FOLLOWING CAESARIAN SECTION UNDER SUB ARACHNOID BLOCKAnish M. Varkey¹**HOW TO CITE THIS ARTICLE:**

Anish M. Varkey. "A Comparative Study between Intrathecal Morphine and Intrathecal Buprenorphine for Post-Operative Analgesia following Caesarian Section under sub Arachnoid Block". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 39, May 14; Page: 6751-6762, DOI: 10.14260/jemds/2015/979.

ABSTRACT: BACKGROUND: Good pain relief following caesarian section is of great importance and intrathecal opioids provide good quality postoperative analgesia for longer duration. So the following study describes a comparative study between intrathecal morphine and intrathecal buprenorphine for postoperative pain relief following caesarian section (CS) under subarachnoid blockade. **AIMS:** The study was conducted to compare intrathecal morphine and buprenorphine for post of analgesia following CS, to achieve analgesia without sedation for better maternal child bondage and to popularize intrathecal opioids. **MATERIALS AND METHODS:** 60 patients posted for CS under SAB were randomly allocated into group A and group B of 30 each, the group A received morphine 0.1 mg and buprenorphine 0.03 mg was given for group B patients along with the local anaesthetic. Subjective assessment of post-operative analgesia was done by direct questioning of the patient and by a five point pain scores. Duration of analgesia was taken as the time interval between the time of injection of intrathecal opiate and the time at which the patient felt pain and requested for additional analgesics. Data's were analyzed using SPSS 16th version. **OBSERVATION AND RESULTS:** The mean duration of post-operative analgesia with intrathecal morphine was 24.19+4.8 hours and that with buprenorphine was only 11.7+3.28 hours. Over weight patients reported a lower mean duration of analgesia. None of the patients in the study showed any bradycardia, hypotension, desaturation or respiratory depression. Intrathecal opiates decreased the parenteral opiate requirements. The main side effects noticed were nausea in about 43% of patients in morphine group and 33% of patients in buprenorphine group. **CONCLUSIONS:** Intrathecal morphine 0.1 mg gives good post-operative analgesia of longer duration than buprenorphine 0.03mg. The quality of analgesia provided by intrathecal morphine was superior to intrathecal buprenorphine. There was no incidence of respiratory depression or sedation.

KEYWORDS: Caesarian section, Subarachnoid block, Intrathecal opioids, Postoperative analgesia.

INTRODUCTION: Surgical trauma is real and severe tissue damage and surgical pain is a universal phenomenon. Yet, paradoxically, after all the effort taken to make the intraoperative period pain free and stress free the patient is left to fend for himself in the post-operative period.

Post-operative pain is uniformly so grossly under treated due to a traditional, though irrational, fear of respiratory depression and also lack of understanding of the pharmacokinetics and dynamics of the opioid analgesics. In the answer to the pain the patient gets a bolus of intramuscular opioids, which takes some more time to produce effective analgesia. Once the patient is relieved of pain, she becomes drowsy goes to sleep during one of the most precious hours of her life, seeing the face of her baby, hugging and breast feeding the baby.

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In our present day of pain management she will not remember seeing the face of her baby and will be in deep slumber in those precious hours of mother hood. In between she will wake up with pain and it is difficult to guess as to what will be her feeling towards the lady who has given her so much of pain. Risk of thromboembolic disease, which is increased during pregnancy, may be further exacerbated by immobility related to pain during the puerperium. Pain may also impair the mother's ability to optimally care for her infant in the immediate postpartum period and may adversely affect early interactions between mother and infant. Pain and anxiety may also reduce the ability of a mother to breast feed effectively.¹

The answer to these problems is provision of post-operative pain relief. In accordance with Morgan (1982) who stressed that any technique of post-operative analgesia should meet the criteria viz -feasibility, effectiveness and safely. In this context intrathecal opiates used for pain is the doubt of safely. The safely perspective are, we are using the lowest recommended dosage which will becomes effective due to the increased pain threshold during pregnancy. Increased progesterone levels decrease the dose of analgesics needed and also, it has got a respiratory stimulant action² which hopefully will antagonize the possible respiratory depression. There may also be a possible preemptive analgesic effect. So it is decided to do a comparative study between intrathecal morphine and intrathecal buprenorphine for postoperative pain relief following caesarian section (CS) under subarachnoid blockade (SAB).

AIMS OF STUDY:

1. To compare effects of intrathecal morphine and intrathecal buprenorphine for post of analgesia following CS.
2. To achieve analgesia without sedation for better maternal child bondage.
3. To popularize intrathecal opioids.

MATERIALS AND METHODS: After Institutional Ethical Committee clearance, the study was conducted in 60 female patients who had undergone caesarian section under sub arachnoid blockade. Detailed history and thorough physical examination were conducted in all patients. Patients belonging to ASA I or II, age between 18-35years, weight 50-75, height 150-170 cm and gestational age >38wks were taken up for the study. Exclusion criteria were patient's refusal, contraindication for spinal anesthesia, allergy to opioid analgesics or local anesthetics, any medical condition resulting in ASA status more than II, already detected fetal anomalies, gross deformity of spine or prior lumbar spine surgery The procedure was explained to each patient and written informed consent was obtained. The 60 patients were randomly allocated into two groups of 30 each, group A and group B. The group A received intrathecal morphine and group B received intrathecal buprenorphine.

Intra venous line was secured and all were pre-medicated with ranitidine 50mg and metoclopramide 10mg IV half an hour before surgery. They were transported from the labour room in left lateral position. Compassionate verbal reassurance was given to alley patient's anxiety. Adequate pain relief was assured to all and a very few were scared of the procedures. All patients were preloaded with 1 liter of 0.9% NaCl solution over 15-20 minutes prior to SAB. Pre induction monitors include NIBP, ECG, and SPO₂. They were positioned in the right lateral position and under aseptic condition SAB was given using a 23G spinal needle at L3-L4 or L4-L5 interspace. 0.5% hyperbaric bupivacaine, 7.5-9 mg was the local anaesthetic used. Preservative free morphine 0.1 mg

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was given for the group A patients and buprenorphine 0.03 mg was given for group B patients along with the local anaesthetic.

After SAB the patients were positioned supine with a wedge under the right buttock to produce a left uterine tilt. Oxygen was administered using a face mask, level of analgesia after 5-7 minutes were around T4-T6. ECG, pulse rate, BP and oxygen saturation were monitored. BP was taken every minute till the delivery of the baby and a fall below 90 mmHg systolic or MBP <20% of baseline was treated with 6 mg of ephedrine IV boluses. Bradycardia; heart rate < 60beats/min was treated with IV atropine 0.6 mg bolus dose and repeated if needed. The average time for delivery of the baby after the subarachnoid block was 7 minutes. Neonatal APGAR scores were taken by the attending pediatrician. None of them had respiratory depression and none required resuscitation. Once the baby was delivered the wedge under the right buttock was taken off and oxytocin administered as per obstetrician's direction. No sedation was given. Oxygen inhalation was continued for some more time. Throughout the intra operative course the monitoring of BP continued every 5-15 minutes. The average duration of surgery was around 1 hour and no patient needed conversion to GA. After the procedure, all patients were monitored in a high dependency unit for 24 hours.

The postoperative advice given was; no sedation, foot end not to be raised, watch for respiratory depression, adequate hydration. Post operatively the patient was assessed for blood pressure, pulse rate, respiratory rate, SPO₂ and visual assessment of tidal volume every 30 minutes for first 12 hours and then every hour until 24 hours, subjective pain ratings at intervals of two hours, subjective sleep rating during the first post-operative night, patients general assessment of the operative course during the first 24 hours, maternal-child bondage, side effects such as pruritus, nausea, vomiting and special attention was given to the problem of respiratory depression and arterial blood gas analysis was planned in doubtful cases.

Subjective assessment of post-operative analgesia was done by direct questioning of the patient and by a five point pain scores:

(1) No pain. (2) Mild pain. (3) Moderate pain. (4) Severe pain. (5) Very severe pain.

Additional parental analgesics were given when the patients complained of pain. First NSAIDS like diclofenac was tried in, if the pain is not relieved, then additional doses of pethidine and phenergan were given. Duration of analgesia taken as the time interval between the time of injection of intrathecal opiate and the time at which the patient felt pain and requested for additional analgesics.

STATISTICAL ANALYSIS: Data's were analyzed using computer software, Statistical Package for Social Science (SPSS) 16th version. Data are expressed in its frequency and percentage. To elucidate the associations and comparisons between different parameters, Chi-Square test was used as a nonparametric test. Analysis of variance (One Way ANOVA) was performed as the parametric test to compare the different parameters with respect to different groups. For all statistical evaluations, a two tailed probability of value, 0.05 was considered as significant. Finally the results in the two groups were compared to draw the conclusion.

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OBSERVATION AND RESULTS:

Patient parameters	Group A Mean +D	Group B Mean +D
Age (yrs)	25+3.6	28+ 3.7
Height (cms)	154+4.2	157+4.5
Weight (Kg)	67+ 5.1	68+4.7

Table 1: Patient parameters in both groups

Types of patients	Group A		Group B	
	No. of Patients	% of total	No. of Patients	% of total
Previous CS	6	20	12	40
Foetal distress	9	30	9	30
CPD	8	26	4	13
Others	7	24	5	17
Total	30	100	30	100

Table 2: Types of patients in both groups

Duration in hours	Group A		Group B	
	No. of Patients	% of total	No. of Patients	% of total
32-36	1	3.3		
28-32	6	20		
24-28	10	33		
20-24	6	20		
16-20	6	20	3	10
12-16	1	3.3	13	43
8-12			9	30
4-8			17	17
Total	30	100	30	100

Table 3: The duration of analgesia in each group

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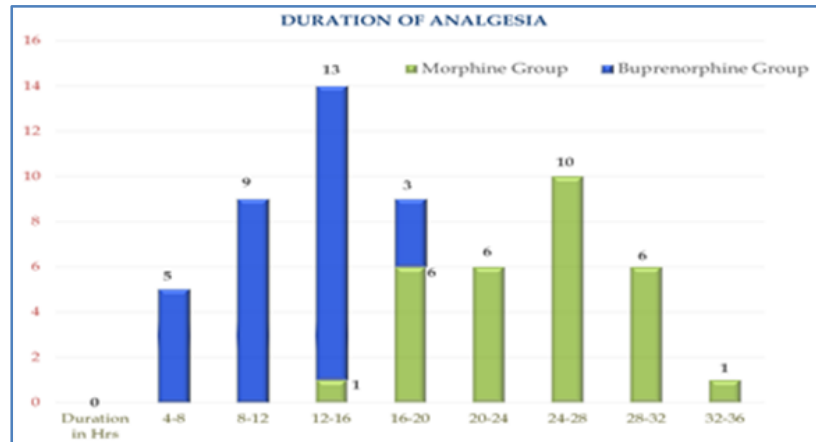


Fig. 1

PAIN SCORES:

Time after injection	Group A (Mean+SD)	Group B (Mean+SD)
3 hours	1+0	1+0
6 hours	1+0	2.13+0.36
12 hours	1+0	3.16+0.8
24 hours	3.36+0.6	4+0

Table 4: The pain scores in both groups over period of 24 hours

6 hours unpaired $t = 9.125$.
 $p < 0.001$ highly significant.

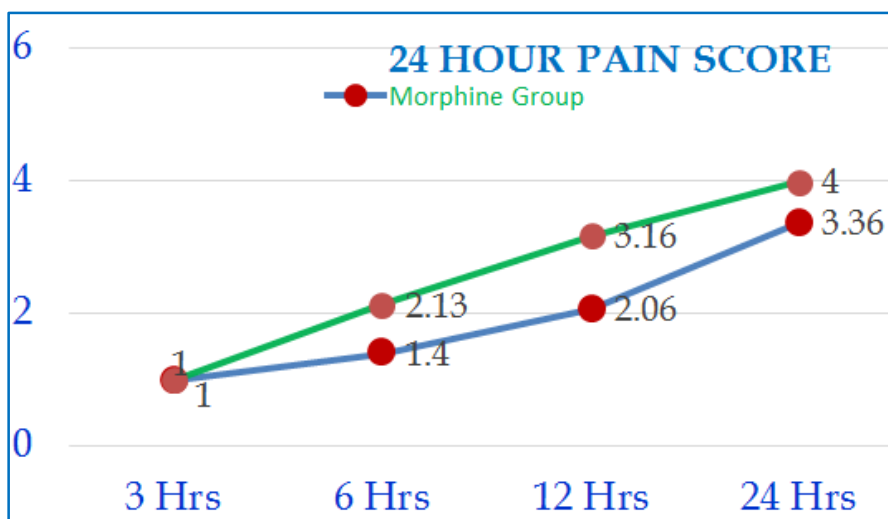


Fig. 2

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Morphine group showed duration of analgesia of about 24.19+4.8 hrs. About 33% of patients in morphine groups showed very good analgesia for 24-28 hrs. 20% showed analgesia upto 28-32 hrs. One patient showed analgesia for about 32 hrs. All the above patients did not require any parenteral opioids or NSAIDS during the first 24 hrs. Subsequently they were given oral diclofenac tablets and all of them were comfortable. 40% of patients showed good analgesia for 16-24 hrs and many of them complained of pain after this period and they were given IV diclofenac Sodium 75 mg and were comfortable for the first 24 hours and then could be managed with oral diclofenac and paracetamol. One patients showed analgesia upto 12 hours only and complained of severe pain after 12 hours. She was managed with IV pethidine 50 mg and IV promethazine 25 mg 6 hourly. Then she was managed with NSAIDS. She was an obese previous CS case.

Buprenorphine group showed duration of analgesia of about 11.7+3.28 hours only. In Buprenorphine group 43% showed analgesia of about 12-16 hours and they were given two shots of IV diclofenac 75 mg 6 hours apart and were comfortable during the first 24 hours. 10% of patients showed analgesia in about 16-20 hours and they were given a single shot of IV diclofenac. Both the above two groups could be managed with oral diclofenac and paracetamol thereafter. The rest of the buprenorphine group needed IV opiates- pethidine 50 mg and promethazine 25 mg was given as the first dose when they complained of pain and then 6th hourly for the first 24 hours.

Side Effects/ Complications	Group B		Group B	
	No. of patients	% of Total	No. of patients	% of Total
Nausea	13	43	10	33
Pruritus	4	13	1	3
Vomiting	3	10	2	6
Head ache	3	10	2	6
Respiratory depression	0	0	0	0
Sedation	0	0	0	0

Table 5: The side effects or complications observed were

The main side effects noticed were nausea in about 43% of patients in morphine group and 33% of patients in buprenorphine group. None of them complained of it but they reported it on direct questioning. Four patients in morphine group and one patient in buprenorphine group had itching which was mild and self-limiting, and often was not spontaneously reported by the patient. None of the patients required treatment for pruritus. Three other in the morphine group and two patients in the buprenorphine group also complained of head ache which responded to usual measures.

Three patients in the morphine group and two patients in the buprenorphine group complained of vomiting. They were given IV ondansetron 4mg and vomiting subsided. Incidence of urinary retention could not be assessed as all the patients in the study group were catheterized during the postoperative period. There were no cases of respiratory depression. One complaint from the side of the nursing staff was that patients were not sleeping though they were free of pain.

DISCUSSION: The identification of opiate receptors in the mesencephalic central gray matter of the brain and the substantia gelatinosa of the posterior horn cells of the spinal cord,³ has led to important research in the area of intrathecal and epidural analgesia with narcotics. A number of recent well

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defined and controlled investigations have confirmed that the analgesia produced by intrathecal opiates is different from and superior to that following parenteral administration. The attractive features of these techniques are that, it produces profound long lasting and segmental pain relief,³ which is not associated with sensory, sympathetic or motor blockade. This method of post-operative analgesia is particularly useful in those undergoing caesarian section because they can have good pain relief, at the same time, will be awake and can breast feed the baby.

This leads to good maternal – child bondage. A large variety of opioids such as morphine,^{4,5,6,7} meperidine,⁸ fentanyl,⁹ buprenorphine.^{10,11} etc., have been tried successfully. However, morphine has been the opioid used in over 80-90% epidural and intrathecal administration. The first clinical study testing intrathecal morphine in this context was published in 1979.¹² Lipophilicity of the drug appears to be an important factor related to the onset and duration of analgesia, as they have greater penetration and also greater affinity for the opiate receptors.¹³ Morphine, which is relatively less hydrophobic than other opioids, has a longer residence time in the cerebrospinal fluid and therefore may reach rostral sites over a longer period than other opioids.¹⁴ Consequently, there is a potential of achieving adequate and long-lasting analgesia with an intrathecal injection of morphine.¹⁵

Buprenorphine, because of its high lipid solubility, high affinity for opiate receptors,¹⁶ and prolonged duration of action seems to be suitable choice for intrathecal administration. Cellena D, Capoga G,¹⁷ and Sunil Dixit,¹⁸ described their experience with spinal buprenorphine for postoperative analgesia after caesarean section.

Hence buprenorphine which has a liposolubility five times to that of morphine is compared with morphine to assess its efficacy with regard to post-operative pain relief. The value of combining local anesthetic and opioids for postoperative pain control has been well established. The combination allows for a reduction in doses of both classes of drugs, thus lessening the likelihood of side effects attributable to each.¹⁹

This study was conducted in 60 female patients who had undergone CS. Out of these 60, patients 30 patients were given 0.1mg of morphine mixed with 0.5% bupivacaine 7.5mg-9mg and 30 patients were given 0.03mg of buprenorphine mixed with 7.5mg-9mg of 0.5% Bupivacaine. The quality and duration of post-operative analgesia and the side effects were noted.

Selection of Dose: Buprenorphine 0.3mg is equivalent to 10mg morphine in analgesia effect. Buprenorphine is 30 times more potent than morphine. It is said that the dose of drug used to produce analgesia through intrathecal route should be such that it will be insufficient when given by parenteral route. And also since it is being used in this study to provide post-operative analgesia for CS patients the fetal blood level attained should be negligible. So only the lowest recommended doses are used. The recommended ratio between clinically common intravenous single injection dose and epidural single injection doses are 10:1 for meperidine, 2-3:1 for morphine and 1:1 for buprenorphine, fentanyl and lofentanyl. A dose as low as 0.1 mg of intrathecal morphine gives excellent analgesia with minimal or no side effects and that subcutaneous morphine is associated with marked depression of the ventilatory variables.²⁰ Hence the doses selected for intrathecal administration were 0.1 mg of morphine, since it is the lowest recommended dose for intrathecal administration,²¹ and 0.03 mg of buprenorphine keeping in mind the above dose ratios.

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Time of Administration of the Intrathecal Opiate: The opiate either buprenorphine or morphine was administered along with local anaesthetic solution, that is 0.5% hyperbaric bupivacaine. So there is only a single injection and the patient is comfortable as well as it is cost effective.

Duration of Analgesia: Post-operative pain was rated subjectively on a scale with five grades. Such a pain scale is a useful standard method for measuring the effects of analgesics. In this study, morphine appears to have a longer duration of analgesia, compared with buprenorphine. The mean duration of post-operative analgesia with intrathecal morphine was 24.19±4.8 hours and that with buprenorphine was only 11.7±3.28 hours. This difference in duration is statically significant. P value less than 0.001.

About 56% of patients i. e., 17 out of 30 in the morphine group had excellent post-operative analgesia and did not require any analgesia supplements in the first 24 hours. 40% of patients of morphine group showed analgesia upto 16-24 hours and they required IV diclofenac 75 mg single shot as the analgesic supplement during the first 24 hours. Only a single patient required narcotic analgesic and she was given 50mg pethidine and promethazine 25mg 2 shots 6 hours apart when she complained of pain after 12 hours of the subarachnoid block.

53% of the patients in the buprenorphine groups showed analgesia more than 12 hours and they were given IV diclofenac and were comfortable during the first 24 hours. The rest of the buprenorphine group needed IV opiates; 1-3 shots of pethidine and promethazine 6 hours apart.

Analgesia with morphine is more intense and more prolonged since morphine has strong receptor binding property and low lipophilicity. Being hydrophilic morphine penetrates the different diffusion barriers more slowly and retards diffusion away from the receptors to a much greater extent than in the case with lipophilic molecules. The two factors governing duration of analgesia are the rate of morphine removal from the receptor site and the magnitude of morphine concentration surrounding the receptor site. The main factor responsible for the long duration of analgesia of morphine appears to be the very high morphine concentration in the vicinity of the receptors²². Due to the superior penetrating ability into the nerve tissue; a lipophilic drug will disappear quickly from the neural tissue and CSF into the blood stream. This redistribution phenomenon is responsible for the inverse relationship between lipid solubility of the drug and duration of analgesia.

Side Effects: The adverse effects following intrathecal administration opiates is due to the rostral spread of the drugs.²³ The most feared of this adverse reaction is late respiratory depression, which may occur 6-12 hours after the injection of the drug. This rostral spread may be less likely to occur with highly lipid soluble drugs like buprenorphine as the drug molecules quickly get attached to the lipid components of the spinal cord, thereby limiting the amount of free drug in the CSF available for rostral diffusion.

However respiratory depression with intrathecal opiates can be minimized by administration the lowest effective dose of the drug and also by using more lipophilic drug. Clinical reports of delayed respiratory depression seemed to be associated with the intrathecal injection of morphine in doses >1.0 mg². In this study, the incidence of respiratory depression was zero. The factors favouring the low incidence of respiratory depression are:

1. Only the lowest possible dose of the drug is administered, which will become effective due to the increased pain threshold and decreased analgesic requirement seen in pregnancy, probably due to the action of progesterone.

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2. Progesterone itself may have respiratory stimulant action, and so it is used for sleep apnoea syndromes.
3. Foot end elevation is not used hopefully to prevent the possible ascent of intrathecal opiate.
4. Close monitoring for respiratory depression, continued for 24 hours after the spinal injection of opiate and naloxone was available for immediate reversal. Anesthesiologist was in the duty room and he visited the patients at hourly intervals.

The main side effect noticed in the study was nausea that was self-limiting and requires no treatment. Nausea was abated by keeping the patient still and slow movements during transfer.

In this study morphine was found to produce analgesia of longer duration than buprenorphine which was statistically highly significant (p value <0.001). Also morphine showed analgesia of a superior quality than buprenorphine as evidenced by the pain scoring at 6 hours after injection, which was also highly significant with a P value less than 0.001. The relatively poor performance of buprenorphine may due to lower dosage (0.03mg); a higher dosage might have given better results.

Since Wang reported the administration of intrathecal morphine for pain relief in 1979,²⁴ There have been several applications of this technique for relief of both chronic,²⁵ and acute pain,^{26,27,28} as well as for pain associated with labour.^{29,30,31} Intrathecal morphine has been employed for postoperative analgesia in a wide range of doses, from 0.5 mg in patients after inguinal herniorrhaphy,³² to 20 mg after laparotomy or thoracotomy³³. Mendieta Sánchez JM1, Fernández-Liesa JI,³⁴ reports, Combining 0.1 mg morphine and bupivacaine for spinal anesthesia during hip arthroplasty significantly decreased the consumption of intravenous morphine during the first 48 hours after surgery. No respiratory depression occurred and the only side effects were urinary retention and mild pruritus and drowsiness. Subarachnoid morphine has been used to provide obstetric analgesia for cardiac patients in a dose of 0.25mg. Jacobsohn E, Lee TW and colleagues studied the effects of low-dose intrathecal morphine (6 microg/kg) for cardiac surgery and found improved postoperative analgesia and pulmonary function and did not delay early extubation.³⁵ Findings in this study are consistent with studies done by Lip et al,³⁶ Capogns et al,³⁷ Cellona et. al.¹⁸

Clinical Observations Probably Important in this Study are:

1. Intrathecal opiates decreased the parenteral opiate requirements, only one patient in the morphine group demanded narcotic analgesia. A great proportion in the buprenorphine group 43% did not required opiates in the first 24 hrs. This can be attributed to the longer duration of higher quality analgesia provided by intrathecal opiates. Also there may be a “pre-emptive” analgesic action, since the opiates were administered prior to surgical incision.
2. Previous CS patients who had undergone conventional subarachnoid blockade followed by IV pethidine reported higher pain scores and shorter duration of analgesia. Many of them reported this technique of intrathecal opiates provided analgesia, but there was not that ‘well-being’ of the previous surgical and anaesthetic experience. This could probably be attributed to the euphoria provided by intravenous opiates, but not by intrathecal.
3. Over weight patients reported a lower mean duration of analgesia, probably there is something to do with the dose calculations.

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None of the patients in our study showed any fall in blood pressure or change in pulse rate. Though the aim was analgesia without sedation, there was a total lack of sedation and additional sedatives were not administered for fear of respiratory depression. Though pain free many patients demanded sedation but were not given

CONCLUSION: Intrathecal morphine 0.1 mg along with 0.5% bupivacaine 7.5-9mg for caesarian section under subarachnoid block gives good post-operative analgesia of longer duration than buprenorphine 0.03mg with 0.5% bupivacaine 7.5-9mg. The quality of analgesia provided by intrathecal morphine was superior to intrathecal buprenorphine. There was no incidence of respiratory depression or sedation.

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