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Original Research Article

Evaluation of the efficacy of 150 micrograms of intrathecal morphine with bupivacaine compared to 250 micrograms for postoperative analgesia following abdominal hysterectomy: a double blinded randomized control study

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ABSTRACT

Background: The synergistic action of local anesthetics and morphine is well known, morphine probably more superior for postoperative analgesia, when compared to other opioids. Preservative-free morphine is now available in India making intrathecal administration possible. The present randomized double blind study was designed to evaluate the effect of adding preservative free morphine to hyperbaric bupivacaine given intrathecally for abdominal hysterectomy.
Methods: Following approval by the institutional review board and institutional research grant committee, eighty patients presenting for elective abdominal hysterectomy were included in this randomized, double blind study. All drugs used for spinal anesthesia were autoclaved as per the departmental protocol. 3.5 ml of hyperbaric bupivacaine 0.5% [heavy] was given in both groups along with preservative free morphine according to study group.
Results: 27.5% (11/40) patients in group A, 17.5% (7/40) patients in group B received one dose of rescue analgesia (ketorolac 10 mg),during the 24 hours for pain relief while 29 patients is group A (72.5%) and 82.5% (33/40) patients in group B received 2 doses of rescue analgesia. 10% patients in Group A (4/40) and 10% patients in Group B (4/40) had a sedation score of 1 (drowsy and arousable).
Conclusions: The mean duration of analgesia in patients who received 250 µgms of intrathecal morphine was 18.725±1.38 hours while in patients who received 150 µgms it is 16.075±1.23 hours. We conclude that 250 µgms of preservative-free intrathecal morphine provides longer duration of analgesia when compared to 150 µgms morphine, with hardly any additional adverse effects.

Keywords: Intrathecal morphine, Bupivacaine, Abdominal hysterectomy

INTRODUCTION

Spinal anesthesia continues to be one of the commonest regional anesthetic techniques because of its rapid onset, safety and simplicity. Ignored until the late twentieth century as a substrate for analgesia, the spinal cord has now emerged as one if not the key target for pain control in clinical anesthesiology. More and more anesthesiologists now give drugs spinally to provide intraoperative anesthesia and post-operative analgesia in various surgical procedures.[1]

The use of neuraxial opioids has increased dramatically in recent years, augmenting the analgesia produced by local anesthetics by binding directly to opiate receptors. Animal and human studies have indicated that opioids

and local anesthetics administered spinally have a synergistic analgesic effect. The synergistic action of local anesthetics and morphine is well known, morphine probably more superior for post-operative analgesia, when compared to other opioids.[2]

Preservative-free morphine is now available in India making intrathecal administration possible. The present randomized double blind study was designed to evaluate the effect of adding preservative free morphine to hyperbaric bupivacaine given intrathecally for abdominal hysterectomy. In India, most of the abdominal hysterectomies are done under regional anesthesia. By adding morphine along with local anesthetic, the duration of analgesia can be increased with minimum side effects and this is also cost- effective.

METHODS

Following approval by the institutional review board and institutional research grant committee, eighty patients presenting for elective abdominal hysterectomy were included in this randomized, double blind study. A pilot study was initially conducted on 20 patients to obtain the sample size required for statistical estimation.

Inclusion criteria

Inclusion criteria were patients of ASA 1 and ASA 2 physical status, uterus <24 weeks size, patient willing to participate in the study and age 30-60 years.

Exclusion criteria

Exclusion criteria were patients of ASA 3 & ASA 4 physical status, large uterus >24 weeks size, age >60 years, known allergy to the study drug, morbid obesity, previous complicated abdominal surgeries, patient not willing for spinal anesthesia and study other contraindication for spinal anesthesia such as coagulopathy, systemic or local infection.

Preoperative preparation

All the patients were seen by the anesthetist on the day prior to surgery. The procedure was explained and informed consent obtained. The visual analogue scale (VAS) and post operative nausea and vomiting (PONV) score was explained to the patients. All patients received tablet ondansetron 8 mg orally along with benzodiazepine one hour prior to surgery as premedication.

Method of randomization

The patients were randomised to one of the 2 groups by a computer generated random assignment.

Method of allocation concealment

The investigator who was giving the drug was given a sealed envelope mentioning the group and method of preparation of the drug. After the drug was administered it was recorded as bupivacaine with study drug 1 or 2. The envelope and the allocation sheet were destroyed.

Blinding and masking

This is a double blind study as the participant and outcome assesors were blinded to treatment allocation.

Preparation of the drug

All the drug solutions were prepared by an anesthesiologist who was not involved with the administration of spinal anesthesia or with observation of the patients. All drugs used for spinal anesthesia were autoclaved as per the departmental protocol. 3.5 ml of hyperbaric bupivacaine 0.5% [heavy] was given in both groups along with preservative free morphine according to study group.

Procedure

In the operating room monitoring was established with pulse oximetry, ECG, non invasive blood pressure. After establishing intravenous (iv) access, patients were preloaded with 10 ml per kg of crystalloids. Under aseptic precautions, and patient in the lateral position, lumbar subarachnoid block was established and the study drug given the study group along with 3.5 ml of hyperbaric local anesthetic bupivacaine 0.5% using 25 gauge whitacre needle, following the intrathecal injection, patients was immediately placed supine Supplemental oxygen (4 litres /min) was administered to all patients using a Hudson's mask. The level of sensory blockade was noted. In case of hypotension following spinal anesthesia and systolic blood pressure of less than 100 mmHg or blood pressure less than 80% from the baseline, iv fluids was administered along with bolus of injection ephedrine 5 mgs boluses intravenously as required.

Assessment of the patient

The following variables were assessed and recorded in the operating room.

- Dermatomal sensory blockade to pin prick was evaluated.
- Extent of motor block was quantified.
- Side effects of intrathecal morphine such as nausea, vomiting, pruritus, arrythimias, shivering, bradycardia, respiratory depression were recorded.
- Hypotension following spinal anesthesia was recorded and treated.
- Nausea and vomiting if present was noted and were treated with intravenous ondansetron 4 mg.
- In the postoperative period, patients were monitored for the quality of pain relief and side effects such as nausea, vomiting, pruritus, sedation, respiratory

depression at 0, 1, 2, 4, 8, 12, 24 hours Pain was assessed using visual analogue scale [VAS] with '0' meaning "no pain" and 10 being the "worst pain imaginable".

Statistical methods

The data was analyzed using the software SPSS 16.0. The statistical significance was analyzed Chi-square test was used.

RESULTS

The results for the 80 patients allocated to the two groups were analysed. Group A received 3.5 ml of 0.5% hyperbaric bupivacaine with 250 mcg of morphine. Group B received 3.5 ml of 0.5% hyperbaric bupivacaine with 150 mcg of morphine.

20% of patients in Group A [8/40] and 17.5% of patients in Group B [7/40] had nausea; there is no statistical difference between Group A and Group B. The incidence of vomiting in group A is 2.5% (1/40) and 5% (2/40) in group 'B'. There is no statistically significant difference in the incidence of vomiting between the two groups.

The incidence of pruritus in Group A is 12.5% (5/40) and group B 7.5% (3/40). There is no statistically significant difference in the incidence of pruritus among the 2 groups.

Table1: Demography of the patients (n=40).

Parameters	Group A	Group B	P value
Age (years)	45.95±5.53	45.3±4.90	>0.05
Weight (kg)	55 ±5.41	54.7± 4.72	>0.05
Height (cm)	156.1±3.31	156.02±2.80	>0.05
Duration of surgery (min)	102.7±11.14	105.75±8.73	>0.05
Duration of analysis (hours)	18.725±1.37	16.075±1.22	<0.05

The mean age in group A is 45.95±5.54 years and in group B is 45.3±4.91 years. The mean weight in Group A is 55.3±5.41 kg and in group B is 54.7±4.72 kg. There is no statistically significant difference in weight between the two groups. The mean height in group A is 156.1±3.31 cm and in group 'B' is 156.02±2.80 cm. There is no statistically significant difference in height between the two groups. Duration of surgery in Group A is 102.75±11.148 minutes and in Group B is 105.75±8.737 minutes. There is no statistically significant difference in duration of surgery between the two groups. Duration of analgesia was taken as time to the first dose of rescue analgesia. In group A it is 18.725±1.38 hrs and in Group B 16.075±1.23 hrs. There is statistically a significant difference in the duration of analgesia between the two groups with a 'p' value of <0.001.

Table 2: Incidence of adverse drug reaction (n=40).

Parameters	Group A	Group B	P value
Nausea	8 (20%)	7 (17.5%)	>0.05
Vomiting	1 (2.5%)	2 (5%)	>0.05
Pruritus	5 (12.5%)	3 (7.8%)	0.808

There is no difference between two groups statistically regarding adverse drug reaction of drug.

Table 3: Additional dose of ondansetron (n=40).

Variable	Group A	Group B	P value
Additional dose of Ondansetron	6 (15 %)	8 (20%)	0.556

15% (6/40) of patients in group A 20% and (8/40) of patients is group B required additional doses of ondansetron in addition to the 8th hourly doses. There is no statistically significant difference is the consumption of additional ondensetron between the two groups.

Table 4: Dose of chlorpheneramine maleate (n=40).

Variable	Group A	Group B	P value
Chlorpheneramine maleate	2 (5%)	2 (5%)	1.00

Two patients received T-chlorpheneramine maleate in each group, there is no statistical difference between the two groups.

Table 5: Rescue analgesia (n=40).

Variable	Group A	Group B
1 dose	11 (27.5%)	7 (17.5%)
2 dose	29 (72.5%)	33 (82.5%)

27.5% (11/40) patients in group A, 17.5% (7/40) patients in group B received one dose of rescue analgesia (ketorolac 10 mg), during the 24 hours for pain relief while 29 patients is group A (72.5%) and 82.5% (33/40) patients in group B received 2 doses of rescue analgesia. Even though there is no statistically significant difference in the rescue analgesia, all patients in the study groups required some oral NSAIDs for the first 24 hours as in both groups the duration of analgesia was less than 24 hours even with the higher dose of intrathecal morphine.

Table 6: Sedation score (n=40).

Variable	Group A	Group B
Sedation score 0	36	36
Sedation score 1	4 (10%)	4 (10%)

10% patients in Group A (4/40) and 10% patients in Group B (4/40) had a sedation score of 1 (drowsy and arousable). There is no statistically significant difference between the two groups. None of them had sedation scores more than 1.

Table 7: Dose of pethedine injection (n=40).

Variable	Group A	Group B	P value
Pethedine injection	1 (2.5%)	5 (12.5%)	0.090

1 patient (2.5%) in group A received injection pethedine and 5 patients (12.5%) in group. Even though there is no statistically significant difference (p<0.09), clinically a few patients' required parenteral opioids, necessitating additional prescription and nursing time.

Respiratory depression

None of the patients in both study groups had clinically significant respiratory depression.

Post dural puncture head ache

None of the patients in both study groups had complaints suggestive of post dural puncture headache (PDPH).

DISCUSSION

In our country most of the transabdominal hysterectomies are done under spinal anesthesia. Intrathecal morphine has proved useful in the treatment of postoperative pain in various surgical populations. However, there are only few studies in literature studying its efficacy in gynecological procedures. Moreover no study is available regarding the use of intrathecal morphine in the Indian population. Hence we thought this study would benefit this group because of the excellent analgesia it is thought to provide for the first 16-24 hours following surgery with minimal side effects as seen from Fukuda et al and others study.[3] It is also a cost effective option (Gadsen et al`s study) Preservative free intrathecal morphine has recently been made available in this part of the country and it is less expensive compared to other opioids or analgesia.[4] Various additives are added intrathecally to improve analgesia and prolong the duration of analgesia, commonly used drugs being fentanyl, pethedine, morphine, clonidine, neostigmine, ketamine, butrophenol. Among the opioids, morphine has more advantages.[5,6] compared to others because it is a highly ionizable and hydrophilic drug having a prolonged effect as a result of its rostral CSF spread and slower disappearance from the CSF and spinal tissue Chadwick et al, have shown this to be true from their studies.[6] Various doses of intrathecal morphine have been tried ranging from 0.075 mgs to 0.5 mgs for providing high quality postoperative analgesia lasting up to 24 hrs.[6-8] The most commonly used doses are between 100-300 micrograms. Palmar et al describes a ceiling effect in the analgesic dose of morphine, after which side effects increase more than analgesia.[9-11] The results for the 80 patients allocated to the two groups were analyzed. There is no statistically significant difference between the two groups in terms of age, height, weight. There is no significant difference in duration of surgery. So the groups were comparable in terms of demographic variables.

The mean duration of analgesia in patients who received 250 µgms of intrathecal morphine was 18.725±1.38 hours while in patients who received 150 µgm it is 16.075±1.23 hours. In the postoperative period, pain was assessed using the VAS. Whenever the patient had VAS more than 4 or when patient complained of pain, Tab Ketorolac 10 mgs was given per orally. Our results are comparable with the studies by Yamaguchi et al.[8]

Even though there was a statistically significant difference in the duration of analgesia between the two groups, clinically 2 more hours of duration of analgesia may not be significant. But the number of patients who had complete analgesia during the first day was more in the 250 µg group compared to the 150 µg group. Gadson et al describe pain of hysterectomy as two components, visceral and somatic, visceral pain arises from the uterus which is best taken care of by NSAIDs and the somatic pain best taken care by opioid.[4] We wanted to assess the efficacy of intrathecal morphine as a sole analgesic in the treatment of postoperative pain relief.

Prolonged postoperative analgesia doesn't come without side effects. Cousins et al, describes nausea, vomiting, pruritius, sedation, urinary retention and respiratory depression as side effects of intrathecal morphine.[4,12] These side effects are mostly "nuisance factors" rather than life threatening.[13]

Review of literature shows the incidence of nausea and vomiting with intrathecal morphine as 35 to 45%.[14,15] In our study the percentage of PONV is 22.5% which is less when compared to the previous studies done by Wang et al and others. Patients in our study belong to the high risk category of PONV, the risk factors being female sex, gynecological surgery, non smoker and parental opioids. All the patients in our study received 8 mgs T. ondensetron preoperatively as prophylaxis for PONV and pruritus. In addition to that, all the patients received 4 mgs ondansetron intravenously eighth hourly and whenever required. This was due to ethical concerns. Despite this, 8 patients in group A and 7 patients in group B had nausea and 1 patient in group A and 2 patients in group B had vomiting. 6 patients in group A and 8 patients in group B required additional doses of ondensetron.

The fact that there was no significant difference in the incidence of PONV between the 2 groups with the increased intrathecal morphine dose of 250 µgm is in contrast to earlier studies by Dahl et al. This may be due to differences in surgical techniques and then ethnical

population.[16-19] Study by Wang et al, have shown that a single dose of dexamethasone can prevent intrathecal morphine induced nausea and vomiting.[14] So it may be worthwhile to combine preoperative dexamethasone and ondansetron for prevention of postoperative nausea and vomiting after intrathecal morphine administration.

Even though a lot of patients had mild pruritis, only five patients from Group A and 3 patients in Group B had severe pruritis. This is in contrast to the previous studies. Choi et al have shown that reducing the dose of intrathecal morphine in LSCS patients from 200 mcg to 50 mcg did reduce the incidence of pruritus to half.[21] In our study, 25% patients from each group had mild pruritius, which settled without treatment. This is much lesser compared to previous studies.[22,23] This may be due to addition of prophylactic ondansetron. Naloxone has been shown to be effective by Jeong et al but none of our patients required naloxone and we were able to treat the pruritius adequately with a single dose of chloropheneramine maleate.[22,23] Yeng et al have shown that a single dose of ondansetron reduced the incidence of intrathecal morphine induced pruritis.[24]

Urinary retention is the commonest side effect of intrathecal opioids. The incidence varies widely from 0-80% and the incidence is higher when intrathecal morphine is used. Rawal et al observed that this is most likely related to interaction with opioid receptors located in the sacral spinal cord.[25]

There is a lot of concern about delayed respiratory depression associated with intrathecal morphine. Delayed respiratory depression occurs 6-12 hours following intrathecal administration of morphine, and may persist for 24 hours, Wide ranges of intrathecal morphine from 0.05-0.5 mgs have been tried and from the available literature it has been shown no respiratory depression occurred with doses less than 0.3 mg.[26]

In many of the earlier studies and case reports respiratory depression was not objectively quantified or defined.[27] In our study respiratory depression was defined as respiratory rate less than 10/minute and Spo2 less than 90%. None of our patients had any respiratory depression including delayed respiratory depression. The incidence of delayed respiratory depression requiring intervention following conventional doses of intrathecal and epidural opioids is shown to be less than 1% by Jacobson et al.[28]

Spinal anesthesia is often associated with postdural puncture headache [PDPH]. In our study, none of the patients had PDPH. This may be due to older age group and intrathecal morphine masking the incidence of PDPH. Kang et al and Youngerman et al have shown that lesser number of attempts and use of intrathecal morphine can reduce the incidence of PDPH. In a recent randomized trial by Lavir et al the incidence of PDPH was 36% in cutting needle group and 3% in pencil point spinal needle group.[29-31]

Over the last three years, the practice of spinal anesthesia has changed in our institution with the availability of 25 G pencil point needle and preservative free morphine.

The incidence of PDPH in our institution in 2004 was 12.4%; and in 2007 it was 7.9%. Many patients had mild to moderate PDPH in both the studies. However none of them required epidural blood patches. In our institution studies conducted with the use of whitacre needle the incidence of PDPH was 4.6% vs 10.9% with quincke 25 G needles. The lesser incidence of PDPH in caesarian sections during 2007 when compared to 2004 is probably due to the use of whittacre needles and intrathecal morphine. Studies by Balestrieri PJ have shown that use of intrathecal morphine reduces the incidence of PDPH.[32]

CONCLUSION

We conclude that 250 µg of preservative free intrathecal morphine provides longer duration of analgesia when compared to 150 µg morphine, with hardly any additional adverse effects. Since preservative free morphine is now freely available in India, 250 µg intrathecal morphine pre emptively along with local anesthetics and oral NSAIDs thereafter round the clock as required, is a good cost effective option for complete postoperative analgesia in patients undergoing transabdominal hysterectomy under subarachnoid block.

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