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A Clinical Study to Evaluate the Effect of Intrathecal Atropine on Post Operative Nausea and Vomiting in Patients Receiving Intrathecal Morphine and Hyperbaric Bupivacaine for Spinal Anaesthesia: Prospective Randomized Trial

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Abstract

Background and Objective: Intrathecal morphine for lower abdominal surgeries provides excellent postoperative analgesia but is associated with significant Post Operative Nausea and Vomiting (PONV). This study was intended to evaluate the effect of intrathecal atropine on PONV in patients receiving intrathecal morphine and hyperbaric bupivacaine for spinal anaesthesia in lower abdominal surgery. **Methods:** 103 patients of ASA physical status I & II posted for elective lower abdominal surgery under spinal anaesthesia were enrolled. They were randomly allocated to two groups - Group A [n=51] - atropine, Group C [n=52] - control. Along with hyperbaric bupivacaine 3ml and morphine 200mcg, group A received atropine100mcg and group C received normal saline, intrathecally. Postoperatively, PONV, haemodynamic parameters, sedation and postoperative pain was assessed over 24 hours. Other adverse effects, if any were also recorded. **Results:** The incidence of PONV was 68% in control group and 34% in atropine group (P value < 0.001). Severity of PONV was greater in group C (28% grade 2 PONV) compared to group A (8% grade 2 PONV)(p<0.001). Cumulative comsumption of metoclopramide [mean (SD), median (IQR)] during 24 hours in group C was 10.6±8.42, 10 (0-20) mg and 5±7.62, 0(0-10) mg in group A (p – 0.001). No significant differences in terms of subarachnoid block characteristics, hemodynamic variables, sedation scores and postoperative pain was observed. The incidence of other side effects was comparable in both groups. **Conclusion:** Intrathecal atropine added to morphine resulted in decrease in incidence and severity of PONV. There was also reduction in requirement of rescue anti emetics.

Keywords: Anaesthesia, Atropine, Bupivacaine, Intrathecal, Lower Abdominal Surgeries, Morphine, Post Operative Nausea and Vomiting (PONV), Spinal

1. Introduction

Intrathecal opioid administration is an attractive analgesic technique since the opioid is injected directly into the cerebrospinal fluid, close to the structures of the central nervous system where it acts. This method is simple and effective mode of postoperative pain management.

Morphine, which is a hydrophilic opioid, has a longer residence time in the cerebrospinal fluid and therefore has long-lasting analgesia with intrathecal injection, when compared with lipophilic opioids such as fentanyl/sufentanil[1]. However, there is an increased risk of adverse effects like nausea and vomiting, pruritus, urinary retention and respiratory depression[2].

Post Operative Nausea and Vomiting (PONV), a common distressing side effect of morphine, can prolong hospital stay, unanticipated admissions and increased health care costs, which can limit its use. Though ignored earlier, the growing emphasis on day-case surgery has focused attention on these complications, which might delay discharge[3-6].

The incidence of PONV in patients who have received intrathecal morphine is 60%–80%[7-12]. Although the prophylactic and therapeutic effects of several drugs have been extensively studied, a decrease in the incidence of PONV after intrathecal morphine remains a major therapeutic challenge[8-12].

Anticholinergic agents are thought to act via inhibition of muscarinic receptors in several regions of the medulla oblongata, which are implicated with nausea and vomiting generation; in addition to the chemoreceptor trigger zone[11]. Anti-cholinergic agents, particularly scopolamine, have been known to decrease opioid related nausea and vomiting, but narrow therapeutic range and inconvenient route of administration (typically transdermal) has limited their application[10]. Some studies have specifically evaluated the antiemetic effect of intravenous (IV) atropine after general or regional anesthesia with opioids, with conflicting results, also the duration of action of intravenous atropine is a concern[12]. Few studies have examined the use of intrathecal atropine for prophylaxis of PONV associated with intrathecal morphine and found significant benefit from intrathecal atropine versus IV atropine or placebo[13,14].

From the knowledge gained by above mentioned studies, this study was undertaken to evaluate the anti emetic effect of intrathecal atropine in patients receiving intrathecal morphine and hyperbaric bupivacaine for spinal anesthesia in lower abdominal surgery.

The primary objective was to evaluate the effect of intrathecal atropine on PONV in patients receiving intrathecal morphine and hyperbaric bupivacaine for spinal anaesthesia in lower abdominal surgery. The effect of intrathecal atropine on haemodynamic parameters, spinal block characteristics, sedation and postoperative pain were secondary objectives.

2. Methods

This was a prospective, randomized, double blind, controlled clinical study involving 103 patients aged between 18 to 50 years of either sex, belonging to American Society of Anesthesiologists (ASA) physical status I and II, undergoing elective lower abdominal surgery under spinal anaesthesia at a tertiary hospital between November 2012 to October 2014. Institutional ethical committee approval was obtained before conduct of study. Patients with BMI <18 or >30 kg/m^2, having systemic disorders (cardiac, renal, hepatic derangement, uncontrolled hypertension, central nervous system and ENT disorders), endocrine disorders (uncontrolled diabetes, thyroid/ adrenal disorders), those with history of migraine, motion sickness, and parturients were excluded from the study. Patients receiving anti emetic therapy, steroids, oral contraceptives and chemotherapy were also excluded from the study.

The study population was randomly assigned to two groups using a computer generated random sequence (Random Sequence Generator, available at www.random.org). Group C (Control group) received 15mg of 0.5% hyperbaric bupivacaine (3ml) with 200mcg morphine and Normal saline, Group A (atropine group) received 15mg of 0.5% hyperbaric bupivacaine with 200mcg morphine and 100 mcg atropine. The random numbers were written on piece of paper and put in enclosed sequentially numbered sealed opaque envelopes to avoid allocation bias.

Pre anaesthetic check up was done one day prior to surgery. Patients were counseled regarding the study, explained the use of PONV scale and written informed consent was obtained from all patients. All patients were kept nil oral for 8 hours prior induction of anaesthesia. Alprazolam 0.5 mg was administered orally the previous night of surgery. On arrival to operation theatre, Electro-Cardio-Gram (ECG), pulseoximeter, and non invasive blood pressure monitors were connected and baseline Heart Rate (HR), systolic (SBP), diastolic (DBP), Mean Arterial Pressure (MAP) and peripheral oxygen saturation (SpO_2) were recorded. Patients received 500 ml of Ringers lactate as co loading. Under strict asepsis and under local anesthesia lumbar puncture was performed at L3-L4 or L4-L5 space using 27G Quincke needle. After confirming a free flow of cerebrospinal fluid, drugs were injected as per group allocation. An anaesthesiologist unaware of group allocation, performed subarachnoid block and injected the drugs. To ensure uniformity, the study drug (or normal saline) was loaded in an insulin syringe which has got 40 markings on it. Morphine 1 mg was taken in

another insulin syringe which has got 100 markings on it. The dose of morphine was 200 mcg (0.2 ml) and that of atropine was 100 mcg (0.167 ml). The total volume of drug in both the group was 3.367 ml (3 ml of 0.5% Bupivacaine + 0.2 ml morphine + 0.167 ml atropine/normal saline). All the drugs used intrathecally were preservative free and were prepared by an anaesthesiologist not involved in administration of anaesthesia and further monitoring of the patient. The drug solutions were prepared based on number in sealed envelope which was opened just before administration of spinal anesthesia. Both patient and the monitoring anaesthesiologist were blinded to the group allocation. Supplemental oxygen 5L/min was administered via face mask throughout the surgery. Following spinal anaaesthesia HR, SBP, DBP, MAP, SPO2, RR were recorded every 5min till the end of surgery. Maximum level of sensory block was assessed 30 min after administration of SAB. Hypotension, defined as 20% decrease in MAP from baseline values, was treated initially with bolus infusion of crystalloids (250 ml) and ephedrine 6 mg IV as needed. Bradycardia, defined as heart rate <50/min was treated with atropine IV 0.6 mg given every 30 seconds until resolution. Patients receiving IV atropine were excluded from the study. Any patient having inadequate block, requiring supplemental analgesics or general anaesthesia was also dropped from the study. Sedation was monitored using Ramsay sedation scale [Annexure I] intraoperatively (at 15 min intervals) and post operatively (at 2nd hourly for 6 hours and 6th hourly for next 18 hours). Post operatively, parameters such as HR, SBP, DBP, MAP, RR, SPO2, sedation, pain and side effects were observed every 30 min till 2hrs, then every 6 hrs till 24 hrs.

The incidence of nausea (unpleasant sensation associated with an urge to vomit) and vomiting (forceful expulsion of gastric contents) was recorded every 6 hours for a period of 24 hours. Severity of nausea and vomiting was evaluated on a modified three point scale, 0 = none, 1 = more than two episodes of nausea and vomiting in one hour period, 2 = more than 3 emetic episodes with in a period of 15 minutes. Patients with PONV score more than 1 were given rescue anti emetic Inj Metoclopramide 10 mg IV. Ondansetron 4 mg was administered IV if vomiting didn't subside within 30 min after administration of metoclopramide. The postoperative analgesia was assessed using Visual Analogue Scale (VAS) 0 to 10 cm score from no pain to worst pain on marked paper strip every 30 mins for 2 hrs and thereafter at 6 hrs interval for 24 hour period. Patients above score 4 received rescue analgesia in the form of inj diclofenac 75mg IM. Time to request for first analgesic and frequency of subsequent doses of the same were noted. Patients were also monitored for adverse effects like pruritus, urinary retention, respiratory depression, xerostomia, palpitations, visual disturbances and any other adverse effects in the 24 hour post operative period. They were appropriately treated.

Sample size was calculated based on a previous study[15]. Assuming the incidence of PONV to be 55% in control group and an effect size of 45% (reduction in incidence of PONV in study group) between the groups, and alpha error at 5%, 45 patients would be required in each group to attain a power of 80%. We enrolled a total of 100 patients with 50 in each group, to compensate for the drop outs.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD or median with interquartile range (IQR) and results on categorical measurements are presented in Number (%). Tests for normality (Shapiro Wilk test) was applied for quantitative variables and Student t test (two tailed, independent) has been used to find the significance of normally distributed study parameters on continuous scale between two groups (Inter group analysis) on metric parameters, where as Mann – Whitney U test applied for those showing skewed distribution. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. P value less than 0.05 was considered statistically significant. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

3. Results

A total of 103 patients were screened and included in the study based on inclusion and exclusion criteria and all patients received allocated intervention. Two patients in group C received atropine for bradycardia and one patient in group A received general anaesthesia due to inadequate level of blockade hence not considered for

Table 1. Demographic parameters, duration and type of surgery

Parameter	Group C	Group A
Age in years (Mean± SD)	34.70±7.18	35.58±6.41
Sex (M:F)	26:24	23:27
BMI (Mean± SD)	22.98±3.02	23.49±2.49
ASA (I:II)	35:15	33:17
Duration of surgery* (Mean± SD)	78.20±25.57	81.72±25.89
Type of surgery#		
Hernia repair	23(46%)	22(44%)
Abdominal Hysterectomy	13(26%)	14(28%)
Myomectomy	2(4%)	1(2%)
Ovarian cystectomy	2(4%)	5(10%)
Appendicetomy	10(20%)	8(16%)

Statistical significance * - p – 0.49, # - p – 0.91.

Table 2. Incidence of PONV in both groups

PONV	Group C	Group A	P value
0 – 6 hrs	33(66%)	14(28%)	0.001
6 – 12 hrs	32(64%)	14(28%)	0.001
12 – 18 hrs	18(36%)	10(20%)	0.074
18 – 24 hrs	10(20%)	8(16%)	0.271

Table 3. Incidence of PONV in both groups

PONV	Group C			Group A			P value
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2	
0 – 6 hrs	17(34%)	19(38%)	14(28%)	36(72%)	10(20%)	4(8%)	0.001
6 – 12 hrs	18(36%)	18(36%)	14(28%)	36(72%)	11(22%)	3(6%)	0.001
12 – 18 hrs	32(64%)	12(24%)	6(12%)	40(80%)	7(14%)	3(6%)	0.201
18 – 24 hrs	40(80%)	7(14%)	3(6%)	42(84%)	6(12%)	2(4%)	0.849

Table 4. Comparison of rescue antiemetics between groups

PONV	Group C	Group A	P value
Metoclopramide 1 dose	15(30%)	9(18%)	0.002
Metoclopramide 2 doses	19(38%)	8(16%)	
Ondansetron	11(22%)	4(8%)	0.51

Table 5. Sensory and motor block characteristics and side effect profile of both groups

Parameters	Group C	Group A	P value
Time for onset of sensory block (min) (Mean±SD)	3.21±0.61	3.09±0.58	0.314
Maximum level of sensory block	T5 (T4-T7)	T5(T4 – T8)	0.432
2 segment sensory regression (min) (Mean±SD)	114.78±10.01	110.90±11.03	0.069
Time for onset of motor block B2 (min) (Mean±SD)	5.65±0.82	5.58±0.89	0.682
Total duration of motor blockade (min) (Mean±SD)	194.30±15.35	196.00±17.55	0.607
Time to request of rescue analgesic (min) (Mean±SD)	546.00±75.42	532.60±73.02	0.369
Ramsay sedation score (Mean±SD)	2.44±0.50	2.4±0.49	0.001
Pruritus	19	17	0.677
Urinary retention	5	6	0.749
Intra operative hypotension	6	7	0.766
Unexplained Anxiety	2	3	1.00

statistical analysis. Statistical analysis included 50 patients in each group. Both groups were comparable with respect to age, gender, BMI and ASA physical status. The duration and type of surgery were comparable between the groups (Table 1).

The overall incidence of PONV was 34% (17/50) in Atropine group and 68% (34/50) in Control. This was clinically and statistically significant. The incidence of PONV was higher in group C compared to group A during the first 12 hours (Table 2).

The severity of PONV was higher in group C compared to group A with 28% patients in group A having no nausea or vomiting in the first 12 hours. In group C, 14 patients had severe nausea and vomiting in first 12 hours which was clinically and statistically significant (Table 3).

The consumption of rescue antiemetics were higher in group C compared to group A (Table 4). Cumulative comsumption of metoclopramide [mean (SD), median (IQR)] during 24 hours in group C was 10.6±8.42, 10 (0-20) mg and 5±7.62, 0(0-10) mg in group A (p – 0.001). The consumption of ondansetron was 1.29±1.89, 0(0-4) in group C and 0.94±1.74, 0(0-0) in group A, p – 0.617.

The sensory and motor block characteristics, intraoperative haemodynamic parameters, post operative duration of analgesia and side effects profile were comparable between the two groups. The mean intraoperative sedation scores comparable clinically though there was statistically significant difference (Table 5, Figure 1A, 1B).

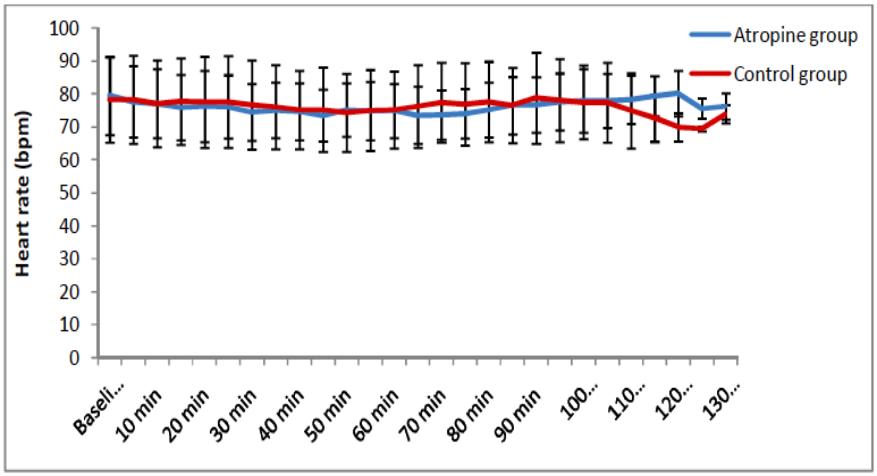

Figure 1A. Comparison of heart rate changes between two groups.

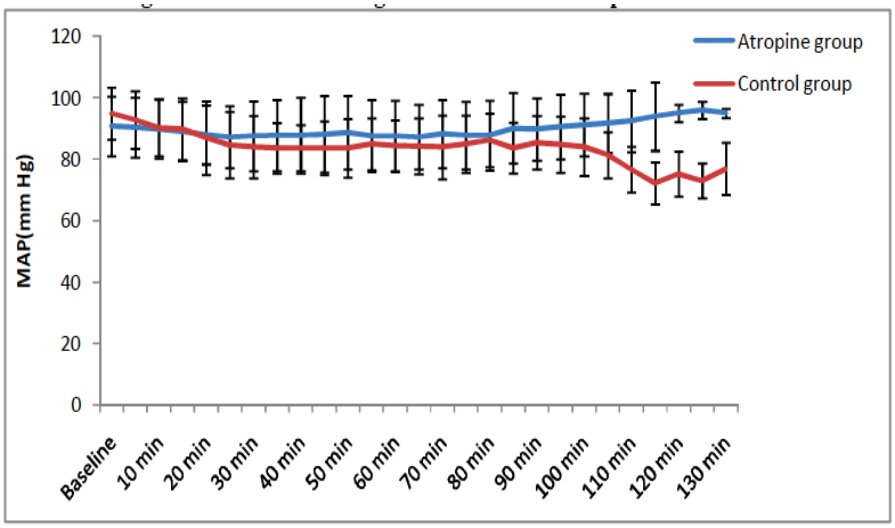

Figure 1B. Comparison of mean arterial pressure between two groups.

4. Discussion

The present study evaluated the effect of intrathecal atropine in preventing PONV after intrathecal morphine along with hyperbaric bupivacaine for spinal anaesthesia in lower abdominal surgery and demonstrated that addition of atropine to intrathecal morphine significantly reduced the incidence and severity of PONV. It also reduced the need for rescue anti emetics in post operative period without causing significant effect on analgesia or haemodynamic parameters. The observations of our study are concurrent with previous studies[10,13-15]. One study reported 69% and 59% reduction in incidence of PONV following intrathecal atropine compared to placebo and intravenous atropine respectively[14]. The profound difference in severity of PONV was noted only in the first 12 hours which can be due to early use of rescue anti emetics in the control group and also the difference in pharmacokinetics of intrathecal atropine and morphine[14].

Multiple risk factors have been identified that increase the incidence of PONV. The incidence of PONV in high-risk patients is 60–70%[15-17]. Apfel, *et al.* identified four risk factors that form the basis for the Apfel scoring system: female gender, history of PONV/motion sickness, non-smoking status, and use of postoperative opioids. Each risk factor increases the likelihood of PONV by 18–22%[16]. However, most of the confounding factors such as age, gender duration and type of surgery were uniformly distributed between the groups in the present study.

Anticholinergic agents are thought to act via inhibition of muscarinic receptors in several regions of the medulla oblongata, which are implicated with nausea and vomiting generation; in addition to the Chemoreceptor Trigger Zone (CTZ)[1]. Cholinergic receptors have been typically associated with motion sickness rather than PONV, yet agonists such as neostigmine have been shown to increase the incidence of postoperative emesis, especially when injected intrathecally, and hence intrathecal atropine may have a role in reduction of PONV by its direct effect on CTZ, or by inhibiting 5HT3 receptors in medulla oblangata.

In two independent studies assessing various doses of intrathecal morphine for lower abdominal surgeries, 200 mcg was shown to be an effective dose with minimal side effects, and increase in dose was associated with increase in incidence of side effects[18,19].

Authors have used different doses of atropine for prevention of PONV. One author found that a dose of 15 mcg along with morphine less than 600 mcg intrathecally would be effective, where as another author demonstrated that intravenous atropine 150 mcg reduced incidence of PONV following opioid based general anaesthesia. The choice of selection of anti emetic and its dose was based on a study by Baciarello M, *et al.*[14] Contrary to the assumptions of authors, intravenous atropine was less effective than intrathecal atropine in preventing PONV, which maybe attributed to its rapid clearance when administered intravenously[14]. There are no pharmacokinetic models to explain the clearance of intrathecal atropine however we assume that the reduced effectiveness beyond 12 hours may be due to clearance of the drug.

There is no uniformity in scoring systems for assessing the severity of PONV. Various authors have used different scoring systems to assess the incidence and severity of PONV. The scoring system used in the present study is a modification of scoring system employed by previous authors[20,21].

There is a theoretical possibility of antagonism of morphine induced analgesia with concomitant administration of atropine however it was not clinically evident. Also there was no difference in incidence of other morphine induced side effects such as pruritus, urinary retention etc suggesting a different mechanism of action for these.

The present study has few limitations. The sample population excluded those with high risk of PONV, such as those with ENT disorders and hence these results should be extrapolated with caution. The sample size was not sufficient to draw a valid conlusion regarding effects of atropine on other parameters such as analgesia and side effect profile. Future studies may be done with varying doses of atropine and morphine to find out an ideal combination.

5. Conclusion

Intrathecal atropine 100 mcg, significantly decreased the incidence and severity of PONV after lower abdominal surgery with subarachnoid bupivacaine and morphine 200 mcg. It also reduced the need for rescue antiemetic therapy compared with placebo.

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