A STUDY OF POST OPERATIVE ANALGESIA AND ADVERSE EFFECTS PRODUCED BY INTRATHECAL NEOSTIGMINE, MORPHINE AND THEIR COMBINATION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

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ABSTRACT

This is a double blind placebo controlled study of 120 patients conducted in the department of anesthesiology POF's Hospital Wah Cantt: from October 2002 to April 2003 to evaluate the post operative analgesia and side effects of IT neostigmine, morphine and their combination in patients undergoing elective caesarean section under spinal anaesthesia. These patients were randomly divided into neostigmine, morphine, combined and saline (control) groups of 30 patients each. Morphine group had the longest analgesia as compared to other groups. The combined group too had a statistically significant prolongation of analgesia as compared to neostigmine (p = .01) and saline group (p = .00). Nausea and vomiting were more frequent in neostigmine group (53%) and combined group (53%) than in the morphine group (36%) and saline group (26%). The frequency of pruritis was not significantly different in combined (50%) and morphine group (46.66%) This study demonstrates that the combination of IT neostigmine 12.5 microgram and IT morphine 50 microgram results in post operative analgesia for longer duration than IT neostigmine 25 microgram alone but not longer than IT morphine 100 microgram alone. The side effects seen with either drug alone are not over come by combining the drugs in half the doses.

Keywords: Analgesia, anaesthesia, intrathecal, morphine, neostigmine, spinal

INTRODUCTION

Despite advances in postoperative pain control strategies, many patients still suffer from post operative pain probably due to difficulties in balancing an effective post operative pain treatment regimen with acceptable side effects [1]. IT morphine has been in use for achieving postoperative analgesia for over a decade [2,3] but despite its efficacy, it's more widespread use has been limited by worrisome side effects including nausea, vomiting, pruritis and delayed respiratory depression [4]. This has prompted further research to develop non opioid analgesics with less worrisome side effects. Through these efforts acetylcholine and more than 25 neurotransmitters that participate in spinal cord modulation of pain processing have been identified [5]. Postoperative analgesic effect of IT neostigmine was first reported by Hood DD et al in 1995 [6]. Intrathecal injection of neostigmine inhibits the metabolism of spinally released acetylcholine and produces analgesia in animals and human without the danger of bothersome side effects, common to spinal opiods [6,7]. The trials with use of IT neostigmine over a period of time for post operative analgesia also revealed certain problems. Among the most common and troublesome side effects encountered with IT neostigmine were nausea and vomiting [8]. Moreover post operative analgesia produced by IT neostigmine was associated with a long delay and its quality was not superior to the one produced by IT morphine [9]. For these reasons researchers have started focusing on the possibility of combining lower doses of IT neostigmine and morphine in an attempt to reduce the intensity and frequency of undesirable side effects in addition to providing effective postoperative pain relief [10,11,12,13].

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We under took this study to compare the postoperative analgesia and side effects produced by IT neostigmine, morphine and their combination with the aim to propose a strategy for effective postoperative pain relief with manageable side effects in patients undergoing elective caesarean section under spinal anaesthesia.

MATERIALS AND METHODS

After approval from ethical comittee of POF's Hospital Wah Cantonment and getting informed written consent of 120 patients of ASA physical status 1, scheduled for elective cesarean section under spinal anaesthesia were included in the study. Patients with obstetric complications or evidence of fetal compromise were excluded. The patients were randomly allocated into four groups of 30 patients each. The test drug was freshly prepared in 1 ml of isotonic saline for each patient. The groups were: 0.9% isotonic sodium chloride (saline group), 25 microgram neostigmine (neostigmine group), 100 microgram morphine (morphine group), or the combination of 12.5 microgram neostigmine and 50 microgram morphine (combined group).

All patients were premedicated with intramuscular injections of ranitidine 40 mg and glycopyrolate 0.2 mg. After successful spinal puncture at L2-3 or L3-4 interspaces with 25-gauge Quincke needle, 1.3 ml of 0.75% hyperbaric bupivacaine [Abocain spinal, Abbott Laboratories (Pakistan) Limited] (9.75 mg) and 1 ml of the study drug was injected in two separate syringes. Then patient was turned supine with left uterine displacement and a level of T4-5 block was achieved.

Maternal blood pressure and heart rate were recorded every minute until delivery and every 5 minute thereafter till the end of surgery, using an automated and noninvasive device (Nihon-Kohden, BSM2301 K Japan). Oxygen saturation (SpO2) was continuously monitored throughout surgery. During the post operative period, blood pressure, heart rate, respiratory rate and oxygen saturation were measured at 15 minute intervals till the complete regression of sensory and motor block and then every hour up to 24 hours in the post anaesthesia care unit. During operation oxygen was routinely administered via a face mask at the rate of 6 L/min. The condition of the neonate was assessed by Apgar score at 1 and 5 min after the delivery.

The sensory block to pinprick and motor block using a modified Bromage scale were assessed. Return of sensory and motor function during the post operative period was assessed every 15 min until complete recovery from spinal anaesthesia. The severity of postoperative pain was assessed every hour until 24 h after the IT injection of the study drug by using a verbal pain rating scale (0, no pain; 1, mild pain; 2, moderate pain; 3, strong pain) or whenever the patient requested analgesia. Post operative analgesia was provided by intramuscular diclofenac 75 mg (Voren, Yung Shin Pharmaceutical Industries Co, Ltd Tachia Taiwan, ROC) to patients with the verbal rating scale 2 or more. The pain and adverse effects were evaluated hourly for 24 hours, except when the patient was sleeping. The time from IT injection to first request for analgesia was recorded and if the patient did not require any analgesia, the time was taken as 24 hours. The severity of nausea was recorded as mild if it was transient and self limiting, moderate if stopped with one intravenous injection of 10 mg metoclopramide, severe if required more than one intravenous injection of 10 mg metoclopramide. Pruritis was also assessed and recorded hourly and intravenous pheniramine maleate (Avil Aventis Pharma Pakistan Ltd Karachi) 25 mg administered for moderate to severe pruritis. The severity of pruritis was recorded as mild if it was transient and self resolving, moderate if stopped with one intravenous injection of 25 mg pheniramine maleate and severe if required more than one intravenous injections of 25 mg pheniramine maleate. Respiratory depression was defined as a respiratory rate <10 breaths/min.

All data are expressed as number or mean +/- S.D or SE. Continuously distributed variables were analyzed using one-way analysis of variance followed by Bonferroni's correction with SPSS 10. $P < 0.05$ was considered statistically significant.

RESULTS

Age, weight, and duration of surgery were similar for all four groups (table-1). There were no significant differences among the four groups in sensorimotor regression times (table-2), maternal blood pressure and heart rate. Hypotension occurred in 38 patients (table-3). In 32 cases out of

38, it occurred within 10 minutes of the spinal block. In all cases it was transient and corrected by raising the legs and by administering the Ringer's solution. Apgar scores at 1 and 5 min were also not significantly different among the four groups.

Morphine group had longest analgesia judged by longest time to first analgesic request (mean of 1001.13 minutes) and the least number of analgesic injection administered in 24 hours as compared to other groups. Both findings were statistically significant. The combined group too had a statistically significant prolongation of analgesia as compared to neostigmine ($p = .01$) and control group ($p = .00$). Time in minutes from spinal anaesthesia to first analgesic request for all four groups is shown in (table-4). Twelve patients in morphine group, four in combined group and two in neostigmine group did not require analgesic injections within the first 24 hours after IT administration of test drugs. Total Consumption of analgesic injections (diclofenac sodium 75 mg) in all four groups for the first 24 hours after the administration of IT study drug is shown in (table-5).

The frequency and severity of nausea and vomiting in the absence of hypotension in each group is shown in (table-6). Nausea and vomitings were more frequent in the neostigmine group (53%) and combined group (53%) than in the morphine group (36.6%) and saline group (26.6%). The frequency and severity of pruritis in all four groups is shown in (table-7). No pruritis was observed in the saline and neostigmine group. There was no significant difference in frequency of pruritis in combined (50%) and morphine (46.66%) groups ($p= .647$). Respiratory depression was not observed in any patient.

DISCUSSION

Intrathecal administration of morphine, neostigmine or their combination for achieving postoperative analgesia in patients undergoing gynecologic, orthopedic and lower abdominal surgery under spinal anaesthesia has been the subject of wide research in the west and USA [3,6,12]. The use of above mentioned IT drugs to improve the spinal anaesthesia and to enhance the duration of postoperative analgesia has not been studied in Pakistan, and this study is first of its kind in Pakistani patients population. Gwirtz KH et al [3] in a study published in 1999 containing a large series of patients including 5969 patients spanned over 7 years reported the efficacy of IT morphine as a very effective postoperative IT analgesic but expressed reservations about widespread use of IT morphine due to serious side effects of pruritis (37%), nausea/vomiting (25%) and respiratory depression (3%) in a significant proportion of his patients. Chung et al [12] in another study encountered similar results with respect to quality of postoperative analgesia but pruritis was seen in 65% of his patients receiving IT morphine alone, although respiratory depression was not observed in any of his patients. In our study the quality of post operative analgesia produced by IT morphine was comparable to the above quoted studies [3,12]. No respiratory depression was seen in any of the patient in our study which is in agreement with the findings of Chung et al [12]. Worrisome pruritis was found in 46.66% of the morphine group in our patients which is also comparable with the above studies [3,12]. The absence of respiratory depression in our study and study of Chung et al may be due to smaller number of patient in these studies as compared to a very large number of patients included in the study of Gwitrz [3].

In an attempt to avoid worrisome side effects produced by IT morphine, first clinical trial of IT neostigmine in healthy human beings was reported in 1995 by Hood DD et al [6]. IT neostigmine produced analgesia by inhibiting the metabolism of spinally released acetylchoine [7]. Ever since its introduction, researchers have been comparing IT neostigmine with IT morphine in terms of their analgesic efficacy and side effects [1,12]. In a study conducted by Chung et al [12] it was reported that 25 microgram of IT neostigmine and 100 microgram of IT morphine given to two separate groups of 20 patients each produced analgesia of almost similar duration. In our study duration of post-operative analgesia produced by 25 micrograms of IT neostigmine was similar to the duration of analgesia produced by similar doses of IT neostigmine in the study of Chung et al [12] however the duration of analgesia produced by 100 micro grams of IT morphine in our patients was significantly prolonged (16.68 hours) as compared to the duration of analgesia (7 hours) produced by similar doses of IT morphine in patients of Chung et al [12]. This difference may be due to the fact that Chung et al [12] in their study used preservative free morphine whereas we

used morphine with the preservative sodium metabisulphite 0.1%. Klamt et al [13] also carried out a study on the efficacy of IT neostigmine in 26 patients and concluded that IT administration of a low dose of neostigmine alone possesses a low clinical efficacy and has no advantage over the routine use of IT morphine which is in agreement with the findings of our study. In our study nausea and vomiting were found in 53.3% patients in neostigmine group and combined group, 36.6% in morphine group and 26.6% patients in saline group. In all the cases nausea and vomiting occurred after the delivery of the baby, mostly in post operative period. Oxytocin 10 IU given after the delivery of the baby might have contributed to some extant for frequency of nausea and vomiting particularly in saline group in the absence of hypotension. These side effects were seen in 65% and 73.3% patients receiving IT neostigmine in studies carried put by Klamt et al [9] and Chung et al [12] respectively which is comparable with our findings.

The focus of current research is on formulating a combination of IT morphine and IT neostigmine so that the side effects of these drugs could be minimized in addition to attaining a prolonged postoperative analgesia. In a study carried out by Lauretti et al [1] it was found out that a combination of 50 microgram IT morphine and 50 microgram of IT neostigmine produced analgesia of significantly prolonged duration (23 hours) with fewer side effects than equianalgesic doses of each drug given separately in a group of

Table-1: Demographic data

Group		Duration of surgery	Age	Weight
Combined	Mean	40.10	28.97	66.67
	S D	10.99	6.05	14.11
	S E	2.01	1.11	2.58
Morphine	Mean	37.70	26.97	70.30
	S D	8.31	4.54	12.27
	S E	1.52	.83	2.24
Neostigmine	Mean	42.97	27.47	69.40
	S D	10.14	6.14	12.62
	S E	1.85	1.12	2.30
Saline	Mean	37.27	26.83	69.60
	S D	10.34	4.12	11.37
	S E	1.89	.75	2.08

Duration of surgery in minutes; Age in years; Weight in Kgs. n=30 in each group; Combined = Neostigmine and Morphine SE: Standard Error of Mean; SD: Standard Deviation

Table-2: Time (minutes) spinal to return of sensation and motor activity

Group		Time spinal to return of motor power	Time spinal to return of sensation
Combined	Mean	229.07	288.07
	S D	72.19	92.33
	S E	13.18	16.86
Morphine	Mean	221.80	245.93
	S D	114.93	94.69
	S E	20.98	17.29
Neostigmine	Mean	211.77	248.67
	S D	72.77	131.95
	S E	13.29	24.09
Saline	Mean	217.53	241.43
	S D	76.78	85.29
	S E	14.02	15.57

n=30 in each group; Combined = Neostigmine and Morphine SE: Standard Error of Mean; SD: Standard Deviation

Table-3: Maternal baseline (pulse and systolic blood pressure), lowest reading of (pulse and systolic blood pressure) and frequency of hypotension after spinal anesthesia

Group		Hypotension	Base line Pulse	Lowest Pulse	Base line Sys BP	Lowest BP
Combined	Mean		118.73	84.80	129.07	91.27
	S D		24.16	15.45	20.86	19.47
	S E		4.41	2.82	3.81	3.55
	N	9	30	30	30	30
Morphine	Mean		120.30	80.23	126.30	86.50
	S D		17.93	9.73	17.53	14.23
	S E		3.27	1.78	3.20	2.60
	N	10	30	30	30	30
Neostigmine	Mean		117.03	81.30	123.37	87.73
	S D		20.24	15.77	23.03	19.42
	S E		3.70	2.88	4.20	3.55
	N	11	30	30	30	30
Saline	Mean		113.45	79.31	123.77	88.87
	S D		23.63	13.34	16.42	12.56
	S E		4.39	2.48	3.00	2.29
	N	8	29	29	30	30

Values are expressed as mean; SD: Standard Deviation; SE: Standard Error of Mean. n= 30 in each group; Blood Pressure in mmHg; N = Number of cases

Table-4: Time in minutes from spinal to first analgesic request

Groups	N	Mean	SD	S E	Significance Between Groups (Bonferroni)
Morphine	30	1001.13	435.32	72.53	Morphine-Neostigmine = .00 Morphine-Combined =.01 Morphine-Saline =.00
Neostigmine	30	429.67	381.70	79.48	
Combined	30	715.23	397.25	69.69	Combined-Neostigmine =.01
Saline	30	267	169.16	30.88	

N=Numbers of patients in each group; SD: Standard Deviation; S E: Standard. Error of Mean

Table-5: Mean consumption of analgesic injections (diclofenac sodium75 mg) in each group

Groups	N	Mean	SD	S E	Significance Between Groups (Bonferroni)	
Morphine	30	.83	.79	.11	Morphine-Saline =.001;	Morphine-Neostigmine = .000
Neostigmine	30	1.53	.68	.14		
Combined	30	1.13	.63	.12		Combined-Saline = .000
Saline	30	1.87	.63	.11		

N=Numbers of patients; Combined= Morphine + Neostigmine; SD: Standard Deviation; SE: Standard. Error of Mean

six patients each undergoing anterior and posterior vaginoplasty. In another study conducted by Chung et al [12] a combination of 50 microgram of IT morphine and 12.5 microgram of IT neostigmine produce analgesia of 11 hours durations compared to six hours in neostigmine group and 7.5 hours in morphine group. In the same study [12] nausea and vomiting were seen in 60% patients in the combined group as compared to 73.7% in neostigmine group and 40% in the morphine group. The frequency and severity of nausea and vomiting were not statistically different between the neostigmine and the combined group in the study of Chung et al [12]. Pruritis was reported in 30% patients in the combined group as compared to 65%patients in morphine group in the same study [12]. In our study the duration of analgesia produced by a combination of 50 microgram morphine and 12.5 microgram of IT neostigmine is 11 hours which is similar to duration of analgesia reported by Chung et al [12] by using the similar doses of these drugs. Moreover the duration of analgesia found in the combination group in the study of Chung et al [12] and Lauretti et al [1] was significantly longer than the neostigmine group which is also in agreement with the findings in our study. However our study contradicts the finding by Lauretti et al [1] and Chung et al [12] that combination group produced even longer duration of analgesia than morphine group. IT Morphine (100 microgram) in our study produced mean analgesia of about 16.68 hours whereas it was 7.5 hours with same doses of IT morphine reported by Chung et al [12]. In another study carried out by Klamt et al [13] it was concluded that a low dose of neostigmine, alone or in combination with a low dose of IT morphine produce an analgesic effect which is not superior to the IT morphine alone. He also found out that adverse effects seen with IT neostigmine alone and IT morphine alone are also not significantly

Table-6: Frequency and severity of nausea and vomiting in each group

Severity	Saline	Neostigmine	Morphine	Combined
No nausea	22	14	19	14
Mild	2	1	2	2
Moderate	6	12	8	12
Severe		3	1	2

Values are expressed as number of cases occurring in each group

Table-7: The frequency and severity of pruritis

Groups	Pruritis				Total
	None	Mild	Moderate	Severe	
Combined	15	10	3	2	30
Morphine	16	11	2	1	30
Neostigmine	30	0	0	0	30
Saline	30	0	0	0	30
Total	91	21	5	3	120

Values are expressed as numbers of patients

reduced by combining lower doses of these drugs. These findings of Klamt et al [13] are in total agreement with the finding of our study.

CONCLUSION

This study provides the evidence that the combination of IT neostigmine 12.5 microgram and IT morphine 50 microgram results in post operative analgesia for longer duration than IT neostigmine 25 microgram alone but not longer than IT morphine 100 microgram alone. The clinical efficacy of IT neostigmine alone or in combination with low dose of IT morphine is lower than the IT use of morphine. The side effects seen with either drug alone are not over come by combining the drugs in half the doses. The severity of the nausea and vomiting might restrict the usefulness of IT neostigmine as the sole analgesic agent. Further studies are required in our patient population to establish these findings regarding the clinical efficacy of these IT drugs for post operative analgesia and side effects in various combinations of doses in variety of procedures.

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