Non-opioid Analgesia, the Effect of Adding Tramadol or Neostigmine as an Adjuvant to 0.5% Bupivacaine in Spinal Anesthesia

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Abstract:

Background: The addition of the non-opioid agents to intrathecal bupivacaine will prolong or may double the time for the first rescue analgesic dose in the postoperative period without the unwanted side effects of opiates which they are usually added as adjuvants to intrathecal local anesthetic. This study was aimed to evaluate the effect of tramadol and neostigmine as an adjuvant to 0.5% intrathecal bupivacaine as effects and side effects.

Method: Ninety patients enrolled in double-blinded controlled clinical trial, divided randomly into 3 groups. Group 1 had received 20 mg bupivacaine. Group 2 had received 20 mg bupivacaine and 20 mg tramadol. Group 3 had received 20 mg bupivacaine with 20 µg neostigmine. The blood pressure, pulse rate, SpO_2 and ECG were monitored. The time of the first analgesic rescue dose of tramadol and diclofenac sodium had been recorded. The time of the first sign of motoric activity had been recorded. The incidence of headache and nausea and/or vomiting had been recorded. One-way ANOVA and Kruscall-Wallace test had been used and $p < 0.05$ was considered significant.

Results: The time of analgesia with group 1 was only 173±35 minutes, while group tramadol and neostigmine had recorded 368±59 and 377±67 minutes respectively ($p < 0.05$). The time of motoric recovery was 153±47 minutes for bupivacaine, 165±48 minutes for tramadol group and 155±46 minutes for neostigmine group ($p > 0.05$). Nausea and/or vomiting incidence was 80% of neostigmine group, while 16.7% and 10% in tramadol group and bupivacaine group respectively.

Conclusion: The addition of tramadol or neostigmine in low doses, prolong the analgesic effect of bupivacaine in spinal anesthesia without any motoric latency. Tramadol is superior to neostigmine as it carries fewer incidences of postoperative nausea and/or vomiting.

Key words: non-opioid analgesia, bupivacaine, tramadol, neostigmine, postoperative nausea and vomiting

Introduction

The addition of opiates in spinal anesthesia is well established to prolong the time of post-operative analgesic effect [1].

Due to the risk of respiratory depression, the non-opiate analgesia had been raised [2]. Tramadol had been used as an adjuvant to local anesthetic agents because it shows no neuro-toxicity [3], with minimal respiratory depression [4] and no pruritus nor itching [5] after intrathecal administration in comparison to opiates. Tramadol is a centrally acting analgesic agent, act on µ receptors with 6000 folds less affinity for the receptor in comparison to morphine [6]. Tramadol affects the noradrenaline, serotonin and 5-hydroxytreptamine reuptake at the spinal cord level potentiating analgesic effect [7, 8, and 9].

Cholinergic mechanism also involved in non-opioid analgesia if administered epidurally or intrathecally without neurotoxicity [10]. Neostigmine produces dose depended analgesia if introduced epidurally or intrathecally with no analgesic effect if introduced intravenously [11]. Intrathecal neostigmine produce a dose dependent nausea [12], for that its' use still restricted to small doses. The anticholinergic effect of neostigmine associated with more hemodynamic stability if it had been used as an adjuvant to local anesthetic agents in cesarean section [13-14]. A dose range from 1-10 µg/kg body weight resulted in prolonged postoperative analgesia, avoiding side effects like nausea and vomiting [15-16]. A dose of 50-100 µg intrathecal neostigmines had shown no analgesic effect. Neostigmine in a dose of 200 µg and more will propagate and prolong the effect of the local anesthetic agent [17].

The action of neostigmine is to inhibit the breakdown of acetylcholine which is increased in the CSF after trauma or operation [18-20].

The aim of the study is to detect and compare the effect of placebo, tramadol and neostigmine as an adjuvant to 0.5% bupivacaine in spinal anesthesia in major surgeries. To detect the effect of those adjuvants on the time of postoperative analgesia, side effects and if there is any motor latency.

Method:

After the ethical improvement and the signed consent form applied to all patients. Ninety cases aged 40-75 years, categorized class ASA II and ASA III, undergo major or super major orthopedic, Lower abdominal, perennial, abdominal and vaginal hysterectomy had been chosen to be enrolled randomly in this study. They had been divided into three groups according to a random allocation table formed by the SPSS PC program version 17. Group 1 (n=30) had received 4 ml of 0.5% bupivacaine with 0.5 ml normal saline (placebo group). Group 2 (n=30) had received 4 ml of 0.5% bupivacaine with 0.5 ml of fluid containing 20 µg/kg B wt. preservative free tramadol (tramadol group). Group 3 (n=30) had received 4 ml of 0.5% bupivacaine with 0.5 ml of fluid containing 2 µg/kg B wt. neostigmine (neostigmine group).

The vital signs of the patient had been recorded. The patient prepared with fluid load of 2 liters of 0.9% normal saline. The patient positioned laterally with proper demarcation at the vertebral column. Staining and toweling of the back of the patient for a proper sterility. L_{3-4} intervertebral space was used and G-22 3.5 inch spinal needle introduced. When clear CSF shown at the hub of the needle, 4ml of the

local anesthetic agent, bupivacaine 0.5% concentration with the adjuvant medication (0.5 ml of 0.9% normal saline or 0.5 ml preservative free tramadol or 0.5 ml neostigmine) injected intrathecaly. The position of the patient changed to supine position immediately with a small pillow to raise the head 15° from the supine level of the body. Diazepam in 5-10 mg dose given intravenously to the patient as sedation. Oxygen applied by simple face mask in a flow of 5 liters per minute. Small increments of intravenous ephedrine had been given, to the patients whose systolic blood pressure dropped below 90 mmHg.

Blood pressure, pulse rate, SpO_2 and ECG monitored through the time of operation. The level of anesthesia marked at the T_{10} level (around the umbilicus). Time of operation had been recorded. Any sign of nausea and vomiting had been recorded and an injection of 10 mg of Metaclopramide given intravenously.

The patient who had received the medications and the doctor who is going to follow up the patients during the postoperative period had been blinded from the type of medication. The time of motor regaining activity was recorded at the first sign the patient showing the ability to move his lower limb. Once the patient started to feel pain, the time is recorded, an analgesic rescue injection of intramuscular 75 mg Diclofenac sodium and intravenous 100 mg tramadol.

All the parametric data had been analyzed by One-way ANOVA test and the non- parametric data by Kruskall-Wallace test. The statistical significance was considered when p less than 0.05.

Results:

The demographic data of the patients are shown in the table (1). There is no statistical significance in between groups. Tables (2) and (3) describing the hemodynamic changes in each group. The results show no statistical significance ($p > 0.05$)

Table (4) show the time of motoric regaining activity (motor latency) and the time of the first rescue dose of analgesia. The results show no statistical significance between the groups in the case of motor latency, the placebo group had recorded 153±47 minutes while tramadol and neostigmine had recorded 185±48 and 155±46 respectively ($P > 0.05$). In the case of postoperative analgesia and the time of first analgesia rescue the placebo group had recorded 153±37 minutes while tramadol and neostigmine groups had recorded 368±59 and 377±67 minutes respectively. This result carrying a statistical significance ($p < 0.05$).

Table No.1 showing the demographic and the preoperative data

	Group of patients					
	Bupivacaine		Tramadol + Bupivacaine		Neostigmine + Bupivacaine	
	Mean±SD	Count	Mean±SD	Count	Mean±SD	Count
Years	59±10		59±11		60±9	
Male/Female						
Male		19		18		21
Female		11		12		9
Kg	78±15		79±15		78±14	
Cm	169±11		170±11		172±10	
Time of operation	82±24		83±27		84±23	
Type						
Orthopedic		20		20		23
G. Surgery		7		5		6
Gynecologic		3		5		1

Table No.2 showing the changes in blood pressure

	Group of patients			P
	Bupivacaine	Tramadol + Bupivacaine	Neostigmine + Bupivacaine	
	Mean±SD	Mean±SD	Mean±SD	
Systolic blood pressure before surgery	140±12	134±12	141±12	0.071
Systolic blood pressure 15 minutes after induction	87±10	81±11	86±12	0.085
Systolic blood pressure at the end of operation	92±9	92±9	96±13	0.292

Table (5) showing the rate of headache and nausea/vomiting between groups. The statistical significance is well noticed in the incidence of nausea/vomiting. The neostigmine group had recorded the highest group, as 80% (24 patients out of 30) had developed PONV while in tramadol and placebo groups was 16.7% (5 patients) and 10% (3 patients only) respectively. This result shows a statistical difference with $p < 0.05$.

Table No. 3 showing the changes in pulse rate

	Group of patients			P
	Bupivacaine	Tramadol + Bupivacaine	Neostigmine+Bupivacaine	
	Mean±SD	Mean±SD	Mean±SD	
Pulse rate before induction	93±8	96±11	93±10	0.540
Pulse rate 15 minutes after induction	74±8	79±10	75±11	0.128
Pulse rate at the end of operation	78±10	81±8	79±8	0.469

Table No.4 showing the time of motoric recovery and the time of first rescue analgesic dose

	Group of patients			P
	Bupivacaine	Tramadol + Bupivacaine	Neostigmine + Bupivacaine	
	Mean±SD	Mean±SD	Mean±SD	
Regain activity after induction	153±47	165±48	155±46	0.603
Time of 1st analgesic dose	173±35	368±59	377±67	0.0001

Table No. 5 showing the incidence of nausea and vomiting

		Group of patients			P
		Bupivacaine	Tramadol + Bupivacaine	Neostigmine + Bupivacaine	
		Count (%)	Count (%)	Count (%)	
Nausea/Vomiting	None	27 (90%)	25 (83.3%)	6 (20%)	0.0001
	Present	3 (10%)	5 (16.7%)	24 (80%)	
Headache	None	19 (63.3%)	19 (63.3%)	23 (76.7%)	0.447
	Present	11 (36.7%)	11 (36.7%)	7 (23.3%)	

Discussion:

In this study, we had compared three groups of patients; all of them had gone under major or super major operation. Bupivacaine is a potent local anesthetic agent, without neurological toxicity with wide safety margin, and can be used in several concentrations to induce a wide range of block, starting from analgesia ending to anesthesia when applied intrathecally or epidurally. The addition of small doses of opiates had shown a propagation of the effect of analgesia of the local anesthetic agents, but still the opiates carrying a wide range of unwanted side effects like nausea, vomiting, respiratory depression, itching and pruritus [1, 4 and 6]. The idea of non-opiate additives had shown a good effect and prolonged the analgesia produced by the local anesthetic agents. While we are still looking for the optimum effect with the least possible and most tolerable side effects those agents may carry when they applied intrathecally. Tramadol is an agent which we can consider as a non-opiate drug, as it shown an affinity to μ opiates receptors, with less than 6000 folds affinity to the receptors in comparison to morphine [6-9]. It produces a double fold prolongation of analgesia. In this study it had been noticed that the first analgesic rescue dose in the group of placebo-bupivacaine was after 220 minutes, while the addition of 10-20 μg/kg body weight tramadol will increase the time up to 510 minutes, with no mentionable unwanted side effects, and no motoric latency. This result goes with the other studies [1-9]. Although one of the worst side effects of tramadol intravenously was nausea and vomiting, in this study only 5 patients out of 30 developed nausea and vomiting which is insignificant in comparison to bupivacaine alone (3 cases out of 30).

Neostigmine, has no analgesic when given alone, but when added to local anesthetic agents, it shows a prolongation of the analgesic effect. In this study, neostigmine when added in a dose of 1-2 μg/kg body weight had raised the analgesic effect up to 500 minutes without any motoric latency, against the study of *Liu ET AL*, which shows a prolongation of motoric and sensory block of bupivacaine. Still nausea and vomiting recorded as a side effect of neostigmine in this study (24 cases out of 30), in

spite of the small dose that had been used (1-2 µg /kg body weight). A single dose of 10 mg metaclopramide was efficient to stop the nausea and vomiting with the patients. This result gose with the studies of *Liu ET AL, Lauretti ET AL and Ross ET AL.*

Conclusion:

The addition of tramadol or neostigmine in small doses as an adjuvant to bupivacaine was a safe procedure and carrying the least side effects without any motoric latency. Tramadol is more superior to neostigmine, as it shows no increase in the incidence of postoperative nausea and vomiting in comparison to bupivacaine group.

The PONV restricting the use of neostigmine.

For further studies to reveal the effect of dexamethasone as an anti-emetic with neostigmine. The effect of neostigmine plus tramadol as an adjuvant to bupivacaine in spinal anesthesia.

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