Comparative Study Between Intrathecal Morphine-Bupivacaine and Tramadol-Bupivacaine in Major Lower Limb Orthopedic Surgery

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Abstract: Background: Spinal anesthesia is the most common performed method in prolonged lower limb surgeries. Bupivacaine is routinely used with addition of a number of adjuvants to increase its duration and potency of analgesia such as opioids and Tramadol. Objective: aimed to compare the effect of intrathecal morphine-bupivacaine and tramadol- bupivacaine on the onset and duration of sensory and motor blokade, as well as postoperative analgesia in major lower limb orthopedic surgery. **Patients and methods:** Patients of either sex, aged 18 to 55 years, American Society of Anasthesiologists (ASA) grade I and II undergoing major lower limb orthopedic surgery were enrolled in this study. January to December 2015 at anesthiology and ICU department in Said Galal, Al-Azhar University Hospital. Patients were randomly categorized into two groups (30 of each): **Group BT:** Received heavy bupivacaine 0.5% 15 mg (3 ml) mixed with Tramadol 25mg (0.5 ml). **Group BM:** Received heavy bupivacaine 0.5% 15mg (3 ml) mixed with morphine sulphate 0.2 mg (0.5 ml). Monitoring of vital parameters, mean blood pressure, respiratory rate, oxygenation, onset of spinal analgesia, level of sensory block, onset of motor block, time of two segment regression post operative analgesia, time of post operative analgesic supplementation after 4 to 8 hours from intrathecal injection, post operative changes in sedation score, respiratory depression and post operative complications (vomting, pruritis, shivering, post dural puncture headache, nurological complications. **Results:** there's no significant difference between both groups as regard time of onset of spinal analgesia, level of sensory block, onset of motor block, time of two segment regression post operative analgesia, time of post operative analgesic supplementation and post operative complications (vomting, pruritis, shivering, post dural puncture headache, nurological complications. But there is a significant difference between them as regard respiratory depression and pruritis. **Conclusions:** Addition of tramadol to heavy bupivacaine can provide the same degree of motor and sensory blockade, the same sensory level, with less side effects and respiratory depression.
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1. Introduction

Spinal anaesthesia with 0.5% hyperbaric bupivacaine is routinely administered nowadays for major lower limb surgery. To increase the duration of analgesia produced by local anesthesia, a number of adjuvants have been added like opioid to provide effective postoperative analgesia, at the cost of increased risk of respiratory depression **(Chakraborty et al., 2008).**

Tramadol, in contrast to a centrally acting opioid analgesic, has minimal respiratory depressant effect, because it has 6000 fold less affinity for μ receptors compared to morphine **(Scott et al, 2000).** It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity. Therefore, tramadol has the potential to provide effective postoperative analgesia, with no risk of respiratory depression after central neuraxial administration **(Tsai et al, 2001).**

Tramadol when used as an adjuvant to intrathecal bupivacaine for transurethral resection of the prostate (TURP) **(Alhashemi et al., 2003)**, did not decrease the postoperative morphine requirements. However, in another study, addition of tramadol to intrathecal bupivacaine significantly prolonged the duration of analgesia **(Chakraborty et al., 2008).** Therefore, the efficacy of intrathecal tramadol as an adjuvant to local anesthetics remains controversial and needs further investigation.

We hypothesized that addition of tramadol to bupivacaine would improve the block characteristics of intrathecal bupivacaine in patients undergoing major orthopedic procedures of the femur when compared to the effect of intrathecal morphine-bupivacaine. The primary outcome measure of the study was duration of sensory block.

2. Patients and Methods

This prospective, randomized study was carried out after local ethics committee approval and written informed consent of the participating subjects from January to December 2015 at anesthesiology and ICU

department and was carried on fourty adult patients in Said Galal, Al-Azhar University Hospital. 60 patients of either sex, aged 18 to 55 years, ASA grade I and II undergoing major lower limb orthopedic surgery were enrolled in this study.

Patients were randomly categorized into two groups (30 each).

Group BT: Received heavy bupivacaine 0.5% 15 mg (3 ml) mixed with Tramadol 25mg (0.5 ml).

Group BM: Received heavy bupivacaine 0.5% 15mg (3 ml) mixed with morphine sulphate 0.2 mg (0.5 ml).

Preoperative:

Demographic data (age, sex, height, weight) and monitoring of vital parameters: mean blood pressure, respiratory rate, oxygenation, onset of spinal analgesia, level of sensory block, onset of motor block, time of two segment regression post operative analgesia, time of post operative analgesic supplementation after 4 to 8 hours from intrathecal injection, post operative changes in sedation score, respiratory depression and post operative complications (vomting, pruritis, shivering, post dural puncture headache, nurological complications) were recorded.

Patients with infections at the site of injection, dermatologic conditions, septicemia or bacteremia, shock or severe hypovolemia, preexisting disease involving the spinal cord, increased intracranial pressure, coagulopathy or allergy to the study medications were excluded from study.

Operative:

All patients were hydrated with normal saline 500 ml after insertion of size 18 gauge cannula after application of standard monitors. Heart rate, arterial blood pressures, oxygen saturation and respiratory rate monitored at baseline and every 5, 10, 20, 40, 60 minutes then at 2, 4, 8, 12, 16 and 24 hours.

The skin of the back will be sterilizes by povidone-iodine solution with an abrasive sponge starting over the selected interspace and proceeding in a widening circle outwards, a sterile field drape is applied and povidone-iodine is wiped from the site with alcohol. A skin wheal was raised by local infiltration of lidocaine 2% 3 ml at level L3–4 or L4–5, with the patient in the sitting position. Spinal puncture will be performed using a 25-gauge spinal needle. Ephedrine 5 mg i.v. will be used as needed to treat hypotension (defined as a 20% decrease in main blood pressure from baseline value). Bradycardia (HR <50 beats /min) will be treated with atropine 0.5 mg i.v. as needed.

Sensory block tested by thermal sensation test every 2 min until the desired level will be reached.

Degree of motor block assessed using a modified bromage scale (1=complete motor block, 2= able to move feet only, 3= able to move knees, 4= able to raise the leg for less than 10 seconds, 5= able to raise the leg for at least 10 sec, 6= no detectable weakness) at 5, 10 min of the intrathecal injection and then every time of vas score evaluation after surgery until recovery of motor block will be detected.

After operation, pain at rest was assessed using a visual analogue scale (VAS) (0 for no pain, 10 for the worst pain the patient had ever experienced).

Level of sedation determined using Modified Wilson Sedation Scale: 1= wide awake, Oriented; 2= Drowsy but easily aroused; 3= Rousable to mild physical stimulation, 4= Unrousable to mild physical stimulation.

VAS and sedation scores were assessed by anesthesia resident blinded to the studied groups every half an hour for 2 hours then hourly for 4 hours. When the VAS score was more than 5 pethedine 0.25mg/ kg will be given intramuscularly and the time is recorded.

The amount of pethedine administered after operation, time to first analgesic dose were recorded.

Post operative complications (vomting, pruritis, shivering, post dural puncture headache, nurological complications) and respiratory depression (defined as a respiratory rate <12 bpm) were recorded.

Statistical analysis

The data were coded, entered and processed on an IBM-PC compatible computer using SPSS (version 20). The level $P < 0.05$ was considered the cut-off value for significance. Chi-square test X^2 was used to test the association variables for categorical data. ANOVA (Analysis of variance) evaluates the quality of several group means; was used to test the difference about mean values of some parameters among multiple groups. Fisher exact test was used instead of chi-square when one expected cell or more less than or equal 5. Unpaired t-test was used to compare quantitative variables, in parametric data (SD<50% mean) Paired t-test was used to compare quantitative variables in the same group. P value <0.05 considered significant.

3. Results

Patient characteristics (Table 1) and HR, MAP and oxygen saturation (Figures 1 - 3) were comparable in the two groups.

There was statistically significant fall in HR and MAP in both the groups after administration of intrathecal drug (Figure 1 and 2). However, their levels between two groups were statistically similar. Bradycardia was seen in only one patient in group BT and in four of the patients in group BM. Hypotension occurred in two patients in group BT and five patients in group BM. There was no statistically significant difference between both groups as regard to mean oxygen saturation (figure 3).

The sensory and motor block characteristics were statistically comparable in the two groups (Table 2).

As regard the onset of spinal analgesia, level of sensory block, onset of complete motor block, time of two segment regression, regression to Bromage zero, total dose of pethedine required postoperatively, time of rescue analgesic there were no significant differences between both groups.

As regard of pain evaluation intraoperatively and post operatively by VAS score, there were no significant differences between both groups (figure 4).

Seven patient (23.33%) in group BM complaining from mild respiratory depression with no patient in group BT. Eighteen patient (60%) had mild degree of pruritis in group BM and no patient in group BT with a significant difference between them (P = 0.034, P <0.01 respectively). The incidence of other postoperative side-effects was comparable in the two groups (table 3). Nausea was seen in two patients (6.67%) in group BT and 3 patients (10%) in group BM (P = 0.971). Three patients had an episode of vomiting (10%) in group BM as compared to one patient (3.33%) in group BT (P = 0.651). Shivering was observed in two patients (6.67%) in group BT and 3 patients (10%) in group BM (P = 0.971). No recorded cases of post dural puncture headache and neurological complication in both groups.

Table (1): Patient characteristics and duration of operation

	Group BT n=30	Group BM n=30	P value
Age (year)	44.30±5.50	46.00±4.24	0.07
Weight (kg)	85.60± 2.58	82.67±8.74	0.085
Height (cm)	166.50± 6.34	165.88±4.20	0.093
Sex (males: females)	24:6	23:7	0.77
ASA (I: II)	25:5	27:3	0.57
Duration of operation (min)	97.95±14.1	102.50±12.8	0.115

ASA = American Society of Anesthesiologists. Values are expressed as mean+SD or as number of patients

Table (2): Sensory and motor block characteristics:

	Group BT n=30	Group BM n=30	P value
Onset of analgesia (min)	6.65±2.85	5.40±3.17	0.114
Level of sensory block	8.8±1.50	8.90±1.21	0.412
Onset of complete motor blocks	16.15±3.70	14.25±3.81	0.054
Time of two segment regression	84.25±22.02	96.95±33.11	0.085
Regression to Bromage zero	184.25±47.82	204.50±53.89	0.129
Total dose of pethedine (mg)	47.5±9.83	43.6±8.68	0.108
Time to first rescue analgesic (hours)	5.89±1.87	6.31±1.11	0.294

Values are expressed as mean+SD

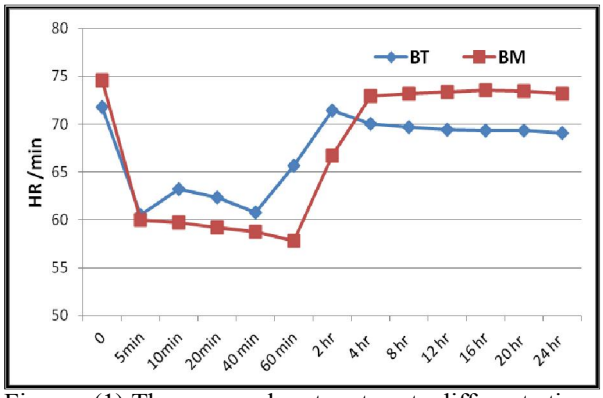

Figure (1):The mean heart rate at different time intervals

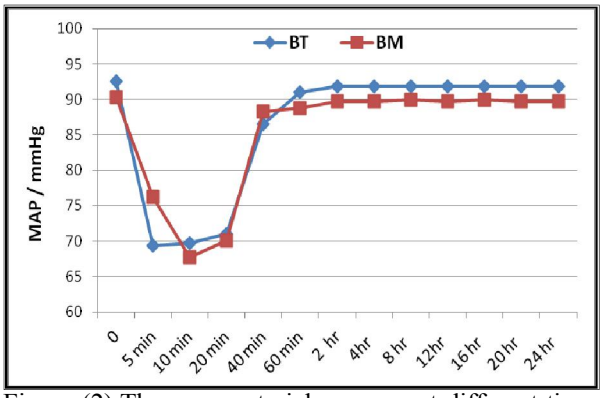

Figure (2):The mean arterial pressure at different time intervals

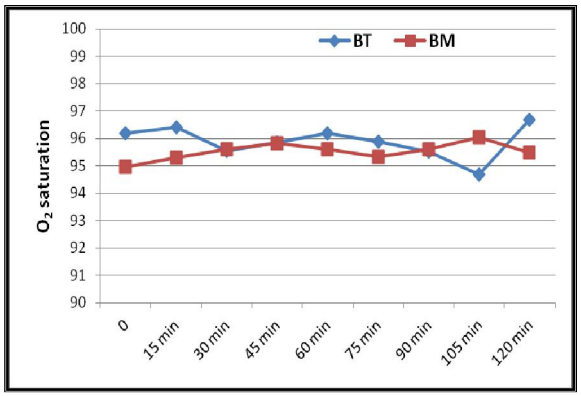

Figure (3): The mean O_2 saturation at different time intervals

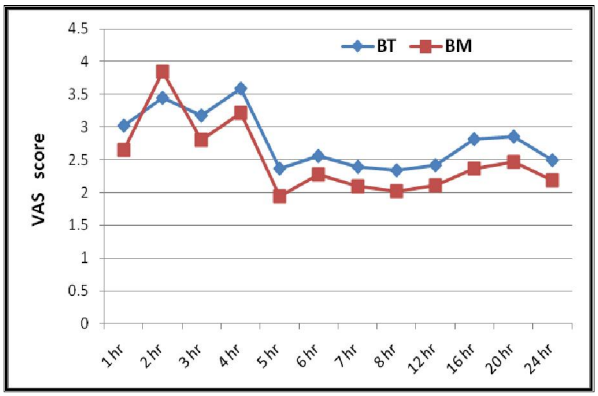

Figure (4): Mean VAS score at different time intervals

Table (3): Postoperative complications in two groups

	Group BT n=30		Group BM n=30		P
	N	%	N	%	
Nausea	3	10.00	2	6.67	0.971
Vomiting	3	10.00	1	3.33	0.651
Pruritis	0	0.00	18	60.00	<0.01*
Shivering	3	10.00	2	6.67	0.971
Respiratory depression	0	0.00	7	23.33	0.034*
Post dural puncture headache	0	0.00	0	0.00	-
Neurological complication	0	0.00	0	0.00	-

4. Discussion

Opioids have been used traditionally as adjuvants to local anesthetics in central neuraxial blocks to provide better anesthesia, improved quality of block without prolongation of motor blockade and to reduce the dose of local anesthetic agent being used. Lipophilic opioids like morphine, fentanyl and sufentanil have been used effectively for this purpose **(Chinachoti et al., 2013).**

However, they are associated with the development of complications such as respiratory depression, nausea, vomiting, pruritus and delayed voiding. Tramadol is a safer opioid which is known to have less respiratory depression **(Mohta et al., 2009).** Various doses of preservative free tramadol have been used alone or as an additive to bupivacaine in the subarachnoid space and have been found to be safe **(Alhashemi et al., 2003; Chakraborty et al., 2008).**

In the present study, a dose of 0.5 ml of tramadol (25 mg) mixed with 3 mL of heavybupivacaine 0.5% (15 mg) as a similar dose of 0.5 ml of morphine sulphate (0.2 mg) mixed with 3 mL of heavy bupivacaine 0.5% (15 mg) were used for major lower limb orthopedic surgeries.

The addition of 25 mg tramadol did not result in prolongation of the duration of action of intrathecal bupivacaine in the present study. There are contradictory reports in the literature on the efficacy of intrathecal tramadol **(Alhashemi et al., 2003; Chakraborty et al., 2008)**. When added to intrathecal bupivacaine, it prolonged the duration of analgesia in women undergoing gynecological (**Chakraborty et al., 2008**) or obstetric procedures **(Subedi et al., 2013)** but did not affect the postoperative morphine requirements or the time to first analgesic requirement in patients undergoing TURP (**Alhashemi et al., 2003**). Various theories have been proposed to explain the efficacy as well as the inefficacy of tramadol as an adjuvant in subarachnoid block. The failure to prolong the duration of analgesia may be because of its lesser affinity for μ receptors **(Scott and Perry, 2000)**, high lipophilicity leading to rapid diffusion out of subarachnoid space (**Alhashemi et al., 2003**) and anti-analgesic effects at low doses **(Wilder-Smith et al., 1998).**

Mechanism of action of tramadol is inhibition of re-uptake of both central and peripheral monoaminergic neurotransmitters (5-hydroxytryptamine and noradrenaline). **(Shipton, 2000).** It also has a local anesthetic like effect, that is blocking of action potential following subcutaneous administration **(Behdad et al., 2013)** and at the peripheral nerves **(Sousa et al., 2012).** However, another study, where tramadol was used as an adjunct to psoas compartment block with levobupivacaine 0.5%, failed to prove a clinical local anesthetic or

peripheral analgesic effect **(Mannion et al., 2005).** Lastly, **Brummet and Williams (2011)** have even recommended against the use of perineural tramadol.

Seven and eighteen patients had mild degree of respiratory depression and pruritis in group BM and no patient in group BT with a significant difference between them ($P = 0.034$, $P < 0.01$ respectively). This finding was in agree with several reports (**Alhashemi et al., 2003; Chakraborty et al., 2008; Mohta et al., 2009; Behdad et al., 2013; Subedi et al., 2013**) they concluded tramadol has less effect on respiratory depression with minimal side effects of pruiritis.

However, the incidence of nausea, vomiting and shivering was higher in the BM group than the BT group (10% vs. 6.67% for nausea, 10% vs. 3.33% for vomiting and 10% vs. 6.67% for shivering, respectively). This difference, although clinically relevant, could not achieve statistical significance. This could be because our sample size was not powered enough to study these side-effects. In agree with our findings; **Scott et al (2000)** have also pointed out that there may be a higher incidence of side-effects such as nausea and vomiting with the use of tramadol**.**

Conclusion

When compare the addition of tramadol 25 mg to heavybupivacaine 15 mg did not improve the sensory or motor block characteristics occurred when adding 0.2 mg morphine sulphate to heavybupivacaine 15 mg. Further trials with increased dose of intrathecal tramadol cannot be recommended in view of clinically significant higher incidence of nausea, vomiting and shivering with 25 mg intrathecal tramadol.

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