Assessment of Tramadol Added to Bupivacaine on Hemodynamics and Duration of Analgesic Effect in Spinal Anesthesia

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ABSTRACT

Background: Tramadol administered intrathecally has been demonstrated to decrease postoperative analgesic requirements. However, its effect on postoperative analgesia after intrathecal administration has not yet been studied extensively.

Objectives: To assess the effects of intrathecally administered tramadol with bupivacaine, on the duration of post-operative analgesia and its hemodynamic effects.

Methods: A prospective, randomized double blinded clinical study. the research was conducted at Baghdad Teaching Hospital and Al Yarmouk Teaching Hospital, and it lasted from August 2021 until August 2022. It involved 60 participants divided into two groups. Group T**,** involves 30 patients who received bupivacaine 0.5% three ml intrathecally premixed with tramadol 25 mg (0.5 ml), which served as active group. Group C, involves 30 patients who received bupivacaine 0.5% three ml intrathecally premixed with 0.5 ml normal saline, which served as placebo.

These 60 patients underwent surgery under spinal anesthesia. Blood pressure, heart rate, oxygen saturation (SpO_2), Visual Analogue Scale (VAS) score, and the time of first analgesia required by the patients were recorded and compared between the two groups.

Results: Mean arterial blood pressure, heart rate, and SpO_2 were assessed during the first 24 hours. There was no significant difference between either group (p-value≥0.05). Median Visual Analogue Scale score was significantly higher in group C compared to group T (3, 3, 4, 4, and 4 vs. 1, 2, 2, 2, and 2 respectively at 3, 6, 12, 18 and 24 hours respectively, p-value<0.05 for all periods of follow-up). The duration of analgesia was significantly longer in group T compared to group C (269.1 ± 39.8 vs. 384.3 ± 45.3 minutes, p-value <0.001).

Conclusions: The use of intrathecal tramadol as an add on medication with 0.5% bupivacaine in spinal anesthesia for minor surgical procedures results in better pain control and longer duration of analgesia effect of bupivacaine, reduction in the postoperative analgesic requirement, and show similar hemodynamic stability in comparison to bupivacaine alone.

Keywords: Bupivacaine, Spinal anesthesia, Pain, Tramadol.

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The use of local anesthetic drugs injected into the subarachnoid space to create a reversible loss of sensation and motor function is known as spinal anesthesia (SA). Local anesthetic injections in the subarachnoid area might cause hemodynamic and respiratory abnormalities. Certain unwanted consequences of spinal anesthesia could be avoided if anesthesia for the operative field could be limited[(1)].

Procedures below the umbilicus, obstetric/gynecologic treatments, genitourinary surgeries, and orthopedic procedures from the hip down are all performed in SA. Furthermore, it is an effective approach for patients who are unable to tolerate general anesthetic medications. August Bier performed the first planned SA for surgery in Kiel in 1898, when he injected 3 cc of 0.5 percent cocaine solution into a 34-year-old laborer[(2)].

Neuraxial blockade applied for surgery has been shown to reduce postoperative mortality and additional serious

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complications after surgery. These include deep vein thrombosis, pulmonary embolism, pneumonia, and respiratory depression, as well as transfusion requirements [3]. Inadequate analgesia during the postoperative period can also lead to numerous adverse consequences, including hemodynamic instability (tachycardia, hypertension, vasoconstriction), increased catabolism, impaired immune response, and altered platelet activation. These are particularly undesirable in patients with numerous pre-existing comorbidities or following cardiac surgery[4].

The addition of opioids to local anesthetic intensifies the quality of the sensory block produced by local anesthetic alone. When used properly, intrathecal (IT) opioids provide analgesia that is often superior to that achieved via the epidural and intravenous (IV) routes. Furthermore, when used in appropriate (low) doses, IT opioids result in a side effect profile similar to that of systemic opioids with one exception; pruritus tends to occur more commonly with IT opioids. Finally, spinal is easier to perform than an epidural[4].

Side effects of spinal opioids, nausea, vomiting, urinary retention, pruritus, and respiratory depression, are the same as intravenous opioids, although pruritus may be more severe with the IT route. Older literature contains case reports of severe respiratory depression progressing to respiratory arrest with IT opioids. It is now known that doses used in such cases were excessive. Indeed, most of the side effects are dose-related, with doses greater than 0.5 mg IT morphine resulting in significant side effects [5]. Pruritus is the one side effect that is uniquely worse with IT opioids as compared with IV opioids, and that seen with sufentanil is worse than with fentanyl[6].

Bupivacaine is an amide-type local anesthetic that is capable of producing prolonged analgesia. This agent provides high quality analgesia in the postoperative period. It was discovered in 1957. Bupivacaine is available as a generic medication and is not very expensive [7].

Local anesthetics are used in regional anesthesia, epidural anesthesia, spinal anesthesia, and local infiltration. Local anesthetics generally block the generation of an action potential in nerve cells by increasing the threshold for electrical excitation. The progression of anesthesia is dependent on factors such as the diameter, degree of myelination, and conduction velocity of nerve fibers. In clinical practice, the order of a loss of nerve function is as follows: pain, temperature, touch, proprioception then skeletal muscle tone [8].

The dose of bupivacaine depends on the procedure, the vascularity of the tissue, the area, the number of segments blocked, the depth or duration of anesthesia needed, and the patient's physical condition. Bupivacaine may interact with ergot medications used for migraine headaches, blood thinners, antidepressants, or monoamine oxidase inhibitors. Immunologic reactions to local anesthetics are rare. Allergic reactions to preservative-free amide-type local anesthetics are rare and usually not reported. A true anaphylactic response appears more common with ester local anesthetics or preservatives; epinephrine-containing local anesthetics reactions are often misdiagnosed as allergic reactions. Patients may also react to preservatives such as methylparaben, which are included with local anesthetics. Methemoglobinemia is typically associated with benzocaine or prilocaine; however, case reports exist implicating bupivacaine in rare instances. At low levels (1% to 3%), methemoglobinemia can be asymptomatic, but higher concentrations (10% to 40%) may accompany cyanosis, cutaneous discoloration (gray), tachypnea, dyspnea, exercise intolerance, fatigue, dizziness, syncope, and weakness. Some more common adverse effects include nausea, vomiting, chills or shivering, headache, back pain, dizziness, sexual dysfunction, restlessness, anxiety, vertigo, tinnitus, blurry vision, tremors which may precede more severe adverse effects such as convulsions, myoclonic jerks, coma, and cardiovascular collapse[9].

The aim of this study is to assess the effects of intrathecally-administered tramadol with bupivacaine, on the duration of post-operative analgesia and its hemodynamic effects.

Methods

A prospective, randomized double-blinded clinical study. The research was conducted at Baghdad Medical City Hospital and Al Yarmouk Teaching Hospital, and it lasted from August 2021 until August 2022. It involved 60 participants divided into two groups:

A. Group T: involved 30 patients who received bupivacaine 0.5% three ml intrathecally premixed with tramadol 25 mg (0.5 ml), which served as active group.

B. Group C: involves 30 patients who received bupivacaine 0.5% three ml intrathecally premixed with 0.5 ml normal saline, which serves as placebo.

Ethical consideration: The scientific council of anesthesia specialization of the Iraqi Board of Medical Specializations gave approval for this study. Written consents were taken from all those who participated in the study.

Inclusion criteria

1. Patients with ASA physical status I–II (according to the American Society of Anesthesiologists classification; ASA I = healthy patient, ASA II = patient with mild systemic disease).
2. Both genders (male and female).
3. Age 20 – 60 years.
4. Weight 60 – 85 kg.
5. Height 160 – 172 cm.
6. Spinal anesthesia for testicular varicocele, anal fissure, vaginal tear repair, and operations of the lower limbs.

Exclusion criteria

1. Lack of cooperation due to any cause.
2. History of allergies to any medication used in the study.
3. Any contraindication to spinal anesthesia.
4. Chronic users of analgesic medications specifically tramadol.

Patients were evaluated and prepared for surgery by taking their medical and surgical history, performing a general examination, and conducting laboratory tests. All patients received 1 mg midazolam IV before the procedure.

- The anesthetic process was described to the patient, and all patients gave their informed verbal consent.
- Before beginning the spinal anesthesia, adequate resuscitation equipment and emergency medications were ready and close at hand.
- All procedures were done under aseptic conditions and techniques.
- Any operation that exceeds one hour duration were excluded.
- ECG, pulse oximeter, and noninvasive blood pressure were employed for intraoperative monitoring.
- Visual Analogue Score was used for assessment of pain.

Before any further procedures, all patients had two large bore IV lines and crystalloid fluids (glucose saline) 10 – 15 mg/kg were given to all patients within 30 minutes as preload. Patients were placed in a setting position. The lumbar area was prepared aseptically and draped. The intervertebral space of L3–L4 was identified, and spinal anesthesia performed with a 25–gauge Quincke needle with midline approach and bevel facing downward. When intrathecal placement of the needle was confirmed with free flow of CSF, 3.0 mL (15 mg) of 0.5% hyperbaric bupivacaine was injected using 5-mL syringe over a period of 60 second (0.3 mL/10 second). After injecting the local anesthetic, the patients returned to supine position. For group T, 25 mg tramadol was added to the 15 mg 0.5% hyperbaric bupivacaine and injected to the patients. And group C patients received bupivacaine 0.5% three ml intrathecally premixed with 0.5 ml normal saline.

Demographical data (age, and gender), BMI (body mass index) were obtained from all participants. All patients were monitored for their; SpO_2, mean arterial blood pressure (MAP), and heart rate (HR), and visual analogue score for pain (VAS) at baseline, every 10 minutes for the first 60 minutes, then every hour for the first 6 hours, and then 3 hours, 6 hours, 12 hours, 18 hours and 24 hours of follow-up.

Additionally, duration of pain free period was recorded (defined as the time the patient asked for additional analgesia [100 mg IV tramadol], or pain above 4 on VAS score.

All analysis was carried out using SPSS version 24.1 and figures drawn using GraphPad Prism 9.1. To compare the difference between two means independent t-test used, while chi square test to test the difference between two categorical variables. P-value was considered to be significant if <0.05.

Results

The study included 60 participants, the patients were divided into two groups, group C contained 30 participants and group T contained 30 participants. There was no significant difference in terms of age, gender, BMI, and ASA, (Table 1).

Mean arterial blood pressure (MAP) was assessed during the first 24 hours, and there was no significant difference between either groups, (Table 2).

Table 1: Demographic distribution of study sample (n=60).

Variables	Group C n = 30	Group T n = 30	P value
Age (y), mean (SD)	37.5(±11.1)	39.9 (±11.8)	0.420
Gender, no. (%)			0.405
Female	11 (36.7)	8 (26.7)	
Male	19 (63.3)	22 (73.3)	
BMI, mean (SD)	28.1 (±3.5)	27.5 (±3.6)	0.506
ASA, no. (%)			0.559
I	21 (70.0)	23 (76.7)	
II	9 (30)	7 (23.3)	

Table 2: Mean arterial blood pressure of study sample (n=60).

Variables	Group C n = 30 mean (SD)	Group T n = 30 mean (SD)	P value
Baseline	81.4±6.0	79.6±6.2	0.257
10 min	67.6±5.3	69.5±6.3	0.212
20 min	69.3±6.5	65.5±8.6	0.055
30 min	69.8±5.8	66.6±6.9	0.054
40 min	71.0±6.9	69.1±6.4	0.253
50 min	71.7±6.8	73.6±6.0	0.264
60 min	73.1±10.3	70.4±7.9	0.263
3 hrs.	77.4±7.1	74.9±9.3	0.252
6 hrs.	77.9±9.3	75.2±9.9	0.284
12 hrs.	78.6±6.2	77.5±10.1	0.620
18 hrs.	80.8±9.7	82.5±9.2	0.482
24 hrs.	79.5±9.3	76.0±7.8	0.110

Heart rate (HR) was assessed during the first 24 hours, and there was no significant difference between both groups. Overall, there was no significant difference between all groups when assessed using two – AVOVA analysis (p-value = 0.431), (Table 3).

SpO2 was assessed during the first 24 hours, and there was no significant difference between both groups, overall. There was no significant difference between all groups when assessed using two – AVOVA analysis (p-value = 0.509), (Table 4).

VAS did not follow normal distribution this required to the median and interquartile range (IQR, 25th to 75th percentile) to represent its value instead of mean and standard deviation. VAS score was significantly lower in group T, from 3 hours till the end of 24 hours, (Table 5).

Duration of analgesia was significantly longer in group T, (Table 6).

The use of rescue tramadol when a break though pain occur was higher in group C compared to group T, (Figure 1).

Table 3: Heart rate of study sample (n=60).

Variables	Group C n = 30 mean (SD)	Group T n = 30 mean (SD)	P value
Baseline	84.5±9.0	85.0±7.7	0.806
10 min	111.7±10.0	109.9±3.4	0.362
20 min	114.9±9.4	113.2±6.6	0.428
30 min	117.3±8.4	114.1±5.9	0.095
40 min	108.1±4.3	106.6±2.4	0.083
50 min	95.3±3.1	93.8±6.0	0.221
60 min	94.4±3.0	93.1±3.9	0.148
3 hrs.	82.3±3.8	80.3±4.8	0.081
6 hrs.	80.8±5.5	78.7±3.0	0.070
12 hrs.	78.7±2.6	77.0±4.9	0.108
18 hrs.	76.9±3.6	75.5±2.9	0.109
24 hrs.	78.1±4.5	77.2±3.2	0.374

Table 4: SpO_2 of study sample (n=60).

Variables	Group C n = 30 mean (SD)	Group T n = 30 mean (SD)	P value
Baseline	97.6±1.0	97.3±0.9	0.234
10 min	97.5±1.0	97.5±0.9	0.836
20 min	97.3±0.9	97.6±0.9	0.227
30 min	97.6±0.9	97.4±0.9	0.248
40 min	97.4±0.9	97.3±0.8	0.859
50 min	97.5±0.9	97.3±1.0	0.399
60 min	97.5±1.1	97.8±0.8	0.167
3 hrs.	97.6±0.9	97.5±0.9	0.844
6 hrs.	97.4±0.9	97.7±0.7	0.164
12 hrs.	97.5±1.0	97.4±0.9	0.639
18 hrs.	97.3±0.8	97.5±0.8	0.469
24 hrs.	97.5±0.8	97.2±0.9	0.191

Table 5: VAS of study sample (n=60).

Variables	Group C n = 30 mean (SD)	Group T n = 30 mean (SD)	P value
Baseline	0 (0 – 0)	0 (0 – 0)	-
10 min	0 (0 – 0)	0 (0 – 0)	-
20 min	0 (0 – 0)	0 (0 – 0)	-
30 min	0 (0 – 0)	0 (0 – 0)	-
40 min	0 (0 – 0)	0 (0 – 0)	-
50 min	0 (0 – 0)	0 (0 – 0)	-
60 min	0 (0 – 0)	0 (0 – 0)	-
3 hrs.	3.0(1.8 - 4.0)	1.0(0.0 - 2.0)	<0.001
6 hrs.	3.0(1.8 - 4.3)	2.0(1.0 - 2.3)	0.001
12 hrs.	4.0(2.0 - 5.0)	2.0(1.0 - 3.0)	<0.001
18 hrs.	4.0(2.5 - 5.0)	2.0(0.8 - 3.0)	0.002
24 hrs.	4.0(2.8 - 6.0)	2.0(0.0 - 3.3)	0.001

Table 6: Duration of analgesia of study sample (n=60).

Variables	Group C n = 30 mean (SD)	Group T n = 30 mean (SD)	P value
Duration of analgesia (min)	269.1 ± 39.8	384.3 ± 45.3	<0.001

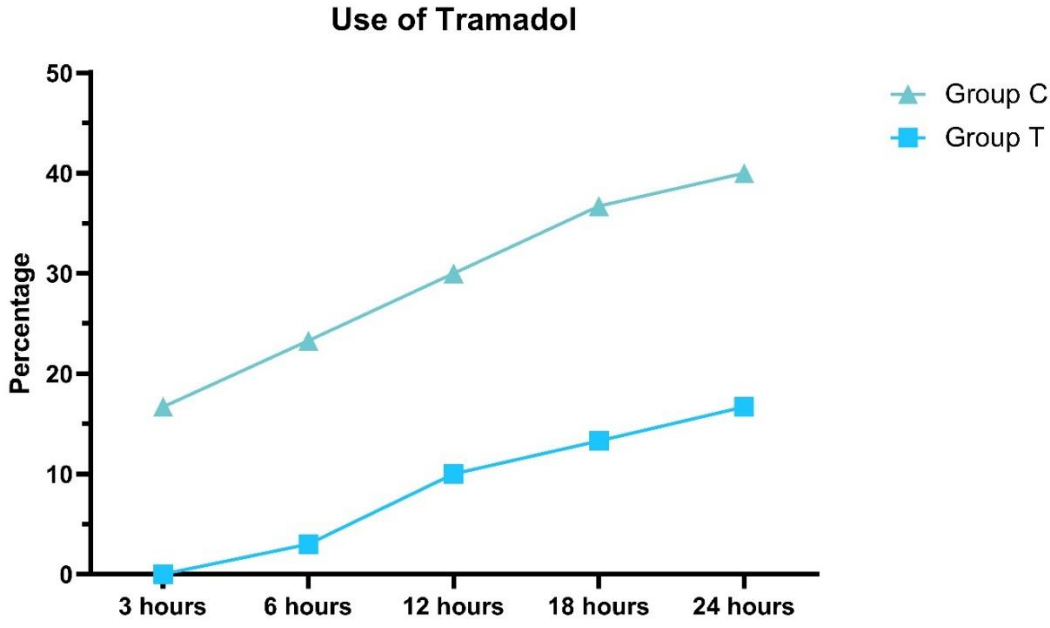

Figure 1: Percentage of need of rescue tramadol.

Discussion

After spinal anesthesia, tramadol, a centrally acting analgesic drug, has a terminal elimination half-life of 5.5 hours and produces clinical analgesia for a period of 10 hours[11,12]. The μ- receptors, and to a lesser degree the δ and κ receptors, are the ones that are stimulated by tramadol. It does this by reducing the reuptake of both norepinephrine and serotonin, which in turn activates the spinal inhibition of pain. Tramadol induces less respiratory depression and pruritus than morphine does, despite the fact that it is only one-fifth as strong as morphine as an analgesic. Other research has shown evidence that tramadol may have a local anesthetic impact on the nerves that make up the peripheral ganglia [13].

According to the findings, the duration of analgesia supplied by intrathecal injection of 25 mg tramadol combined with 15 mg of 0.5 percent hyperbaric bupivacaine was much longer than that provided by intrathecal bupivacaine alone (384.3 ± 45.3 vs. 269.1 ± 39.8 minutes). This was in agreement with several other studies, such as the one conducted by Chakraborty et al.

Sixty-four patients having transurethral resection of the prostate were studied by Alhashemi and Kaki, who found that the tramadol group had a longer time to initial analgesia after receiving bupivacaine 0.5 percent 3 ml intrathecally premixed with tramadol 25 mg compared to saline 0.5 ml (7.6 vs. 6.3 hours) [14].

A total of 186 patients with ASA I or II who were scheduled to undergo emergency open appendicectomy were evaluated in the research by Afolayan et al. Intrathecally administered tramadol 25 mg was combined with 3 ml of 0.5 percent hyperbaric bupivacaine in one group, while normal saline was used in the other. Patients in the tramadol group took noticeably more time before asking for pain relief (238.39 vs. 146.59 minutes) [15].

Other studies tested the effect of tramadol compared of other opioids, like in Ozer et al. study in which the anesthetic and analgesic efficacy of intrathecal tramadol hydrochloride was assessed against a local anesthetic. In this study, they found that the saline group experienced more pain than patients in the tramadol HCL and fentanyl groups ($p<0.05$). The incidence of complications was similar, they found no significant difference in MAP, HT, and SpO_2 between the three groups, and no significant differences in onset of analgesia[16].

Chatrath et al. [17] compared the addition of 25 mcg fentanyl and 25 mg tramadol with the administration of levobupivacaine during combined spinal-epidural anesthesia in labor. Adding tramadol to a local anesthetic provided prolonged analgesia with minimal side effects. Fentanyl, when used as adjuvant to a local anesthetic, has a rapid onset of analgesia but may have certain fetomaternal side effects. Frikha et al. [18] compared tramadol and sufentanil used in combined spinal-epidural analgesia in terms of the duration of analgesia and frequency of adverse maternal or fetal effects. A dose of 2.5 mcg intrathecal sufentanil combined with 2.5 mg bupivacaine provided rapid-onset and profound analgesia during the first stage of labor without adverse maternal or fetal effects. Administration of 25 mg intrathecal tramadol with 2.5 mg bupivacaine had longer-lasting analgesia. The major side effect was vomiting Subedi et al. [19] evaluated the effect of intrathecal tramadol on spinal block characteristics and neonatal outcome after an elective caesarean section. Tramadol 10 mg, as an adjunct to bupivacaine for subarachnoid block for caesarean section, showed a longer duration of analgesia with a reduced incidence of shivering compared with intrathecal fentanyl 10 μg [19].

Afolayan et al. evaluated the effectiveness of intra-operative analgesia produced by intrathecal tramadol and fentanyl during bupivacaine spinal anesthesia for an open appendectomy. They demonstrated that intrathecal trama-dol (25 mg) could safely replace intrathecal

fentanyl (25 µg) in the management of visceral pain and discomfort during a subarachnoid block for an appendectomy. The pain-free period, however, was significantly longer in the fentanyl patient group than the tramadol group [15].

In conclusion; the use of intrathecal tramadol as an add on medication with 0.5% bupivacaine in spinal anesthesia for minor surgical procedures results in better pain control and longer duration of analgesia effect of bupivacaine, reduction in the postoperative analgesic requirement, and show similar hemodynamic stability in comparison to bupivacaine alone

We recommend using tramadol in a 25 mg dose premixed with bupivacain in spinal anesthesia for better pain control and lower postoperative analgesic requirement.

Further studies are needed to determine the benefits and safety of tramadol as an add-on in large patients' number, different types of operation, and different types of patients.

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