A DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE ANALGESIC EFFECTS OF TRAMADOL AND BUPRENORPHINE IN PATIENTS UNDERGOING LOWER ABDOMINAL AND LOWER LIMB SURGERIES UNDER SPINAL ANESTHESIA WITH 0.5% BUPIVACAINE

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Abstract

Background: Intrathecal opioids are routinely used as adjuncts to local anesthetics (LA) in spinal anesthesia (SA). Buprenorphine is a mixed opioid agonist-antagonist with high affinity for mu and kappa opiate receptors while tramadol (TDL) is an opioid having low affinity for opioid receptors. The effects of intrathecal TDL with bupivacaine were compared to intrathecal buprenorphine with bupivacaine for post-operative analgesia in lower abdominal and lower limb surgeries.

Methods: A total of 132 patients undergoing specified surgeries (lower abdominal/limb) under SA were randomized to receive 3 ml of hyperbaric bupivacaine premixed with either 60 mcg buprenorphine (Group BB), tramadol 10 mg (Group BT), or 0.2 ml normal saline (Group BS). Postoperative details of visual analog scale (VAS) score for pain, time to first analgesic requirement, total analgesic requirement, and adverse effects for 24 hours post-operative period were recorded.

Results: Prolonged post-operative analgesia was observed in Group BB (549.09±103 min) compared to Group BT (446.48±77.40 min) and Group BS (312.73±30.45 min). The reduction in post-operative shivering was noted

	in TDL group. Post-operative rescue analgesic requirement was significantly lesser in group buprenorphine (P=0.042). **Conclusion:** Intrathecal buprenorphine showed a longer duration of action with lesser postoperative rescue analgesic requirement as an adjunct to bupivacaine for subarachnoid block than intrathecal tramadol.

Introduction

Mitigating and controlling pain is one of the most important issues presently being addressed by the scientific community and healthcare professionals. Pain is a consistent and prominent complaint of many individuals following most surgical interventions.[1] Till date, various modalities have been tried to relieve postoperative pain. SA with various drugs to prolong the length of action have been attempted. The first operation with SA was performed by August Bier on August 16, 1898 at The Royal Surgical Hospital of the University of Kiel, Germany.[2]

SA is reliable, easy to perform, safe, and time tested due to which it is considered as the most preferred regional anesthesia technique. It is economical, less infectious, has a low failure rate and produces rapid onset of anesthesia and muscle relaxation.[1,3] SA with hyperbaric (0.5%) bupivacaine is normally administered for lower abdominal/lower limb (LALL) surgeries. To surge the period of analgesia produced by LA, several adjuvants are added. Intrathecal opioid administration has been practically proven to provide effective postoperative analgesia for different surgical procedures, although at the cost of increased jeopardy of respiratory depression**.**

Buprenorphine is a mixed agonist antagonist narcotic with high affinity at both μ and κ opiate receptors. Buprenorphine, being compatible with CSF, does not produce adverse reactions when administered intrathecally. At low doses, buprenorphine produces minimal adversities with a long period of action, making it a suitable choice for intrathecal administration.[4] In contrast, TDl, a centrally acting opioid has minimal respiratory depression[5] because it has 6000 times less affinity for opioid μ receptors as opposed to morphine. In cord, it also inhibits nor-epinephrine and serotonin reuptake and has no reported neural toxicity.[6] TDL is more widely available across the world because of lesser government regulations.[7] When administered epidurally, TDL has been demonstrated to provide adequate postoperative analgesic effect after chief abdominal surgery and caesarean section.[8] However, its effect on post-operative pain after administration intrathecally has not been well studied.

This study was to assess the effects of intrathecal TDL with bupivacaine compared to intrathecal buprenorphine with bupivacaine on duration of postoperative analgesia in lower abdominal and lower limb (LALL) surgeries.

Methods

The study was conducted on 132 patients undergoing LALL surgeries at a tertiary hospital between October 2014 and September 2016 after obtaining written informed consent. During preoperative evaluation, patients were educated about assessment of perioperative pain using a visual analogue scale (VAS), ranging from 0 (no pain) and 10 (worst pain). Patients were randomly divided into

three groups BB, BT and BS by picking lots on the day of surgery. Group BB received 3 ml of 0.5% bupivacaine (heavy) plus 60 mcg buprenorphine intrathecally, group BT received 3 ml of 0.5% bupivacaine (heavy) plus 10 mg of preservative-free TDL intrathecally, whereas group BS received 3 ml of 0.5% bupivacaine (heavy) plus 0.2 ml normal saline (control group).

To facilitate blinding, a resident anesthetist not involved in the study prepared the solutions for SA. After securing intravenous access with an 18G cannula, patients were preloaded with 10 ml/kg of Ringer Lactate over 10 minutes. Pulse oximetry, electrocardiogram and noninvasive blood pressure were applied and baseline values recorded. Under strict aseptic precautions, SA was performed using a 25G Quincke's needle inserted at L3-4 or L4-5, with patient in sitting position. After free flow of cerebrospinal fluid, the study solution was administered, following which patients were placed supine. Supplemental oxygen was delivered at 4 L/min through face mask. Vital parameters were monitored intraoperatively. The onset of sensory blockade was tested by pin prick test (PPT) at the level of L1. The level of sensory anesthesia, defined as loss of sensation to PPT was noted bilaterally, and duration of sensory blockade was recorded. The length of sensory blockade was counted from the time of injection of the drug to the time when the patient was able to appreciate pain in the S1 dermatome (i.e., the heel). Hypotension (fall in SBP >20% from baseline), and bradycardia (HR<50/min) was cured with intravenous bolus of ephedrine 6 mg and atropine 0.6 mg respectively. Nausea, vomiting, shivering, pruritus and respiratory depression (RR<12min) were recorded. Nausea or vomiting was treated with IV ondansetron 4 mg and pruritus with IV chlorpheniramine 10 mg.

After the operation, pain at rest was assessed using a VAS (0 for no pain and 10 for worst pain). VAS score was assessed every fourth hour for a total of 24 hours. At each level of pain assessment, patients were asked for need of additional support or medication, irrespective of VAS score obtained. If patients wanted analgesia, they were asked to request for analgesics from the nurse and not to wait for the next scheduled VAS score assessment. Pain was treated with TDL 50 mg slow IV. No other analgesics and/or sedative agents were allowed during the first 24 hours after surgery. The amount of TDL administered after operation, time to first analgesic dose and the occurrence of any intraoperative or postoperative adverse events such as nausea, vomiting, itching, respiratory depression (RR<12 /min), post dural puncture headache (PDPH) or any other adverse events were documented. Results obtained were statistically analyzed using R Studio 3.5.3. Values with $p < 0.05$ were considered statistically significant.

Results

A total of 132 patients were included in this study. The three groups were similar in terms of demographic profile. The mean age of study participants in the present study was 43.36±13.13 years.

Significant difference was observed in weight, time for analgesia and time for sensory regression among the three groups (**Table 1**). There was no statistically significant difference between age and height of the patients among the three groups.

In this study, 18.2% of patients in group BB, 11.4% of patients in group BT and 15.9% of patients in group BS had hypotension (systolic blood pressure, SBP <20% of baseline). These observations were not statistically significant when compared among the three groups, as seen in **Table 2** (p=0.662). One patient each in group BB and group BT had bradycardia (heart rate < 50 beats per

minute) which was managed with inj. atropine 0.6 mg IV. The results were not statistically comparable among the three groups (p=1.000). In group BB, 25% had an earlier onset of sensory analgesia when compared to 1% of patients in group BT and 3% in group BS. This observation was not statistically significant when group BB was compared with group BT and group BS (p=0.079).

The total dose of rescue analgesic (TDL) requirement during first 24 hours after surgery was high in control group (193.8 6±39.24 mg) compared to buprenorphine (173.86±45.10 mg) and TDL (180.68±30.91 mg) group. The observations were statistically significant (P=0.042), **Table 3.**

Mean VAS score at four hours was significantly lower in group BB (2.14±0.67) when compared to group BT (3.61±2.06) and group BS (5.57±7.67). As observed in **Table 4**, VAS scores at 8, 12, 16, 20 and 24 hours were comparable.

Four patients in group BT (9.1%) and one patient in group BB (2.3%) complained of nausea and vomiting. The incidence of postoperative shivering was significantly lesser in group BT when compared to group BB (13.6%) and group BS (11.4%), which were comparable. There were no reports of other side effects such as pruritus, post dural puncture headache (PDPH), respiratory depression and neurological complications in any of the groups (Figure 1).

Discussion

In the present study, adding intrathecal buprenorphine to bupivacaine produced similar effect of anesthesia with prolonged postoperative analgesia, comparable to intrathecal TDL (with same dose of bupivacaine). Buprenorphine upsurges the sensory nerve block without affecting motor system and causing hemodynamic alterations.[2] Buprenorphine increased the duration of analgesia in this study, in agreement with the study conducted by Capogna et al.[9]

The onset of sensory block was tested by PPT method, the commonest method of testing the onset of sensory blockade. The early onset of anesthesia in the current study was by addition of buprenorphine, due to its high lipid solubility and high affinity for opiate receptors.[9, 10]

On comparing intraoperative variables, one patient each in the TDL and buprenorphine group had bradycardia, which was managed with inj. atropine 0.6 mg. Hypotension, defined as a fall in SBP more than 20%, was noted in all the three groups. However, these observations were statistically insignificant. Hypotension is an anticipated sequel of neuraxial blockade. Wang C et al.[11] in their experimental work found that the decrease in sympathetic efferent activity after SA is dose related to bupivacaine and not to the added intrathecal opioid. In the present study, the significant fall in BP is due to the effect of bupivacaine rather than intrathecal opioid. Most researchers have evaluated the hemodynamic effects of intrathecal opioids and have found them to be safe. Ravishankar et al[12] and Chakraborty et al[13] found no significant change in pulse rate and blood pressure in their respective studies.

The effect of intrathecal TDL on post-operative analgesia has shown varying results. Several studies have reported effective post-operative analgesia with intrathecal TDL, including Alashemi and Kaki[14] who found it to be effective in reducing morphine requirements following transurethral resection of prostate. In this study, VAS scores at the fourth postoperative hour was significantly lower in the buprenorphine group (p=0.003). The time to first rescue analgesic dose was also significantly prolonged in the buprenorphine group as compared to the TDL and control groups (p<0.001). This suggests that TDL did not potentiate the LA effects of bupivacaine. Gunduz and

colleagues[15] found that TDL does not prolong the duration of action of bupivacaine when co administered caudally. However, Kapral and colleagues[16] have reported that the addition of TDL to mepivacaine 0.1% for brachial plexus anesthesia prolongs the duration of block. This is attributed to the LA-like effects of TDL on the peripheral nerves.

There could be a number of reasons due to which TDL failed to provide effective post-operative analgesia. Firstly, the TDL dose used in this study could have been too small to detect clinically relevant analgesic effect. A large dose of TDL may have increased the incidence of nausea and vomiting.[17] Whether using a large dose of intrathecal TDL would have reduced the post-operative analgesic requirement needs to be determined. Secondly, TDL has a reduced affinity for μ receptors[18,19], which is the site for the action of spinally administered opioids. Thus, the analgesic efficacy could have decreased after intrathecal administration which is supported by the findings of the study conducted by Grace and Fee,[20] who failed to demonstrate analgesic efficacy of epidurally administered TDL in patients undergoing total knee replacement. Thirdly, the lipophilic properties of TDL would have resulted in rapid diffusion of drug out of the subarachnoid space. Rapid drug clearance from subarachnoid space has been reported for fentanyl and sufentanil.[21] There is a possibility that the analgesic effects of TDL disappear before the SA gets regressed. Buprenorphine, due to its high lipid solubility, high affinity for opioids and prolonged duration of action is a suitable choice for intrathecal administration. The total dose of rescue analgesic (TDL) requirement during first 24 hours after surgery was significantly higher in the control group when compared to buprenorphine and TDL groups (p=0.042).

The secondary objective of this study was to learn the adverse effects of the drugs during the first 24 hours following administration. In the present study, six (13.6%) patients in buprenorphine and five (11.4 %) patients in control group developed post-operative shivering, but none of the patients in the TDL group developed shivering. This finding was statistically significant. This can be explained by the fact that TDL inhibits norepinephrine and serotonin uptake that facilitates descending inhibitory spinal pathways which modify thermoregulatory control and shivering.[22,23]

Four patients in the TDL group and one patient in the buprenorphine group had post-operative nausea/vomiting. Although nausea and vomiting are frequently reported side effects of TDL, this finding was not significant in this study. This occurrence of nausea/vomiting depend on other major factors like dose, time and mode of administration, pain intensity, previous motion sickness, the type of surgical procedure planned and anesthesia.[24] None of the patients reported other adverse effects like pruritis, PDPH, respiratory depression, and neurological complications.

The main advantage of a spinal opioid is the absence of sympathetic block and postural hypotension, allowing patients to ambulate earlier. The intrathecal route is technically easier to achieve, and a single injection produces pain relief of a sufficient duration. In the present study, intrathecal buprenorphine provided prolonged post-operative analgesia without any notable raise in adversities. The quality of surgical anesthesia and post-operative analgesia were excellent. Thomas et al. assessed the efficacy of buprenorphine as a post-operative analgesic using the Magill's classification.[25] The longer duration of action for buprenorphine is due to its high affinity for narcotic receptors.[26]

Conclusion

The current study concluded that addition of either intrathecal TDL or buprenorphine to hyperbaric bupivacaine produces comparable intraoperative hemodynamic changes, minimal intraoperative and postoperative side effects. TDL produced a significantly reduced incidence of post-operative shivering when compared to buprenorphine.

References

1. Ravindran R, Sajid B, Ramadas KT, Susheela I. Intrathecal Hyperbaric Bupivacaine with Varying Doses of Buprenorphine for Postoperative Analgesia after Cesarean Section: A Comparative Study. Anesth Essays Res 2017;11**(4)**:952-957.
https://doi.org/10.4103/aer.AER_82_17
PMid: 29284855
2. Wulf HFW. The centennial of spinal anesthesia. Anesthesiol 1998;89**(2)**:500–503.
https://doi.org/10.1097/00000542-199808000-00028
PMid: 9710410
3. Siddaiah J, Pujari V, Madalu A, Bevinaguddaiah Y, Parate L. A comparative study on the effect of addition of intrathecal buprenorphine to 2-chloroprocaine spinal anesthesia in short duration surgeries. J Anaesthesiol Clin Pharmacol 2019;35**(4)**:533.
https://doi.org/10.4103/joacp.JOACP_65_19
PMid: 31920240
4. Lanz E, Simko G, Theiss D, Glocke MH. Epidural buprenorphine--a double-blind study of postoperative analgesia and side effects. Anesth Analg 1984;63**(6)**:593–8.
PMid: 6375465
5. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and pethidine. Eur J Anaesthesiol 1998;15**(1)**:64–8.
https://doi.org/10.1046/j.1365-2346.1998.0233a.x
PMid: 9522144
6. Tsai YC, Chang PJ, Jou IM. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. Anesth Analg 2001;92**(6)**:1547–51.
https://doi.org/10.1097/00000539-200106000-00040
PMid: 11375844
7. Bamigbade TA, Langford RM. The clinical use of tramadol hydrochloride. Pain Rev 1998;5**(3)**:155–82.
https://doi.org/10.1191/096813098668122984
8. Siddik-Sayyid S, Aouad-Maroun M, Sleiman D, Sfeir M, Baraka A. Epidural tramadol for postoperative pain after Cesarean section. Can J Anaesth 1999;46**(8)**:731–5.
https://doi.org/10.1007/BF03013907
PMid: 10451131
9. Celleno D, Capogna G. Spinal buprenorphine for postoperative analgesia after caesarean section. Acta Anaesthesiol Scand 1989;33**(3)**:236–8.
https://doi.org/10.1111/j.1399-6576.1989.tb02897.x
PMid: 2728828
10. Capogna G, Celleno D, Tagariello V, Loffreda-Mancinelli C. Intrathecal buprenorphine for postoperative analgesia in the elderly patient. Anaesthesia 1988;43**(2)**:128–30.
https://doi.org/10.1111/j.1365-2044.1988.tb05482.x
PMid: 3354808

11. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiol 1979;50**(2)**:149-51.
https://doi.org/10.1097/00000542-197902000-0001
PMid: 373503
12. Parthasarathy S. and Ravishankar. M. Single dose intrathecal tramadol in the management of post appendicectomy pain. Anaesthesiol Clin Pharmacol 2002;18**(4)**:419-422.
13. Susmita C, Jayanta C, Dipasri B. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. Indian J Pharmacol 2008;40**(4)**:180-182.
https://doi.org/10.4103/0253-7613.43166
PMid: 20040953
14. Alashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. Br J Anaesth 2003;91**(4)**:536-540. https://doi.org/10.1093/bja/aeg213 PMid: 14504156
15. Gunduz M,Ozcengiz D, Ozbek H,Isik G. A comparision of single dose caudal tramadol,tramadol plus bupivacaine and bupivacaine administration for postoperative analgesia in children. Paediatr Anaesth 2001;11**(3)**:323-326.
https://doi.org/10.1046/j.1460-9592.2001.00647.x
PMid: 11359591
16. Kapral S, Gollmann G, Waltl B et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. Anaesth Analg 1999;88**(4)**:853-856.
https://doi.org/10.1097/00000539-199904000-00032.
PMid: 10195537
17. Delilkan AE, Vijayan R. Epidural tramadol for post-operative pain relief. Anaesthesia 1993;48**(4)**:328-331
https://doi.org/10.1111/j.1365-2044.1993.tb06955.x
PMid: 8494137
18. Raffa RB, Friderichs E,Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and non opioid component s independently contribute to the mechanism of action of tramadol, an atypical opioid analgesic. J Pharmacol Exp Ther 1992;260**(1)**:275-285.
PMid: 1309873
19. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs 2000;60**(1)**:139-176.
https://doi.org/10.2165/00003495-200060010-00008
PMid: 10929933
20. Grace D, Fee JP. Ineffective analgesia after extradural tramadol hydrochloride in patients undergoing total knee replacement. Anaesthesia 1995;50**(6)**:555-558.
https://doi.org/10.1111/j.1365-2044.1995.tb06053.x
PMid: 7618676
21. Sandler AN. Clinical pharmacology of opioids. Pharmacokinetic and pharmacodynamic aspects. Curr Opin Anaesth 1994;7:339-342.
22. Mathews S, Al Mulla A, Varghese PK., Radim K, Mumtaz S. Postanaesthetic shivering –a new look at tramadol. Anaesthesia 2002;57**(4)**:394-398.
https://doi.org/10.1046/j.1365-2044.2002.2457_3.x
PMid: 11949644

23. De Witte J, Deloof T, De Veylder J, Housmans PR. Tramadol in the treatment of post anaesthetic shivering. Acta Anaesth Scand 1997;41**(4)**:506-510. https://doi.org/10.1111/j.1399-6576.1997.tb04732.x PMid: 9150780
24. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anaesthesia: a review. Anaesthesiology 2003;98**(2)**:530-547. https://doi.org/10.1097/00000542-200302000-00036 PMid: 12552215
25. Thomas W, Abraham V, Kaur B. Intrathecal buprenorphine for postoperative analgesia. Indian J. Anaesth 1997;41:188-194.
26. Khan FA, Hamdani GA. Comparision of intrathecal fentanyl and buprenorphine in urological surgery. J Pak Med Assoc 2006;56**(6)**:277-81. PMid: 16827252

Table 1: Comparison of various parameters in study groups

Variables	Group BB	Group BT	Group BS	P value
Age	44.98±13.34	42.20±12.57	42.88±13.61	0.571
Height (cm)	160.73±4.98	159.77±4.74	158.93±3.47	0.4609
Weight (kg)	62.45±6.26	64.30±5.64	61.36±5.70	0.0353*
Analgesia time (minutes)	549.09±103.06	446.48±77.40	312.73±30.45	<0.001*
Sensory regression (minutes)	238.98±19.19	228.52±15.57	213.30±18.71	<0.001*

*Significance; Hyperbaric bupivacaine premixed either with buprenorphine (BB), tramadol (BT) or normal saline (BS)

Table 2: Comparison of presence of hypotension, bradycardia and tome for onset of sensory block in study groups

Variable	Group BB	Group BT	Group BS	P value
Hypotension				
No	36(81.8%)	39(88.6%)	37(84.1%)	0.662
Yes	8(18.2%)	5(11.4%)	7(15.9%)	
Bradycardia				
No	43(97.7%)	43(97.7%)	44(100%)	1.000
Yes	1(2.3%)	1(2.3%)	0(0%)	
Onset of sensory block				
1–2 minutes	7(15.9%)	1(2.3%)	3(6.8%)	0.079
>2–4 minutes	37(84.1)	43(97.7%)	41(93.2%)	

*****Significance; Hyperbaric bupivacaine premixed either with buprenorphine (BB), tramadol (BT) or normal saline (BS)

Table 3: Total dose of rescue analgesic distribution in study groups

Total dose (mg)	Group BB	Group BT	Group BS	P value
<120	7(15.9%)	1(2.3%)	2(4.5%)	0.042*
120–250	37(84.1%)	43(97.7%)	42(95.5%)	
Mean ± SD	173.86±45.10	180.68±30.91	193.86±39.24	

*Significance; Hyperbaric bupivacaine premixed either with buprenorphine (BB), tramadol (BT) or normal saline (BS)

Table 4: Comparison of VAS Score in study groups

Time	Group BB	Group BT	Group BS	P value
4 h	2.14±0.67	3.61±2.06	4.48±2.09	0.003*
8 h	3.98±1.96	3.41±1.59	3.48±1.44	0.226
12 h	4.23±1.83	4.50±1.82	4.93±1.85	0.196
16 h	4.59±1.90	4.41±2.05	4.48±2.19	0.916
20 h	4.39±1.71	4.32±1.93	4.73±2.00	0.553
24 h	4.77±1.82	5.30±2.10	5.45±1.86	0.226

*Significance; VAS-Visual analog scale; *Significance; Hyperbaric bupivacaine premixed either with buprenorphine (BB), tramadol (BT) or normal saline (BS)

Figure legend

Figure 1: Post-operative complications in study groups

PDPH-Post dural puncture headache