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Original Research Paper

Anesthesiology

"SAFETY AND EFFICACY OF INTRATHECAL TRAMADOL WITH HYPERBARIC BUPIVACAINE FOR GYNECOLOGICAL SURGERIES UNDER SPINAL ANESTHESIA: A RANDOMIZED CONTROL TRIAL."

Dr. Bhumika Pathak Associate Professor, Department of Anesthesiology, Pramukh Swami Medical College, Shree Krishna Hospital.

Dr. Parth B. Bhatt* Resident, Department of Anesthesiology, Pramukh Swami Medical College, Shree Krishna Hospital. *Corresponding Author

Dr. Madhavi Chaudhari Professor,Department of Anesthesiology, Pramukh Swami Medical College, Shree Krishna Hospital.

ABSTRACT

Introduction: Spinal anesthesia with long acting 0.5% hyperbaric bupivacaine is most commonly administered for gynecological surgeries. To prolong post op analgesia, Tramadol a weak mu receptor agonist with minimal risk of respiratory depression was studied as an additive.

Method: 40 Patients aged 18 to 75 years, of ASA physical status I-III undergoing gynecological surgeries under spinal anesthesia, were randomly divided into two groups (n=20 each). Group BT received 3 ml of Hyperbaric Bupivcaine (15mg) + 0.5 ml Tramadol (25mg) intrathecally and Group BN received 3 ml of Hyperbaric Bupivcaine (15mg) + 0.5 ml of Normal Saline intrathecally. Onset, duration and quality of sensory block, side effects, duration of post-operative analgesia (VAS score) were evaluated and compared.

Results: There was late onset, and peak in sensory blockade in Group BT as compared to Group BN (85 seconds v/s 61.5 seconds and 15.6 v/s 12.35 minutes, $p<0.05$), total duration of sensory blockade was prolonged in Group BT compared to Group BN (168.6 v/s 148.1 minutes, $p<0.05$). Hemodynamics and other side effects were comparable in both the groups except incidence of nausea and vomiting was more in Group BT. Time of post-operative analgesia was prolonged in Group BT as compared to Group BN.

Conclusion: Addition of 25 mg of Tramadol to 15 mg of Hyperbaric Bupivacaine intrathecally for gynecological surgeries prolongs the sensory block and also improves post operative analgesia with some amount of side effect like intraoperative nausea and vomiting with preserved hemodynamics.

KEYWORDS : Gynecological surgeries, intrathecal Tramadol, hyperbaric bupivacaine, post-op analgesia.

INTRODUCTION

Spinal anesthesia with local anesthetic 0.5% hyperbaric bupivacaine is most commonly administered for gynecological surgeries as it produces good muscle relaxation and complications of general anesthesia can be avoided. In most of the gynecological surgeries visceral pain and discomfort is due to manipulation and stretching of peritoneum and intestine, which requires block as high as T_6 [1]. Hence there is need of intrathecal opioid as an adjuvant to 0.5% hyperbaric bupivacaine for management of visceral pain and discomfort [2,3,4]. Tramadol is weak mu receptor opioid agonist with 6000 fold less affinity compared to morphine, so there is minimal risk of respiratory depression after central neuraxial administration [1]. So, the aim of this randomized controlled study was to evaluate the safety and efficacy of tramadol with respect to onset and duration of sensory block, postoperative analgesia and side effects.

MATERIAL AND METHODOLOGY

After obtaining approval from Institutional Ethics Committee (IEC/HMPCMCE/112/Faculty/12/227/19) a prospective, randomized controlled trial was conducted. The present study was conducted after obtaining written and informed consent from patients in the department of Anesthesiology of Shree Krishna Hospital, Karamsad, Gujarat. Trial was registered under Clinical Trial Registry India (CTRI registration No. CTRI/2020/08/027221).

Total 40 patients of aged 18-75 years with ASA grade I-III undergoing gynecological surgeries were included in this study.

Patients having hypersensitivity to local anesthetics and absolute and relative contraindications to spinal anesthesia were excluded from this study.

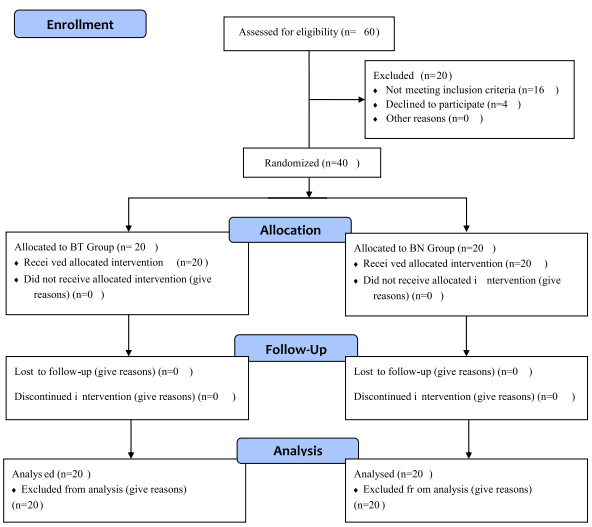
Randomization and Grouping

Total 40 patients were randomly divided into two groups- Group BT and Group BN based on computer generated randomization (WINPEPI Software).

Group BT Bupivcaine (heavy) 3ml+ Tramadol (25mg) 0.5ml = Total Volume 3.5 ml in group BT

Group BN Bupivacaine (heavy) 3ml +Normal Saline 0.5ml = Total Volume 3.5 ml in group BN

CONSORT Flow Diagram



Pre-operative Evaluation

A detailed pre-anesthetic examination was done comprising of history, clinical examination (general physical examination, systemic examination, airway examination and evaluation of surface anatomy of the site of insertion of spinal

needle), routine baseline investigations (complete haemogram, random blood sugar, serum creatinine, serum electrolytes, and Electrocardiogram (ECG)) were done. Participant information sheet in patients' preferred language was shown to them and procedure was explained in detail and written consent for the same was obtained. All patients were kept Nil By Mouth (NBM) 8 hours prior to surgery.

Pre- operative Preparations

Pre operatively peripheral intravenous access was secured with intravenous cannula. All patients were started with crystalloid solution like Ringer's Lactate or Normal Saline. Baseline vital parameters like Heart rate (HR), non invasive blood pressure (NIBP), peripheral arterial oxygen saturation (Spo2), were recorded in the pre-operative room. Patients were explained about the spinal anesthesia in detail.

Intra operative

After all the above mentioned pre-operative preparations patients were shifted to Operation theatre and Electrocardiogram, Pulse oximeter, Non invasive blood pressure monitors were attached. Co-loading with crystalloid solution like Ringer's Lactate or Normal Saline at 10-15 ml/kg of body weight started. Under all aseptic and antiseptic precautions and infiltrating the area with local anesthetic, Spinal anesthesia was performed in sitting position, using midline or para-median approach with 23 Gauge Quincke type of spinal needle in L2-L3 intervertebral space. The study drug was administered after confirmation of free flow of CSF.

Immediately after the administration of spinal anesthesia patient was turned supine. Sensory block was assessed by loss of pin prick sensation using a short beveled 24 gauge needle every 5 minutes till first 20 minutes after administration of intrathecal injection and then every 40 minutes till 2 hours.

Following parameters were assessed and noted –

1. Time of injection was noted as time "0"**(T_0).**
2. **Onset of sensory block (T_1)**- Time from administration of drug to onset of loss of pin prick sensation at L1 dermatome.
3. **Time taken for sensory blockade to reach up to T6 level(T_2)**- Time from administration of drug till the loss of pin prick sensation at the level of T6 dermatome.
4. **Time to peak level(T_3)**- Time from administration of drug till the loss of pin prick sensation at the highest level achieved.
5. **Regression to T10 Level time(T_4)**- Time from administration of drug till the recovery of pin prick sensation as pain at T10 level.
6. **Total duration of sensory block(T_5)**- Time from onset of sensory blockade till recovery of pin prick sensation as pain at T10 dermatome level.

Baseline heart rate and blood pressure and spo2 were recorded before administration of the drug. Intra-operatively heart rate and blood pressure and spo2 were recorded every 5 minutes till 30 minutes and thereafter every 10 minutes till 3 hours and thereafter every 1 hourly.

Hypotension(decrease of > 20% in mean arterial blood pressure from baseline), Bradycardia (decrease of > 20% in heart rate from baseline) and Respiratory depression (decrease of Spo2 < 94% or Respiratory rate < 9 breaths per minutes). Total number of cases who experienced these were noted and treated accordingly.

Patients were also monitored for other side effects like Nausea, Vomiting, Shivering, Pruritus, Urinary retention and Arrythmias. In case of Nausea or vomiting Inj. Ondansetron 4 mg intravenously administered.

Post operative

After the completion of surgery patients were shifted to Post Anesthesia Care recovery room and were monitored for assessment of analgesic effect of drug by VISUAL ANALOGUE SCALE (VAS) Score. VAS score was assessed and documented every 40 minutes interval till 6 hours post operatively. Time to first analgesic requirement (measured from the administration of drug T_0) was defined as VAS score > 3 on rest or VAS score >5 on movement.

STATISTICAL ANALYSIS:

All the data from all patients was entered on an excel sheet. Data was analyzed statistically using independent unpaired 'T' test with 95% Confidence Interval and 38 degree of freedom. And a 'P' value of < 0.05 was regarded as statistically significant. We used STATA 14.2 software for the statistical analysis.

OBSERVATION AND RESULTS

There were no drop outs in this study. All the patients in both the groups were comparable and there was no statistically significant difference between two groups in terms of demographic data like Age, Weight, Height, BMI, Duration and Type of surgery.

Sensory Characteristics

1) Onset of Sensory block(T_1)

- Mean difference of duration of onset of sensory block between two groups was 23.5 seconds.

Table.1 Comparison Of Mean Time For Onset Of Sensory Block In Both Groups

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Time for onset of sensory block inseconds	85±12.61	61.5±11	<0.05

2) Time taken for sensory blockade to reach up to T6 level(T_2).

- Mean difference of duration to reach t6 level between two groups was 2.55 minutes.

Table.2 Comparison Of Time For Sensory Block To Reach T6 Level In Both Groups

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Time for sensory blockade to reach T6 level in minutes	12.35±2.15	9.8±2.01	<0.05

3) Time for sensory blockade to reach peak level(T_3)

- Mean difference of duration to reach peak level between two groups was 3.25 minutes.

Table.3 Comparison Of Time For Sensory Block To Reach Peak Level In Both Groups

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Time for peak sensory blockade level in minutes	15.6±2.45	12.35±2.15	<0.05

4) Regression to T10 time(T_4)

- Mean difference of duration to regression up to t10 level between two groups was 20.5 minutes.

Table.4 Comparison Of Time For Sensory Block To Regress To T10 Level In Both Groups

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Time for sensory blockade regression to T10 Level in minutes	168.6±10.26	148.1±10.47	<0.05

5) Total duration of sensory block(T_s)

- Mean difference of duration between two groups was 20.5 minutes.

Table.5 Comparison Of Total Duration Of Sensory Blockade In Both Groups

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Total duration of sensory blockade in minutes	168.6±10.26	148.1±10.47	<0.05

Intra-operative hemodynamic characteristics and side effects

- Incidence of intra-operative hemodynamic changes like hypotension, bradycardia, arrhythmias, and respiratory depression were not noted in both the groups.
- Intra-operative Nausea noted in 7 patients in Group BT as compared to only 1 patient in group BN which was statistically significant.
- Vomiting noted in only 1 patient in group BT as compared to none in group BN.
- Other side effects like shivering, urinary retention, pruritus were not noted in any of the patients.

Table.6 Comparison Of Complications In Both Groups

Complications	Group BT		Group BN	
	No.	%	No.	%
Hypotension	0	0	0	0
Bradycardia	0	0	0	0
Respiratory depression	0	0	0	0
Arrythmia	0	0	0	0
Nausea	7	35	1	5
Vomitting	1	5	0	0
Pruritus	0	0	0	0
Shivering	0	0	0	0
Urinary retention	0	0	0	0

Post-operative analgesia

1) Time for first post-operative analgesia

- Mean difference of time for first post operative analgesia between two groups was 29.45 minutes.

Variable	Group BT (Mean±SD)	Group BN (Mean±SD)	P value
Time for 1st post-operative analgesia in minutes	219.1±10.65	189.65±9.20	<0.05

Table.7 Comparison Of Mean Time For 1st Post-operative Analgesia In Both Groups

2) Visual Analogue Score Post-Operatively

Table.8 Comparison Of Post-operative Vas Score In Both Group

Time (postoperatively) in Hrs	Group BT (no. of patients)		Group BN (no. of patients)	
	VAS 0-3	VAS 4-10	VAS 0-3	VAS 4-10
0-1	18	2	11	9
1-2	7	13	11	9
2-3	19	1	16	4
3-4	20	0	19	1
4-5	20	0	19	1
5-6	20	0	20	0

DISCUSSION

Tramadol is a synthetic phenylpiperidine analogue of codeine. It stimulates the μ-receptor and also δ- and κ-receptors to a lesser extent. We used tramadol that is a sterile preparation and which does not contain neurotoxic preservatives agent like sodium metabisulphite, methylparaben or chlorocresol, hence there is no neurotoxicity [5].

Safe and effective dose range of intrathecal Tramadol to prolong post-operative analgesia is not available till date. Various doses of intrathecal tramadol were studied by **Priyanka Gupta et al, 2018** and concluded that there was a significant dose-dependent prolongation of duration of sensory block (121, 137, and 150.5 min; P = 0.001), motor block (242.83, 298.5, and 344 min; P < 0.001), and analgesia (289.17, 357, and 404.67 min; P < 0.001) with escalating doses of intrathecal tramadol that is 0 mg, 10 mg and 20 mg respectively. So, we studied the 25 mg intrathecal dose of tramadol.

Our results showed that addition of 25 mg of Tramadol to 15 mg of Hyperbaric bupivacaine in spinal anesthtesia causes Delayed onset (85 seconds v/s 61.5 seconds, p<0.005) and late peak (15.6 minutes v/s 12.35 minutes, p<0.05) level of sensory blockade as well as delayed regression of sensory blockade to T_{10} level (168.6 minutes v/s148.1minutes, p<0.05) as compared to hyperbaric bupivacaine with normal saline.

Tramadol is available as sterile non-pyrogenic solution which contains durg Tramadol hydrochloride 50 mg and Water for injection to make it a solution. Adding water to hyperbaric bupivacaine changes the baricity of the drug and makes it hypobaric, while adding normal saline to the hyperbaric bupivacaine makes it isobaric [6]. This change in baricity probably leads to changes of Spinal block characteristic like delayed onset and regression of sensory block in Tramadol group patients as compared to normal saline group patients.

The results of the present study was in agreement with the study conducted by the **A. Subedi et al, 2013** where the mean onset time to T6 level was more with tramadol group as compared to fentanyl group (6 minutes v/s 5 minutes), late peak in tramadol group (8 minutes v/s 7 minutes) also time to regression to T10 was more in tramadol group compared to fentanyl group (130 minutes v/s 120 minutes). This study was conducted on patients undergoing Cesarean section and therefore dose of 0.5% hyperbaric bupivacaine was less in this study (2ml) and dose of tramadol used was 10 mg, this may be the reason of less time for sensory level regression to T_{10}in this study as compared to our study.

POST-OPERATIVE ANALGESIA

Post-operative analgesic effect was prolonged by addition of 25 mg of tramadol with bupivacaine (time for first post-operative analgesia was 219.1 minutes v/s 189.65 minutes, p<0.05) as compared to bupivacaine with normal saline.

Our result of prolongation of post-operative analgesia with addition of Tramadol to Hyperbaric bupivacaine was probably due to fact that Tramadol has multiple mechanisms of action via μ receptors in dorsal horn and on afferent nerve fibers and also by activating spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin [7]. Its direct serotonin releasing action is also been documented [8].

This result was in agreement with other studies like **A. Subedi et al, 2013,** which showed prolonged post-operative analgesia with tramadol compared to fentanyl (300 minutes v/s 260 minutes) in patients undergoing cesarean section. However, pregnancy-induced anti-nociception is multi-factorial and results from elevation endogenous neuropeptides, serotonin in plasma and CSF, and enhanced spinal noradrenergic activity; this could be the basis of the prolonged post-operative analgesia with tramadol in this study as compared to our study [9,10,11].

Susmita chakraborty et al, 2008 studied effect of addition of 20 mg of tramadol to 3 ml 0.5% hyperbaric bupivacaine showed longer duration of analgesia with tramadol compared to normal saline group (380 minutes v/s 210 minutes, respectively) in patients undergoing major gynecological surgeries. The difference between the duration

of analgesia between this study and our study may be due to the fact that they have considered VAS score of >4 for administration of rescue analgesia.

JM Afolayan et al, 2014 studied the effect of addition of 25 mg tramadol to 3ml of 0.5% hyperbaric bupivacaine in spinal anesthesia, which concluded that pain free period was more in tramadol group as compared to normal saline group (238.39±61.28 minutes v/s 146.59±36.62 minutes) in patients undergoing open-appendectomy.

Our result was in difference with the study of **J. A. Alhashemi et al, 2003** which concluded that addition of 25 mg tramadol to 3ml of 0.5% hyperbaric bupivacaine in spinal anesthesia in patients undergoing transurethral resection of prostate was not different from 0.5 ml of saline in its effect on postoperative morphine requirement where time to first analgesic requirement was 6.3 hours in saline group and 7.6 hours in tramadol group which was not statistically significant. The cause of more time for first post-operative analgesia as compared to our study may be because of the fact that this study used 20-25 μg intravenous Fentanyl as needed for intra-operative breakthrough pain. Also, this study only studied the post-operative morphine requirement according to patient's demand irrespective of VAS score. So, there was no difference in post-operative morphine requirement for 24 hours in both groups.

Intra-operative hemodynamic changes

Intra-operative hemodynamic changes were comparable in two groups, there was no statistically significant difference in pulse rate, blood pressure, respiratory rate between two groups.

This intra-operative hemodynamic stability in terms of preserved respiratory rate is due to fact that Tramadol has minimal respiratory depressant effect,[12,13] as it has 6000 fold less affinity for MOP(mu/μ) receptors compared to morphine [14,15].

The result was similar with the studies carried out by **Geetanjali S Masamaddi et al, 2016** for hemodynamic and sedative effects of intrathecal Tramadol with Bupivacaine and Bupivacaine alone in patients undergoing elective lower abdominal surgery and concluded that Tramadol (25 mg) with 3 ml of 0.5% hyperbaric bupivacaine intrathecally provides a better post-operative analgesia with preserved hemodynamic stability (no statistically significant difference in pulse rate, Respiratory rate, systolic and diastolic Blood pressures in both groups).

Side Effects

In our study we found out that intra-operatively incidence of nausea and vomiting was higher in patients receiving tramadol with hyperbaric bupivacaine in spinal anesthesia as compared to patients receiving hyperbaric bupivacaine with normal saline. Incidence of Nausea and vomiting showed statistically significant difference between two groups. There was high number of incidence of nausea (in 7 patients v/s 1 patient) and vomiting (in 1 patient v/s 0 patients) in patients who received hyperbaric bupivacaine with tramadol as compared to hyperbaric bupivacaine with normal saline.

Tramadol binding to Oipoid receptors present in Chemoreceptor Trigger Zone present in medulla oblongeta and its sertonergic property causes vomiting/nausea as side effect.

This result was in agreement with the study **Priyanka Gupta et al, 2018** which used 3 various doses of tramadol that is 0, 10 and 20 mg with 3 ml of 0.5% hyperbaric bupivacaine in lower limb orthopedic surgeries and concluded that a dose-dependent but insignificant increase in the incidence of peri-operative nausea and vomiting was observed with addition of tramadol.

Our study result was in contrast with study of **J. A. Alhashemi et al, 2003** in which 25 mg tramadol added to 3ml of 0.5% hyperbaric bupivacaine in spinal anesthesia in patients undergoing transurethral resection of prostate and it showed that there was no difference in incidence of intra-operative nausea and vomiting in both tramadol and saline group.

Incidence of other side effects like pruritus, arrhythmia and urinary retention showed no statistically significant in both groups, and there was no incidence of any of these side effects. All the patients undergoing gynecological surgeries were catheterized pre-operatively. So, the incidence of urinary retentions could not be assessed.

CONCLUSION

Addition of 25 mg of Tramadol to 15 mg of Hyperbaric Bupivacaine in subarachnoid block for gynecological surgeries prolongs the sensory block and also improves post operative analgesia with some amount of side effect like intraoperative nausea and vomiting with preserved hemodynamics.

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