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Comparative study of intrathecal fentanyl mixed with bupivacaine, tramadol mixed with bupivacaine, midazolam mixed with bupivacaine for peri and post-operative pain relief in lower limb and lower abdominal surgery

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Abstract
Background: Pain relief is of much importance in patients undergoing surgery during perioperative and post-operative period. Various methods have been evolved for providing post-operative pain relief. After effective pain relief a smoother post operative period and early discharge from the hospital is anticipated. Intrathecal and epidural narcotics have been widely used to relieve pain and provide post-operative analgesia. Intrathecal and epidural narcotics have been widely used to relieve pain and provide post-operative analgesia. Here three drugs tramadol, fentanyl, and midazolam used as adjuvant with bupivacaine in intrathecal injection for post operative pain lelief and comparative study had been done.
Material and Methods: After the study protocol was approved by the Ethical clearance committee of the IGIMS, Sheikhpura, Patna. Study design was prospective, randomised and double blind techniques. A group of 100 patients undergoing lower abdominal and lower limb surgery were included in the study. Every patient was fully explained about the anaesthesia and surgical procedure before inclusion in the study. The patients were in the (25 – 65) years age group and belonged to the American Society of Anaesthesiologist (ASA) physical status class I- II and scheduled for lower abdominal and lower limbs surgery were randomly allocated to four groups with equal number: group B [Bupivacaine (0.5)% 3 cc +.4 cc normal saline], group BT [Bupivacaine (0.5)% 3 cc + 25 mg tramadol], BM [Bupivacaine (0.5)% 3 c.c + 2 mg midazolam], BF [Bupivacaine (0.5)% 3 cc + 20 µg fentanyl]. All additive drugs used intrathecally were preservative free. All intrathecal punctures were performed in the lateral (Right or Left) position with a (25G) Quinke needle, using the midline approach at the L_3-L_4 intervertebral space.
Results: The study revealed that administration of additives in group BM and group BF did prolong analgesia. In group B, duration of analgesia and mean duration of rescue analgesic requirement was (3.22 $\pm$ 1.16) hrs. For group BM it was (12.1$\pm$ 2.34) hrs, for group BF (7.6 $\pm$ 2.86) hrs, for group BT (3.65 $\pm$ 1.42) hrs. Degree and duration of motor blockade was slightly prolonged in group BM and there was mild modulation in group BF.
Conclusion: Addition of adjuvants (fentanyl, midazolam) to intrathecal bupivacaine for perioperative pain relief does prolong postoperative analgesia and improves the intraoperative quality of analgesia than bupivacaine alone.

Keywords: Spinal anesthesia, hyperbaric bupivacaine; intrathecal fentanyl; intrathecal midazolam; lower abdominal surgery; postoperative analgesia

Introduction
In very day to day clinical practice, as well as in many medical and surgical procedures, one of the most common complaints encountered is pain. Pain is an unpleasant subjective sensation which can only be experienced and not expressed. There have been developed so many kinds of things to decrease and control pain as pain is the most important cause of disability and is the source of significant financial burden for the patients. Pain relief is of much importance in patients undergoing surgery during peri-operative and post-operative period. Various methods have been evolved for providing post-operative pain relief. After effective pain relief a smoother post operative period and early discharge from the hospital is anticipated.
Post operative pain relief can be obtained by many methods. Intrathecal and epidural narcotics have been widely used to relieve pain and provide post-operative analgesia

following the initial reports of their clinical efficacy in 1979 [1]. Pain relief by these methods have been shown to improve surgical outcome by excellent pain relief, decreased post operative catabolism, decreased incidence of post operative adverse manifestations, improved vascular graft blood flow and improved pulmonary function.

Intrathecal and epidural narcotics like morphine had used for long time back, either at the time of spinal/epidural block along with local anaesthetic injection for surgical anaesthesia or, as a separate technique of providing analgesia when general anaesthesia is administered. Although this method of pain relief has shown good results in clinical practice, it is still subject to certain draw backs, the most serious of which appears to be delayed respiratory depression. The other major problems with intra spinal opioids is pruritus, development of tolerance and inefficiency against certain types of pain. So always there is search of some other drugs with different chemical structure, which have same effects and devoid of these side effects. These type of drugs are being tried and introduced either intrathecally or epidurally. Three such drugs are Fentanyl, tramadol, midazolam, of these three drugs – the first two are opioid receptor agonists and midazolam is a benzodiazepine [2-5].

Aims and Objective

A comparative study in between the groups containing the respective drugs to evaluate the potency and duration of post operative analgesic action of intrathecal drugs – Fentanyl, Tramadol, Midazolam with Bupivacaine.

Any adverse reaction caused by the drugs like early and delayed respiratory depression, skin pruritus, urinary retention, post-operative nausea vomiting and shivering.

Materials and Methods

After the study protocol was approved by the Ethical clearance committee of the IGIMS, seikhpura, Patna. A group of 100 patients undergoing lower abdominal and lower limb surgery were included in the study. Every patient was fully explained about the anaesthesia and surgical procedure before inclusion in the study. The patients were in the (25 – 65) Years age group and belonged to the American Society of Anaesthesiologist (ASA) physical status class I-II.

Study design was prospective, randomised and double blind techniques. All the postoperative variables were assessed by the same post anaesthesia care unit person, who was unaware about the anaesthesia techniques and drugs used for the patients, to avoid individual variation in the assessment.

The patients were randomly allocated to four groups (group B, BF, BT, BM) with equal numbers n = 25.

Patients were excluded from the study if they have-

1. A history of allergy or contraindication to any of the study drugs.
2. Pregnant or nursing mothers
3. Any evidence of major Cardiovascular, Pulmonary, hepatic, renal, endocrinal or metabolic disorders.
4. Suffering from bleeding diathesis and neurological disorders.
5. Patients with gross spinal abnormality.

Preparation

After fasting for at least (6-8) hours, the patients did not receive any sedatives, anxiolytics or analgesics orally or parenterally on the day of surgery.

Anaesthesia technique

In preoperative holding area, the dorsal vein of hand was cannulated with 18G cannula and all the patients were hydrated with lactated Ringers solution calculated on the basis of body weight of the patients and hours of preanaesthetic fasting.

Monitors like pulse oximeters, Non invasive Blood Pressure (NIBP), Electrocardiography (ECG), and capnography were attached before induction of anaesthesia (spinal or intrathecal blockade) to see the baseline parameters.

All intrathecal punctures were performed in the lateral (Right or Left) position with a (25G) Quinke needle, using the midline approach at the L_3-L_4 intervertebral space. All additive drugs were given using a tuberculin syringe. Then all the patients received intrathecal drugs (Local anaesthetic and additive analgesics according to their groups)

There were four groups

Groups	Drugs used intrathecally
B (group I)	Bupivacaine 3cc (.5%) + (.4 cc) saline
BF (group II)	Bupivacaine 3 cc (.5%) + 20 μg fentanyl (.4cc) [.4 μg/kg]
BT (group III)	Bupivacaine 3cc (.5%) + 25 mg tramadol (.5cc) [.5 mg/kg]
BM (group IV)	Bupivacaine 3cc (.5%) + 2mg midazolam (.4cc) [.04 mg/kg]

Intraoperative monitoring

Monitoring of Blood Pressure (BP), Oxygen Saturation (SPO2), End tidal Carbon dioxide (ETCO2), Respiratory Rate (RR), Heart Rate (HR), Electro Cardiography (ECG), Visual analogue scale (VAS Score), Sedation Score, Bromage Score, Onset of block was done. Other adverse effects eg observed. Nausea vomiting, respiratory depression, urinary retention, shivering were also pruritus, and treated accordingly (vasopressors, antiemetic etc).

Every parameter was assessed before giving block and was consider as the baseline value (0 minute measurement), then measured at 5 minutes interval for first 30 minutes, then 15 minutes interval upto the end of surgical procedur. After that patient was sent to postanesthesia care unit (PACU) for further assessment and treatment (based on aforementioned parameters).

Monitoring in PACU

In PACU, all mital parameters monitoring and special monitoring like sedation score, pain- VAS Score, Bromage score, any other adverse effects, retention of urine respiratory depression, pruritus, PONV were assessed by trained anaesthesia personnel and other trained paramedical personnel.

All scoring system were assessed and calculated by trained personnel in the PACU at 1^{st}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 12^{th}, 24^{th} postoperative hours

Whenever the patient required analgesia in post operative period, patient was given analgesic according to patient demand or pain- VAS Score(rescue analgesia). Rescue analgesia was provided by injection Diclofenac -sodium (75 mg) i.m (if pain on VAS Score was between (40 –50) and in severe break through (VAS > 50) pain then morphine (3

mg) was given slow i.v. bolus.
The following scoring systems were used for assessment of potency and duration of Analagesic action of intrathecally administered drugs.

A. Visual analogue scale (VAS)

Score: 0 ← 100 (mm) (No pain) (Worst pain)

B. Bromage scale (Motor Blockade) – (0-3)
0 = Able to straight leg raise against resistance (No motor block)
1 = Unable to straight leg raise but able to flex knee
2 = Unable to flex knee but able to dorsiflex ankle
3 = Unable to move hip, knee or ankle

C. Sedation Score (0-3)
0 = Patient is awake and talkative
1 = Patient is awake but uncommunicative
2 = Patient is drowsy, quiet and easily arousable
3 = Patient is asleep

Observations

Table 1: Demographic data of each group (Mean + SD)

	Items	Group B	Group BT	Group BM	Group BF	't' test 'p' value
1	No. of Patients	25	25	25	25	*
2	Age (Years)	48.55 ± 10.73	43.05 ± 13.94	49.65 ± 11.00	47.5 ± 9.85	*
3	Body W. (Kg.)	54.15 ± 12.88	55.8 ± 14.51	63.35 ± 5.83	55.30 ± 14.41	*
4	Height (Cm.)	156.10 ± 4.7	159.9 ± 7.33	159.75 ± 6.75	154.55 ± 5.17	*
5	Duration of Surgery (Hour)	1.57 ±0.23	1.66 ± 0.27	1.74 ± 0.29	1.68 ± 0.25	*
6	ASA Status (I/II)	23/2	21/4	23/2	22/3	*

[p< 0.01].

Table 1 shows different patient data in different groups. Each group consisted of 50 patients. There was no statistically significant difference in the valvues between the groups with respect to age, body weight, height and duration of surgery. The difference between the means & between the study groups and control groups is statistically insignificant. Student 't' test used for comparison. Regarding ASA status, when compared statistically (X_2 test) no significant different was found.

Table 2: Onset of sensory block in different groups

Group	Onset of Sensory block (min.)
Group B	3.1 ± 1.87
Group BT	3.0 ± 1.22
Group BM	3.2 ± 1.43
Group BF	3.0 ± 1.36

Table 2 shows that there is no significant difference between the groups with time of onset of sensory block.
There was no significant difference in the Highest sensory level achieved (T_4-T_{10}) and Sensory regression to L1 from highest sensory level (min) is not significantly different In groups B(120 ± 6.2 mg) BT(124 ± 8.6 m), BM (126± 9.2m), but is prolonged in group BF (176± 6.8) mins.

Table 3: (Time of Administration Of Rescue Analgesic (Vas 50)-Mean Duration ± S.D.)

Group	(Mean ± S. D) of R. A.
B	(3.22 ± 1.16)hrs.
BT	(3.65 ± 1.42)hrs.
BM	(12.1 ± 2.34) hrs.
BF	(7.6 ± 2.86)hrs.

Conclusion: P< .001 in groups BM, BF implying statistical significance.
P>.05 in group BT implying statistical insignificance.

Table-3 Shows that mean duration of administration of first rescue analgesic differs in the groups. In the group BM it is (12.1 ± 2.34) hours and in the group BF it is (7.6 ± 2.86) hrs compared to the control group B (3.22 ± 1.16) hours. It shows significant (P< 0.5) prolongation of analgesic effect in the groups BM and BF, compared to the group B and Group BT.
Since there was no statistically significant difference (P>.05) between groups B & BT, BT was not included in further analysis with anova.
The mean duration of analgesic action or mean duration of first analgesic administration has been statistically compared by student's t test, ANOVA and ANOVA was followed by Duncan's test.

According to student's t test

Table 4: T values between groups are as follows

Groups	't' value *
B-BF	10.039
B-BM	24.96
BF-BM	8.77

*Table 4 shows that the above 't' values in between groups are highly significant (p< .001)

According to ANOVA
Groups B, BF, BM are analysed.

Table 5: Shows the ANOVA analysis within the column and between the Column.

Source	Df	Sum of squares	Mean sum of squares	F
Between columns	2	1971	985.7	203.84 *
Within columns	147	710.9	4.836	

* Highly significant at p< .001.

Table 6: ANOVA test was followed by Duncan's multiple range test.

Groups	'R' value *
BF-B	4.38 > 1.133
BM-BF	4.5 > 1.133

Table 6 shows 'R' values are significant in both the intergroup analysis.
The duration of motor blockade is slightly prolonged in group BF (5.1 ± 2.1) hours and also in group BM (5.8 ± 1.8)

hours than in the control group B (4.2 ±.96)hours.
The sedation score is significantly (P< 0.05) prolonged in groups BM (9.8± 1.8)hours and group BF(7.2 ± 1.)hours than control group B (4.1 ± 2.4) hours. The sedation score is also not only prolonged but higher in score in group BM than in others.
Heart rate was maximally affected with group BM and control group B. In order of providing haemodynamic stability, the groups are as BF, BT > B> BM.

Table 7: (Side effects seen in different groups)

	Shivering	Pruritus	PONV	Urinary Retention	Early Respiratory depression	Complaint of Discomfort
Group B	12%	02%	04%	06%	00%	06%
Group BT	04%	04%	18%	10%	04%	16%
Group BF	04%	10%	10%	14%	08%	02%
Group BM	00%	00%	00%	02%	00%	00%

Table 7 shows incidence of different side effects in each group. Shivering was maximum in control group B (12%), least in group BM (O), less in group BF and group BT. Incidence of Pruritus was maximum in group BF (10%), then group BT (4%), group b (2%), group BM (O). PONV was maximum in patients of group BT (18%). Followed by group BF (10%). It was less in the control group B (4%) and absent in group BM. Incidence of Urinary retention was also higher in group BF (14%) and group BT(10%). Early respiratory depression was also observed in group BF (8%), group BT (4%).

Discussion

This is the study of prospective pain relief using intratheal anaesthesia with local anaesthertic Bupivacaine combined with opioid group of drugs like fentanyl, tramadol and benzodiazepine group like midazolam.
Fentanyl acts through opioid receptors at presynaptic and post synaptic sites in CNS and spinal cord. Tramadol is a synthetic opiod. It relieves pain by opioid as well as additional mechanism, while midazolam produces antinociceptive effects. This could be GABA mediated.
As observed by Morgan, saline retains isobar city of a local anaesthetic solution. Therefore, a volume of (.4 cc) of normal saline was added to the control group of bupivacaine as the other groups also received an extra volume of (.4 cc) of each drug in the other three groups, namely – BT, BF, BM.
Dose of Bupivacaine was fixed at 15mg or 3cc of (.5%) bupivacaine as that dose was needed for lower abdominal surgeries and also covered for lower limb surgeries. The dose of intrathecal fentanyl used in this study is 20µg. Intrathecal lipophilic opioids (Fentanyl) and Midazolam have been studied as adjuvant with local anaesthetic (bupivacaine) in spinal anaesthesia and may provide improved intra and post-operative analgesia.
Fentanyl acts on µ receptors in substantia gelatinosa in spinal cord, at presynaptic and postsynaptic sites in CNS (brainstem & spinal cord). Fentanyl prolongs the sensory bupivacaine spinal block as observed from the study of H. Singh, J. Yang *et al*. 1995. The mean duration for rescue analgesics in the group-BF was (7.6 ± 2.86) hrs. longer than that in the control group (3.22 ± 1.16) hours. but less than that in the group-BM (12.1 ± 2.34) hours Intraoperatively, as observed during gynaecological procedures it causes less discomfort and less vagal stimulation and eliminates visceral pain effectively [6].
Mild modulation of motor blockade may be due to its action through peripheral tissues and its analgesic action. Mild sedation is also observed. It may be due to the systemic absorption of the drug. Arterial hypoxemia and hypercarbia may develop despite normal breathing rate. It may manifest as excessive sedation as depressed level of cousciousness (produced by hypercarbia). Moreover, lipid soluble opioids like fentanyl are limited in their cephalad migration by up table into the spinal cord (CSF tabes 1-2 hrs to reach cisterna magna & 3-6 hrs to reach 4th and lateral ventricles from lumb as region). Therefore, delayed respiratory depression was not observed in any of the cases. Ventilatory depression (as evidenced by decreased S_pO_2, (<90 mm Hg) rising E_TCO_2) was early and was observed in 2 cases. Systemic absorption of fentanyl depresses carotid sinus baroreceptor reflex control of heart resulting in bradycardia.
The intrathecal tramadol in group-BT did not make any difference in the onset of block, attainment of height of block or no significant prolongation of VAS score as compared to the control group. Motor blockade was not affected.
Intrathecal midazolam acts on the benzodiazepine receptors which are present throughout the nervous system including the spinal cord and on the local GABA activity. Antinociceptive action is mediated via BZD/GABA-A receptor complex which are abundantly present in lamina II of dorsal horn ganglia of spinal cord. Intrathecal midazolam probably also causes release of an endogenous opioid acting at spinal delta receptor as naltrindole, a delta selective opioid antagonist suppresses analgesic effect of intrathecal midazolam. It also is effective in suppressing reflex response to visceral pain in humans in caesarian section. Studies have shown that intrathecal midazolam causes segmental cord level analgesia [7-9].
Intrathecal midazolam has been shown to be practically free of any neurotoxicity as observed by Batra YK, Jain K. in 1999 and Valentine JM in 1996. They observed that no adverse or irreversible damage to spinal cord and meninges after administration of midazolam through intrathecal route. There was no incidence of shivering, pruritus, PONV, respiretory depression. Therefore, it is observed that group-BM causes the most significant prolongation of postoperative analgesia along with less incidence of adverse effects and better sedation intra and postoperatively [10-12].

Conclusion

With the principle objective of reducing postoperative pain and distress in the group of patients, the study “Comparative study of intrathecal fentanyl mixed with bupivacaine, tramadol mixed with bupivacaine, midazolam mixed with bupivacaine for peri- and post operative pain relief in lower limb and lower abdominal surgery” was carried out in the department of Anaesthesiology, IGIMS, Patna. The study was to evaluate the potency and duration of analgesic action of the drugs when administered intrathecally and a

comparative study is done in between them.

Hundred patients with physical status of ASA grade I and II, scheduled for lower abdominal and lower limbs surgery were randomly allocated to four groups with equal number: group B [Bupivacaine (0.5)% 3 cc +.4 cc normal saline], group BT [Bupivacaine (0.5)% 3 cc + 25 mg tramadol], BM [Bupivacaine (0.5)% 3 c.c + 2 mg midazolam], BF [Bupivacaine (0.5)% 3 c.c + 20 µg fentanyl]. All additive drugs used intrathecally were preservative free.

In conclusion, addition of adjuvants (fentanyl, midazolam) to intrathecal bupivacaine for perioperative pain relief does prolong postoperative analgesia and improves the intraoperative quality of analgesia than bupivacaine alone. The side effects observed with groups for example PONV, pruritus with group-BF, amnesia with group-BM were easily manageable. There were no remarkable effects on respiratory system and haemodynamic stability. Addition of tramadol to bupivacaine did provide for haemodynamic stability but there was no significant prolongation of analgesia and side effects like PONV was observed. With respect to intraoperative quality of analgesia, both midazolam and fentanyl provided excellent results as adjuvants to bupivacaine. Therefore, in view of providing better and prolonged postoperative analgesia with better sedation, midazolam is the adjuvant of choice [13].

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