ORIGINAL RESEARCH

Comparison of the Effects of Midazolam (1mg) and Fentanyl (25 Mcg) as Additives to Intrathecal 3ml of 0.5% Bupivacaine (15mg) For Spinal Anaesthesia

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ABSTRACT

Background: This clinical study was undertaken to compare the effects of intrathecal midazolam and fentanyl as additives to intrathecal bupivacaine 0.5 % for spinal anaesthesia.

Materials and Methods: This prospective, randomized, comparative study was conducted on 100 adult patients of ASA physical status 1 & 2 in the age group of 18 years to 60 years, at MAMATA GENERAL HOSPITAL, KHAMMAM. on patients admitted for elective surgery from the period october 2017 - september 2019. Patients belonging to Group A received 3 ml (15 mg) of hyperbaric bupivacaine (0.5 %) + 0.2 ml (1 mg) of preservative free midazolam + 0.3 ml of normal saline and Group B received 3 ml (15 mg) of hyperbaric bupivacaine (0.5 %) + 0.5 ml (25 μg) of fentanyl. Patients were preloaded with intravenous Ringer's lactate solution 15 ml / kg just before administering subarachnoid block. Subarachnoid block was administered in L3-L4 intervertebral space with 25G Quincke's needle. Standard monitoring was carried out in the form of pulse oximetry, ECG and non-invasive arterial blood pressure monitoring. Pulse rate, respiratory rate, arterial blood pressure and oxygen saturation were recorded every 5mins for first 10mins, every 10mins for next half an hour and then every 15mins intra operatively. The following parameters were observed - onset and duration of sensory blockade, maximum level of sensory blockade achieved, two segment regression, onset and duration of motor blockade, duration of effective analgesia and any side effects associated with these drugs like nausea, vomiting, pruritis, bradycardia, and hypotension. Computer generated randomization was used to allocate patients into two groups. Statistical analysis was done using T-test and fischers exact test. P value of less than 0.05 was considered to be significant

Results: The present study concludes that there were no differences in the onset of sensory and motor blockade, maximum level of sensory blockade achieved, and time for two segment regression. 25μg intrathecal fentanyl was found to provide a longer duration of sensory and motor blockade and prolonged the time for first rescue analgesia as compared to 1mg intrathecal midazolam. There was no significant difference between the two groups with respect to the occurrence of side effects.

Conclusion: Hence, we suggest that addition of intrathecal fentanyl is excellent additive to Bupivacaine for prolongation of duration of anaesthesia without any deleterious effects.

Keywords: Fentanyl, Bupivacaine, Midazolam, Bradycardia, Subarachnoid Block, Hemodynamic Parameters, Hypotension.

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INTRODUCTION

Spinal anaesthesia with lignocaine was highly popular earlier for short surgical procedures as it had a predictable onset and provided dense sensory and motor blockade of moderate duration. Unfortunately, some reports of neurotoxicity had cast doubts on the intrathecal use of lignocaine. The phenomenon of 'transient neurological symptoms' may be associated with all local anaesthetics; but it is 7-9 times more common with lignocaine than with bupivacaine1. In view of controversy and uncertainty surrounding the use of intrathecal lignocaine, hyperbaric bupivacaine (0.5%) has replaced lignocaine as the gold standard drug for the safe conduct of spinal anaesthesia in recent times.

Post-operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal hyperbaric bupivacaine (0.5 %) by adding various drugs such as Opioids, Clonidine, Ketamine, Neostigmine, Conotoxin ziconotide etc.[1] However each drug has its own limitations and a need for alternative method or drug always exists. Recently Conotoxin ziconotide gained registration for intrathecal use in specific pain conditions.

Opioids are the other group of drugs other than local anaesthetics widely used neuraxially to provide either analgesia alone or more commonly in combination with other agents. Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as the forerunner. Neuraxial administration of opioids along with local anaesthetics improves quality of intraoperative analgesia and also provides postoperative pain relief of longer duration.[2]

Animal studies have also demonstrated antinociceptive synergism between intrathecalopioids and local anaesthetics during visceral and somatic nociception.[3]

Fentanyl, a highly lipophilic opioid, has rapid onset of action following intrathecal administration. It does not tend to migrate to the fourth ventricle in sufficient concentration to cause delayed respiratory depression when administered intrathecally.[2]It is associated with less side effects compared to morphine. It has become very popular additive to hyperbaric bupivacaine in recent times. However, fentanyl has side effects like pruritus, nausea and vomiting and even a possible serotonin syndrome related to intrathecal fentanyl has been reported.[4]Duration of the effect of intrathecal fentanyl is dose dependent. In spinal anaesthesia, hyperbaric bupivacaine combined with fentanyl 6.25 micrograms or more facilitates precise peri operative analgesia.[5]

Discovery of benzodiazepine receptors in the spinal cord triggered the use of intrathecal midazolam for analgesia.[6]Several studies have shown that intrathecal or epidural administration of midazolam produces a dose dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory depression or significant sedation. Intrathecal midazolam caused spinally mediated antinociception involves endogenous neurotransmitters acting at spinal cord delta opioid receptors.

Preservative free midazolam is also being used in recent times as an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. It is associated with fewer side effects compared to neuraxial opioids.

As there are only a handful of studies comparing intrathecal midazolam with neuraxial opioids, the present study was undertaken to compare the effects of intrathecal midazolam (1 mg) and fentanyl (25 μg) as additives to intrathecal hyperbaric bupivacaine (15 mg) for spinal anaesthesia in adult patients of either sex belonging to ASA physical status classification class 1 & 2 aged between 18 to 60 years, posted for elective lower limb, lower abdominal,

gynaecological and urological surgeries under spinal anaesthesia at MAMATA GENERAL HOSPITAL, KHAMMAM.

Aims
To compare the effects of intrathecal midazolam (1mg) and fentanyl (25 μg) as additives to intrathecal3ml of 0.5% hyperbaric bupivacaine (15mg) for spinal anaesthesia.

Objectives:
To compare
1) Onset and duration of sensory blockade with both drugs.
2) Onset and duration of motor blockade with both drugs.
3) Duration of effective analgesia with both drugs.
4) To assess the perioperative hemodynamic changes.
5) Any side effects associated with the drugs.

MATERIALS & METHODS
Study Design: Prospective, Randomized Study.
Place of Study: Hospital based. The study is conducted at MAMATA GENERAL HOSPITAL, KHAMMAM. on patients admitted for elective surgery.
Period of Study: The study was conducted from october 2017to September 2019.
Method of Collection of Data: Following institutional ethical and scientific committee approval, patients were thoroughly explained regarding the nature of study. The study was conducted after informed written consent is taken from patients in both groups under senior anaesthesia consultant guidance in the hospital. All emergency drugs and equipments were kept ready before the procedure.
100 normotensive patients of ASA physical status classification class 1 & 2, in the age group of 18 years to 60 years, of either sex, posted for elective lower limb, lower abdominal, gynaecological and urological surgeries under spinal anaesthesia were included in the study.
Using computer generated randomization technique these patients will be divided into two main groups of 50 patients each.

Group A - Bupivacaine+ Midazolam Group.
Group B - Bupivacaine + Fentanyl Group.

Inclusion criteria:
1. ASA physical status classification class 1 & 2.
2. Age group of 18 –60 yrs.
3. Patients giving valid informed consent.
4. Those patients scheduled to undergo elective lower abdominal, lower extremity, gynaecological or urological surgeries under subarachnoid blockade.

Exclusion criteria:
1. Patients belonging to ASA grade 3 and grade 4.
2. Patient refusal.
3. Patients physically dependant on narcotics.
4. Patients with history of drug allergy.
5. Patients with gross spinal abnormality, localized skin sepsis, hemorrhagic diathesis or neurological involvement / diseases.
6. Patients on potent anti-platelets or on anticoagulants.
7. Head injury cases.

8. Patients with cardiac, pulmonary, hepatic or renal disorders.
9. Patients with peripheral neuropathy.
10. Extremes of age.
11. Patients having inadequate subarachnoid blockade and who are later supplemented by general anaesthesia.

Method of study
Preanaesthetic check-up was carried out with a detailed history, general physical examination and systemic examination. Airway assessment and examination of spine were done.
The following laboratory examinations were done:-
• Haemoglobin.
• Urine analysis.
• Blood sugar.
• Blood urea.
• Serum creatinine.
• Coagulation profile.
• Blood grouping and Rh typing.
• ECG-for patients over 40 years of age.
• Chest X- ray.

Preoperatively-
• Patient's informed consent was taken.
• Nil per oral status was confirmed.

The procedure of spinal anaesthesia was explained and the patient was informed to communicate to the anaesthesiologist about perception of any pain or discomfort during surgery.
• They were premedicated with tab. Alprazolam 0.25 mg and tab. ranitidine 150 mg orally 12 hours before giving spinal anaesthesia.
In the pre-operative room, intravenous line was secured and the patients were preloaded with I.V 15 ml / kg Ringer's lactate, 30 minutes prior to spinal anaesthesia.
Procedure: Under strict aseptic precautions, in each case after giving local infiltration at L2-3 or L3-4 interspace with patient in lateral position, lumbar puncture was performed by inserting 25 gauge Quincke's spinal needle into subarachnoid space and the study drugwas injected over 20 seconds.
Patients belonging to group A received 3ml of 0.5% hyperbaric bupivacaine (15mg) + 0.2ml (1mg) of preservative free midazolam + 0.3 ml of normal saline. Patients belonging to group B received 3ml of 0.5% hyperbaric bupivacaine (15mg) + 0.5ml (25 μg) of fentanyl. After injection patient is immediately turned to supine position.

Assessments of parameters include the following:
Standard monitoring was carried out in the form of pulse-oximetry, ECG and non-invasive blood pressure monitoring. Pulse rate, respiratory rate, blood pressure and oxygen saturation were recorded every 5mins for first 10 mins, every 10 mins for next half an hour and then every 15 mins intra operatively. Bolus doses of inj mephenteramine 6 mg i.v. was given to maintain arterial blood pressure within 20 % of base line and inj atropine 0.6 mg i.v. was given when the patient developed bradycardia (HR< 50 beats/min)38,44. No other sedative or analgesic was given in the study period.

Sensory Blockade: The level of sensory blockade was assessed by pin pricks in mid clavicular line bilaterally using 27 guage hypodermic needle, as loss of sensation every 2 min for first 10 min and then every 5 min till the level stabilized. The onset of sensory blockade was considered as the time taken from intrathecal injection to the highest level of the sensory blockade6. The duration of sensory blockade was taken from the time of intrathecal injection till regression of the level to S2 dermatome52. Time taken to achieve peak sensory level and time till 2- segment regression of the blockade were noted.

Motor Blockade:
Time taken for onset and duration of motor blockade (from the time of intrathecal injection till no motor weakness could be detected) was noted. It was assessed by straight leg raising while lying supine and was graded according to Bromage scale.

Post-operative analgesia:
Post-operative analgesia was assessed using a visual analogue scale (VAS) every 15 min. The patient was asked to mark on a 10 cm horizontal scale with no pain corresponding to 0 at one end and the worst pain to 10 at the other end. This was explained to the patient in his vernacular language. The patient's mark of severity of pain on the line was measured.
The duration of effective analgesia (the time from subarachnoid injection to the first dose of rescue analgesic) will be recorded.Injection diclofenac sodium 1.0 mg / kg intramuscular was the rescue analgesic given if VAS score was found to be 4 or more.

Table 1: Visual Analogue Scale Score

VAS Score	Intensity of pain
0 – 1	No pain to slight pain
1 – 3	Mild pain.
4 – 6	Moderate pain.
7 – 10	Severe pain.

The pulse rate, blood pressure, respiratory rate and oxygen saturation will be monitored intra and postoperatively at regular intervals till the sensory blockade lasts. Established side effects of the drugs used like nausea, vomiting, pruritus, bradycardia, hypotension, respiratory depression, urinary retention, sedation etc. will be monitored intra and post operatively for 12 hours in the recovery room and then shifted to the ward. Neurological examination was done to rule out any neurological deficits at discharge.

Statistical Analysis
The raw data was entered into a Microsoft Excel spreadsheet and analyzed using Graphpad Instant (Version 3.10), Graphpad Prism 6 (version 6.03) and Graphpad Statmat_2 (version 2.00) for Windows Seven. Appropriate statistical tests were done to compare between qualitative data and quantitative data. The qualitative data were presented in the form of number and percentage and the quantitative data were presented in the form of mean and standard deviation.
- t-tests were used to analyze differences between two groups
- Differences in parameters such Heart rate, Systolic BP, Diastolic BP,VAS score over a period of time were analyzed using ANOVA (analysis of variance)
- Fischer's exact test for parameters such as sedation score, nausea, vomiting, pruritus.
Consideration ofp values: <0.05 = significant and>0.05 = Not significant

RESULTS

Data was collected and statistical analysis was performed as explained in the methodology of the study. The results and interpretations are as explained below.

Table 2:Age distribution

Age Groups	Number of patients in two groups	Percentage
18 – 30	12	12.0
30 – 40	28	28.0
40 – 50	28	28.0
50 – 60	32	32.0
Total	100	100.0

Parameters	Group A	Group B
	Mean ±SD	Mean ±SD
Age (years)	42.82 ± 10.83	43 ± 10.583

p value is 0.933(statistically insignificant).

Table 5: Sex Comparison

Groups	SEX		Total
	Male	Female	
Group A (n=50)	28	22	50
	56%	44%	100%
Group B (n=50)	30	20	50
	60%	40%	100%
Total	58	42	100

p value is 0.839(statistically insignificant)

Table 3: Types of Surgery

Type of Surgeries	Group A	Group B	Total
Gynaecology	10	13	23
Lower Abdomen	14	10	24
Urology	5	5	10
Lower limb	21	22	43
Total	50	50	100

Table 4: Demographic profile of two groups with mean and S.D. values

Parameters	Group A (Midazolam 1mg)	Group B (Fentanyl 25µg)	P Value	Statistical significance
Number of patients	50	50	-	-
Age	42.82 ± 10.83	43 ± 10.583	0.933	Not significant
Weight (kg)	62.58 ± 6.21	64.38 ± 4.78	0.104	Not significant
Height (cms)	162.680 ± 4.86	161.880 ± 4.86	0.413	Not significant
Surgical time (min)	85.4± 28.92	94.2± 34.49	0.170	Not significant
ASA Grade I/II	31/19	36/14	-	-

Thus, the age, weight and height of the patients in both groups were comparable which shows that the patients of equal age, weight and height were enrolled in our study.

Sensory Blockade-Onset and Duration
Table 5: Sensory blockade – Onset

Time in minutes	Group A	Group B
Minimum	2.07	2.29
Maximum	4.47	4.7
Mean + SD	3.55+0.56	3.41+0.61

p value is 0.234(Statistically insignificant).

The mean onset of sensory blockade in group A was 3.55±0.56 min and in group B, mean onset of sensory blockade was 3.41±0.61min. There was no significant difference between the two groups with respect to the onset of sensory blockade as p value is> 0.05 (here it is 0.234).

Table 6: Sensory blockade – Duration

Time in minutes	Group A	Group B
Minimum	181	192
Maximum	235	258
Mean + SD	206.56 + 13.33	230.06 + 13.64

p value < 0.0001 (Statistically significant).

The mean duration of sensory blockade, as assessed by regression of the level till S2 was significantly longer in the fentanyl group (230.06 minutes) as compared to the midazolam group (206.06minutes) (p<0.0001).

Maximum level of sensory blockade:
Table 7: Maximum level of sensory blockade

Maximum level of sensory blockade	Group A	Group B
T6	18	21
T8	23	22
T10	9	7
T12	0	0
Grand Total	50	50

Thus in our study we found that there was no significant difference in maximum level of sensory blockade achieved in between midazolam and fentanyl groups.

Motor Blockade-Onset and Duration
Table 8: Onset of Motor Blockade

Time in minutes	Group A	Group B
Minimum	2.36	2.57
Maximum	5.42	5.97
Mean + SD	4.45+0.63	4.28+0.64

p value is 0.183 (Statistically insignificant).
The mean onset of motor blockade in group A was 4.45±0.63 min and in group B, mean onset of motor blockade was 4.28±0.64 min. There was no significant difference between the two groups with respect to the onset of motor blockade as p value is > 0.05 (here it is 0.183).

Table 9: Duration of Motor Blockade

Time in minutes	Group A	Group B
Minimum	197	212
Maximum	251	277

| Mean + SD | 225.56±14.125 | 251.88 + 15.80 |

p value < 0.0001 (Statistically significant)

The mean duration of motor blockade was found to be significantly longer with fentanyl (251.88 minutes) as compared to midazolam (225.56 minutes) (p<0.0001)

Post op analgesia:
Table 10: Duration of effective analgesia

Time in minutes	Group A	Group B
Minimum	215	225
Maximum	275	286
Mean + SD	246.2±14.3	264.32 + 15.38

p value < 0.0001 (Statistically significant)

The time for first rescue analgesia was significantly longer in fentanyl group (264.32±15.38min)as compared to midazolam group (246.2±14.3min), (p value< 0.0001).

Two Segment Regression Of Sensory Blockade
Table 11: Time for two segment regression

Parameters	Group A Mean ±SD	Group B Mean ±SD	p value
Time for 2 segment regression in minutes	94.46±14.95	100.14±14.98	0.0607

p value is 0.0607 (Statistically in significant).

The time taken for two segment regression was 94.46 min in group A and in group B was 100.14 min. There was no significant difference between the two groups with respect to the time taken for two segment regression as p value is >0.05 (here it is0.0607).

Table 12: Characteristics of Spinal Blockade

Parameters	Group A (Midazolam)	Group B (Fentanyl)	p value
Sensory blockade Onset of in min	3.55±0.56	3.41±0.61	0.234
Sensory blockade Duration in min	206.56±13.33	230.06±13.64	<0.0001*
Peak sensory level	T6	T6	
Duration of effective analgesia in min	246.2±14.3	264.32±15.38	<0.0001*
2 segment regression	94.46±14.95	100.14±14.98	0.0607
Onset of motor blockade in min	4.45±0.63	4.28±0.64	0.183
Duration of motor blockade in min	225.56±14.12	251.88±15.80	<0.0001*

* Statistically significant

Heart Rate
Table 13: Heart Rate (beats per minute)

Group		Preoperative reading	5min	10min	20min	30min	60min
A	Mean±SD	73.84± 7.427	69.62±	71.90±	72.26±	72.94±	72.82±

				11.719	9.545	8.506	8.016	8.285
B	Mean±SD	74.08± 7.87	70.00± 12.936	72.30± 9.677	72.56± 8.291	72.56± 8.437	72.32± 8.095
	p value	0.876	0.878	0.836	0.859	0.818	0.761

p-value (Statistically insignificant).

Blood Pressure
Table 14: Changes in SBP (mm of hg)

Group		Preoperative reading	5 Min	10 min	20 min	30 min	60 min
A	Mean±SD	116.78± 12.960	108.40± 16.497	107.96± 12.523	113.26± 11.423	115.20± 10.521	111.68± 11.545
B	Mean±SD	116.76± 13.510	106.88± 17.857	110.00± 15.296	113.80± 11.740	115.92± 10.849	113.00± 14.715
	P value	0.994	0.659	0.467	0.619	0.816	0.737

pvalue (Statistically insignificant).

There were not much differences in the systolic blood pressure observed upto 60 minutes after the administration of the drugs.

Table 15: Changes in DBP (mm of Hg)

Group		Preoperative reading	5 min	10 min	20 min	30 min	60 min
A	Mean±SD	74.84± 9.749	69.50±11.655	69.04± 9.304	73.30± 8.853	74.04± 8.690	70.84± 8.714
B	Mean±SD	74.84± 10.118	68.54±13.123	70.06± 8.863	73.14± 9.342	74.64± 9.102	72.00± 8.953
	P value	1.000	0.700	0.576	0.513	0.930	0.737

pvalue (Statistically insignificant).

There were not much differences in the diastolic blood pressure observed for 60 minutes after the administration of the drugs.

Comparison of SpO_2 between two groups:
Table 16: Changes in Spo2:

Group		Preoperative reading	5min	10 min	20 min	30 min	60 min
A	Mean±SD	98.34± 1.022	98.24± 1.205	98.40± 1.030	98.62± 0.602	98.84± 0.618	98.46± 0.952
B	Mean±SD	98.46± 0.908	98.32± 1.220	98.34± 1.002	98.44± 0.884	98.68± 0.868	98.40± 0.926
	p value	0.536	0.742	0.768	0.750	0.237	0.291

pvalue (Statistically insignificant).

There were not much differences in the oxygen saturation observed for 60 minutes after the administration of the drugs.

Sedation score:
Table 17: Distribution of sedation scores

Sedation score	Group A	Group B
One	0	0
Two	26	25
Three	20	22
Four	4	3
Five	0	0
Six	0	0

p value is 0.50 (statistically insignificant).

Majority of people in both groups did not have any significant sedation. There were no statistical differences in the sedation scores between the two groups (p>0.05).

Peri operative side effects
Table 18: Perioperative side effects

Side effect	Group A n(%)	Group B n (%)	p Value
Bradycardia	3(6)	4(8)	1
Hypotension	6(12)	8(16)	0.774
Nausea	2 (4)	4(8)	0.677
Vomiting	0	0	-
Pruritus	0	2(4)	0.494
Respiratory Depression	0	0	-
Urinary Retention	0	0	-
Neurological Deficits	0	0	-

p> 0.05 (statistically in significant)

DISCUSSION
In the present study, the effects of addition of different adjuvants to Bupivacaine were observed to find out the best additive among them.
Subarachnoid block with bupivacaine has been most extensively used for lower abdominal and lower limb surgeries because of its simplicity, speed, reliability and minimal exposure to depressant drugs. However, a single intrathecal injection of bupivacaine provides analgesia for only 2-2.5 hours. Most patients require further analgesia during post operative period.
Various adjuvants to intrathecal local anaesthetics such as ketamine, clonidine, neostigmine are often added to enhance the duration and quality of spinal anesthesia. Their use is limited because of significant adverse effects such as pruritus, urinary retention, respiratory depression, haemodynamic instability, nystagmus, nausea and vomiting.
Neuraxial administration of opioids along with local anaesthetics improves quality of intra operative analgesia and also provides post operative pain relief for longer duration.[6] Highly hydrophilic opioids such as morphine, though provides very good intra and post operative analgesia, its use becomes limited because of delayed respiratory depression that it causes due to rostral spread in intrathecal space.[2]
Fentanyl, a highly lipophilic opioid, has rapid onset of action following intrathecal administration. It is associated with fewer side effects compared to morphine. It has become very popular additive to hyperbaric bupivacaine in recent times. However, fentanyl has side

effects like pruritus, nausea and vomiting and even a possible serotonin syndrome related to intrathecal fentanyl has been reported.[4] The dose of intrathecal opioid added to the local anesthetic is important not only for the quality of surgical anesthesia but also for the onset and duration of the block. Opioids interrupts pain transmission in the dorsal horn, while local anesthetics block conduction in the motor and sensory nerves. Therefore, adding an opioid to the local anesthetic may offer local anesthetic sparing effects and lead to shorter onset time and prolonged duration for sensory block. shorter onset time and longer regression time in patients in whom opioid was added to local anesthetics.

The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentamericgamma-aminobutyric acid (GABA A) receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA A receptor. This receptor is a chloride ionophore that, when activated, typically stabilises the transmembrane potential at, or near, the resting potential. In neurons, this typically serves to decrease excitability. Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation.[7] The present cumulative experience with intrathecal midazolam across species broadly confirms the safety thereof, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effect.Midazolam is a potent short acting imidazo benzodiazepine that has been shown to have antinociceptive effects when administered intrathecally both in laboratory animals and in humans. Preservative free midazolam is also being used in recent times as an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. It is said to be associated with less side effects compared to neuraxial opioids.[8]

This clinical study, which was a randomized, prospective study, was done in 100 patients belonging to the age group of 18-60 years of both sexes of ASA physical status classification class 1 & 2 scheduled to undergo elective lower abdominal, lower limb, gynaecological and urological surgeries and compared the effects between fentanyl 25 µg and midazolam 1mg as additives to hyperbaric bupivacaine 0.5 % 15 mg for spinal anaesthesia.

Patients belonging to group A received 3ml of 0.5% hyperbaric bupivacaine (15mg) + 0.2 ml (1 mg) of preservative free midazolam + 0.3 ml of normal saline. Patients of group B received 3ml of 0.5% hyperbaric bupivacaine (15mg) + 0.5 ml (25 µg) of fentanyl. After injection, patient was immediately turned to supine position.

Harbhej Singh et al,[9] in 1995, BN Biswas et al in 2002,[10] Khanna MS et al,[11] in 2002 have chosen 25 µg of fentanyl as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study, we chose 25 µg of fentanyl as an additive to hyperbaric bupivacaine.

MH Kim et al in 2001, Bharti N et al in 2003, Nidhi Agrawal et al in 2005 and Vandana et alin 2008 have chosen 1mg of midazolam for the study as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study we chose 1 mg midazolam as an additive to hyperbaric bupivacaine.[12-15]

The principal findings of this study are that:

The two groups were comparable with regards to age, gender, weight, height, ASA grade and duration of surgery. Hence patients of equal age, weight, height & sex were enrolled in the study.

		Group A	Group B	P Value
i	Mean Duration of surgery (in minutes)	85.4	94.2	0.170
ii	Mean onset of sensory blockade (in minutes)	3.55	3.41	0.234
iii	Mean Duration of sensory blockade (in minutes)	206.56	230.06	<0.0001

iv	Mean Onset of Motor blockade (In minutes)	4.45	4.28	0.183
v	Mean Duration of Motor blockade (In minutes)	225.56	251.88	<0.0001
vi	Mean Time for two segment regression (In minutes)	94.46	100.14	0.0607
vii	Mean Time of Post-operative analgesia (In minutes)	246.2	264.32	<0.0001
viii	Peri operative complications			
	Hypotension (%)	12	16	1
	Bradycardia (%)	6	8	0.774
	Nausea (%)	4	8	0.677
	Pruritus (%)	0	4	0.494

Onset of sensory blockade:
The mean onset of sensory blockade in midazolam group was 3.55min and in fentanyl group, mean onset of sensory blockade was 3.41 min. Similar values were obtained with regard to the onset of sensory blockade in midazolam group in the studies conducted by Nidhi Agrawal et al in 2005 and Aikta Gupta et al in 2008.[14,16] Similar values were obtained with regard to the onset of sensory blockade in fentanyl group in the studies conducted by Uma srivastava et alin 2004 and K.Kurmanadh and K.srilakshmi in 2017.[1,17]

In another study by Codero et al,[16] the authors report a significantly longer time taken for onset of block whenmidazolam was added as an adjunct as compared to fentanyl (17.1 min vs. 13.2 min, respectively, with P = 0.023), which again has been demonstrated by our study. In this study, the dose of midazolam used as an adjunct was double than what was used in our study (2 mg vs 1 mg of midazolam).

There were no differences between the two groups with respect to the onset of blockade as significance value obtained was more than 0.05 (here it is 0.234).

Duration of sensory blockade:
The mean duration of sensory blockade in group A was 206.56 min and in group B mean duration of sensory blockade was 230.06 min. There was significant difference between the two groups with respect to the duration of blockade as P value <0.0001.

In their study in 2008, Vandana et al,[15]also found out that there was significant difference in the duration of sensory blockade when midazolam and fentanyl were administered as adjuvants to intrathecal hyperbaric bupivacaine.

The present study finding is in accordance with the study conducted by Vandana et al.[15]

Durations of effective analgesia:
The mean duration of effective analgesia in group A was 246.2 min and in group B, mean duration of effective analgesia was 264.32 min. There was significant difference between the two groups with respect to the duration of effective analgesia as P value obtained <0.0001.

Side effects:
Considering the perioperative hemodynamic variables the result of our study is comparable with studies done by Vandana et al,[15] Anjali Bhure who also did not find statistically significant difference in heart rate,[18] arterial blood pressure in their studies. Incidence of hypotension and bradycardia is found to be similar in both groups.

There was no significant difference between the two groups with respect to the occurrence of nausea as the P value obtained was > 0.05. Nausea was more commonly associated with fentanyl group though none of the patients in both groups developed vomiting.

4% of people in fentanyl group developed pruritus where as none in midazolam group developed it. Pruritus was mild and didn't require any treatment.

Majority of people in both groups did not have any significant sedation. There were no statistical differences in the sedation scores between the two groups (p>0.05).Kim and Lee and Bharti et al did not find any significant difference in sedation levels between the midazolam and the control groups.[12,13]

In studies conducted by K.Kurmanadh, K.Srilakshmi,[18] there were no significant differences between the two groups with respect to the occurrences of bradycardia, hypotension and in sedation scores as the significance values obtained from Fisher's exact test were more than 0.05 for each of these variables. There were significant differences between the two groups with respect to the occurrence of nausea as the significance value obtained from Fisher's exact test was less than 0.05. Nausea was more commonly associated with fentanyl group though none of the patients in both groups developed vomiting. 14% of people in fentanyl group developed pruritus whereas none in midazolam group developed it. The association of pruritus with fentanyl was statistically significant as the significance value from Fisher's exact test was less than 0.05. Pruritus was mild and did not require any treatment. None of the patients had any postoperative complications like urinary retention,

None of the patients in our study had any post operative complications like urinary retention, respiratory depression, lower limb weakness or any other neurological deficitis.

The mechanism of intrathecal opioid induced respiratory depression is due to the rostral spread. Various studies have found different incidences of sedation following intrathecal midazolam.The incidence of sedation was higher in the intrathecal fentanyl group than in the intrathecal midazolam group. Present study shows results similar to that obtained by Vandana et al,[15] Anjali Bhure.[18]

Present study shows thatthe time for first request of rescue analgesia was found to be significantly longer in the fentanyl group as compared to the midazolam group.

Similar values were obtained with regard to the duration of effective analgesia in midazolam group in the studies conducted by Prakash smita et al,[19] in 2006 and in fentanyl group in studies conducted by Biswas BN et al in 2002.[2]

Time for Two Segment Regression:
The time taken for two segment regression was 94.46min in group A and in group B was 100.14 min. P value obtained was 0.0607. The present study finding is in accordance with the study conducted by Vandana et al,[15](90 min for midazolam group and 90.60 min for fentanyl group).

Motor blockade:
The mean onset of motor blockade in midazolam group was 4.45min and in fentanyl group, mean onset of motor blockade was 4.28 min. The mean duration of motor blockade in group A was 225.56 min and in group B, was 251.88 min. P value obtained was <0.0001.

In present study we found that, duration of motor blockade were clinically and statistically significant in between the two groups and were comparable with Vandana et al.[15]

Haemodynamic stability:
There was no significant variations in the haemodynamic stability of patients.

In a previous study conducted by Sawhney S, Singh RK, Chakraberty S et al,[20] in 2019on a group of elderly patients, it was reported that if 4.0 mg of isobaric bupivacaine was combined with 20 μg of fentanyl, it provided adequate anaesthesia and analgesia without producing any haemodynamic instability.

Side effects:

Considering the perioperative hemodynamic variables the result of our study is comparable with studies done by Vandana et al, Anjali Bhure who also did not find statistically significant difference in heart rate, arterial blood pressure in their studies. Incidence of hypotension and bradycardia is found to be similar in both groups.

There was no significant difference between the two groups with respect to the occurrence of nausea as the P value obtained was > 0.05. Nausea was more commonly associated with fentanyl group though none of the patients in both groups developed vomiting.

4% of people in fentanyl group developed pruritus where as none in midazolam group developed it. Pruritus was mild and didn't require any treatment.

Majority of people in both groups did not have any significant sedation. There were no statistical differences in the sedation scores between the two groups (p>0.05).Kim and Lee,[12] and Bharti et al,[13] did not find any significant difference in sedation levels between the midazolam and the control groups.

In studies conducted by K.Kurmanadh, K.Srilakshmi,[17] there were no significant differences between the two groups with respect to the occurrences of bradycardia, hypotension and in sedation scores as the significance values obtained from Fisher's exact test were more than 0.05 for each of these variables. There were significant differences between the two groups with respect to the occurrence of nausea as the significance value obtained from Fisher's exact test was less than 0.05. Nausea was more commonly associated with fentanyl group though none of the patients in both groups developed vomiting. 14% of people in fentanyl group developed pruritus whereas none in midazolam group developed it. The association of pruritus with fentanyl was statistically significant as the significance value from Fisher's exact test was less than 0.05. Pruritus was mild and did not require any treatment. None of the patients had any postoperative complications like urinary retention,None of the patients in our study had any post operative complications like urinary retention, respiratory depression, lower limb weakness or any other neurological deficitis.

The mechanism of intrathecal opioid induced respiratory depression is due to the rostral spread. Various studies have found different incidences of sedation following intrathecal midazolam.The incidence of sedation was higher in the intrathecal fentanyl group than in the intrathecal midazolam group. Present study shows results similar to that obtained by Vandana et al,[15] Anjali Bhure.[18]

Limitations:

- The obvious limitation of our study includes the absence of a control group (in which patients would have received 3 ml of hyperbaric bupivacaine along with 0.5 ml of saline intrathecally).
- The inclusion of a control group would have further supported our findings. We also recognize the fact that the wide variability in the age of the patients included in the study is a confounding factor in relation to perception of pain as pain perception varies for various age groups.
- We studied postoperative analgesia in the subjects till duration for first request of rescue analgesia only and did not record the number of doses and the total dose of rescue analgesic required to relieve pain in each group.
- Further studies can be aimed at finding the minimal possible doses of intrathecal fentanyl and midazolam in conjunction with hyperbaric bupivacaine that will provide adequate anesthesia and analgesia.

CONCLUSION

Despite advances in the knowledge of pathophysiology, pharmacology and the development of more effective techniques for the management of perioperative analgesia, many patients

continue to experience distressing pain in the postoperative period. It is shown that relief of pain with neuraxial blockade with a local anesthetic like bupivacaine alone is limited to the initial postoperative period. When adjuvants like midazolam and fentanyl are added to local anesthetic, pain relief can be extended well into the post operative period. The present study demonstrated that intrathecal administration of midazolam or fentanyl to hyperbaric bupivacaine had similar onset of sensory and motor blockade with relative haemodynamic stability.

Intrathecal fentanyl was found to provide a significantly longer mean duration of sensory and motor blockade and prolonged the time for first rescue analgesia as compared to midazolam. Hence, we suggest that addition of intrathecal fentanyl is excellent additive to Bupivacaine for prolongation of duration of anaesthesia without any deleterious effects.

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