Comparison of Intrathecal Midazolam and Fentanyl used as an adjuvant with Hyperbaric Bupivacaine in infraumbilical surgeries: A prospective, randomized, double-blind, interventional study

Dr. Mahesh Kumar Meena[1], Dr. Rajeev Sharma[2], Dr. Vinod Kumar Meena[3], Dr. Dilip Raj[4§]

[1,3]Post graduate Student, Department of Anaethesia, SMS Medical College, Jaipur (Rajasthan), India
[2]Professor, Department of Anaethesia, SMS Medical College, Jaipur (Rajasthan), India
[4]Associate Professor, Department of Community Medicine, SMS Medical College, Jaipur (Rajasthan), India
[§]Corresponding author's Email: diliprajhadia@yahoo.com

Abstract— *Post-operative pain management remains a challenge. Various combination of medicines are used to reduce post operative pain. So study was designed to compare the effect of Midazolam and Fentanyl adjuvant to Bupivacaine in reducing pain in infra-umblical surgeries It was observed in thia study that duration of analgesia was 197.6±9.8 minutes when bupivacaine was used alone, while it increased to 272.8±10.9, and 286±10.4 minutes when bupivacaine was used in combination with fentanyl and midazolam respectively. The total duration of analgesia in midazolam group was significantly more than Fenetanyl and Saline group. Present study demonstrated that midazolam produce longer duration of post-operative analgesia when compared to fentanyl. Mean VAS scores at various intervals were compared in all the three groups, it was found without significant variation till 2 hours of surgery but after that upto 3 hours it was minimum (<0.05) in Midozolam group and after 3 hours it significantly less (<0.05) in Fenetanyl group. So it can be concluded from this study that adding Midozolam with Bupivacaine is good for analgesia.*

Keywords: Midazolam and Fentanyl adjuvant to Bupivacaine, Infra-umblical Surgeries, Analgesia.

I. INTRODUCTION

Post-operative pain management remains a challenge despite recent advances in our understanding of the physiology of acute pain, the newly developed opioid and non-opioid analgesics , novel methods of drug delivery (systemic, regional and local) and more widespread use of interventional pain managment.[1]

The concept of multimodal "opioid-sparing" analgesic techniques (so-called balanced analgesia) was introduced more than 15 years ago[2] with the aim of improving analgesia by combining analgesics with additive or synergistic effects. Midazolam is potent short acting, water soluble benzodiazepine, which has been used for potentiating the analgesic effect of local anesthetic induced neuraxialsblockade.[3] Its use as postoperative analgesic by intrathecal route was first studied by Valentine J.M, Lyon.[3] Spinal analgesic effect of midazolam is mediated by benzodiazepine-GABA receptor complex within the spinal cord. GABA receptors are abundant in dorsal root nerve cells and maximum concentration found in lamina-II of dorsal horn ganglia.[4,5,6] Intrathecal Midazolam also has anti-nociceptive effect mediated via spinal opiate receptors.[5] Midazolam, despite of being the commonest benzodiazepine used in anesthesia and preoperative care, is a relatively newer addition to the list of adjuvant used in subarachnoid block. Addition of intrathecal midazolam to bupivacaine significantly improves the duration and quality of spinal anesthesia and provides prolonged preoperative analgesia without any significant side effects.

Fentanyl is a synthetic opioid related to the phenylpiperidines. The actions of fentanyl and congeners are similar to those of other m-receptor agonists. Fentanyl is a popular anesthetic because of its relatively short time to peak analgesic effect, rapid termination of effect after small bolus doses, and cardiovascular safety. [7]

So this study was designed to compare the effect of Midazolam and Fentanyl adjuvant to Bupivacaine in reducing pain in infra-umblical surgeries.

II. METHODOLOGY

This hospital based prospective randomized double blind, interventional study was conducted in the Department of anesthesia, SMS Medical College, Jaipur (Rajasthan) India, in the year 2017.

Sample size was calculated as 46 subjects in each of 3 groups at alpha error-0.05 and power- 80%, assuming difference in means to be detected 11.8 min S.D.18.2 of total duration of analgesia (as per the seed articles), so for the study purpose 46 subjects was taken for each of group bupivacaine+fentanyl group, bupivacaine+midazolam group and bupivacaine+normal saline group.

For study purpose 20-60 years aged having weight 40-80 Kg and ASA grade I & II going for infra-umblical surgeries were scrutinized. Patients unfit for anesthesia and having infection site infection were excluded from study.

After taking proper consent of eligible patients, randomization was done by chit in box method. A total of 138 chits (46 per group) were made, each chit mentioning a particular study group. One of my colleagues asked the patient to pick up a chit from the box. Patient was allocated to group mentioned on the chit. Study drug was prepared by my colleague and was administered by me to the patient. In group (F) 2 ml of 0.5% hyperbaric Bupivacaine + 0.5ml(25mcg) of Fentanyl, in group (M) 2 ml of 0.5% hyperbaric Bupivacaine + 2mg (0.4ml midazolam +0.1ml NS) and in group (S) 2 ml of 0.5% hyperbaric Bupivacaine +0 .5 ml of Normal saline was given after infra-umblical surgeries.

After pre-anesthetic check up and preperation, vitals were noted just before lumbar puncture. Spinal anaesthesia was performed at L3-L4 interspace (L4-L5 in case of failure) with the patient in left lateral position by using a 24 Gauge Quincke needle under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anaesthetic solution, which was administered over 30 seconds. All patients were immediately placed in a supine position following the injection with a head down tilt to achieve level of block of T10. Monitoring is done using continous electrocardiography (lead II & V), heart rate, non-invasive blood pressure and continous pulse oximetry and patients were given 4.0 L/min of oxygen by venti-mask.

Vitals were checked every 2 minutes for first 10 minutes then every 10 minutes till surgery and then every 30 minutes for 4 hours postoperatively.

When adequate spinal block was achieved, the time from the end of intrathecal injection to readiness for surgery was recorded. Then the patient will be positioned for planned surgery.

Statistical analysis: All the statistical analysis of data was done with statistical programming software – SPSS (Statistical Package for the Social Science) version 20.0.0 (SPSS Inc., Chicago, Illinois, USA). The continuous variables (quantitative data) like age, weight, height, blood pressure, heart rate, time were presented as mean and standard deviation and analyzed by ANOVA test. The categorical variables

(qualitative data) like ASA grade, sedation score were presented in frequency and percentage and were analyzed with Chi-Square test (for nominal data), Kruskal Wallis test (for ordinal data). For significance, "p" value <0.05 was accepted as significant.

III. RESULTS

In this study all the three groups were comparable (p>0.05) as per age wise, sex wise, weight wise and ASI grade wise distribution. (Table 1)

Mean surgery time in Fentanyl group, Midazolam and Saline group was 83.6, 84.5 and 85.7 minuts. This difference was also not without significant (p>0.05). (Table 1)

Table 1
Comparison of characteristics of all the three groups of study

S. No.	Variables	Fentanyl Group (F) N=46	Midazolam Group (M) N=46	Saline Group (S) N=46	P value	LS
1	**Age (yrs) Mean ± SD**	40.7 ±12.3	39 ± 11.7	39.9 ±12.5	0.804*	**NS**
2	**Sex (M:F)**	25:21	26:20	25:21	0.971**	**NS**
3	**Weight (Kg) Mean ± SD**	61.1 ± 11.3	63.6 ± 11.8	58.4 ± 12.4	0.113*	**NS**
4	**ASA Grade I:II**	22:24	23:23	23:23	0.971**	**NS**
5	**Surgery time**	83.6 ±7.8	84.5 ± 8.9	85.7 ± 8	0.495*	**NS**

**ANOVA* ***Chi square*

When variables related to anasthesia were compared in all the three groups,, it was found that Midozolam group had significantly more time for sensory block than Fenetanyl and Saline group. But Fenetanyl group had significantly more time for sensory block than Midozolam and Saline group. Starting of sensory sensations were earliest in Midozolam group than Fenetanyl and Saline group whereas motor sensations were earliest in Saline group than Midozolam and Fenetanyl and Saline group. (Table 2)

Mean duration of anesthesia was significantly more (<0.001) in Midozolam group than Fenetanyl and Saline group. Likewise it was found significantly more (<0.001) in Fenetanyl than Saline group. (Table 2)

Table 2
Comparison of variables related to anesthesia of study groups

Variables	Group (F) N=46		Group (M) N=46		Group (S) N=46		P value (Post hoc test)		
	Mean	SD	Mean	SD	Mean	SD	Group F&M	Group F&S	Group M&S
Sensory Block (minutes)	193.7	13.8	213.5	11.7	167	10.3	<0.001	<0.001	<0.001
Motor Block (minutes)	148.5	8.3	141.9	8.3	131	6.2	<0.001	<0.001	<0.001
Sensory onset (minutes)	6.91	0.86	6.26	0.77	8.11	0.80	<0.001	<0.001	<0.001
Motor onset (minutes)	8.54	0.50	7.59	0.50	6.52	0.51	<0.001	<0.001	<0.001
Duration of Analgesia	272.8	10.9	286	10.4	197.6	9.8	<0.001	<0.001	<0.001

When hemodynamic parameters at various interval were compared in all the three groups, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial pressure (MAP) and Heart rate (HR) in all the three groups were without significant difference at various interval. (Figure 1, 2, 3&4)

Figure 1

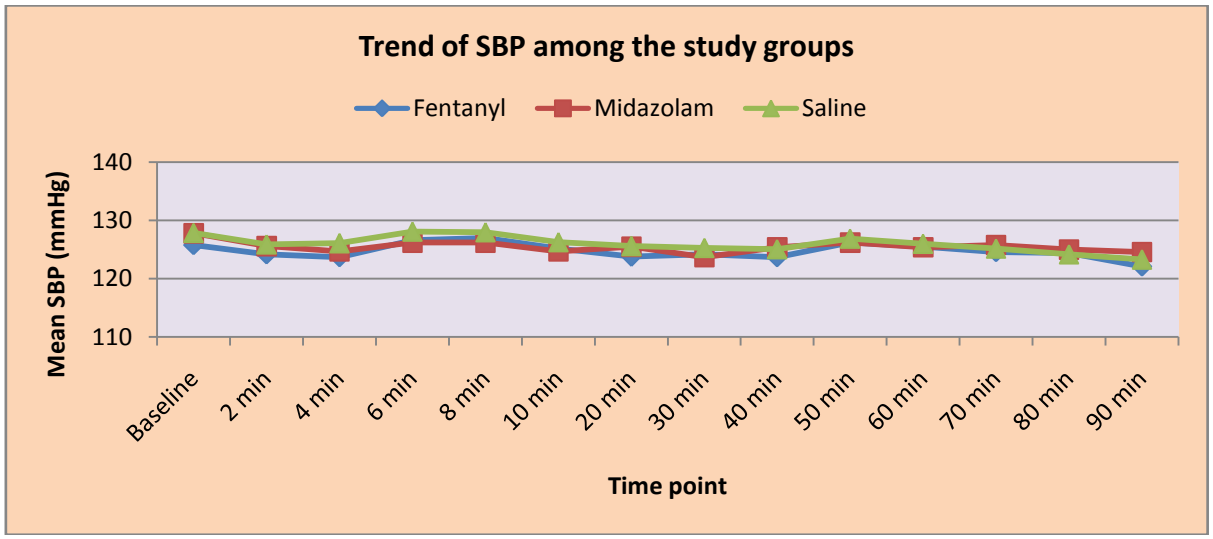


Figure 2

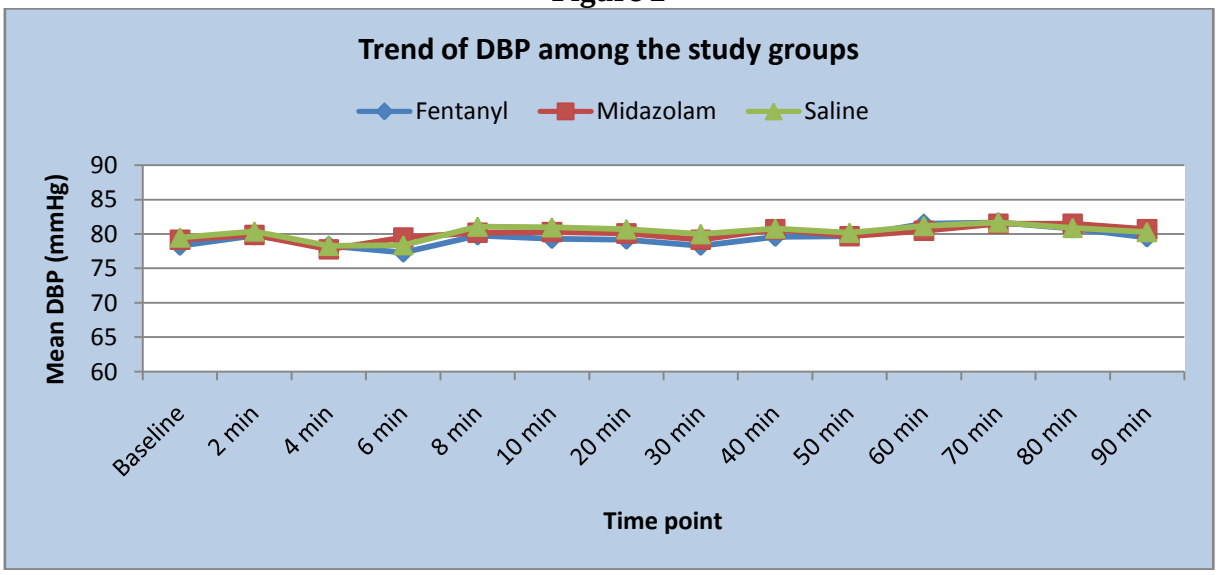
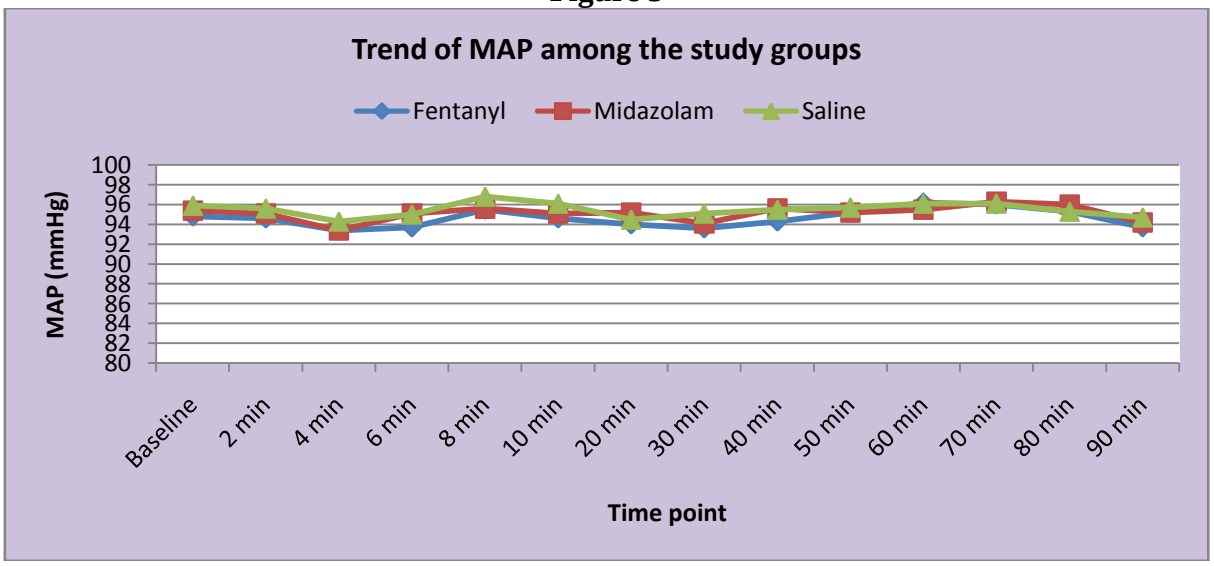


Figure 3



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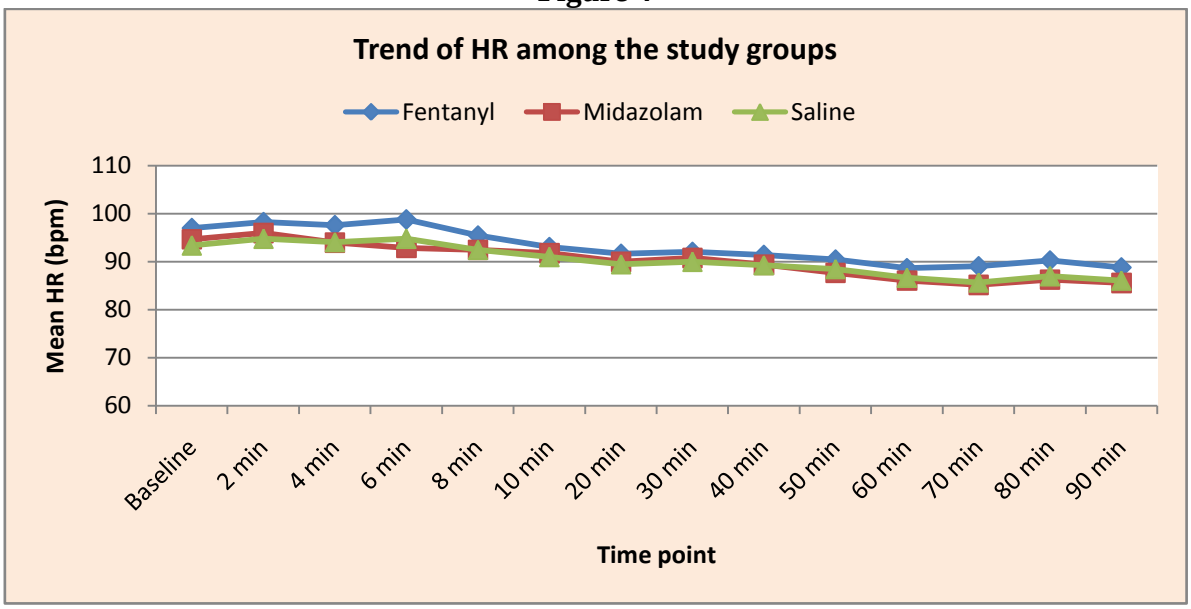


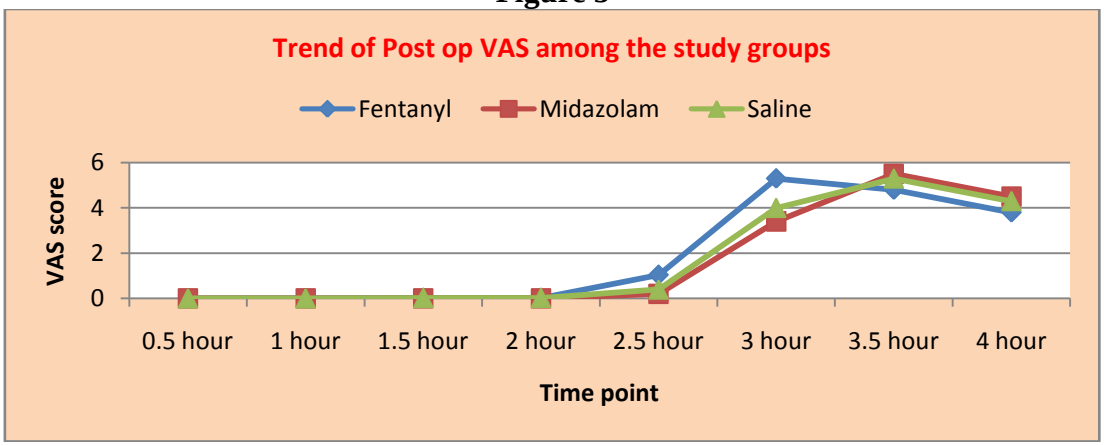
When mean VAS scores at various intervals were compared in all the three groups, it was found without significant variation till 2 hours of surgery but after that upto 3 hours it was minimum (<0.05) in Midozolam group and after 3 hours it significantly less (<0.05) in Fenetanyl group. (Table 3& Figure 5)

Table 3
Comparison of trend of Post operative VAS among the study groups

S. No.	Time point	Fentanyl Group (F) N=46	Midazolam Group (M) N=46	Saline Group (S) N=46	P* value LS
1	**0.5 hour**	0	0	0	-
2	**1 hour**	0	0	0	-
3	**1.5 hour**	0.02 ± 0.15	0	0.02 ± 0.15	0.608 **NS**
4	**2 hour**	0.02 ± 0.15	0	0.02 ± 0.15	0.608 **NS**
5	**2.5 hour**	1.04 ± 1.93	0.2 ± 0.83	0.39 ± 1	0.007 **S**
6	**3 hour**	5.3 ± 2.1	3.4 ± 3.2	4 ± 3.2	0.008 **S**
7	**3.5 hour**	4.8 ± 1	5.5 ± 1.1	5.3 ± 1.1	0.009 **S**
8	**4 hour**	3.8 ± 1	4.5 ± 1.1	4.3 ± 1.1	0.009 **S**

**ANOVA*

Figure 5



IV. DISCUSSION

Regional anaesthesia for infra umbilical surgeries is associated with a short duration of analgesia post operatively, which can be extended by i.m and i.v analgesics once patient experiences pain and demands for its relief.

In present study duration of analgesia was 197.6±9.8 minutes when bupivacaine was used alone, while it increased to 272.8±10.9, and 286±10.4 minutes when bupivacaine was used in combination with fentanyl and midazolam respectively. The total duration of analgesia in midazolam group was more when compared to Alokasamantary et al[8] in which the total duration of analgesia for midazolam was 236.9±64.9 minutes. Present study demonstrated that midazolam produce longer duration of post-operative analgesia when compared to fentanyl.

Similar to present study, Kim et al. also found that the addition of 1 or 2 mg of midazolam to intrathecalbupivacaine provided analgesia of approximately 2 and 4.5 hours respectively.

In another study Prakashet al[9] reported that 2 mg of intrathecal midazolam, when used as an adjunct to bupivacaine in patients undergoing caesarean delivery, could provide a moderate prolongation of postoperative analgesia with decreased incidence of postoperative nausea and vomiting.

Onset of sensory block in patients who received fentanyl and midazolam (6.91±0.86 mins and 6.26±0.77mins respectively) as adjuvants were significantly faster when compared to those patients who received bupivacaine (8.11±.8mins) only. Present finding is strengthened by the studies done by Alokasamantary et al and Sivevskiet al.[10] However the onset of sensory block was comparable between patients of midazolam and fentanyl group.

Onset of motor block was 6.52±.51, 7.59±0.5, 8.54±0.5 minutes in patients receiving bupivacaine alone, bupivacaine with midazolam and bupivacaine with fentanyl respectively. In present study the **Duration of motor block** was 131±00, 141.9±8.2 and 148.5±8.3 minutes in patients of bupivacaine alone, midazolam and fentanylgroup respectively, which demonstrated the increased duration of motorblock due to fentanyl in comparison to bupivacaine alone, while midazolam produces comparable duration of motor block when bupivacaine used alone as substantiated by study done by Neerja Bharti[11] as well as by Sunder L Negi ment.[12]

In present study the **Duration of sensory block** demonstrate the increased duration of sensoryblock due to midazolam in comparison to bupivacaine alone. These findings were strengthened by the studies done by Alokasamantary et al and Sivevski et al. However the duration of sensory block was comparable between patients of midazolam and fentanyl group

Present study demonstrated no clinically significant difference in the hemodynamic parameters and adverse effects among the 3 groups.

V. CONCLUSION

It can be concluded from this present study that duration of analgesia in midazolam group was significantly more than other Fenetanyl and Saline group. Present study concludes that midazolam produce longer duration of post-operative analgesia when compared to fentanyl. Mean VAS scores at various intervals were compared in all the three groups, it was found without significant variation till 2 hours of surgery but after that upto 3 hours it was minimum (<0.05) in Midozolam group and after 3

hours it significantly less (<0.05) in Fenetanyl group. So it can be concluded from this study that adding Midozolam with Bupivacaine is good for analgesia.

VI. CONFLICT OF INTEREST

None declared till now.

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