ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 3, Issue – 6, November - December - 2020, Page No. : 129 – 142

Comparative Study of Intrathecal Preservative Free Midazolam Versus Clonidine As An Adjuvant To Hyperbaric 0.5% Bupivacaine For Infraumbilical Surgeries

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Aim: Comparing preservative free Midazolam and Clonidine as an adjuvant to Hyperbaric Bupivacaine 0.5% to compare the onset and duration of sensory and motor block, hemodynamic changes and duration of post operative analgesia.

Method: Randomized observational study on 60 patients of ASA grade I & II, 18-60 years of age of either sex undergoing elective infraumbilical surgeries. Randomization was done by odd & even numbers, in sealed opaque envelopes. Execution of Randomization was done at the time of giving spinal anaesthesia. Thirty patients in each group.

Group A (Midazolam group) will receive 3ml (15mg) 0.5% hyperbaric bupivacaine and 0.2 ml (1mg) preservative free midazolam.

Group B (Clonidine group) will receive 3ml (15mg) 0.5% hyperbaric bupivacaine and 0.2 ml (30 mcg) preservative free clonidine.

Results : Time for first analgesia in group A was 368± 18.64 min as compared to 317.7 ± 12.78 min in group B. Onset and highest sensory level was 116.1 ± 10.95 sec and 7.9 ± 0.61 min respectively in group A while it was 128.3 ± 11.77 sec and 8.6 ± 0.61 min respectively In group B. Onset for motor blockade was 104.9± 8.88 sec in group A as compared to 112.3 ± 11.04 sec in group B. Decrease in Heart Rate and Blood Pressure were more in Clonidine than Midazolam group at 25- 50 min of administration of study group.

Conclusion: Intrathecal Midazolam provides perioperative stable hemodynamics, less adverse effects, prolonged sensory blockade and postoperative analgesia than clonidine.

Keywords: Midazolam, clonidine, Bupivacaine Heavy, postoperative analgesia.

Introduction:

Bupivacaine is the most commonly used local anaesthetic agent having satisfactory sensory and motor blockade with limited duration of action. "Various adjuvants that are added to local anaesthetic agents are adrenaline, phenylephrine, opiods, α2 agonists, neostigmine, ketamine, magnesium sulphate."[1, 2] This study was undertaken to evaluate and compare the efficacy and potency of intrathecally Bupivacaine with preservative

free Clonidine (30mcg) and preservative free Midazolam (1mg) for onset and duration of sensory and motor block, hemodynamic stability, duration of effective analgesia, including post operative analgesia and any adverse effects with each combination in patients undergoing infraumbilical surgeries.

Materials and Method

On approval from NHL Institutional review board, we carried out this study on 60 patients of ASA grade I & II, between 18-60 years of age of either sex and height in the range of 150-180 cm undergoing elective infraumbilical surgeries after explaining the procedure and obtaining consent from them.

Patient exclusion criteria

- Patient refusal.
- Patient on chronic analgesic therapy.
- Patient with gross spinal deformity.
- Patient with peripheral neuropathy.
- Patient taking sympathomimetics / sympatholytic drugs.
- Pregnancy /lactation.
- Known allergy to local anaesthetics.
- Hypersensitivity to study drugs.
- H/o chronic headache /backache.
- Local infection at the site.
- Coagulation disorder.
- Surgeries which last longer than 3 hrs.
- ASA grade III, IV, V.
- H/o drug / Alcohol abuse.
- Patient with systemic hypertension, hepatic dysfunction, renal dysfunction, endocrine dysfunction, cardiac dysfunction.
- Patient using alpha 2-adrenergic receptor antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors or noted to have dysrhythmias on ECG.
- Patient who were morbidly obese.
- Patient who were hemodynamically unstable.

Random allocation of patients was done in two groups

Group A: 30 patients in group A (Midazolam group) will receive 3ml (15mg) 0.5% hyperbaric bupivacaine and 0.2 ml (1mg) preservative free midazolam.

Group B: 30 patients in group B (Clonidine group) will receive 3ml (15mg) 0.5% hyperbaric bupivacaine and 0.2 ml (30 mcg) preservative free clonidine. Total volume intrathecally given was 3.2 ml in both the groups.

Study Protocol

It is a randomized observational study. Randomization was done by odd & even numbers, in sealed opaque envelopes. Execution of Randomization was done at the time of giving spinal anaesthesia. Microsoft Excel 2007 was used for statistical analysis. Data was expressed as Mean ± Standard Deviation. Data were compared using student t-test. *P* value < 0.05 considered statistically significant(S) and *P*<0.001 considered highly significant (HS). *P* value >0.05 is considered Not significant (NS).

Pre Anaesthetic Assessment

- Preoperative history and physical examination of patient was done.
- Patients having history of allergy to any drug or contraindications for spinal anaesthesia were excluded from study.
- Laboratory investigations like CBC, blood sugar, Renal function tests, serum electrolytes, X ray chest, ECG were viewed.
- Patient was explained the procedure and was informed to communicate about the perception of any discomfort or pain during surgery.
- Patient was explained about VAS score with 1 to 10 scale.

- Written and informed consent was taken from the patients as well as his/her relatives.
- Patients were kept Nil by Mouth for 6 hours.

In the operation theatre

- IV line taken and each patient were preloaded with 10 ml/ kg of Ringer's lactate solution over 30 minutes before procedure.
- Pulse Oximeter, Non-invasive blood pressure monitoring and ECG were attached and base line reading taken.

Equipment

- Cotton swabs with swab holding forceps. Disposable 25G lumbar puncture needle.
- Disposable 5 cc syringe
- An ampoule of hyperbaric Bupivacaine 0.5%, preservative free clonidine and preservative free Midazolam.

Technique

- Under all strict aseptic and antiseptic precaution, with patient in sitting position, lumbar puncture was performed at L2-L3 or L3-L4 intervertebral space with 25G Quincke spinal needle and selected drug was given slowly. After completion of procedure, patient was laid down in supine position. Time was noted for subarachnoid injection of drug.
- Pulse, BP, SPO_2 and RR were recorded every 0,2,4,6,8, 10, 15,20,25,30, 40, and 60 minutes after giving spinal anaesthesia and then every 30 minutes till 240 mins and thereafter at 60 mins interval upto 600 mins and then at 720 mins, and 1440 mins in post operative ward where further monitoring was continued.

Evaluation

Onset of sensory blockade: Time required to loss of pinprick sensation at the level of sensory dermatome T10 were noted.

Highest level of sensory block and time to attain it were recorded. It was assessed by bilateral pin prick method along the midclavicular line using a short beveled 26 G hypodermic needle at 2 mins interval till surgical anaesthesia was achieved.

Further sensory testing was performed at 30 mins intervals till the recovery of S_2 dermatome.

Onset of Motor Blockade will be defined as the time from injection of study drug to the time to achieve Bromage grade1.

Bromage criteria		
Scale	Criteria	Degree of block
0	Free movement of legs and feet with ability to raise extended legs.	None
1	Inability to raise extended leg and knee flexion decreased, but full flexion of feet and ankle is present.	Partial (33%)
2	Inability to raise leg or flex knees, but flexion of ankle and feet present.	Partial (66%)
3	Inability to raise leg, flex knees or ankle or move toes.	Complete paralysis

- After adequate level of block, surgery was started and beginning time of surgery was noted.
- **Motor blockade Onset (Time required to produce grade 3 motor block)** and duration from grade 3-0 was noted.
- Time to two segment regression was noted.
- Time to S2 regression was noted.

- Depending on the weight of patient, IV fluids were administered and replaced according to loss during surgery.
- Duration of Surgery- it is time duration between injection of study drug to the skin closure
- After completion of surgery, patients were shifted to post operative ward, where patients were monitored.
- Total duration of analgesia: Time of injection of study drug to first demand for rescue analgesia by patient.
- Intraoperative complications like bradycardia, hypotension, sedation, shivering, nausea, vomiting, dryness of mouth and respiratory depression was noted in patients.
- Hypotension was defined as systolic blood pressure > 30% decrease in baseline value.
- Hypotension was treated with Ephedrine 6mg iv stat.
- Tachycardia was defined as heart rate >100/mins and bradycardia was defined as heart rate < 60/mins or >20% decline than baseline value.
- Bradycardia was treated with Inj. Glycopyrollate 0.2mg i.v.
- Nausea and vomiting if occurred was treated with Inj. Ondansetron 4mg i.v.
- Warm fluids and covering of patient was used to treat shivering.
- After surgery, patients were monitored for 24 hours postoperatively.
- Postoperatively pain measurement was assessed by VAS scale. And First rescue analgesic was given in the form of inj. Tramadol (1mg/kg)iv and inj. Ondansetron (0.08mg/kg)iv.
- Total number of analgesic requests in 24 hours noted.
- **Sedation** was assessed by **OAA/S** score periodically upto 360 minutes**.**

Responsiveness	**Score**
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not responds to mild prodding/shaking	1

- **Pruritus:** For severe form of pruritus, antihistaminic was kept ready.
- Time for 1st rescue Analgesia was noted.
- Total number of analgesic requests noted.
- **Post dural puncture headache(PDPH)** : Headache was classified as PDPH if it was aggravated by erect or sitting position, relieved on lying flat, mainly occipital or frontal and increased on coughing, sneezing, or straining.
- **VAS score** was assessed according to 10 point scale as shown below

0	1	2	3	4	5	6	7	8	9	10
Pain free	Very Mild	Discomforting	Tolerable	Distressing	Very Distressing	Intense	Very Intense	Utterly Horrible	Excruciating Unbearable	Unimaginable Unspeakable
No Pain	Minor Pain			Moderate Pain			Severe Pain			

Observation & Results

Table 1: Demographic Data

Variables	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
Age (years)	32.2 ± 6.56	33.7 ± 8.02	0.43	NS
Height(cm)	169.5 ± 6.79	167.4 ± 8.02	0.26	NS
Weight (kg)	61.5 ± 7.76	62.0 ± 8.11	0.8	NS
Sex ratio(M:F)	21/9	22/8	-	-
ASA Grade I Grade II	20 10	21 9	- -	- -
Duration of Surgery	142 ± 22.19	143.0 ± 25.75	0.87	NS

Table 1 shows demographic data between group A and group B. The two groups were comparable in Age, Height, Weight, Sex, ASA (American Society of Anesthesiologist) grade and duration of surgery and there was no statistical significant difference between the two groups (*P*>0.05). **SD**- Standard Deviation

Table 2: Baseline Vital Parameters

	Group A (Mean± SD)	Group B (Mean± SD)	*P*- Value	Inference
Heart Rate (per minute)	82.9 ± 4.23	83.1 ± 3.7	0.84	NS
SBP (mmHg)	127.3 ± 5.11	126.3 ± 3.51	0.38	NS
DBP (mmHg)	82.5 ± 2.91	82.9 ± 2.33	0.49	NS
MAP (mmHg)	97.4 ± 3.29	97.4 ± 2.28	0.97	NS
RR (/min)	15.5 ± 1.55	15.7 ± 1.49	0.73	NS
SPO_2 (%)	97.8 ± 0.92	97.9 ± 0.9	0.77	NS

Table 2 shows Baseline Vital Parameters between groups A and B. There was no statistical significant difference with regard to Baseline Heart Rate, SBP,DBP,MAP,RR and SPO_2 between the two groups (*P*>0.05).

Table 3: Characteristics of Motor Blockade

	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
Time Of Onset Of Motor Blockade (sec)	104.9± 8.88	112.3 ± 11.04	0.005	S
Time For Bromage Grade 3 Motor Blockade (min)	7.7± 0.53	8.1 ± 0.49	0.0021	S
Duration of Motor Block Regression From Bromage (Grade 3-0) (min)	238 ± 12.52	249.7 ± 10.66	0.0005	HS

Table 3 shows Characteristics of Motor Blockade between groups A and B. The time of onset of Motor Blockade is prolonged in Group B (112.3 ± 11.04) sec as compared to Group A (104.9± 8.88) sec which is statistically significant (P<0.05) while Time for Bromage grade 3 motor blockade was prolonged in Group B (8.1 ± 0.49) min than group A (7.7± 0.53) min which is statistically significant (P<0.05). Duration of Motor block regression from Bromage grade 3 to 0 was more in group B (249.7 ± 10.66) min as compared to group A (238 ± 12.52) min which is statistically highly significant (P<0.001).

Table 4: Characteristics of Sensory Blockade

	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
Time Of Onset Of Sensory Block (sec)	116.1 ± 10.95	128.3 ± 11.77	0.0001	HS
Time For Highest Sensory Block (min)	7.9 ± 0.61	8.6 ± 0.61	<0.001	HS
Time For Two Segment Regression (min)	127.3 ± 8.29	115.7 ± 8.58	<0.001	HS
Time For S2 Segment Regression (min)	295 ± 12.8	284.3 ± 15.01	0.004	S

Table 4 shows Characteristics of Sensory Blockade which shows time of onset of Sensory block is prolonged in group B(128.3±11.77) sec as compared to group A (116.1± 10.95)sec (P<0.001). Time for highest Sensory Block is prolonged in group B (8.6 ± 0.61) min as compared to group A (7.9 ± 0.61) min (P<0.001).Time for Two segment regression and time for S2 segment regression is more in group A (127.3 ± 8.29) min and (295 ± 12.8) min respectively as compared to group B (115.7 ± 8.58) min and (284.3 ± 15.01) min respectively which is statistically significant (P<0.05).

Table 5: Perioperative Heart Rate (per Minute)

Time	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
0 min	82.1 ± 3.88	83.3 ± 3.46	0.22	NS
2 min	81.2 ± 3.77	82.3 ± 2.68	0.18	NS
4 min	79.3 ± 3.26	80.5 ± 3.01	0.12	NS
6 min	78.9 ± 3.7	78.2 ± 3.38	0.46	NS
8 min	78.3 ± 4.67	76.9 ± 2.66	0.15	NS
10 min	77.2 ± 4.83	75.4 ± 1.75	0.06	NS
15 min	76 ± 6.5	74.3 ± 1.72	0.16	NS
20 min	75.7 ± 6.59	72.9 ± 1.87	0.02	S
25 min	75.8 ± 6.32	70.9 ± 2.61	<0.001	HS
30 min	75.6 ± 4.38	66.8 ± 4.05	<0.001	HS
40 min	75.7 ± 2.73	64.9 ± 6.03	<0.001	HS
60 min	74 ± 1.75	68.6 ± 5.95	<0.001	HS
80 min	73.3 ± 1.32	69 ± 5.97	<0.001	HS
100 min	73.7 ± 2.11	66.9 ± 4.76	<0.001	HS

120 min	73.5 ± 1.94	67.9 ± 3.98	<0.001	HS
150 min	74.5 ± 1.89	69.3 ± 3.17	<0.001	HS
180 min	75.7 ± 2.56	70.1 ± 2.62	<0.001	HS
240 min	79.1 ± 3.27	73.1 ± 1.71	<0.001	HS
300 min	79.8 ± 2.43	75.4 ± 2.77	<0.001	HS
360 min	79.5 ± 1.66	77.6 ± 3.33	<0.001	HS
480 min	80.7 ± 2.26	81.7 ± 2.35	0.12	NS
600 min	80.5 ± 3.16	81.7 ± 2.39	0.09	NS
720 min	79.3 ± 2.95	80.6 ± 3.2	0.09	NS
1440 min	80.4 ± 2.65	81.5 ± 2.4	0.1	NS

Table 5 shows Perioperative change in Heart Rate, with Group B showing decrease in Heart Rate as compared to Group A which is statistically highly significant from 25 minutes to 360 minutes (P<0.001).

Table 6: Perioperative SBP (mmHg) (Systolic Blood Pressure)

Time	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
0 min	125.8 ± 4.82	125.7 ± 3.75	0.9	NS
2 min	122.6 ± 4.21	121.2 ± 2.76	0.13	NS
4 min	115.2 ± 4.09	116.9 ± 3.99	0.102	NS
6 min	114.3 ± 4.32	113.1 ± 3.51	0.46	NS
8 min	114.1 ± 4.62	112.2 ± 2.8	0.06	NS
10 min	113.1 ± 4.86	111.5 ± 2.27	0.10	NS
15 min	112.1 ± 5.69	110.6 ± 2.24	0.19	NS
20 min	110.7 ± 8.21	107.4 ± 2.88	0.04	S
25 min	111.5 ± 8.27	103.2 ± 4.05	<0.001	HS
30 min	112 ± 7.3	98.7 ± 4.59	<0.001	HS
40 min	112.5 ± 5.22	96.9 ± 4.78	<0.001	HS
60 min	112.9 ± 1.95	99.7 ± 5.27	<0.001	HS
80 min	112.8 ± 1.86	97.3 ± 3.73	<0.001	HS
100 min	113.3 ± 1.86	96.8 ± 3.74	<0.001	HS
120 min	114.3 ± 2.61	98.9 ± 3.05	<0.001	HS
150 min	115.7 ± 2.91	103.5 ± 2.27	<0.001	HS
180 min	117.9 ± 2.97	106.5 ± 2.66	<0.001	HS
240 min	119.9 ± 2.29	110.1 ± 3.08	<0.001	HS
300 min	120.9 ± 2.5	112.1 ± 3.75	<0.001	HS
360 min	120.8 ± 2.76	114.5 ± 3.36	<0.001	HS
480 min	120.1 ± 2.03	120.9 ± 3.35	0.26	NS

600 min	120.1 ± 3.58	121.4 ± 2.84	0.11	NS
720 min	119.9 ± 4.77	121.6 ± 3.12	0.11	NS
1440 min	120.8 ± 4.25	122.3 ± 2.45	0.10	NS

Table 6 shows changes in Perioperative SBP which shows decrease in systolic Blood Pressure in group B more than group A, which is statistically highly significant from 25 mins to 360 mins (*P*<0.001).

Table 7: Perioperative DBP (Diastolic Blood Pressure)

Time	Group A (Mean± SD)	Group B (Mean± SD)	*P*-Value	Inference
0 min	82.1 ± 3.15	82.4 ± 2.31	0.7	NS
2 min	79.8 3.11	80.9 ± 2.55	0.13	NS
4 min	73.5 ± 3.44	74.7 ± 2.37	0.12	NS
6 min	72.5 ± 2.57	72.1 ± 1.93	0.42	NS
8 min	73.0 ± 3.05	71.9 ± 1.48	0.07	NS
10 min	72.5 ± 3.47	71.3 ± 1.32	0.1	NS
15 min	70.9 ± 4.29	70.8 ± 1.54	0.93	NS
20 min	70.8 ± 4.72	67.4± 2.58	0.001	S
25 min	70.9 ± 4.54	65.1 ± 3.09	<0.001	HS
30 min	70.9 ± 4.6	62.7 ± 3.26	<0.001	HS
40 min	71.9 ± 3.81	61.9 ± 2.49	<0.001	HS
60 min	72.1 ± 1.93	62.4 ± 2.8	<0.001	HS
80 min	72.3 ± 1.67	61.2 ± 1.54	<0.001	HS
100 min	72.8 ± 2.38	60.7 ± 0.98	<0.001	HS
120 min	73.4 ± 2.42	62.1 ± 1.44	<0.001	HS
150 min	74.1 ± 2.4	63.4 ± 1.19	<0.001	HS
180 min	77.6 ± 2.7	64.8 ± 2.07	<0.001	HS
240 min	79.4 ± 2.74	68.7 ± 2.32	<0.001	HS
300 min	79.9 ± 2.34	70.3 ± 3.02	<0.001	HS
360 min	80.3 ± 1.83	73.7 ± 3.11	<0.001	HS
480 min	79.2 ± 2.33	78.6 ± 2.53	0.34	NS
600 min	79.7 ± 2.56	79.3 ± 1.99	0.5	NS
720 min	80 ± 3.9	79.5 ± 1.94	0.55	NS
1440 min	80.7 ± 3.76	80.3 ± 1.97	0.66	NS

Table 7 shows changes in Perioperative DBP between two groups , with decrease in diastolic blood pressure being more in group B as compared to group A from 25 min to 360 min, which is statistically highly significant (*P*<0.001).

Table 8: Perioperitive Respiratory Rate And Spo2

Time	Group A		Group B		*P*-Value		Inference	
	RR (/min) (Mean±SD)	SPO2(%) (Mean±SD)	RR(/min) (Mean±SD)	SPO2(%) (Mean±SD)	RR(/min) (Mean±SD)	SPO2(%) (Mean±SD)	RR(/min) (Mean±SD)	SPO2(%) (Mean±SD)
0 min	14.7 ± 1.11	97.6± 0.82	14.7± 1.11	97.7± 0.84	1	0.53	NS	NS
2 min	14.7 ±1.09	97.4± 0.67	14.3 ±1.03	97.6± 0.82	0.23	0.3	NS	NS
4 min	14.6 ± 1.07	97.2± 0.57	14.2± 1.1	97.1± 0.40	0.15	0.29	NS	NS
6 min	14.5 ±1.04	97.2± 0.57	14.2 ±1.1	97.3± 0.61	0.23	0.51	NS	NS
8 min	14.7 ± 1.09	97.2± 0.5	14.4± 1.1	97.3± 0.6	0.35	0.64	NS	NS
10 min	14.4 ± 1.22	97.1± 0.51	13.9 ±1.11	97.1± 0.78	0.12	1.00	NS	NS
20 min	13.8± 1.32	97.3± 0.47	13.3 ±1.11	97.1± 0.61	0.09	0.15	NS	NS
30 min	13.5 ± 1.28	97.3± 0.47	13.1 ±1.14	97.1± 0.76	0.29	0.22	NS	NS
40 min	13.4 ± 1.19	97.3± 0.45	12.9± 1.01	97.1± 0.91	0.1	0.28	NS	NS
60 min	13.3 ± 1.11	97.2± 0.41	12.9 ±1.01	97± 0.81	0.14	0.31	NS	NS
100 min	13.4± 1.19	97.1± 0.35	13.1± 1.01	96.9± 0.78	0.35	0.2	NS	NS
120 min	13.4± 1.19	97.1± 0.31	13.2 ±1.0	97.2± 0.82	0.48	0.4	NS	NS
150 min	13.5 ± 1.17	97.2± 0.38	13.2± 1.0	97.1± 0.97	0.34	0.86	NS	NS
180 min	13.9± 1.44	97.3± 0.47	13.5± 0.9	97.2± 1.01	0.13	0.74	NS	NS
240 min	13.7± 1.46	97.5± 0.68	13.3± 0.96	97.5± 0.86	0.21	0.86	NS	NS
300 min	13.7± 1.46	97.5± 0.68	13.5 ±0.86	97.8± 0.9	0.52	0.26	NS	NS
360 min	13.7± 1.46	97.6± 0.76	13.8± 0.61	98± 0.85	0.81	0.11	NS	NS
480 min	13.7 ±1.46	97.7± 0.76	14.3± 0.69	98± 0.91	0.07	0.12	NS	NS
600 min	13.9 ± 1.34	97.8± 0.79	14.3± 0.69	98.2± 0.83	0.23	0.11	NS	NS
720 min	14.2 ±1.32	97.9± 0.8	14.3± 0.69	98.2± 0.83	0.8	0.21	NS	NS
1440 min	14.4 ±1.33	97.9± 0.8	14.3± 0.69	98.2± 0.83	0.62	0.21	NS	NS

Table 8 shows Perioperative change in Respiratory Rate and SpO2 between two groups which were normal and comparable in both groups and there is no statistical difference between two groups (P>0.05).

Table 9: Perioperative OAA/S Sedation Score

Time	Group A (Mean ± SD)	Group B (Mean ± SD)	*P*-Value	Inference
0 min	5.0 ± 0.0	5.0 ± 0.0	-	-
2 min	5.0 ± 0.0	5.0 ± 0.0	-	-
4 min	5.0 ± 0.0	5.0 ± 0.0	-	-
6 min	5.0 ± 0.0	5.0 ± 0.0	-	-
8 min	5.0 ± 0.0	5.0 ± 0.0	-	-
10 min	4.9±0.31	4.8±0.38	0.45	NS

15 min	4.9 ± 0.35	4.8 ± 0.43	0.32	NS
20 min	4.8 ± 0.41	4.7 ± 0.48	0.25	NS
25 min	4.7 ± 0.45	4.2 ±0.73	0.002	S
30 min	4.7 ± 0.47	4.1 ± 0.78	0.0003	HS
40 min	4.7 ± 0.47	3.8 ± 0.79	<0.001	HS
60 min	4.7 ± 0.48	3.8 ± 0.76	<0.001	HS
80 min	4.7± 0.45	4.1±0.55	<0.001	HS
100 min	4.8±0.38	4.44 ± 0.56	<0.001	HS
120 min	4.9 ± 0.35	4.7 ± 0.48	0.06	NS
150 min	5.0 ± 0.00	4.9 ± 0.31	0.07	NS
180 min	5.0 ± 0.00	5.0 ± 0.00	-	-
210 min	5.0 ± 0.00	5.0 ± 0.00	-	-
240 min	5.0 ± 0.00	5.0 ± 0.00	-	-
300 min	5.0 ± 0.00	5.0 ± 0.00	-	-
360 min	5.0 ± 0.00	5.0 ± 0.00	-	-

Table 9 shows OAA/S Sedation Score in both groups which is highly significant between both groups from 30 min to 100 min (*P*<0.001) however In First 8 Minutes and after 150 Minutes, OAA/S Score Is 5 In Both Groups.

Table 10: Duration of Post-Operative Analgesia and Total Analgesic Requests

Parameters	Group A (n=30) (Mean±SD)	Group B (n=30) (Mean±SD)	*P*-Value	Inference
Time to first analgesic request (min)	368± 18.64	317.7 ± 12.78	<0.001	HS
Total Analgesic Requests (no.)	1.9 ± 0.61	3.2 ± 0.48	<0.001	HS

Table 10 shows Duration of Post Operative Analgesia and Total Analgesic Requests which is more in group A (368± 18.64)min and (1.9 ± 0.61) no. respectively as compared to group B (317.7 ± 12.78)min and (3.2 ± 0.48) respectively which is statistically highly significant (*P*<0.001).

Table 11: Perioperative Adverse Effects

Adverse Effects	Group A	Group B
Hypotension	4 (13.3%)	8 (26.7%)
Bradycardia	4 (13.3%)	10(33.3%)
Nausea, vomiting	3(10%)	5 (16.7%)
Pruritis	0	0
RS depression	0	0
Shivering	4(13.3%)	3(10%)

Table 11 shows Perioperative Adverse Effects between both groups, with incidence of Hypotension and Bradycardia being more in Group B, 26.7% and 33.33 % respectively as compared to group A ,13.3 % and 13.3% respectively. The incidence of Nausea and vomiting was 16.7% in group B as compared to 10% in group A while

Shivering was observed in 13.3 % in group A as compared to 10% in group B.

Discussion

Intrathecal preservative free Clonidine has been successfully used as an adjuvant with preservation of cardiovascular reflexes, reduced post operative analgesic requirement and prolongation of the duration of bupivacaine induced sensory and motor blockade. Intrathecal preservative free midazolam has been shown to have analgesic properties and potentiate the effects of intrathecal local anesthetic. "The mechanism by which midazolam provides analgesia has been explored in several recent studies, it acts through gamma-aminobutyric acid (GABA) receptors present in the dorsal horn of the spinal cord with the highest density of these receptors found within the lamina II of the dorsal horn ganglia, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation. It may also have central antinociceptive effect via the activation of spinal δ opioid receptors."[3,4,5,6] Neuraxialanaesthesia is a safe and effective alternative to general anaesthesia when surgical site is located in infraumbilical region. To improve spinal anaesthetic efficacy, adjuvants used enhance and prolong analgesia, to lower dose requirements and to reduce dose dependent side effects of local anaesthetics. Intrathecal preservative free Midazolam has been shown to have analgesic properties and potentiates the effects of intrathecal local anaesthetic. The mechanism by which midazolam provides analgesia has been explored in several studies.

Good child CS et al [7] studied that "intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal delta receptor".

Edward m and serrao et al [8]observed that "Antinociception actions of intrathecal midazolam are mediated via BZD/GABA receptors".

N Nader et al [9] **in 2001** showed "suppression of plasma and CSF concentration of TNF-α during the perioperative period on preoperative administration of clonidine resulting in perioperative analgesia and decreased sympathetic tone".

In recent years, Clonidine which is a selective partial agonist for adrenoreceptor has been used to prolong duration of spinal anaesthesia. It is known to potentiate both sensory and motor block of local anaesthetics. The analgesic effect of intrathecal preservative free clonidine is mediated through activation of post synaptic receptor in substantia geletinosa of spinal cord.

Drug and Dosage

- **Joshi SA, Khadke VV et al** [4] have used 3ml (15mg) 0.5% Hyperbaric Bupivacaine for lower abdominal surgeries.
- **Tucker et al** [6] suggested that intrathecal midazolam in humans and identified safe dose of intrathecal midazolam as less than 0.03mg/kg.
- **Kanazi et al** [10] studied the effect of low dose clonidine (30mcg) added to intrathecal bupivacaine Heavy 0.5%, produces the prolongation of sensory and motor blockade.

Neurotoxicity Concerns

- **Tucker et al** [6] evaluated 574 patients who received intrathecal midazolam and observed the patients for one month for a wide range of neurotoxicity and conclude that upto 2 mg of intrathecal midazolam did not increase the occurrence of neurological symptoms .We have 1 mg preservative free midazolam along with 3ml (15 mg) 0.5% Bupivacaine Heavy.
- **In 1999 Hodgson PS et al** [11] concluded that clonidine seems to be a safe spinal drug in humans.

Characteristics of Sensory Blockade

- **In our study Time to onset of sensory block** was

116.1 ± 10.95 sec in group A and 128.3 ± 11.77 sec In group B which was statistically highly significant (*P*<0.001).

- **In our study Time to achieve highest sensory level** was 7.9 ± 0.61 min in group A and 8.6 ± 0.61 in group B, which was highly significant (*P*<0.001).
- **In our study Time for two segment regression** was 127.3 ± 8.29 min in group A as compared to 115.7 ± 8.58 min in group B, which was statistically highly significant (*P*<0.001).
- Similar to our study **Gupta et al in 2015 [12] and Agrawal et al [13] in 2005** used "Intrathecal midazolam and reported prolonged sensory and motor block duration."
- **In our Study Time for S2 segment regression** was 295 ± 12.8 min in group A as compared to 284.3 ± 15.01 min in group B which is statistically significant with time for S2 regression being more in group A as compared to group B(*P*<0.05).
- **N Bharti et al [5]** showed "Time to S2 segment regression as significantly longer with intrathecal midazolam ,218 min as compared to bupivacaine alone, 165 min (*P*<0.001)".

CHARACTERISTICS OF MOTOR BLOCKADE

- **In our study Time for onset for motor blockade** was 104.9± 8.88 sec in group A as compared to 112.3 ± 11.04 sec in group B.(*P* value<0.05).
- **In our study time For Motor Bromage Grade 3 to 0 (Duration of Motor Block)** was 238 ± 12.52 min in group A as compared to 249.7 ± 10.66 min in group B which is highly significant(*P*<0.001).
- **Joshi SA, Khadke VV et al [4]** showed "duration of motor block of 293.8 ±108.69 min with intrathecal midazolam as compared to 322.92 ± 135 min with intrathecal clonidine".

Post Operative Analgesia

- **In our study, time for first analgesic request** in group A was 368± 18.64 min as compared to 317.7 ± 12.78 min in group B(*P*<0.001).
- **Joshi SA, Khadke VV et al [4]** showed "prolongation of duration of analgesia by intrathecalmidazolam (391.64 ± 132.98 min) as compared to intrathecalclonidine (296.6 ± 52.77 min) which was satistically highly significant (p<0.001)".

Perioperative Haemodynamics

In our study decrease in Heart Rate and Blood Pressure were more in group clonidine than in midazolam group at 25- 50 min of administration of study group (*P*<0.001).

Decrease in Blood Pressure was noted in Midazolam group at 40 mins, which was 12% of baseline value and in clonidine group, it was 23% of baseline value.

Decrease in Heart Rate in clonidine group at 40 minutes was of 22% than the baseline values while in Midazolam group it was 8.7% of baseline.

- **Joshi SA, Khadke VV et al [4]** observed "bradycardia (36%) and hypotension (44%) with low dose clonidine (30mcg) while intrathecal Midazolam showed bradycardia (10%) and Hypotension (16%) which was satistically siginificant(*P*<0.05)".
- **In our study Table 6 shows Respiratory rate and SpO_2** were stable and comparable in both groups(*P*>0.05).

Perioperative Adverse Effects

Nausea and Vomiting

- In our study Nausea and vomiting was noted in 10% of group A as compared to 16.7% in group
- **Joshi SA, Khadke VV et al [4]** showed "28% incidence of post operative Nausea and Vomiting in

both intrathecal midazolam and Clonidine".

OAA/S sedationscore

- In our study Sedation was observed and compared by OAA/S sedation score and it was more in group B as compared to group A(P<0.001) However in first 8 minutes and after 150 minutes, OAA/S score is 5 in both groups.
- Joshi SA, Khadke VV et al [4] observed "sedation in 4% patients with intrathecal Midazolam as compared to 20% patients with intrathecal clonidine".

In our study

Hypotension **was noted in 13.3% in group A as compared to 26.7% in group B.**

Bradycardia was noted in 13.3% in group A as compared to 33.3% in group B.

- **Joshi SA, Khadke VV et al [4]** observed "bradycardia (36%) and hypotension (44%) with low dose clonidine (30mcg) while intrathecal Midazolam showed bradycardia (10%) and Hypotension(16%)".
- **Shivering** was noted in 13.3% in group A as compared to 10% in group B.
- **Pruritis and Respiratory depression** was not noted in any of the groups.
- **Transient Neurological Symptoms and Post Dural Puncture Headache** was not noted in any of the group.

Conclusion

In nutshell, Intrathecal preservative free midazolam (1mg) and Clonidine (30mcg), both are good adjuvants to 0.5% Heavy Bupivacaine. Intrathecal Midazolam provides perioperative stable hemodynamics, less adverse effects, prolonged sensory blockade and better postoperative analgesia than intrathecal clonidine. Intrathecal Clonidine provides longer duration of motor blockade as compared to intrathecal Midazolam.

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How to citation this article: Dr. Manisha S. Kapdi, Dr. Parikh Tapan P., Riddhi Sabhadiya, Resident, Ajay Limbachiya , "Comparative Study Of Intrathecal Preservative Free Midazolam Versus Clonidine As An Adjuvant To Hyperbaric 0.5% Bupivacaine For Infraumbilical Surgeries", IJMACR- November - December - 2020, Vol – 3, Issue -6, P. No. 129 – 142.