International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2021; 4(4): 100-107
Received: 05-10-2021
Accepted: 07-11-2021

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Comparative study of intrathecal fentanyl and midazolam for postoperative pain relief after lower abdominal surgery

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DOI: https://doi.org/10.33545/26643766.2021.v4.i4b.437

Abstract
Background: For surgeries on the lower limbs and abdomen, spinal anesthesia is recommended. Due to its lower neurotoxicity, lignocaine is the most often used local anesthetic for subarachnoid blockade. Even with high sensory block, intrathecal lignocaine may not be enough to provide sustained analgesia following surgery. Therefore, a variety of adjuvants, such as fentanyl, ketamine, midazolam, clonidine, opioids, and neostigmine, are used to extend the duration of the local anesthetic's effect.
Aims and objectives
1. To evaluate and compare the efficacy, utility and safety of single bolus dose of intrathecal Fentanyl (25 μ gm) and Intrathecal midazolam (2 mg) and To compare it with Control group of Placebo (0.5 ml) of normal saline in various lower abdominal surgeries under spinal anaesthesia
2. To know the quality and duration of post-operative pain relief following intrathecal fentanyl and midazolam
3. To see the incidence and severity of side effects following intrathecal administration of midazolam and fentanyl

Materials and Methods: This is a prospective, parallel group clinical trial that is randomized, observer and participant blind, and prospective. Three groups were randomly assigned to 75 ASA grade I and II patients who were scheduled for lower abdominal surgery.
Conclusion: Additional of intrathecal midazolam or fentanyl provided post-operative analgesia significantly longer than lignocaine alone and duration of analgesia was comparable between midazolam and fentanyl. Quality and degree of analgesia was better and both. Additional of fentanyl does not have any significant effect on onset, duration and regression of motor block. Additional of midazolam has significant effect on onset duration and regression of motor block. The onset of motor block was earlier and duration and regression of motor block was prolonged.

Keywords: Lower neurotoxicity, lower abdominal surgery, lignocaine

Introduction
While local, regional (spinal or epidural), or general anesthesia can be used for lower abdominal and lower limb surgeries, neuraxial blockade is the recommended kind of anesthesia. Due to its quick onset, excellent blockade, low risk of infection from the catheter in situ, low failure rate, and affordability, spinal block is still the preferred procedure. However, spinal anesthesia with only local anesthetics is associated with a relatively short duration of action, making early analgesic intervention necessary in the postoperative period. This presents a significant challenge for postoperative pain control. Many adjuvants have been investigated in an effort to extend the duration of spinal anesthesia [1].
Midazolam, a water-soluble benzodiazepine/type Gamma-aminobutyric acid (GABA)-A, has an analgesic action through GABA-A receptor complex and reduces the excitability of the spinal cord. Midazolam may be used as a perfect epidural and intrathecal analgesic for persistent postoperative pain because of its widespread availability and good patient tolerance. Midazolam had been proved to potentiate the analgesic effect of local anesthetics when added to it in both central neuraxial (intrathecal, epidural, and caudal) and peripheral nerve blocks techniques [2].
Opioids like fentanyl have been shown in some studies to enhance the quality of subarachnoid block when added to hyperbaric bupivacaine; however, there are drawbacks to using opioids in local anesthetic solutions, including pruritus and respiratory depression [3].

In the present study, an attempt has been made to evaluate the use of intrathecal fentanyl and midazolam in terms of achievement and maintenance of block and postoperative analgesia among patients undergoing lower abdominal surgeries.

Aim

The present study was undertaken

1. To evaluate and compare the efficacy, utility and safety of single bolus dose of intrathecal Fentanyl (25μ gm) and Intrathecal midazolam (2 mg) and to compare it with Control group of Placebo (0.5 ml) of normal saline in various lower abdominal surgeries under spinal anaesthesia.
2. To know the quality and duration of post-operative pain relief following intrathecal fentanyl and midazolam.
3. To see the incidence and severity of side effects following intrathecal administration of midazolam and fentanyl.

Methodology

The study was undertaken in 75 adult patients of either sex between age group of 25-65 years belonging to ASA grade I and II undergoing lower abdominal surgery under spinal anaesthesia. These patients were divided into three groups of twenty-five each.

Exclusion criteria

The following patients were excluded from the study

- Patient not willing for regional anaesthesia.
- Patients on chronic analgesic therapy.
- Patient who could not understand visual analogue scale.
- Patient had spinal deformities, local infection of skin, history of spinal injury and spinal surgery.
- History of headache, dizziness nausea of vomiting.
- Any systemic or neuro muscular disorder.
- Patients with abnormal coagulation profile.
- Failed previous regional anaesthetic technique.

Study Design

These patients were divided into three group of 25 each depending on the intrathecal drug injected and the total dose of drug given was 2.0 ml in each group separately.

- **Group I:** (Control group n=25)1.5ml (75 mg) of hyperbaric lignocaine (5%) with Placebo 0.5 ml (Normal saline).
- **Group II:** (n=25) 1.5 ml (75mg) of hyperbaric lignocaine (5%) with midazolam 2 mg (0.4 ml) (preservative free) with 0.1ml (Normal saline).
- **Group III:** (n=25) 1.5ml (75 mg) of hyperbaric lignocaine (5%) with fentanyl 25μgm (0.5 ml) (preservative free)

Results

Demographic Distribution of Patients

Table 1: Age Distribution

Age Groups (in years)	Group I	Group II	Group III
38-40	8	6	6
41-43	4	6	6
44-46	6	5	5
47-50	6	7	7
51-60	1	1	1
Total	25	25	25
Range	35-50	38-50	38-50
Mean + SD	44.12±5.50	44.56±4.93	45.0±5.37
Comparison	I & II	II & III	I & III
T value	0.64	0.28	0.37
P value	>0.05	>0.05	>0.05
Significance	NS	NS	NS

Table 1 shows that mean age of patient was 44.12±5.50 years in group I, 44.56±4.93 in group II and 45.0±5.37 in group III. Statistical analysis showed that the difference in mean age in all the three groups was not significant (p>0.05)

Table 2: Sex Distribution

Sex	Group I		Group II		Group III	
	No.	%age	No.	%age	No.	%age
Male	17	68	19	76	18	72
Female	8	32	6	24	7	28
Total	25	100	25	100	25	100

Table 2 shows that majority of patients were males in all the three groups. In group I 68%, in group II 76% and in group III 72% were males. The distribution of the female patients was group I 32%, in group II 24% and in group III 28%. Three groups were thus comparable as far as the distribution of sex ratio was concerned.

Table 3: Comparison of postoperative pain score (vas score reached at 5 or>) at different time intervals in all the groups (post- operative)

Time		Group I						Group II						Group III					
Hr.	Min.	No.	Range	Mean	't'	'p'	s	No.	Range	Mean	't'	'p'	s	No.	Range	Mean	't'	'p'	s
1	15	0	0	-	10.09	<0.001	HS	0						0					
	30	6 (24%)	0-5	3.08±1.52	64.86	<0.001	HS	0						0					
	45	16 (64%)	4-6	4.84±0.37				0						0					
	60	3 (12%)	5-5.0	5.0±0				0						0					
2	15	0						0						0					
	30	0						25	0-2	0.20±0.57	1.73	<0.01	HS	0					
	45	0						3 (12%)	0-5	2.48±1.55	7.34	<0.001	HS	1 (4%)	0-5	1.64±1.52	5.37	<0.01	HS
	60	0						14 (56%)	3-5	4.36±0.90	24.22	<0.001	HS	8 (32%)	2-5	3.79±1.06	17.85	<0.001	HS
3	15	0						8 (32%)	5-0	5.0±0				12 (48%)	3-5	4.68±0.60	39.21	<0.001	HS
	30	0						0						4 (16%)	5-0	5.0±0			
	45	0						0						0					
	60	0						0						0					

All the patients in all three groups had been given rescue analgesics injection tramadol 50 mg i.v. when vas score reached at 5 or >5 and on demand of the patient.

Table 4: Number of patients having vas score 5 or >5at different time intervals

Time interval		Group I		Group II		Group III	
		No.	%age	No.	%age	No.	%age
1 hour	15 min	0	0	0	0	0	0
	30 min	06	24	0	0	0	0
	45 min	16	64	0	0	0	0
	60 min	3	12	0	0	0	0
Total		25	100				
2 hour	15 min	-	-	0	0	0	0
	30 min	-	-	0	0	0	0
	45 min	-	-	3	12	1	4
	60 min	-	-	14	56	8	32
3 hour	15 min	-	-	8	32	12	48
Total				25	100		
	30 min	-	-	-	-	4	16
	45 min	-	-	-	-	-	-
Total						25	100

The Comparison of post-operative pain score (VAS) at different time intervals in all three groups as shown in Tables 3 and 4.

There was no pain in first 15 minutes of a post-operative hour in all three groups.

But in group I the mean VAS score at different time intervals of 30,45 and 60 mins of first post-operative hour in total number of 6 patients (24%), 16 patients (64%) and 3 patients (12%) was 3.08±1.52, 4.84±0.37 and 5.0±0 respectively. All the patients were given rescue analgesics injection tramadol 50mg IV when vas score 5 or >5 at different time intervals in different number of patients. At the end of first post-operative hour, the total number of 25 patients (100%) reached the VAS score 5 or >5 after giving injection tramadol, they were not further included for evaluation but were given analgesic on demand. There was no pain in any of the patient till the end of first hour in group II & III.

In group II, there was no pain in any patient at 1 hour and 15 minutes post-operative hour. The mean VAS score at 30,45,60 minute of second postoperative hour and first 15 minutes interval of third postoperative hour had total number of 25 patients, 3 patients (12%), 14. Patients (56%) and 8 patients (32%) was 0.20±0.57, 2.48±1.55, 4.36±0.90 and 5.0± respectively. All the patients were given rescue analgesic Injection tramadol 50mg IV, when VAS score was 5or>5. At different time intervals and different number of the patients. At the end of first 15min of third hour total number of 25 patients (100%) had VAS score 5 or >5, after given injection tramadol, they were not included for further evaluation, but were given repeat analgesic on demand.

In group Ill there was no pain in first hour and 30 minutes postoperatively. The mean VAS score at 45 minutes, 60 minutes of second and 15, 30 minutes of third postoperative hour in total number of 1 patients (4%), 8 patients (32%) and 12 patients (48%), 4 patients (16%) was 1.64±1.52, 3.79±1.06 and 4.68±0.60, 5.0±0 respectively. All the patients were given rescue analgesic, when VAS 5 or >5 at different time interval in different number of patients. At the end of 30 minutes of third hour total number of the 25 patients (100%) had reached the VAS score 5 or >5 and those already received analgesic were not included for a further evaluation but were given repeat analgesic on demand.

Table 5: Comparison of vas score (post-operative) in between all three groups immediately post-operative period at different time intervals

Time	Group	Mean ± SD	Comparison	T	P	S
1 Hour 15 min	I	0	I & II	-	-	-
	II	0	1 & III	-	-	-
	III	0	II & III	-	-	-
30 min	I	3.08±1.52	-	-	-	-
	II	0	1 & III	-	-	-
	III	0	II & III	-	-	-
45 min	I	4.84±0.37	I & II	-	-	-
	II	0	1 & III	-	-	-
	III	0	II & III	-	-	-
60 min	I	5.0±0	I & II	-	-	-
	II		1 & III	-	-	-
	III		II & III	-	-	-
2 Hour 15 min	I		I & II	-	-	-
	II		1 & III	-	-	-
	III		II & III	-	-	-
30 min	I		I & II	-	-	-
	II	0.20±0.57	1 & III	-	-	-
	III	-	II & III	-	-	-
45 min	I	-	I & II	-	-	-
	II	2.48±1.55	1 & III	-	-	-
	III	1.64±1.52	II & III	1.92	>0.05	NS
60 min	I	-	I & II	-	-	-
	II	4.36±0.90	1 & III	-	-	-
	III	3.79±1.06	II & III	1.95	>0.05	NS
3 Hour 15 min	I	-	I & II	-	-	-
	II	5.0±0	1 & III	-	-	-
	III	4.68±0.60	II & III	1.45	>0.05	NS
30 min	I	-	I & II	-	-	-
	II	-	1 & III	-	-	-
	III	5.0±0	II & III	-	-	-

Table 5 shows the comparison of VAS score at different time intervals in three groups. In first 15 minutes of first hour there was no pain in any group. In group I at 30, 45, 60 minutes of first hour, VAS score was 3.08±1.52, 4-.84±0.37 and 5.0±0 respectively. There was no pain in group II and III the VAS score was 0. When VAS score reached 5 · or >5, inj. Tramadol 50 mg IV was given.

The VAS score was 0 up to 15 minutes of second hour in group II and 15, 30 minutes of 2 hour in group III.

In group II, at 30, 45 and 60 minutes of second hour, VAS score was 0.20±0.57, 2.48±1.55 and 4.36±0.90 respectively. By comparing with group II to group III, the statistically it was not significant (p>0.05). At 15 minutes interval of 3 hour the VAS score was 5.0±0, on statistical comparison with group III, it was not significant (p>0.05), at which the rescue analgesic Inj. Tramadol 50 mg IV was given.

In group III at 45 and 60 minutes of second hour, VAS score was l.64±1.52 and 3. 79±1.06 respectively. By comparing with group II to group III, the statistically it was not significant (p>0.05). At 15 and 30 minutes interval of 3 hour the VAS score reached 4.68±0.60 and 5.0±0, on statistical comparison with group II, it was not significant (p>0.05), at this time the rescue analgesic lnj. Tramadol 50 mg IV was given.

Table 6: Side Effects

Side Effects	Group I		Group II		Group III	
	No.	% ages	No.	% ages	No.	% ages
Nausea	2	8	-	-	3	12
Vomiting	-	-	-	-	1	4
Sedation	-	-	20	88	-	-
Pruritis	-	-	-	-	1	4
Urinary-retention	-	-	-	-	-	-
Headache	-	-	-	-	-	-
Changes in colour	-	-	-	-	-	-
Respiratory depression	-	-	-	-	-	-
Others	-	-	-	-	-	-

Table 6 shows the incidence of postoperative side effects. The incidence of nausea was 8% in group I and 12% in group III. No patient in group II had nausea.

The incidence of vomiting was 4% in group III and no patient had vomiting in group I and group II.

The incidence of sedation was 80% in group II. This was however not of serious concern as all patients were easily arousable on verbal command. No patient had any sedative effect in group I and III.

Pruritis was seen only in one patient (4%) in group II[It was mild, self-limiting and disappered within 15 minutes without any treatment. No patient had pruritus in group I and II. Pruritis did not require any active treatment and it resolves itself.

None of the patients in any group had urinary retention, headache, pallor, cyanosis or respiratory depression throughout the period of study.

Table 7: Comparison of pulse rate at different time interval from baseline in all the three groups (intra-operative)

	Time Interval	Groups	Range/min	Mean ± SD	Mean Change ± SD	't'	'p'	S
Pre-op.	B/L	I	74-98	83.76±6.95	-	-	-	-
		II	74-96	84.08±6.41	-	-	-	-
		III	76-96	83.92±5.70	-	-	-	-
1 HRS.	5 m	I	58-94	81.16±9.05	2.60±5.58	1.13	>0.05	NS
		II	58-94	82.12±8.70	1.96±4.81	0.90	>0.05	NS
		III	58-94	81.72±8.43	2.20±5.03	1.08	>0.05	NS
	10 m	I	60-92	81.32±9.23	2.44±5.41	1.05	>0.05	NS
		II	62-92	82.60±8.10	1.48±4.46	0.74	>0.05	NS
		III	60-92	82.04±8.01	1.88±4.83	0.95	>0.05	NS
	15 m	I	62-92	81.76±8.27	2.00±4.47	0.92	>0.05	NS
		II	64-94	82.80±7.52	1.28±3.40	0.67	>0.05	NS
		III	64-92	81.76±7.17	2.16±4.31	1.06	>0.05	NS
	20 m	I	66-92	82.20±7.44	1.56±3.83	0.76	>0.05	NS
		II	68-94	83.72±6.55	0.36±2.87	0.19	>0.05	NS
		III	68-90	81.60±5.91	2.32±3.90	1.41	>0.05	NS
	25 m	I	70-92	83.08±6.69	0.68±3.88	0.35	>0.05	NS
		II	72-92	83.36±5.87	0.72±1.98	0.34	>0.05	NS
		III	72-92	83.24±6.30	0.68±3.59	0.56	>0.05	NS
	30 m	I	74-92	83.16±5.63	0.60±4.08	0.33	>0.05	NS
		II	74-92	83.52±5.42	0.56±3.18	0.27	>0.05	NS
		III	74-92	83.40±5.35	0.52±3.28	0.47	>0.05	NS
	40 m	I	72-92	83.36±5.47	0.40±3.88	0.22	>0.05	NS
		II	76-90	82.84±5.19	1.24±3.30	0.71	>0.05	NS
		III	72-92	83.36±5.44	0.56±3.30	0.50	>0.05	NS
	50 m	I	72-90	83.00±5.11	0.76±4.33	0.42	>0.05	NS
		II	76-90	83.44±4.45	0.64±3.77	0.32	>0.05	NS
		III	72-90	83.00±5.01	0.92±3.78	0.83	>0.05	NS
	60 m	I	74-92	83.52±5.44	0.24±4.41	0.18	>0.05	NS
		II	74-94	84.12±5.37	0.04±3.34	0.02	>0.05	NS
		III	74-92	83.52±5.44	0.40±3.52	0.33	>0.05	NS

Table 7 shows intraoperative comparison of pulse rate at different time intervals form baseline in all three groups. The mean preoperative pulse rate of group I was 83.76±6.95 per min, group II 84.08±6.41 per min and group III 83.92±5.70 per min. There was slight decrease in the pulse rate all three groups. By comparison of fall in pulse rate in between the groups, there was no statistically significant difference (p>0.05). No patient had episode of bradycardia i.e. pulse rate <60 per minute.

Table 8: Comparison of systolic blood pressure (sbp) at different time intervals from baseline in all the three groups (intra-operative)

	Time Interval	Groups	Range/min	Mean ± SD	Mean Change ± SD	't'	'p'	S
Pre-op.	B/L	I	100-136	112.48±10.95	-	-	-	-
		II	100-134	112.80±10.89	-	-	-	-
		III	100-136	112.72±15.34	-	-	-	-
1 HRS.	5 m	I	96-124	107.60±5.94	4.88±11.87	1.95	>0.05	NS
		II	96-124	108.40±6.35	4.4±12.71	1.74	>0.05	NS
		III	96-130	108.48±8.25	4.24±9.3	1.69	>0.05	NS
	10 m	I	102-122	108.24±4.90	4.24±8.76	1.76	>0.05	NS
		II	96-132	109.44±6.91	3.36±9.35	1.30	>0.05	NS
		III	100-128	108.24±6.2	4.48±8.56	1.85	>0.05	NS

	15 m	I	100-136	109.76±7.96	2.72±8.48	1.00	>0.05	NS
		II	100-132	108.72±6.97	4.08±7.44	1.57	>0.05	NS
		III	100-130	109.04±7.23	3.68±8.47	1.45	>0.05	NS
	20 m	I	102-136	111.52±9.35	0.96±6.43	0.33	>0.05	NS
		II	102-130	109.52±8.08	3.28±5.09	1.20	>0.05	NS
		III	102-130	110.16±7.97	2.56±5.9	0.97	>0.05	NS
	25 m	I	100-134	112.96±10.45	0.48±4.77	0.15	>0.05	NS
		II	100-130	11.40±9.74	2.40±2.38	0.82	>0.05	NS
		III	100-130	110.96±9.00	1.76±3.97	0.39	>0.05	NS
	30 m	I	100-136	113.36±11.47	0.88±4.76	0.31	>0.05	NS
		II	102-132	111.84±10.40	0.96±2.77	0.31	>0.05	NS
		III	100-132	111.68±10.09	1.04±3.11	0.31	>0.05	NS
	40 m	I	102-136	113.36±11.68	0.88±4.32	0.31	>0.05	NS
		II	102-134	111.84±10.22	0.96±2.31	0.31	>0.05	NS
		III	100-134	111.44±10.88	1.28±2.44	0.36	>0.05	NS
	50 m	I	102-136	113.36±10.96	0.80±4.72	0.30	>0.05	NS
		II	102-132	112.08±9.82	0.72±2.15	0.27	>0.05	NS
		III	102-134	111.44±10.02	1.28±2.97	0.36	>0.05	NS
	60 m	I	102-138	113.28±11.26	0.80±4.72	0.28	>0.05	NS
		II	102-130	111.92±9.47	0.88±2.38	0.32	>0.05	NS
		III	100-132	112.0±10.67	0.72±3.25	0.19	>0.05	NS

Table 8 shows intraoperative comparison of SBP at different time intervals from baseline in all three groups. The mean pre-operative SBP of group I was 112.48±10.95 mmHg, group II 112.80±10.89 mmHg and group III 112.72±15.34 mmHg. There was decrease in the SBP all three groups. In first 15 to 20 minutes of first hour. By comparison of fall in SBP in between the groups, there was no statistically significant difference (p>0.05). No patient had hypotension i.e. fall of BP >20 from baseline or <90mmHg. All three group, already preloaded with Haemaccel (3.5% Polygeline) 500ml solution within 20-30 minutes before giving the spinal anesthesia.

Table 9: Comparison of diastolic blood pressure (dbp) at different time intervals from baseline in all the three groups (intra-operative)

	Time Interval	**Groups**	**Range/min**	**Mean ± SD**	**Mean Change ± SD**	**'t'**	**'p'**	**S**
Pre-op.	B/L	I	74-88	81.44±7.0	-	-	-	-
		II	74-90	81.68±4.19	-	-	-	-
		III	78-88	81.68±3.14	-	-	-	-
1 HRS.	5 m	I	76-88	80.40±3.74	1.04±1.64	0.98	>0.05	NS
		II	72-88	80.48±3.88	1.20±1.29	1.04	>0.05	NS
		III	76-88	80.72±3.50	0.96±2.09	1.01	>0.05	NS
	10 m	I	74-86	80.24±3.12	1.20±2.0	1.15	>0.05	NS
		II	74-88	80.56±3.62	1.12±1.64	0.99	>0.05	NS
		III	72-86	80.80±3.60	0.88±2.77	0.94	>0.05	NS
	15 m	I	76-88	80.80±3.05	0.64±2.05	0.66	>0.05	NS
		II	74-88	80.96±3.74	0.72±2.57	0.70	>0.05	NS
		III	76-88	81.04±3.06	0.64±2.49	0.56	>0.05	NS
	20 m	I	76-86	80.64±3.14	0.80±2.0	0.82	>0.05	NS
		II	72-88	80.80±3.91	0.88±2.16	8.96	>0.05	NS
		III	74-86	81.20±3.60	0.48±2.46	0.50	>0.05	NS
	25 m	I	76-88	80.96±3.61	0.48±2.53	0.41	>0.05	NS
		II	74-86	80.72±3.50	0.96±2.00	0.82	>0.05	NS
		III	74-88	81.44±3.58	0.24±2.40	0.21	>0.05	NS
	30 m	I	74-88	81.12±3.74	0.32±1.60	0.30	>0.05	NS
		II	72-88	80.48±4.44	1.20±1.15	1.04	>0.05	NS
		III	76-88	81.12±3.51	0.56±2.20	0.53	>0.05	NS
	40 m	I	76-88	81.52±4.05	0.08±2.41	0.07	>0.05	NS
		II	70-88	80.40±4.58	1.28±1.81	1.03	>0.05	NS
		III	76-86	81.28±3.25	0.40±2.16	0.47	>0.05	NS
	50 m	I	74-86	81.04±4.08	0.40±2.82	0.69	>0.05	NS
		II	72-88	80.32±4.42	1.36±1.60	1.09	>0.05	NS
		III	78-86	81.52±2.02	016±2.76	0.14	>0.05	NS
	60 m	I	74-88	81.76±4.73	0.32±3.35	0.30	>0.05	NS
		II	72-88	80.56±3.89	1.12±1.83	0.99	>0.05	NS
		III	78-84	81.20±1.73	0.48±2.60	0.50	>0.05	NS

Table 9 shows intraoperative comparison of DBP at different time intervals from baseline in all three groups. The mean pre-operative DBP of group I was 81.44±7.0mmHg, group II 81.68±4.19 mmHg and group III 81.68±3.14 mmHg. There was decrease in the DBP all three groups in first 15 to 20 minutes of first hour. By comparison of fall in DBP in between the groups, there was no statistically significant difference (p>0.05). No patient had

hypotension i.e. fall of B*P*>10 mmHg of baseline. All three groups, already preloaded with Haemaccel (3.5% Polygeline) 500 ml solution within 20-30 minutes before giving the spinal anesthesia.

Table 10: Comparison of respiratory rate at different time intervals from baseline in all the three groups (intra-operative)

	Time Interval	Groups	Range/min	Mean ± SD	Mean Change ± SD	't'	'p'	S
Pre-op.	B/L	I	18-22	19.76±1.05	-	-	-	-
		II	18-22	19.72±0.97	-	-	-	-
		III	18-22	19.80±1.0	-	-	-	-
1 HRS.	5 m	I	18-22	19.40±1.15	0.36±1.49	1.15	>0.05	NS
		II	18-22	19.20±1.11	0.52±1.32	1.74	>0.05	NS
		III	18-22	19.24±1.12	0.56±1.32	1.88	>0.05	NS
	10 m	I	18-22	19.40±0.95	0.36±1.25	1.15	>0.05	NS
		II	18-22	19.28±0.97	0.44±1.15	1.58	>0.05	NS
		III	18-22	19.32±0.98	0.48±1.15	1.70	>0.05	NS
	15 m	I	18-21	19.32±0.80	0.44±1.26	1.66	>0.05	NS
		II	18-21	19.28±.097	0.44±1.58	1.58	>0.05	NS
		III	18-21	19.20±0.95	0.60±1.52	1.98	>0.05	NS
	20 m	I	18-22	19.24±1.05	0.52±1.08	1.74	>0.05	NS
		II	18-22	19.28±1.02	0.44±1.12	1.58	>0.05	NS
		III	18-22	19.24±1.05	0.56±1.12	1.85	>0.05	NS
	25 m	I	18-22	19.28±0.93	0.48±1.26	1.39	>0.05	NS
		II	18-22	19.32±0.90	0.40±1.29	1.51	>0.05	NS
		III	18-22	19.28±0.89	0.52±1.29	1.77	>0.05	NS
	30 m	I	18-22	19.52±1.04	0.24±0.92	0.80	>0.05	NS
		II	18-22	19.56±1.08	0.16±0.98	0.54	>0.05	NS
		III	18-22	19.48±1.08	0.32±0.90	1.12	>0.05	NS
	40 m	I	18-22	19.56±1.19	0.20±1.22	0.74	>0.05	NS
		II	18-22	19.40±1.19	0.32±1.02	1.02	>0.05	NS
		III	18-22	19.40±1.22	0.40±1.22	1.19	>0.05	NS
	50 m	I	18-21	19.64±0.99	0.12±0.88	0.29	>0.05	NS
		II	18-21	19.44±1.00	0.28±0.61	0.99	>0.05	NS
		III	18-21	19.56±1.00	0.24±0.59	0.84	>0.05	NS
	60 m	I	18-21	19.56±1.08	0.20±1.15	0.74	>0.05	NS
		II	18-21	19.44±1.12	0.28±1.06	0.99	>0.05	NS
		III	18-21	19.56±1.12	0.24±1.05	0.84	>0.05	NS

Table 10 shows intraoperative comparison of respiratory rate at different time intervals from baseline in all three groups. The mean preoperative respiratory rate of group I is 19.76±1.05, group II 19.72±0.97 and group III 19.80±1.0. There was slight decrease in the respiratory rate in all three groups. By comparison of fall in respiratory rate in between the groups. There was no statistically significant difference (p>0.05). No patient had respiratory depression i.e. decrease of respiratory rate <10 per minute.

Table 11: Comparison of spo2 at different time intervals from baseline in all the three groups (intra-operative)

Time Interval		Groups	Range In %	Mean ± SD	't'	'p'	S
Pre-op.	B/L	I	98-100	99.60±0.64	-	-	-
		II	99-100	99.80±0.40	-	-	-
		III	99-100	99.80±0.40	-	-	-
1 hour	5m	I	98-100	99.56±0.58	0.43	>0.05	NS
		II	99-100	99.68±0.47	1.14	>0.05	NS
		III	99-100	99.68±0.47	1.14	>0.05	NS
	10m	I	99-100	99.64±0.48	0.29	>0.05	NS
		II	99-100	99.64±0.56	1.18	>0.05	NS
		III	99-100	99.64±0.48	1.44	>0.05	NS
	15m	I	98-100	99.48±0.58	0.72	>0.05	NS
		II	99-100	99.72±0.45	0.62	>0.05	NS
		III	99-100	99.76±0.43	0.29	>0.05	NS
	20m	I	98-100	99.40±0.64	0.78	>0.05	NS
		II	99-100	99.76±0.43	0.39	>0.05	NS
		III	99-100	99.68±0.47	1.14	>0.05	NS

Table 11 shows intraoperative comparison of SpO2 at different time interval from baseline in all three group. The mean pre-operative SpO2 of group I was 99.60±0.6, group II 99.80±0.40 and group III 99.80±0.40. There was decrease in the SpO2 all three group. By comparison of fall in SpO2 in between the groups, there was no statistically significant difference (p>0.05).

Discussion

The present study was undertaken to compare the efficacy

utility, safety and side effects of intrathecal fentanyl (25 ugm) and midazolam 2 mg in combination with lignocaine for comparison of post-operative pain relief after lower abdominal surgery. 75 adult patients of ASA grade I & II were divided into three groups of 25 patients in each group according to the drug given intrathecally.

Group-I patients were given 1.5 ml of 5% hyperbaric lignocaine (75 mg) + 0.5 ml of N.S.

Group-II patients were given 1.5 ml of 5% hyperbaric lignocaine (75 mg) + midazolam 2.0 mg (0.4 ml) + 0.1 ml of N.S.

Group-III patients were given 1.5 ml 5% hyperbaric lignocaine (75 mg) + 25 µgm of fentanyl.

To tide over pain many conventional drugs have been tried by various routes for providing analgesia. Intrathecal Opioids and benzodiazepines have so far stood the test of time for providing good pain relief post-operatively. The identification of specific opioid receptors in the substantis gelatinosa in posterior horn cells of spinal cord opened new pathways for providing analgesia (Pert and Synder, 1973) [17] and intrathecal benzodizepines induced analgesia was spinally mediated and binding sites were GABA recepors (Edwards and Serrao *et al*, 1990) [4].

Side effects- nausea, vomiting, sedation, pruritis, headache, urinary retention, arrythmias, involuntary movements, respiratory depression were also noted.

Onset of analgesia is related to the physio-chemical properties of individual agents like pKa (dissociation constant) and lipid solubility (Miller, 1994). The onset of action of local anaesthetics is mainly dependent onthe diffusion of non-ionised lipid-soluble form of the local anaesthetic across the nerve membrane [5].

There is an inverse relation between pKa and onset time (Wylie and Churchill Davidson, 1995). Local anaesthetics with pKa close to the physiological pH, have a more optimal ratio of ionised to non-ionised fraction and thereby a quicker onset. GABA receptors are abundant in the dorsal root nerve cells, maximum concentration is found with the Lamina-II of dorsal nerve cells [6]. Midazolam (preservative free) in 2mg dose was selected since this dose of midazolam given intrathecally has been found to be safe and effective for analgesia effect (Serrao *et al*, 1992; Batra, *et al*, 1999) [4, 7]. Addition of midazolam to epidural/intrathecal infusion provides better analgesia, amnesia and sedation than local anaesthetic alone without major side effects (Nishyam *et al*, 1995 and Valentine et a, 1996) [8].

Spinal opioids like fentanyl and others given intrathecally had greater spinal anaesthesia success rate, faster onset of surgical block improved intraoperative analgesia than LA alone, without increased motor block because of their synergistic interaction between spinal opioids and LA alone. They have antinociceptive effects via different mechanisms and this forms the basis of the combining the two opioids to produce analgesia by inhibition of synaptic transmission in nociceptive afferent pathways via A & and c fibres by opening presynaptic K+ channels to inhibit transmitter release and thus reduce the calcium influz. There is also direct post synaptic effect with hyperpolarisation and reduced neuronal activity along with inhibition of substance-P release in the dorsal horn of spinal cord. LA act primarily by impeding sodium access to the exon interior by occluding the transmembrane sodium channels. (Butterwoth *et al*, 1993) [9].

Miller (1994) has reported onset of analgesia with 5% hyperbaric lignocaine was achieved in less than 5 minutes [5].

Raine *et al* (2001) reported that the onset of analgesia with 1.5 ml of 5% hyperbaric lignocaine intrathecally was with average mean of 2.73 minutes [10].

Shrivastava *et al* (2004) reported that onset of analgesia with 1.5 ml of 5% hyperbaric lignocaine plus 0.5 ml of normal saline was 5.49 ± 2.13 minutes [11].

The results of present study in group I for onset of analgesia was comparable with Miller *et al* (1994) [5], Shrivastava *et al* (2004) [11] but not comparable with Raine *et al* (2001) [10] may be due to no addition of normal saline to lignocaine.

Sen *et al* (2001) reported that intrathecal 2 mg. Of midazolam for postoperative pain relief in caesarean section delivery potentiates the onset of analgesia [12].

Vaswani *et al* (2002) using lignocaine 1.5 ml + 2.5 mg midazolam intrathecaly observed onset of analgesia the average mean was 2.26 ±0.19 minutes [13].

The results of present study were comparable with above studies in group II except Vaswani *et al* (2002) because the dose of midazolam used was more as compared to present study [13].

Cohen *et al* (1993) observed segmental sensory block and hypotension in parturients and reported that lipophilic opioids (fentanyl/sulfentanil, etc.) are only 10-20 time more potent after intrathecal sulfentanil injection [14].

Scott *et al* (1994) [15] studied intrathecal dose response in lower extremity revascularisation procedure using continuous spinal technique at close of 0.5, 10, 20, 40, 50 ugm of the fentanyl and observed that the onset of analgesia in patients with 40-50 ugm was excellent within 10 minutes. A significant greater number of the patients reported satisfactory analgesia within 3 minutes as compared to patient with 20 ugm fentanyl group (4 minutes) with lignocaine 2% isobaric or 5% hyperbaric.

Spencer Liu *et al* (1995) [16] had observed that the fentanyl prolongs lidocaine spinal anesthesia without prolonging recovery. Fentanyl produces sensory analgesia by inhibition of synaptic transmission in nociceptive afferent pathway (A, &, C fibres) and yet does not inhibit the conduction in sympathetic pathway which explains the prolonged sensosry regression.

Shrivastava *et al* (2004) reported that onset of analgesia 1.5 ml of 5% hyperbaric lignocaine plus 0.5 ml (25 ugm) of fentanyl was 3.68 minutes [11].

The result in this present study, in Group III addition of fentanyl (25 ugm) to the lignocaine potentiate the sensory block and prolongs the postoperative analgesia without affecting the motor recovery. Results of the Cohen *et al* (1993) [14], Scott *et al* (1994) [15], Spencer Liu *et al* (1995) [16], and Shrivastava *et al* (2004) [11] are comparable with present study. Early onset of analgesia with midazolam as well as fentanyl as compared to plain lidocaine were explained on the basis than both drugs acts on their respective receptors i.e. GABA and opoid receptors respectively.

Conclusion

Additional of intrathecal midazolam or fentanyl provided post-operative analgesia significantly longer than lignocaine alone and duration of analgesia was comparable between midazolam and fentanyl. Quality and degree of analgesia was better and both. Additional of fentanyl does not have any significant effect on onset, duration and regression of

motor block. Additional of midazolam has significant effect on onset duration and regression of motor block. The onset of motor block was earlier and duration and regression of motor block was prolonged. The incidence of hypotension was not significant after preloading done with heamaccel 500 ml in the any of the drug used. Nausea and pruritis encountered in group I and group III respectively was not significant. But the sedation in group II was significant but all the patients were arousable on verbal command. Other side effect like vomiting, urinary retention, arrythmias, involuntary movements and cardio respiratory depression respectively was not reported. No other side effect were observed with any of the drugs.

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How to Cite This Article
Kaur J, Singh H, Kaur A, Comparative study of intrathecal fentanyl and midazolam for postoperative pain relief after lower abdominal surgery. International Journal of Medical Anesthesiology. 2021;4(4):100-107.