Original Research Article

Comparative evaluation of the effect of intrathecal ketamine and fentanyl added to bupivacaine in elective hernia repair surgeries

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Abstract

Background: Addition of adjuvants in spinal anaesthesia spares the local anaesthetic dose and produces good postoperative analgesia. **Aim:** To compare the duration of prolongation of postoperative analgesia between Ketamine and Fentanyl when added to hyperbaric bupivacaine for elective inguinal hernia surgeries. **Material and Methods:** This is a non randomised prospective triple arm single blind comparative study including 90 patients undergoing elective inguinal hernia repair surgery. Patients satisfying inclusion criteria, with written consent were divided into three groups : Group B receiving a spinal drug volume of 3ml hyperbaric 0.5 % bupivacaine with 0.5 ml normal saline, Group F receiving a spinal drug volume 3ml hyperbaric 0.5 % bupivacaine with 25 mcg fentanyl (0.5ml), Group K received a spinal volume 3ml hyperbaric 0.5% bupivacaine with 25 mg preservative free Ketamine (0.5ml). The time of onset of sensory and motor blockade, duration of sensory and motor blockade, time of requirement of first dose analgesic, total analgesic requirement were recorded apart from the vital hemodynamic and saturation monitoring. Requirement for ephedrine and incidence of adverse effects were also recorded. **Results:** Addition of Ketamine and Fentanyl to Bupivacaine prolongs the onset of sensory and motor blockade; prolongation is greater with fentanyl than with ketamine. Ketamine and Fentanyl when added to hyperbaric bupivacaine prolongs the duration of motor and sensory blockade; prolongation being greater with ketamine than fentanyl. The total ephedrine requirement and the total analgesic requirement in the first 24 hours period was significantly lower in the Ketamine group compared to Fentanyl or control group. **Conclusion:** Intrathecal Ketamine is a better adjuvant to hyperbaric bupivacaine than intrathecal fentanyl in prolonging the duration of blockade and postoperative analgesia in patients undergoing inguinal hernia repair under spinal anaesthesia.

Key Words: Spinal anaesthesia, Ketamine, Fentanyl, Onset, Duration of block, Analgesia.

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INTRODUCTION

Spinal anaesthesia, till date, remains the most preferable technique of choice for all infraumbilical surgeries, by most anaesthesiologists. The only disadvantage being the profound motor blockade that remains after the procedure. Reducing the dose of hyperbaric bupivacaine results in rapid recovery, but inadequate surgical anaesthesia.[1] Addition of adjuvants like opioids, alpha 2 agonists, ketamine, neostigmine and vasoconstrictors help enhance the analgesia, with a lowered side effect profile.[2,3,4,5,6] Till date, opioids are the most commonly used adjuncts in spinal anaesthesia, but its use is often associated with side effects.[7] The use of opioids may result in a reduction in the pain threshold, causing a

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delayed hyperalgesia.[8] Ketamine is an N-methyl D-aspartate receptor (NMDA) antagonist with good analgesic and local anaesthetic properties. In addition to NMDA receptors, it also interacts with opiate, cholinergic, adrenergic and serotonin receptors.[9,10,11,12,13] It has been proved that single or multiple doses of preservative free racemic ketamine has no adverse neurological effects, but instead may also have neuroprotective effects.[14,15,16]

MATERIALS AND METHODS

90 patients posted for inguinal hernia surgeries at Government Kilpauk Medical College Hospital and Government Royapettah hospital from August 2017 to February 2018 were assessed for the inclusion and exclusion criteria and were included in the study after obtaining written informed consent.

Sample Size: 90, calculated using the OPENEPI software (The confidence level was estimated at 95%, Power of study at 80%,minimum sample size required for the study was calculated to be 90.n=30 in Group K, n= 30 in Group F and n=30 in Group B arm)

Study Design: A prospective, Non–Randomized, Triple Arm, Single-Blind, Controlled study

Inclusion Criteria

1. Patients undergoing elective inguinal hernia repair surgeries under subarachnoid block
2. Age between 18 to 60 years
3. Males
4. ASA class 1 and 2

Patients who have given valid informed consent

Exclusion Criteria

1. Patients not satisfying inclusion criteria
2. Patients with an allergy or sensitivity to opioid group of drugs and local anaesthetics.
3. Patients with spinal deformities
4. Any contraindication to spinal anesthesia
5. Patients with neurological disorders
6. Impaired ability to communicate (e.g., confusion, poor hearing or language barrier)
7. Patients who are unconscious or severely ill.
8. Patients with Coagulation disorders.

Materials

1. 25G Quincke spinal needles
2. Inj 0.5% Hyperbaric Bupivacaine available as ampoules (each ampoule contains 4cc of Bupivacaine, each ml contains 5mg of bupivacaine with 80mg of dextrose)
3. Inj. Ketamine (preservative free), available as ampoules (each ampoule contains 2ml, 50mg/ml)
4. Inj. Fentanyl, available as ampoules (one ampoule contains 2 ml, each ml contains 50mcg of Fentanyl)
5. Inj. Ephedrine, available as ampoules (each ampoule contains 1ml, 30mg/ml); diluted with 4cc of distilled water to 6mg/ml
6. Inj. Atropine sulphate, available as ampoules (each ampoule contains 2ml, 0.6mg/ml)
7. Boyles apparatus
8. Laryngoscope with different blade sizes
9. Endotracheal tubes
10. Drugs for general anaesthesia

Methodology: Patients satisfying the above inclusion criteria were counselled about the purpose, risks and benefits of the procedure and study.. After getting consent, patients willing to be included in the study were enrolled and analyzed. A total of 90 patients were included in the study. Patients were divided into three groups of 30 in each based on computerized random number into group B, group F and group K. GROUP B received a spinal drug volume of 3cc of hyperbaric 0.5 % bupivacaine with 0.5cc of normal saline GROUP F received a spinal drug volume of 3cc of hyperbaric 0.5% bupivacaine with 25 mcg of fentanyl (0.5ml) GROUP K received a spinal drug volume of 3cc of hyperbaric 0.5% bupivacaine with 25mg of preservative free ketamine (0.5ml) This study was designed as a prospective, comparative study. Patients were preoperatively evaluated, clinically examined and proper investigations were done prior to the assessment. Procedures were explained in detail and written consent was obtained. All patients were kept nil per oral for atleast 6 hours before the procedure. Patients were shifted inside the operation theatre half an hour before the scheduled procedure. All patients were pre-medicated with intramuscular injection glycopyrollate 0.2mg. Baseline vitals such as pulse rate, non-invasive blood pressure, saturation in room air, respiratory rate, ECG pattern were recorded. Intravenous access was obtained with 18G IV cannula and IV fluid started. All patients were preloaded with 5-7 ml/kg lactated Ringer's solution before administering spinal anesthesia. Using all aseptic precautions, a 25-gauge Quincke needle was inserted intrathecally via a midline approach into the L4-5 interspaces while the patient was in sitting position.

- **Sensory blockade** was assessed by the pin prick test. The onset of sensory block was defined as the time between intrathecal injection to the absence of pain at T10. The maximum level of sensory blockade was assessed by pinprick after 20 minutes of intrathecal injection. The duration of sensory blockade was taken as the time for

sensory block to regress from the maximum height to the T10 dermatome.

- **Motor blockade** was assessed by the Modified Bromage scale
- GRADE 0: No motor loss
- GRADE 1: Inability to flex hip
- GRADE 2: Inability to flex knee
- GRADE 3: Inability to flex ankle
- The time of onset of motor blockade was defined as the time from intrathecal injection to the time taken to reach Bromage 1. The duration of motor blockade was taken as the time taken to reach back to Bromage 0.
- The duration of spinal analgesia was defined as the period between spinal injection and the first time the patient complained of pain in the post operative period.
- The pulse rate, blood pressure were monitored for every 2 minutes for 10 minutes after intrathecal injection, and thereafter every 5 minutes till the end of the surgery. Injection Ephedrine 6mg was administered intravenously when the systolic blood pressure fell below 90 mm Hg. Injection Atropine sulphate 0.6mg was administered intravenously if the heart rate fell below 50 beats per minute.
- Post operative analgesia was standardised in all patients; Inj Tramadol 100mg was given intramuscularly, after the patient complained of pain.
- The incidence of adverse effects were also noted- nausea, vomiting, delirium, sedation, pruritus, urinary retention, respiratory depression

Data Analysis: Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired t test. Categorical variables were analyzed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analyzed using SPSS version 16 and Microsoft Excel 2007

Table 1: Null hypothesis

Null Hypothesis: H0	Intrathecal ketamine is equal in effect to intrathecal fentanyl as an adjuvant to bupivacaine for post operative analgesia in patients undergoing hernia repair
Alternate hypothesis: H1	Intrathecal ketamine is better compared to intrathecal fentanyl as an adjuvant to bupivacaine for post operative analgesia in patients undergoing hernia repair

OBSERVATIONS AND RESULTS

Table 2: Age

Group	Age		ANOVA	P value
	Mean	SE		
Ketamine	44.73	2.16	0.858	0.427
Fentanyl	43.20	1.60		
Bupivacaine	41.13	2.04		

Table 3:

Comparing the groups	T test	P value
Ketamine vs Fentanyl	0.570	0.571
Ketamine vs Bupivacaine	1.210	0.232
Fentanyl vs Bupivacaine	0.797	0.429

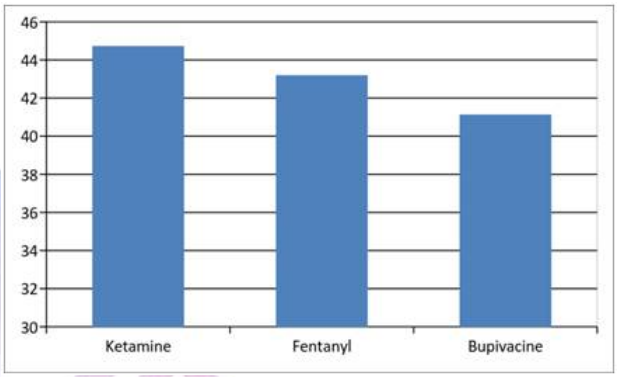

Figure 1:

Among the patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was no statistical difference in relation to age distribution between the three groups with a p value >0.05 as per the unpaired t test. Therefore we fail to reject the null hypothesis that there is no age difference between the intervention groups.

Table 4: Onset time of sensory blockade

Group	Onset time of sensory blockade (seconds)		ANOVA	P value
	Mean	SE		
Ketamine	101.20	1.48	94.088	0.0001
Fentanyl	125.60	2.53		
Bupivacaine	93.23	0.69		

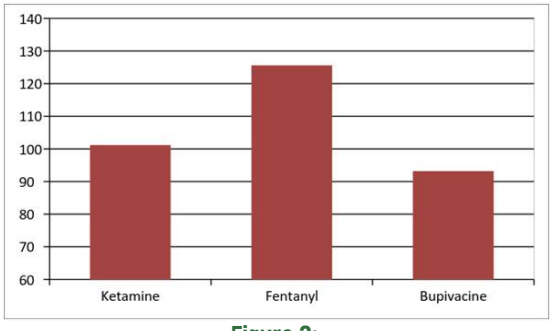

Figure 2:

Table 5:

Comparing the groups	T test	P value
Ketamine vs Fentanyl	-8.326	0.0001
Ketamine vs bupivacaine	4.870	0.0001
Fentanyl vs Bupivacaine	12.347	0.0001

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the onset of sensory blockade in the ketamine and fentanyl groups compared to the control group, with p value <0.05 as per the ANOVA test. Therefore, we reject the null hypothesis that there is no difference in the onset time of sensory blockade in the three groups. The onset time of sensory block was longest in Group F (125.60±2.53 sec) compared to Group K (101.20± 1.48 sec), with a p value of 0.0001 as per t test.

Onset of Motor Blockade

Table 6:

Group	Onset time of motor blockade (seconds)		ANOVA	P value
	Mean	SE		
Ketamine	77.03	0.61		
Fentanyl	87.30	1.06	66.634	0.0001
Bupivacaine	73.00	0.98		

Table 7:

Comparing the Groups	T test	P value
Ketamine vs Fentanyl	-8.401	0.0001
Ketamine vs Bupivacaine	3.501	0.001
Fentanyl vs Bupivacaine	9.930	0.0001

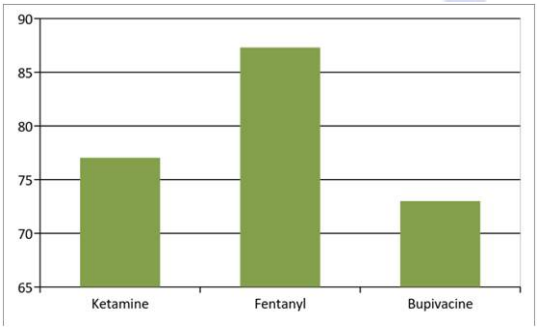

Figure 3:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the onset of motor blockade in the ketamine and fentanyl groups compared to the control group, with p value <0.05 as per the ANOVA test. Therefore, we reject the null hypothesis that there is no difference in the onset time of motor blockade in the three groups. The onset time of motor block was longest in Group F (87.30±1.06 sec) compared to Group K (77.03± 0.61 sec), with a p value of 0.0001 as per t test.

Table 8: Duration of sensory block

Group	Duration of sensory blockade (minutes)		ANOVA	P value
	Mean	SE		
Ketamine	171.33	3.73		
Fentanyl	143.67	1.50	195.489	0.0001
Bupivacaine	107.50	1.45		

Table 9:

Comparing the Groups	T test	P value
Ketamine vs Fentanyl	7.499	0.0001
Ketamine vs Bupivacaine	17.381	0.0001
Fentanyl vs Bupivacaine	17.341	0.0001

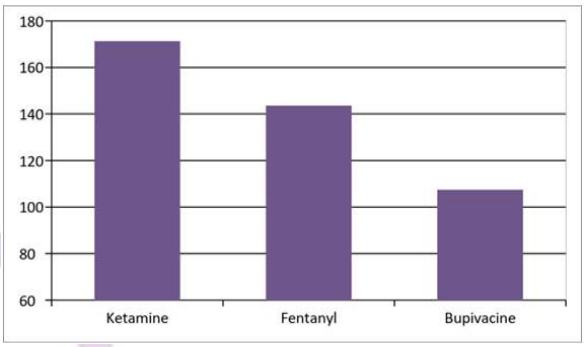

Figure 4:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the duration of sensory blockade in the ketamine and fentanyl groups compared to the control group, with p value <0.05 as per the ANOVA test. Therefore, we reject the null hypothesis that there is no difference in the duration of sensory blockade in the three groups. The duration of sensory blockade was longest in Group K (171.33±3.73 min) compared to Group F (143.67± 1.50 min), with a p value of 0.0001 as per t test.

Table 10: Duration of motor blockade

Group	Duration of motor blockade (minutes)		ANOVA	P value
	Mean	SE		
Ketamine	225.83	2.26		
Fentanyl	186.17	1.90	200.245	0.0001
Bupivacaine	173.83	1.53		

Table 11:

Comparing the Groups	T test	P value
Ketamine vs Fentanyl	13.431	0.0001
Ketamine vs Bupivacaine	19.041	0.0001
Fentanyl vs Bupivacaine	5.060	0.0001

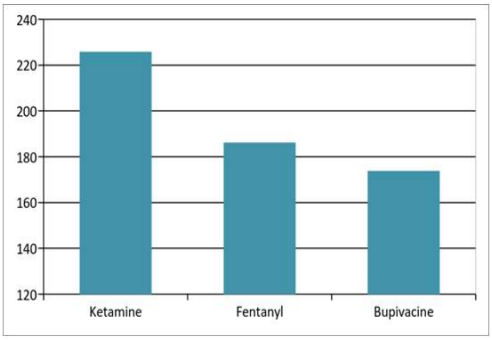

Figure 12:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the duration of motor blockade in the ketamine and fentanyl groups compared to the control group, with p value <0.05 as per the ANOVA test. Therefore, we reject the null hypothesis that there is no difference in the duration of motor blockade in the three groups. The duration of motor blockade was longest in Group K (225.83±2.26 min) compared to Group F (186.17± 1.90 min), with a p value of 0.0001 as per t test.

Table 12: Request for first analgesic

Group	First analgesic		ANOVA	P value
	Mean	SE		
Ketamine	357.00	7.17		
Fentanyl	287.33	3.53	258.907	0.0001
Bupivacine	203.33	2.16		

Table 13:

Comparing the Groups	T test	P value
Ketamine vs Fentanyl	8.713	0.0001
Ketamine vs Bupivacaine	20.508	0.0001
Fentanyl vs Bupivacaine	20.295	0.0001

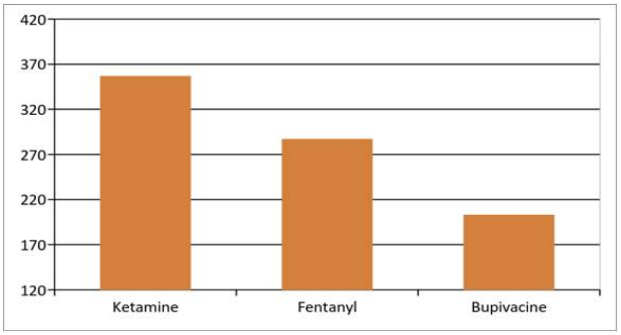

Figure 13:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the request for first analgesic in the ketamine and fentanyl groups compared to the control group, with p value <0.05 as per the ANOVA test. Therefore, we reject the null hypothesis that there is no difference in the time for request for first analgesic in the three groups. The time for request for first analgesic was longest in Group K (357.00±7.17 min) compared to Group F (287.33± 3.53 min), with a p value of 0.0001 as per t test.

Table 13: Total analgesic requirement

Group	Total Analgesic doses				Chi square	P value
	1	2	3	4		
Ketamine	30	0	0	0		
Fentanyl	10	18	2	0	113.20	0.0001
Bupivacine	0	2	22	6		

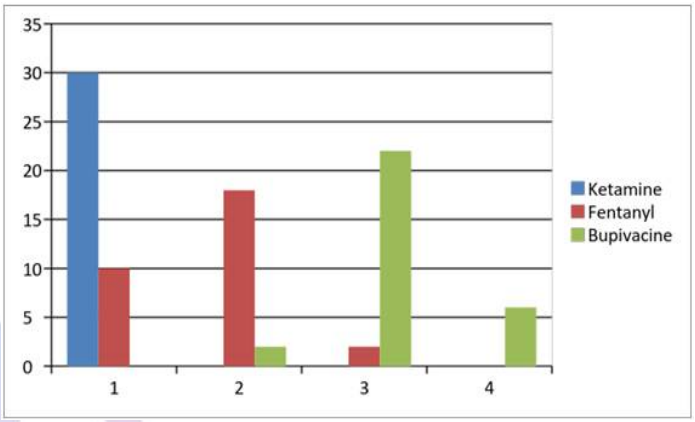

Figure 14:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the total analgesic requirement in the ketamine group compared to the fentanyl and control group, with p value <0.05 as per the Chi-square test. Therefore, we reject the null hypothesis that there is no difference in the total analgesic requirement in the three groups.

Table 14: Total ephedrine requirement

Group	Ephedrine in mg			Chi square	P value
	0	6	12		
Ketamine	30	0	0		
Fentanyl	14	14	2	52.463	0.0001
Bupivacaine	5	12	13		

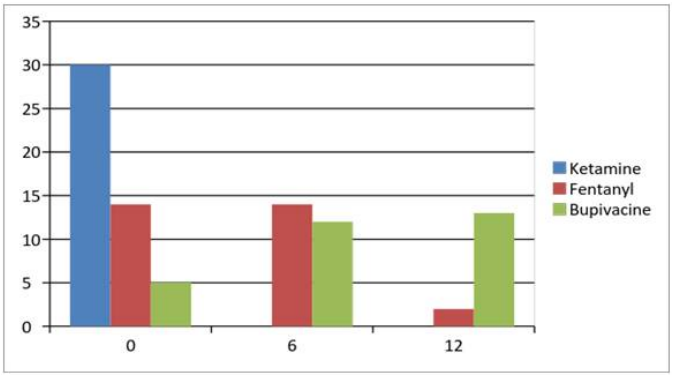

Figure 15:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the total ephedrine requirement in the ketamine group compared to the fentanyl and control group, with p value <0.05 as per the Chi-square test. Therefore, we reject the null hypothesis that there is no difference in the total ephedrine requirement in the three groups.

Table 15: Post operative adverse effects

Adverse Effect	Group B	Group F	Group K
Pruritus	-	14	-
Drowsiness	-	2	2
Psychomimetic changes	-	-	-
Hypotension	-	-	-
Bradycardia	-	-	-
Respiratory depression	-	-	-
Nausea	-	-	1
Urinary retention	-	1	

Table 16:

Group	Adverse effect		Chi square	P value
	Present	Absent		
Ketamine	3	27		
Fentanyl	17	13	31.76	0.0001
Bupivacaine	0	30		

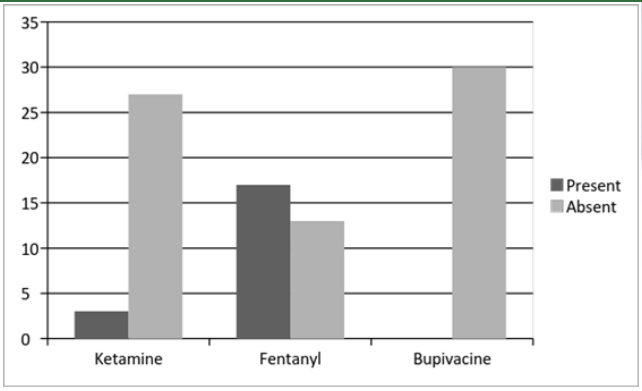

Figure 16:

Among the three groups of patients undergoing spinal anaesthesia for inguinal hernia surgeries, there was a statistically significant difference in the total incidence of post- operative adverse effects in the ketamine and fentanyl group compared to the control group, with p value <0.05 as per the Chi-square test. Therefore, we reject the null hypothesis that there is no difference in the incidence of post- operative adverse effects in the three groups.

DISCUSSION

Spinal anaesthesia or sub arachnoid block till date remains the most favoured mode of anaesthesia for most infraumbilical surgeries, unless otherwise contraindicated. It offers several advantages over general anaesthesia, the major ones being-reduction in the stress response to surgery, reduction in the blood loss and better post-operative pain relief. The main disadvantage of spinal anaesthesia is the profound motor blockade that remains after surgery. Reducing the dose of local anaesthetic used for spinal anaesthesia may help overcome this problem, but results in inadequate pain relief. Addition of adjuvants to intrathecal bupivacaine helps in prolonging the duration of spinal anaesthesia, along with reducing the density of motor blockade. Various adjuvants are being used- like opioids, alpha 2 agonists, neostigmine, the most common being opioids. However, opioids are known for a number of adverse effects, the most dreadful being respiratory depression. In addition, repeated use of opioids can reduce the threshold of pain perception, and results in a hyperalgesic response. Ketamine is an N-methyl D-aspartate receptor antagonist, which has analgesic and local anaesthetic properties. It also interacts with opioid, cholinergic and adrenergic receptors. Recent studies have proved that preservative free ketamine does not cause any neurotoxicity; but instead may have neuroprotective effects. In this prospective study, the effect of adding ketamine to intrathecal bupivacaine on the duration of postoperative analgesia was compared with that of fentanyl. 90 patients satisfying the inclusion criteria were chosen and divided into three groups. Group K received 3cc of 0.5% hyperbaric bupivacaine with 0.5mg/kg of preservative free ketamine; Group F received 3cc of 0.5% hyperbaric bupivacaine with 25mcg of fentanyl citrate; Group B received 3cc of 0.5% hyperbaric bupivacaine with 0.5cc of normal saline. The mean age was 44.73±2.16 in Group K; 43.20±1.60 in Group F and 41.13±2.04 in Group B. Hence all the three groups were comparable with respect to age as the P value was greater than 0.05. The time for onset of sensory blockade which was assessed by the absence of sensation to pin prick at the T10 dermatome was 101.20±1.48 seconds in Group K; 125.60 ±2.53 in Group F and 93.23±0.69 seconds in Group B. This implies that the addition of ketamine or fentanyl to bupivacaine prolongs the onset of sensory blockade. There was a statistical difference between Group K and F in the onset of sensory blockade implied by the T test value of -8.326 and a P value of 0.0001; the prolongation of onset of sensory blockade is greater with fentanyl than with ketamine. The time for onset of motor blockade which was assessed by the modified Bromage score was 77.03±0.61 seconds in Group K; 87.30 ±1.06 in Group F and 73.00±0.98 seconds in Group B. This implies that the addition of ketamine or fentanyl to bupivacaine prolongs the onset of motor blockade. There was a statistical difference between Group K and F in the onset of motor blockade implied by the T test value of -8.401 and a P value of 0.0001; the prolongation of onset of motor

blockade is greater with fentanyl than with ketamine. The total duration of sensory blockade after spinal anaesthesia was 171.33±3.73 minutes in Group K; 143.67 ±1.50 in Group F and 107.50±1.45 minutes in Group B. This implies that the addition of ketamine or fentanyl to bupivacaine prolongs the duration of sensory blockade. There was a statistical difference between Group K and F in the duration of sensory blockade implied by the T test value of 7.499 and a P value of 0.0001; the prolongation of sensory blockade is greater with ketamine than with fentanyl. The total duration of motor blockade after spinal anaesthesia was 225.83±2.26 minutes in Group K; 186.17 ±1.90 in Group F and 173.83±1.53 minutes in Group B. This implies that the addition of ketamine or fentanyl to bupivacaine prolongs the duration of motor blockade. There was a statistical difference between Group K and F in the duration of motor blockade implied by the T test value of 13.431 and a P value of 0.0001; the prolongation of motor blockade is greater with ketamine than with fentanyl. The first request for analgesia after spinal anaesthesia was made after 357.00±7.17 minutes in Group K; 287.33±3.53 in Group F and 203.33±2.16 minutes in Group B. This implies that the addition of ketamine or fentanyl to bupivacaine prolongs the duration of spinal analgesia. There was a statistical difference between Group K and F in the request for first analgesic after spinal anaesthesia implied by the T test value of 8.713 and a P value of 0.0001; the prolongation of the duration of spinal analgesia is greater with ketamine than with fentanyl. The total analgesic requirement in the first 24 hour period after spinal anaesthesia was significantly lower in the ketamine group when compared to the fentanyl or control group. In Group K, all the thirty patients had made an analgesic request only once in the first 24 hours. In Group F, 10 patients had made an analgesic request once; 18 patients twice and 2 patients thrice in the first 24 hours. In Group B, 2 patients had made an analgesic request twice, 22 patients thrice and 6 patients had made an analgesic request four times in the first 24 hours. Thus, the values were statistically significant as implied by the Chi-square test value of 113.20 and a P value of 0.0001. The total ephedrine requirement after spinal anaesthesia was significantly lower in the ketamine group when compared to the fentanyl or control group. In Group K, ephedrine was not required in any of the thirty patients. In Group F, 6 mg of ephedrine was used in 14 patients; 12 mg ephedrine was used in 2 patients. In Group B, 6 mg ephedrine was used in 12 patients; 12 mg ephedrine was used in 13 patients. Thus, the values were statistically significant as implied by the Chi-square test value of 52.463 and a P value of 0.0001. The incidence of adverse effects was statistically significant in the fentanyl and ketamine group when compared to the control group. In Group K, 2 patients had complained of drowsiness; while one patient complained of nausea. In Group F, 14 patients complained of pruritus; 2 patients complained of drowsiness; while one patient complained of urinary retention.

SUMMARY

It was interpreted from the study that,

- addition of preservative free ketamine to intrathecal bupivacaine prolongs the onset of sensory and motor blockade after spinal anaesthesia
- addition of preservative free ketamine to intrathecal bupivacaine prolongs the duration of sensory and motor blockade after spinal anaesthesia
- addition of preservative free ketamine to intrathecal bupivacaine prolongs the duration of spinal analgesia and delays the first analgesic requirement
- the total analgesic requirement is reduced with intrathecal ketamine
- hemodynamic parameters are more stable when ketamine is added to intrathecal bupivacaine

CONCLUSION

It is concluded that intrathecal ketamine is a better adjuvant to bupivacaine than intrathecal fentanyl in prolonging the duration of postoperative analgesia after spinal anaesthesia in patients undergoing inguinal hernia repair.

REFERENCES

1. Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z: Intrathecal fentanyl with small-dose dilute bupivacaine: better anaesthesia without prolonging recovery. Anaesthesia and Analgesia; 1997, 85:560-565.
2. Sens, Ozmert G, Aydin ON Baran N, Caliskan E: The persisting analgesic effect of low does intravenous ketamine after spinal anaesthesia for CS. European J Anesthesiology; 2005, 22:518-523.
3. Khezri MB, Rezaei M, DelkhoshReihany M, Haji SeidJavadi E: Comparison of postoperative analgesic effect of intrathecal clonidine and fentanyl added to bupivacaine in patients undergoing caesarean section: a prospective randomized double-blind study. Pain Res Treat.doi: 10.1155/2014/513628.
4. Khezri MB, Ghasemi J, Mohammadi N: Evaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing caesarean section. Acta Anaesthesiology Taiwan; 2013, Dec. 51(4):155-60.
5. Safari F, Dabbagh A, Sharifnia M: The effect of adjuvant midazolam compared with fentanyl on the duration of spinal anaesthesia with 0.5% bupivacaine in opium

abusers. Korean Journal of Anaesthesiology; 2012, 63(6):521-526.
6. Hindle A: Intrathecal opioids in the management of acute postoperative pain. Continuing Education in Anaesthesia, Critical Care and Pain; 2008, 8(3):81-85.
7. Chaney MA: Side effects of intrathecal and epidural opioids. Can J Anesth; 1995, 42:891-903.
8. Laulin JP, Célèrier E, Larcher A, Le Moal M, Simonnet G: Opiate tolerance to daily heroin administration: apparent phenomenon associated with enhanced pain sensitivity. Neuroscience; 1999, 89:631-6
9. Hirota K, Lambert DG: Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesthesiology; 1996, 77:441-444.
10. Kamal MM, El-Fawy D: The effect of adding ketamine to bupivacaine in spinal anaesthesia in day-case surgery. Ain-Shams J Anaesthesiology: 2014, 7:530-3.
11. Finck AD, Ngai SH: Opiate receptor mediation of ketamine analgesia. Anaesthesiology; 1982, 56:291-297.
12. Vranken JH, Troost D, de Haan P, Pennings FA, van der Vegt MH, Dijkgraaf MG, et al: Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S (1) ketamine. Anaesthesiology; 2006, 105:813-8.
13. Borgbjerg FM, Svenssson BA: Histopathology after repeated intrathecal injections of preservative free ketamine in the rabbits: a light and electron microscopic examination. Anaesthesia and Analgesia; 1994
14. Yu QJ, Zhou QS, Huang HB, Wan YL, Tian SF, Duan DM: Effects of ketamine on the balance of ions Ca2, Mg2, Cu2and Zn2in the ischemia-reperfusion affected spinal cord tissues in rabbits. Neurochem Res; 2009, 34:2192-6.
15. Malinovsky JM, Lepage JY: Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anaesthesiology; 1993,78:109-15.
16. Rojas AC, Alves JG, Moreira E, Lima R, Esther Alencar Marques M, Moreira de Barros GA, Fukushima FB, et al: The effects of subarachnoid administration preservative-free S-ketamine on spinal cord and meninges in dogs. Anaesthesia and Analgesia; 2012, 114:450-5.
17. MarziehBeigomKhezri, ElhamTahaei and Amir HosseinAtlasbaf, Middle east journal of anaesthesiology, February 2016, Comparison of postoperative analgesic effect of intrathecal ketamine and fentanyl added to bupivacaine in patients undergoing caesarean section: A prospective randomized double-blind study
18. Ahmed SobhyBasuni, "Addition of low dose ketamine to midazolam and low dose bupivacaine improves haemodynamics and postoperative analgesia during spinal anaesthesia for caesarean section", Journal of Anaesthesiology and clinical pharmacology, Feb 2016, issue 1
19. Unlugenc H, Ozalevli, Gunes Y. A double blind comparison of intrathecalS(±) ketamine and fentanyl combined with bupivacaine 0.5% for caesarean section. European J Anaesthesiology. 2006;23: 1018-1024.
20. Shrestha SK, Bhattarai B, Shah R. Comparative Study of Hyperbaric Bupivacaine Plus Ketamine Vs Bupivacaine Plus Fentanyl for Spinal Anaesthesia During Caesarean Section. Kathmandu University Med J 2013; 44(4):287-291.
21. Kathirvel S, Sadhasivam S, Saxena A. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia 2000;55: 899-910.
22. Togal T, Demirbilek S, Koroglu A. Effects of S (±) ketamine added to bupivacaine for spinal anaesthesia for prostrate surgery in elderly patients. European J Anaesthesiology. 2004; 21: 193-197.
23. Khezri MB, Ghasemi J, Mohammadi NEvaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing caesareansection, Acta Anaesthesiology Taiwan. 2013 Dec; 51(4):155-60
24. Kamal MM, El-Fawy D. The effect of adding ketamine to bupivacaine in spinal anaesthesia in day care surgery, Ain-Shams J Anaesthesiology 2014; 7: 530-3.

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