Original Article

Effects of ketamine hydrochloride (preservative free) and fentanyl citrate added to low dose hyperbaric bupivacaine for sub-arachnoid block in lower uterine caesarian section – a comperative study

SM Rafiqul Islam[1*], Hasina Begum[2], Md. Mustafa Kamal[3], Md. Shah Alam Bhuiyan[4], UH Shahera Khatun[5]

[1]Dept. of Anaesthesiology, Enam Medical College & Hospital, Savar, Dhaka, [2]Dept. of Anaesthesiology, Dhaka Dental College & Hospital, [3] Dept. of Anaesthesia, Analgesia and Intensive Care Medicin, BSMMU, [4]Dept. of Anaesthesiolog & ICU, Burn Unit, Dhaka Medical College Hospital, [5]Dept. of Anaesthesiology & ICU, Dhaka Medical College & Hospital.

***Address of correspondence**:

Abstract

Background *Caesarian section is one of the most common operations Now a days for delivery of baby sub-arachnoid block is the better choice. World wide Commonly used bupivacaine with fentanile.*

Objective *The present study was designed to observe the effects of intrathecal ketamine hydrochloride with bupivacaine+complne bupivacaine with fentanyl to observe quality of block eioth duration block during caesarian section.*

Methods *Ninety ASA 1 parturients scheduled for elective caesarian section were randomly selected. There are thirty patients in each group. The base line haemodynamic parameters, heart rate, blood pressure respiratory rate SpO_2 and indication of operation were recorded The control group BN (n = 30) received 1.75 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml normal saline intrathecally. While the study group, fentanyl group BF (n = 30) received 1.75 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml (25 mg) injection fentanyl, BK received 1.75 ml of 0.75% hyperbaric bupivacaine plus 0.5 ml (25 mg) of ketamine hydrochloride.*

Results *Duration and quality of sensory and motor block, post-operative analgesia, haemodynamic changes and sedation levels were assessed. There was no significant difference in duration of motor blockade in three groups. Quality of analgesia, sensory block was significant (P<0.05) in BK and BF group than BN group. The quality of block was excellent throughout the surgical procedure in 80% BK group 60% in BF group and 53.3% in control (BN) group. Incidence of hypotension was less in group BF (26.6%) and BK (20%) than group BN (40%). Ketamine had an upper level of sensory block than fentanyl.*

Conclusion *Injection ketamine 25 mg can be used as an adjunct to low dose spinal bupivacaine during caesarian.*

Key words: *SAB, Post-operative analgesia, ketamine, fentanyl.*

(JBSA 2011; 24(2): 53-59)

Introduction

Caesarian section is one of the most common operations in the child bearing age of a woman. The choice of anesthetic technique for caesarean section depends on patient preference, coexisting medical conditions, reasons for surgery, the degree of urgency and the anesthesiologist's judgment and experience. Regional anesthesia for caesarean section has become the preferred technique because general anesthesia has been associated with higher maternal mortality. Regional anesthesia is advantageous in terms of less neonatal exposure to potentially depressant drugs, decreased risk of maternal pulmonary aspiration and an awaken mother at the birth of her child[1].Hyperbaric bupivacaine is the most common

local anesthetic used in subarachnoid block for caesarean section adding an adjunct (opioids or non opioids) has allowed reduction in the dose of bupivacaine and provides cardiovascular stability[2]. In the context of "augmentation strategies" a wide variety of opioids and non opioids are used as an adjunct to subarachnoid block to improve the quality of anaesthesia and prolongation of analgesia in the post operative period[3].Opioids added to local anesthetic for subarachnoid block was first introduced into clinical practice in 1979 with morphine sulphate as a forerunner. Morphine is a hydrophilic agent, may not be optimal as intrathecal drug for intraoperative analgesia because of less lipid soluble drug have a slower rate of onset of action and the drug may reach the medulla and cause delayed ventilatory depression[4]. Fentanyl, a lipophilic opioid, has rapid onset of action following intrathecal administration. It does not tend to migrate to fourth ventricle in sufficient concentration to cause delayed respiratory depression[5]. So, fentanyl is suitable as intrathecal drug for intraoperative analgesia and also prolongs analgesia in the early postoperative period[6].Recently, a non-opioid, NMDA receptor antagonist, ketamine (preservative free) is used for central neuraxial block. Ketamine as an analgesic has gained major attention during last few years because it is the most potent blocker of NMDA receptor's available for clinical use[7]. Epidural route for the administration of ketamine has become popular because of its safety and efficacy[8].Using the epidural route would give the highest concentration of ketamine at the spinal segments with the minimum systemic effects. Also, the elimination half life of epidural ketamine is longer than that following I.V administration and its CSF concentration is double that in plasma[7]. There are some concerns about the safety of the intrathecal use of ketamine and its preservative, benzal-konium chloride. A recent case report of a terminally ill cancer patient who received a continuous infusion of intrathecal ketamine with preservative for three weeks reported sub-pial vacuolar myelopathy[9]. Preservative-free ketamine has been shown to be devoid of neurotoxic effects after single and repeated administration[10, 11, 12]. This study was carried out to evaluate and compare the quality of sensory & motor block between intrathecal ketamine Hcl and fentanyl with low dose hyperbaric bupivacaine.

Methods

This study was conducted after obtaining approval from the institutional ethical committee. ASA physical status 1 parturient at term undergoing elective caesarean section willing to be included in the study. History of allergy to these drugs, bleeding diathesis, Pregnancy induced hypertension, COPD, history of taking tricyclic antidepressant drugs were excluded from the study. Patients were randomly selected into three groups by card sampling, 30 in each group. BN, BF & BK. Group BN received 0.5% hyperbaric bupivacaine 1.75 ml (8.75mg) + 0.5 ml normal saline, group BF received 0.5% hyperbaric bupivacaine 1.75ml (8.75mg) + 0.5ml Fentanyl (25μg) & group BK received 0.5% hyperbaric bupivacaine 1.75ml (8.75mg) + 0.5 ml Ketamine (preservative free) Hcl (25mg). After taking informed consent from parturient during preoperative visit she was instructed for overnight fasting and Inj. metoclopramide 10mg intramuscularly 1 hour before operation. In the operating room an intravenous canula of 18G was inserted and (pre-operative note was taken regarding pulse, blood pressure, heart, lungs, respiratory rate and SpO_2). Pre-loaded with 15ml kg^{-1} Ringer's lactate solution. Under all aseptic precaution lumbar puncture was performed with 25 gauge Quincke's spinal needle in L_{3-4} space in sitting position and study drugs were injected. After noting the time of injection, patient was immediately placed in supine position. A wedge was placed under the right hip. All patients were received supplementation of O_2 (3 liter per minute) via facemask. Immediately after administration of spinal anesthesia pulse rate, blood pressure and rate of respiration was recorded. Then Pulse rate, blood pressure, rate of respiration, SpO_2 was recorded every 3 minute for first 20 minutes, at 10 minutes interval for remainder of operation and thereafter at 30 minutes interval until the patient complains of pain. The occurrence of discomfort and side effects likes pruritus, nausea or vomiting, shivering, chest pain, restlessness, nystigmus etc. were recorded upto 24 hours. Hypotension defined as a decrease in systolic BP to less than20% from the baseline, was treated with bolus of IV Ephedrine 6mg as required. In any patient intensity of pruritus was assessed as mild (itching was only a minor concern), moderate (itching was a primary concern although bearable) or severe (unbearable,

patient requiring treatments). Sedation was assessed by Ramsay Sedation scale. Incidence of any other discomfort and side effects were also recorded. Height of the sensory block was assessed by pin prick method at 20 minutes after administration of spinal anesthesia. The quality of motor block was assessed by bromage scale. The quality of anesthesia was assessed depending on quality of motor block (onset time, bromage scale) and quality of sensory block (onset time, level of block) and on incidence of side effects, and by interviewing the parturient for their satisfaction, Verbal Rating Scale (VRS). Accordingly quality of anesthesia was categorized as excellent / good / fair / poor. Duration of effective analgesia (time from subarachnoid injection to first dose of rescue analgesic) was recorded as the patients request for first dose of analgesic. APGAR score was recorded at 1 and 5 minute after delivery of the baby.

Mean±SD was calculated for the variable at observation time in each group. The data yielded from this study were compiled and analyzed using chi-square ($\chi 2$) and one way ANOVA test. P value less than 0.05 was considered significant. Analysis was done by using statistical package for social science (SPSS); version 12.0.

Results

Patients in three groups were homogeneous regarding demographic characteristics.

In Table - I In sensory block, 20%, 40%, 33.3% and 6.7% of the patients in Group-BN had block at T_5, T_6, T_7 and T_8 level respectively. In Group-BF 13.3%, 50%, 20% and 16.7% of the patients had block at T_4, T_5, T_6 and T_7 level respectively. In Group-BK, 26.7%, 66.7% and 6.7% of the patients had block at T_4, T_5, and T_6 level respectively.

Table-I : *Sensory block and quality of motor block in three group*

Parameters	Group-BN	Group-BF	Group-BK	P value	
Level of sensory block at 20 min.					
T_4		4 (13.3)	8 (26.7)		
T_5	6 (20.0)	15 (50.0)	20 (66.7)	9.48	0.029
T_6	12 (40.0)	6 (20.0)	2 (6.7)		
T_7	10 (33.3)	5 (16.7)			
T_8	2 (6.7)				
Quality of motor block (Bromage scale)					
Grade-2	8 (26.7)	8 (26.7)	5 (16.7)	0.884	0.347
Grade-1	22 (73.3)	22 (73.3)	25 (83.3)		

Regarding quality of motor block, in Group-BN 26.7% and 73.3% of the patients had block of grade-2 and grade-1 respectively in Bromage Scale. In Group-BF 26.7% and 73.3% patients had block of grade-2 and grade-1 respectively. While in Group-BK 16.7% and 83.3 of the patients had block of grade-2 and grade-1 respectively.

Table-II On set time of motor block were 7± 1.80, 6± 1.11 and 4± 1.01 in group BN, BF and BK respectively. The mean on set time of sensory block was 6± 1.01, 5± .80 and 3± .90 in group BN, BF and BK respectively & there was statistically significant difference in mean on set time of motor block and mean on set time of sensory block among three groups.

Table II : *Onset time of motor block and sensory block*

Parameter	Group-BN	Group-BF	Group-BK	Sources of variation	SS	df	P-value
On set time of motor block	7± 1.80	6± 1.11	4± 1.01	Between Groups	126.422	2	.000*
				Within Groups	160.200	87	
				Total	286.622	89	
On set time of sensory block	6± 1.01	5± .80	3± .90	Between Groups	64.939	2	.000*
				Within Groups	71.908	87	
				Total	136.847	89	

P<0.05 is significant.

Table III shows the mean duration of motor and sensory block in three groups.

Duration of motor block was 98 ± 10.40, 109 ± 16.42 and 104 ± 14.86 in group BN, BF and BK respectively. The mean duration of sensory block was 111 ± 14.62, 160 ± 31.85 and 147 ± 20.91 in group BN, BF and BK respectively& there was statistically significant difference in mean duration of motor block and mean duration of sensory block among three group

Table IV shows duration of motor and sensory block in BF and BK groups.

Pruritus (46.7%) was the only side effect observed in patients belonging to Group-BF.

The incidence of Nystigmus & strange feeling was 20% & 10% of the patients in Group BK only.

In Table IV shown quality of anesthesia was categorized as excellent, good, fair and poor depending on quality of motor and sensory block, per-operative anesthesia and parturient satisfaction on verbal rating scale (VRS) and also on the incidence of side effects. In Group-BN 53.3% had excellent anesthesia, 30% and 16.7% of the patients had good and fair scale of anesthesia respectively. In Group-BF 60% of the patients had excellent and 40% of the patients had good scale of anesthesia. In Group-BK 80% of patients had excellent scale of anesthesia and 20% of the patients had good scale of anesthesia.

Quality of anesthesia in two groups- BF and BK was statistically insignificant (P= 0.091).

Table V shows that the V.R. of duration of effective Analgesia (P = 0.000) is greater than the critical value of $F_{0.05,2,87}$ (3.10), then it may be concluded that the mean duration of effective analgesia compared in three groups had statistically significant difference.

Table III

Duration of motor block and sensory block

Parameter	Group-BN	Group-BF	Group-BK	Sources of variation	SS	df	P-value
Duration of	98± 10.40	109± 16.42	104± 14.86	Between Groups	1927.222	2	0.010*
motor block				Within Groups	17364.167	87	
				Total	19291.389	89	
Duration of	111± 14.62	160± 31.85	147±20.91	Between Groups	38301.667	2	0.000*
sensory block				Within Groups	48300.833	87	
				Total	86602.500	89	

Data were expressed as mean ± SD, p<0.05 = significant, * = significant.

Table IV

Quality of Anesthesia in three groups

Parameters	Group-BN	Group-BF	Group-BK	c^2 value	P value
Excellent	16 (53.3)	18 (60.0)	24 (80.0)	2.857	0.091
Good	9 (30.0)	12 (40.0)	6 (20.0)		
Fair	5 (16.7)	0	0		

Table V : *APGAR score in three groups:*

APGAR	Group-BN	Group-BF	Group-BK	χ^2 value	P value
After 1 minute					
7	1 (3.3)				
8	8 (26.7)	8 (26.7)	7 (23.3)	2.843	0.828
9	5 (16.7)	7 (23.3)	5 (16.7)		
10	16 (53.3)	15 (50.0)	18 (60.0)		
After 5 minute					
8	1 (3.3)	0	0		
9	3 (10.0)	4 (13.3)	3 (10.0)	2.225	0.694
10	26 (86.7)	26 (86.7)	27 (90.0)		

Comparison among three groups had statistically insignificant difference in APGAR Score at 1 minute (P=0.828) after delivery and at 5 minutes (P=0.694) after delivery.

Table VI : *Duration of effective Analgesia*

Sources	SS	df	MS	V.R.	P-value
Between Groups	45743.901	2	22871.950	44.027	0.000*
Within Groups	44676.908	86	519.499		
Total	90420.809	88			

Table VII : *Incidence of hypotension in three groups*

Parameters	Group-BN (n=30)	Group-BF (n=30)	Group-BK (n=30)	P value
Ephedrine given	12 (40.0)	8 (26.7)	6 (20.0)	0.220

Data are presented as frequencies. Values within parentheses are expressed as percentage over column total.

Figure 1 shows that the changes in pulse rate of group BK was lower than that of group BN and group BF. It also shows that the gap of pulse rate was high among the three groups after 90 min. of per operative period (group BK was max. and group BF was min.), though the gap was comparatively low in the baseline period.

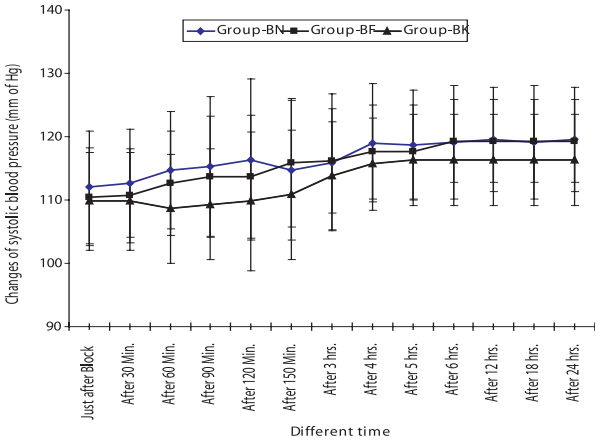

Fig 2 *Changes of systolic blood pressure (mm Hg) (per operative)*

Figure 2 shows that the changes of systolic blood pressure of group BK was lower than that of group BN and group BF after 90 min. of per operative period (group BK was max. and group BF was min.).

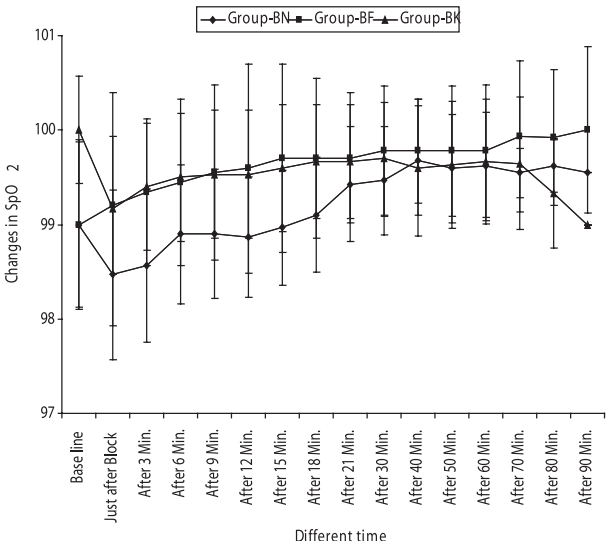

Fig- 2: *Changes in SpO_2 (per operative)*

Figure 3 shows that the changes in SpO_2 of group BK was lower than that of group BN and group BF after 90 min. period, though the SpO_2 was comparatively high in the baseline period.

Incidence of post operative side effects: pruritus (43.3%) was the only side effect observed in patients belonging to Group-BF. Incidence of nausea was 16.7% in Group BF only. Incidence of vomiting was also 3.3% in Group BF only. Dizziness was observed in 20% of the patients only in Group BN. Incidence of strange feeling was 13% in Group BK only. Incidence of shivering was 20% and 16.6% in Group BN and BF respectively.

Discussion

In the present study, patients were randomly allocated in three groups-BN, BF and BK, in group BN 0.5 ml normal saline + 1.75 ml 0.5% hyperbaric bupivacaine, in group BF 0.5 ml (25ìg) fentanyl + 1.75 ml 0.5% hyperbaric bupivacaine, and in group BK 0.5 ml (25 mg) ketamine (preservative free) + 1.75 ml 0.5% hyperbaric bupivacaine were used for induction of subarachnoid block. Final height of the block was assessed by pin prick in 20 min. after block, because bupivacaine fixed at this time and no further progression of the block occurred.

In BK group 26.7% patients had sensory block at T_4 and in BF group 13.3% patients had sensory block at T_4 while in BN group (Control) no patients had sensory block at T_4 level. So, ketamine (preservative free) and fentanyl had higher level of sensory block than control group which was statistically significant (P=.000). Again ketamine (preservative free) group had higher level of sensory block than fentanyl group which was statistically significant (P=.029). There was no statistically significant difference (P=0.347) in assessment motor block among three groups observed by bromage Scale. This result is consistent in terms of level of sensory block with the study conducted by Kathirvel et al [13] and Biswash et al. [6].

Cardiovascular effect of spinal block was measured in terms of number of patients developed hypotension and required treatment with Inj. ephedrine. Hypotension was defined as reduction systolic blood pressure to 20% or more than the base line. In group BK 20% and in group BF 26.7% while 40% of patients in group BN developed hypotension. The incidence of hypotension among three groups was statistically insignificant (P = 0.220). In BK & BF group, though dose of the bupivacaine was not reduced, cardiovascular stability in respect of hypotension was found insignificant.

There have been reports of respiratory depression when intrathecal lipophilic opioid has been used for labour analgesia byLu et al.[14] & Hays & Pabner[15]. But during caesarean delivery significant respiratory depression has not been observed by Dahlgren et al.[16] & Hunt et al[17]. Intrathecal ketamine (preservative free) didn't induce respiratory depression reported by Kathirvel & Shadasivam [13] even after massive dose of 250 mg Mankowitz et al.[18]. In our study no patient in any groups experienced respiratory depression.

The incidence of discomfort and side effects observed during the study was less in BK & BF groups than BN group (Control Group).

Quality of anesthesia was categorized as excellent, good, fair and poor depending on assessment of motor block, level of sensory block and the incidence of side effects. Quality of anesthesia was better in BF & BK than control group BN which was statistically significant (P = 0.008). On the other hand BK group had better quality of anesthesia than group BF which was statistically insignificant (P = 0.091).

Neonatal APGAR score was similar among three groups.

Mean duration of effective analgesia in group BN, BF & BK were 128±13.78, 181±30.17 and 169 ± 21.14 minute respectively which was statistically highly significant (P = 0.000). On the other hand, there were small difference in postoperative analgesia in group BF & BK which was not statistically significant (P = 0.072).

There were two important observations in the study. One was in BK group there was no nausea and vomiting in peroperative and postoperative period. And another observation was that there was less incidence of hypotension in BF and BK group than BN group with same dose of bupivacaine. These two observations may be further evaluated.

Limitation of this study is that only one dose of ketamine (preservative free) was used. Dose-

response study was not carried out because previous study has already shown that ketamine (preservative free) dose-dependency potentiates the local anesthetic effect. Similar dose response relationship in study where 20, 40 or 60 ìg of fentanyl was administered and prolongation of effect was found in higher doses but with increased pruritus reported by Belzrena et al.[21] Sample size was also small in this study.

Concluded that subarachnoid ketamine (25 mg) with low dose hyperbaric bupivacaine is an alternative to subarachnoid fentanyl with low dose hyperbaric bupivacaine for elective caesarean section in terms of quality of block, haemodynamic stability, incidence of side effects, quality of anesthesia, duration of post operative analgesia and foetal outcome.

References:

1. Morgan EG, Mikhali MS, Murray MJ. Maternal and foetal physiology anaesthesia. In: clinical anaesthesiology, 3rd edition, New York: Mc Grow-Hill, 2002; 805
2. Dyer RA, Joubert A, Ivan A. *Low-dose spinal anesthesia for Cesarean section*. *Anesthesiology* 2004; 4: 303-308
3. Saxena, AK, Arava, SK. *Current concepts in Neuraxial Administration of opioids and non-opioids: an overview and Future Perspective*, Indian J. Anaesth 2004; 48:13-24
4. Alan, RA, David J, Rowbotham, Smith G, *'Postoperative pain'*, Textbook of anaesthesia, 4th edition, Churchill Livingstone 544-554
5. Etches, RC, Sandler, AN, Daley, MD. *Respiratory depression and spinal opioids*. Can J. Anaesth 1989; 36:165-85
6. Biswas, BN, Rudra, A, Bose, BK, et al. *Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during caesarean delivery and in early post- operative period*. Indian J. Anaesth. 2002; 46: 469-472
7. Ghaffar, AME, Abdulatif M et al. *Epidural ketamine reduces post- operative epidural PCA consumption of fentanyl/bupivacaine*. Can J. Anesthesia 1998; 45: 103-109
8. Nagubm, Abu-Gyamfi, Y, Absood, GH, Faragh, Gyasi, HK, *Epidural ketamine for postoperative analgesia*. Can J. Anesthesia 1986; 33: 16-21
9. Karpinski, N, Hansen, DJL, Masliah E. *Subpial vacuolar myelopathy after intrathecal ketamine: report of a case*. Pain 1997; 73: 103-5
10. Borgbjerg, FM, Svensson, BA, Frigast C, Gordh T. *Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabit: a light and electron microscopic examination*. Anesthesia and Analgesia 1994; 79: 105-11
11. Malinovski JM, Lepage JY, Cozain A, et al. *Is ketamine or its preservative responsible for neurotoxicity in the rabbit?* Anesthesiology 1993; 78: 109-15
12. Brock-Unte JG, Mankowitz E, Kallichurum S, Dowing JW. *Effects of intrathecal saline and ketamine with and without preservative on the spinal roots of monkey*. South African Medical Journal 1982; 61: 360-61
13. Kathirvel S, Shadasivam S*A, Saxena, et al. Effects of intrathecal Ketamine added to bupivacaine for spinal anesthesia*. Anesthesia 2000; 55: 899-910
14. Lu JK, Schafer PG, Gurdner TL, et al. *The dose response pharmacology of intrathecal sufentanil in female volunteers*. Anesth analg 1997; 85: 372-79
15. Hays RL, Pabner GM. *Respiratory depression after intrathecal sufentanil during labour*. Anesthesioloy 1994; 79: 1288-93
16. Dahlgren G, Hultsrand C. *Intrahecal sufentanil, fentanyl or placebo added to bupivacaine for caesarean section*. Obstet Anesth 1997; 85: 1288-1293
17. Hunt CO, Namitry JS, Bader AM, et al. *Peroperative analgesia with subarachnoid fentanyl bupivacaine for caesarean delivery*. Anesthesiology 1989; 71: 535-40
18. Mankowitz E, Brock-Unte JG, Connet, JE, Thompson, GR, et al. *Epidural ketamine, A preliminary report*. South African Med J, 1982; 61: 441-2.
19. Bader AM, Thormill M, Datta S. *The antiematic efficacy and safety of prohylacitc metoctopramide for elective caesarean delivery during spinal anaesthesia*. Reg Anaesth 1992; 17: 126-30
20. Eisenach JC, DeKock M, Klimscha W. *Alpha (2) adrenergic agonists for regional anesthesia*. A clinical review of clonidine Anesthesiology 1996; 85: 655-74.
21. Belzrena SD. *Clinical effects of intrathecally administered fentanyl in patients undergoing caesarean section*. Anesth analg 1992; 74: 653-657