Pre-emptive Epidural Analgesia with Bupivacaine, Diltiazem and Ketamine Singly or In Combination- A Randomised Trial.

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Abstract

Background: A randomized control study was designed to compare postoperative epidural analgesia by preemptive use of epidural administration of local anesthetic- bupivacaine alone and in combination with NMDA blocker- ketamine or calcium channel blocker- diltiazem singly or both in combination .

Methods: Sixty female patients in age group 35-50 yrs with ASA grade I and II, posted for open abdominal hysterectomy were randomly distributed in four groups after ethical committee approval and written consent. They were given epidurally 0.4 ml /kg of 0.5 % Bupivacaine in Control group, 0.4 ml /kg of 0.5 % Bupivacaine + Ketamine 5mg in BK group , 0.4 ml /kg of 0.5 % Bupivacaine + Diltiazem 10 mg in BD group and 0.4 ml /kg of 0.5 % Bupivacaine + Ketamine 5 mg + Diltiazem 10 mg in BKD group.

Results: BK group had significant pain free period (8.8 ± 1.37) post operatively as compared to rest three groups ($P < 0.01$). BD group (5.8 ± 0.94) also had comparable pain relief. BK group needed three to four number of top-up's in first 24 hours (3.37 ± 0.46) where as BD group needed five to seven number of top-up's in next 24 hours (5.93 ± 0.70) ($P < 0.01$). BK group and BKD group patients were sedated resulting in reduced number of top-ups required in first 24 hours.

Conclusion: Ketamine and diltiazem were found to be synergetic with bupivacaine for preemptive epidural analgesia. Diltiazem was better option over ketamine when sedation is not desirable.

Key-Words: Pre-Emptive Analgesia, Epidural, Ketamine, Diltiazem.

Introduction

An important goal of modern anaesthesia is to ensure that the patient undergoing surgery awakens from anaesthesia totally pain free and that this state is maintained satisfactorily in the post-operative period as well. Good pain control not only speeds up the recovery of patients but also shortens their length of hospital stay. Pre-emptive analgesia is an attractive concept of addressing pain even before it starts.

There is substantial amount of evidence that N-methyl-D-aspartate (NMDA) receptor is important in sustaining and magnifying excitability of neurons in the spinal cord.[1] Excitatory neurotransmitters, acting through N-Methyl-D aspartate (NMDA) receptors have been related to the development and maintenance of pathological pain states after tissue injury especially hyperalgesia and allodynia.

Calcium channel conductance at neuronal level is essential for neurotransmitter effectivity and for nociceptive perception. A disruption of calcium ion movement interferes with sensory processing and contributes to antinociception [1, 2, 3].

These observations have encouraged the evaluation of NMDA receptor antagonists [4], and calcium channel blockers[5], in different pain

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states. Studies using epidural ketamine with bupivacaine for preemptive analgesia are limited and to our knowledge limited studies have used epidural diltiazem prompting us to design this study. This study was taken up postulating addition of NMDA antagonist ketamine and/or calcium channel blocker- diltiazem to epidural bupivacaine would improve analgesic quality as well as reduce postoperative analgesic consumption.

Material and Methods

A prospective randomized control study was designed to compare postoperative analgesia by preemptive use of epidural administration of local anesthetic-bupivacaine alone or in combination with NMDA blocker- ketamine or calcium channel blocker- diltiazem singly or both in combination. After obtaining the approval from the Institutional ethics committee the present study was undertaken in 60 female patients.

Inclusion Criteria: Patients aged between 35-45 years in ASA grade I and II posted for abdominal hysterectomy.

Exclusion Criteria: Patients with H/O chronic backache, coagulopathy, local sepsis, spinal deformities, cardiovascular problems and those patients using the study drugs pre-operatively were excluded .

After valid informed consent, the selected patients were randomly allocated by block randomization method to four groups of 15 patients each and group 1 acted as the Control group.

Block size :4 Allocation Ratio: 1:1:1:1. For allocation concealment, randomization was done by third person other than the Anaesthesiologist who administered the drugs and later on made the observations. All the patients were explained the use of visual analogue scale and Prince Henry Scale preoperatively. Drugs administered epidurally 30 minutes before induction of general anaesthesia for preemptive analgesia are shown:

Group 1 (Control group): 0.4 ml /kg of 0.5 % Bupivacaine.

Group 2 (BK group) : 0.4 ml /kg of 0.5 % Bupivacaine + Ketamine 5mg.

Group 3 (BD group): 0.4 ml /kg of 0.5 % Bupivacaine + Diltiazem 10 mg.

Group 4 (BKD group): 0.4 ml /kg of 0.5 % Bupivacaine + Ketamine 5 mg + Diltiazem 10 mg.

Both the patient and the anesthesiologist were blinded to the study solutions. Syringes were prepared by the third person who did randomized allocation, immediately before the epidural injection, ensuring total volume of 20ml and labeled as "Epidural Study Drug" and the patient's name. Anticholinergic, benzodiazepines and opioid premedication was avoided to prevent interference with intraoperative and postoperative assessment. All the baseline parameters were recorded. After fulfilling all the pre-requisties of regional anaesthesia, under all aspetic precautions in sitting position, epidural space was identified using a midline approach at L3-4 inter space with 18 G Tuohys epidural needle by loss of resistance to air technique. An 18 G epidural catheter was inserted in cephaloid direction gently to an intraepidural distance of 3-4 cm in all the patients. Patients were then put in supine position and a test dose of 3 ml of 2 % lignocaine with adrenaline (1:2,00,000) was given. All the patients were given respective study drugs 30 minutes prior to induction of general anaesthesia. The extent of sensory blockade was assessed by pinprick method and after desired sensory blockade (T6 ± 1) was acheived, conventional general anaesthesia was administered. Induction was done with inj. thiopentone sodium 4 mg/kg followed by intubation facilitated by inj. Vecuronium 0.1mg/kg. Anaesthesia was maintained with O2, N2O and halothane. Neuromuscular block was reversed at the end of surgery by inj.neostigmine 0.05 mg/kg and inj.glycopyrrolate 0.01mg/kg. Intraoperatively systemic analgesics were avoided in all groups. Routine monitoring was done throughout the intraoperative period with special attention for signs of inadequate analgesia such as tachycardia, hypertension and excessive lacrimation. Haemodynamic parameters (SBP,DBP and PR) were recorded both before and after the incision and later at frequent intervals. Postoperatively all the patients received analgesia through epidural catheter with fixed dose of 20 ml of 0.2 % of local

anaesthetic- bupivacaine as and when required in first 48 hrs using pain score. All patients were monitored for haemodynamic status in the postoperative period. Pain was assessed using the Prince Henry Score, Visual analouge scale and sedation score every 4 hours till 48 hours postoperatively.

Prince Henry Score: It is graded as

0- when patient has no pain on taking a deep breath or on coughing.
1- when patient had no pain at rest nor on taking a deep breath but had pain coughing .
2- when patient had no pain at rest but pain on taking a deep breath.
3- when patient had mild pain at rest.
4- when patient had severe pain at rest.

Visual Analouge Scale:

It consists of a scale marked from 0 to 100 mm where 0 indicates no pain and 100 indicates worst pain.

Sedation Score: It is graded as

0 - Awake patient.
1 - Drowsy patient.
2 - When patient is sleeping but responds to verbal Commands.
3 - Sleeping but responding to tactile stimulus.
4 - Unresponsive patient.

When the visual analogue score was 20 or the Prince Henry score was 2 on assessment, the analgesic drug was given epidurally even if the patient did not ask for it. Epidural catheter was removed post operatively after 48 hours. Efficacy of different drug combinations as regards post operative pain relief indicated by duration of analgesia i.e: 1st top-up requirement and total analgesic requirement in first and next 24 hours period i.e: number of top-ups required in the first and next 24 hours was noted and compared in all groups. Patients satisfaction was assessed by questioning patients at the end of 48 hours about pain relief, postoperative sedation, comparison of pain relief with previous experience if any.

Data analysis

Descriptive statistics for all the continous variables was expressed in terms of mean and standard deviation. Differences in group mean of baseline subject characteristics (age in years and weight in kgs.) were tested using ANOVA F-test for continuous variables. Mean duration of analgesia and mean no. of top-ups required in first 24 hours and next 24 hours for each group was compared using simple linear regression. Hemodynamic parameters (systolic blood pressure, diastolic blood pressure and pulse rate) were measured at baseline, pre-incision and post-incision and the difference in the mean at these three time points was tested using linear regression with generalized estimating equations to take care of clustering of the observations at individual patient level. Comparison of mean hemodynamic parameters at different time points was done separately for each group. The level of significance was set at 0.05. The statistical analysis was done using STATA 11 IC.

Results

Our study included 60 patients divided into 4 groups belonging to ASA Grade I and II who were posted for elective abdominal hysterectomy. Range of age was 35 to 45 years and weight was 42 to 58 kgs in all groups. Table I shows baseline, pre-incision and post-incision haemodynamic prarameters. In all groups, pre-incision haemodynamic parameters were lower than the baseline and post-incision parameters were lower than the pre-incision, suggesting adequate analgesic effect. The first analgesic requirement in the post-operative period was compared in all 4 groups. BK group had significant pain free period (8.8 ±1.37 hrs.) post operatively as compared to the rest three groups ($P< 0.05$) BD group (5.8 ± 0.94 hrs.) also had comparable pain relief. Though BKD group (7.53 ± 1.14) did not offer any advantage over BK group it is better than BD group. BK group needed least number of top-up's in first 24 hours (3.37 ± 0.46) where as BD group needed least number of top-up's in next 24 hours (5.93 ± 0.70). The total number of top-up's required for BK group in the first 24 hours were doubled in the next 24 hours which was correlated with decreasing sedation. Control group received the maximum amount of drug in 48 hours (395.73 ± 20.81 mg) while BK group received the minimum amount of drug in 48 hours (281.87 ± 30.79 mg) (Table II).

The sedation scores taken at the end of every 4 hours showed that in BK group and BKD group patients were sedated. BK group patients were sedated upto grade 2 in initial 24 hours which correlated with the reduced number of top-ups required in first 24 hours. No side effects were noted in any of the above groups. When patients were assessed for satisfaction, BK group patients were most satisfied followed by BD group (Table III).

Discussion

Nociceptive stimulation causes neuro-transmitter release, which is coupled with activation of voltage-dependent calcium conductance in synaptic terminal membranes of neurons. A disruption of calcium influx into the cells interferes with normal sensory processing and contributes to antinociception.

Peripheral tissue injury provokes both peripheral and central sensitization. Peripheral sensitization is a reduction in the threshold of nociceptor-afferent peripheral terminals and central sensitization is an activity dependent increase in the excitability of spinal neurons [6]. There is considerable evidence that excitatory amino acids and neuropeptides are involved in nociceptive transmission in the dorsal horn of the spinal cord [7, 8]. The actions of excitatory amino acids are mediated by the N-methyl-n-aspartate (NMDA) receptor and non-NMDA receptors. Activation of NMDA receptors leads to Ca++ entry into the cell and initiates a series of central sensitization such as wind-up and long-term potentiation in the spinal cord in the responses of cells to prolonged stimuli. This central sensitization may be prevented by preemptive analgesia not only with NMDA antagonists such as ketamine, but also with calcium channel blockers that block Ca++ entry into cells.

Recently increasing attention has been focused on new methods of pain relief to improve patient care. Good pain control can speed up the recovery of patients and shorten their hospital stay. Evidence from the basic research in the mechanism of pain suggests that administration of analgesic drugs much before surgical stimulus may be more effective than giving them after the stimulus. This is reffered to as "PRE-EMPTIVE ANALGESIA " and is one of the new treatment protocols. The accepted method for postoperative analgesia till now was to begin the analgesic treatment when the pain starts in the post-operative period. Pre-emptive analgesia is an attractive concept of addressing pain even before it starts.

We planned this study to compare postoperative epidural analgesia after open abdominal hystrectomy by preemptive use of epidural administration of bupivacaine alone or in combination with ketamine or diltiazem singly or both in combination. Opioids were avoided because they could have prevented or attenuated central sensitization, thus leading to questionable results [9,12]. A sub-anesthetic ketamine dose, defined as intravenous or epidural bolus below 1 $mg.kg^{-1}$ is related to analgesic effects, as compared to a higher dose which has psychomimetic symptoms and dissociative anaesthesia [13]. At subanesthetic (i.e. low) doses, ketamine exerts a specific NMDA blockade and hence modulates central sensitization induced both by the incision and tissue damage and by perioperative analgesics such as opioids[14]. We used very low dose of ketamine (5mg) along with bupivacaine. No studies have evaluated the effects of epidural bupivacaine and verapamil before Choe H.et al [15], who administered lumbar epidural bupivacaine or bupivacaine plus verapamil to investigate the possible role of the calcium channel blocker, verapamil, in postoperative pain. Later on Lin XM [16], also used epidural Bupivacaine + Verapamil. We decided to test diltiazem by epidural route along with bupivacaine and compare it with ketamine and bupivacaine. Analgesia was adequate in all the groups during intraoperative period as pulse rate and blood pressure remained stable. Both ketamine and diltiazem proved to be an effective adjuvant to plain bupivacaine for epidural analgesia as control group showed the shortest duration of postoperative pain free period (4.6 ± 0.74 hrs.) and required maximum number of top-ups in first (6.0 ± 0.85) and next 24 hours (8.13 ± 0.83). Ketamine proved to be better than diltiazem

as BK group showed the longest duration of postoperative pain free period (8.8 ± 1.37 hrs.) and required minimum number of top-ups in first 24 hours (3.37 ± 0.46). Sedation was also noted during this period (Sedation score more than 2 in 9 patients and 1 in 6 patients) which would have contributed for the pain relief as the requirement of top-ups increased in next 24 hours (6.8 ± 0.77). As against this, number of top-up's in BD group did not vary much in the study period of 48 hours.(4.93 ± 0.80 and 5.93 ± 0.70 respectively), showing well balanced level of analgesia without associated sedation. Duration of postoperative pain free period was less (5.8 ± 0.94 : 8.8 ± 1.37) and total consumption of bupivacaine was more (304.27 ± 37.96 : 281.87 ± 30.79) in BD group as compared to BK group. Neverthless as sedation was not noted in this group, (sedation score 0 in 93.33% patients) diltiazem can be a better option over ketamine in whom sedation is not desirable. Combining ketamine and diltiazem with bupivacaine did not offer much advantage. Contrary to our results Kawana Y et al [17], who also administered low doses ketamine (4, 6, 8 mg) found that ketamine administered epidurally was inadequate for postoperative pain relief after gynecologic operations. This may be due to the fact they administrerd ketamine singly while we administered it along with bupivacaine. Choe H. et al [15] and Lin XM [16] also had similar results like us regarding use of calcium channel blocker though they used verapamil and we used diltiazem.

In conclusion both NMDA antagonist ketamine and calcium channel blocker diltiazem were found to be synergestic with local anesthetic bupivacaine when used for preemptive epidural analgesia and provided excellent intraoperative and postoperative analgesia in patients who had undergone abdominal hysterectomy. Diltiazem was found to be a better option than ketamine when sedation is not desirable in postoperative period. A detailed study in larger number of patients is recommended for full exploitation of analgesic effects of diltiazem.

Table I : Comparison of Haemodynamic Parameters

Haemodynamic Parameters		Control Group (n=15)	BK Group (n=15)	BD Group (n=15)	BKD Group (n=15)
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Baseline	SBP(mm of Hg)	123.43 ± 8.65	121.65 ± 6.25	128.93± 6.44	119.06 ± 6.57
	DBP(mm of Hg)	80.8 ± 5.10	81.2 ± 3.78	79.86 ± 8.46	77.73 ± 4.95
	PR/min	78.4 ± 5.52	81.2 ± 3.49	80.6 ± 5.78	81.0 ± 5.90
Pre-Incision	SBP(mm of Hg)	117.06±8.09**	120 ± 7.41	114.26±7.62**	115.33±6.56**
	DBP(mm of Hg)	76.53 ± 4.70**	78.4 ± 3.57**	74.8 ± 7.86**	76.26 ± 5.65
	PR/min	77.6 ± 5.9	80.46 ± 3.75††	78.33 ± 6.27	80.66 ± 5.73
Post-Incision	SBP(mm of Hg)	113.6 ± 6.16**	118.1 ± 7.74**	112.8 ± 6.76**	114.3 ± 5.4**
	DBP(mm of Hg)	74.93 ± 4.12**	76.93 ± 4.06**	74.4 ± 5.8**	75.73 ± 5.6
	PR/min	76.4 ± 6.07*	82.27 ± 4.25 ¶	79.33 ± 5.15	79.33 ± 4.82

BK Group = Bupivacaine + Ketamine group SBP = Systolic Blood Pressure
BD Group = Bupivacaine + Diltiazem group DBP = Diastolic Blood Pressure
BKD Group= Bupivacaine + Ketamine + Diltiazem group PR = Pulse Rate
* P-value significant at 0.05 ** p-value significant at 0.01 (When Baseline SBP, DBP and PR are compared to pre incision and post incision SBP, DBP and PR respectively)
¶ P-value significant at 0.05 †† p-value significant at 0.01 (When SBP, DBP and PR are compared in all groups)

Table II : Comparison of duration of analgesia and number of top-ups required in first and next 24 hours.

	Control Group (n=15)	**BK Group** (n=15)	**BD Group** (n=15)	**BKD Group** (n=15)
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)
First top-up requirement (Mean duration in hours)	4.6 ± 0.74 (3.5 - 6)	8.8 ± 1.37** (6 - 12)	5.8 ± 0.94 ** (4 - 8)	7.53 ± 1.14** (6 - 10)
No of top-ups in first 24 hours	6.0 ± 0.85 (5 - 8)	3.37 ± 0.46** (3 - 4)	4.93 ± 0.80** (4 - 6)	5.36 ± 0.80** (4 - 7)
No of top-ups in next 24 hours	8.13 ± 0.83 (7 - 10)	6.8 ± 0.77** (6 - 8)	5.93 ± 0.70** (5 - 7)	7.53 ± 1.13 6 - 9)
Total dose of bupivacaine required in postoperative period in mg	395.73 ± 20.81 (364 - 420)	281.87 ± 30.79 (252 - 336)	304.27 ± 37.96 (252 - 364)	358.4 ± 35.42 (308 - 420)

BK Group = Bupivacaine + Ketamine group
BD Group = Bupivacaine + Diltiazem group
BKD Group= Bupivacaine + Ketamine + Diltiazem group

* P-value significant at 0.05 ** p-value significant at 0.01

Table III :Number of patients showing sedation score in first and next 24 hours.

Sedation score in first 24 hours	**Control Group** (n=15)	**BK Group** (n=15)	**BD Group** (n=15)	**BKD Group** (n=15)
0	15	0	14	0
1	0	6	1	12
2	0	7	0	2
3	0	2	0	1
4	0	0	0	0
Sedation score in next 24 hours				
0	15	12	15	13
1	0	3	0	2
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0

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