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Original Article

PRE-EMPTIVE ANALGESIA : EFFECT OF LOW DOSE KETAMINE AS PRE-EMPTIVE ANALGESIA IN POSTOPERATIVE PAIN MANAGEMENT AFTER LOWER ABDOMINAL SURGERY

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SUMMARY:

A Prospective randomized placebo-controlled study was done at Dhaka Medical College Hospital to evaluate the effects of low dose Ketamine as pre-emptive analgesia in post operative pain management after lower abdominal surgery.

Sixty patients scheduled for elective total abdominal hysterectomy under General Anaesthesia were randomly divided into three equal groups. In Group-A, patients received 0.5 mg/kg ketamine I/V 90 seconds before incision, in Group-B, patients received the same dose after incision and in Group-C, patients were regarded as controlled, received 0.5 ml distilled water before incision.

The patients were premedicated orally by giving Tab. diazepam 5mg with sips of water one hour before induction of anaesthesia. General anaesthesia was induced with thiopental sodium 3-5 mg/kg. Suxamethonium 1.5 mg/kg was given to facilitate endotracheal intubation. The neuromuscular block was continued with vecuronium. Anaesthesia was maintained with N_20 (60-70%) and halothane in 0_2. Halothane was adjusted to maintain the MAP and heart rate within 20% of the pre-induction value. Opioids were not administered during the induction or during the operation. At the end of the anaesthesia, residual neuromuscular block was antagonized with intravenous neostigonine 0.05 mg/kg in atropine 0.02 mg/kg. In the post operative ward following parameters were recorded for 24 hours: recovery status, time of first analgesic demand, pain intensity by VAS & VRS, total opioid consumption, sedation score, haemodynamic status and, complications like nausea, vomiting, delirium and hallucination. Upon the first complaint of moderate pain (>5 on VAS), pethidine 1.5 mg/kg was administered intramuscularly & then repeated 4 hourly. If pain intensity remained >5 on VAS scale, rescue analgesic Pethidine 10 mg was administered intravenously. Time of first demand for analgesic among three groups: Gr- A(pre-incision): 68.4$\pm$ 6 min; Gr-B (post-incision): 37.4$\pm$ 3.3 min; and Gr-C (Control): 18.9 $\pm$ 2.1 min. It is statistically significant (P<0.00) i, e, delayed in Gr. A. Total opioid consumption in 24 hours was: Gr. A: 8.6 $\pm$ 0.11 mg/kg, Gr. B: 9.0 $\pm$ 0.11 mg/kg and in Gr. C: 9.9 $\pm$ 0.14 mg/kg. (P<0.00) i , e, less in Gr. A. The incidence of hallucination and delirium were present in Gr. A & Gr. B but more in Gr. B than Gr. A. Nausea and vomiting were present in three groups. So, it can be concluded that pre-emptive use of ketamine significantly reduces postoperative pain and spare opioid consumption in the postoperative pain management.

INTRODUCTION:

The concept of 'preemptive analgesia' suggests that "the best management of postoperative pain begins preoperatively"[1]. It signifies that analgesia, when it is given before the painful stimulus has effects that outlast the presence of the analgesic in the body[2]. The aim of such treatment is to prevent the spinal cord from reaching a hyper excitable state in which it responds excessively to afferent inputs. Experimental evidence suggests that preemptive analgesia can effectively attenuate peripheral and central sensitization to pain[1]. The importance of peripheral and central modulation in nociception has fostered the concept of 'Preemptive Analgesia' in patients undergoing surgery. This may involve infiltration of the wound

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with local anaesthetic, central neural blockade, administration of effective doses of opioids, NSAIDS or ketamine.

Ketamine as an analgesic gained major attention during last few years as it blocks NMDA receptors. The NMDA receptors are the receptors of pain memory that maintain neuroplasticity and hyperalgia after the end of initial painful stimulus[3].

Many studies on 'preemptive analgesia' were done with ketamine through different routes. But this study was designed to compare the effect of low dose ketamine at two different time e.g. before and after surgical incision with placebo.

MATERIALS AND METHODS:

After obtaining written informed consent, sixty patients aged between 35-55 years with ASA physical status I & II scheduled for elective total abdominal hysterectomy (TAH) under general anaesthesia were recruited in a double blind, placebo-controlled study. The protocol was approved by the ethics committee of DMCH. The patients with history of hypertension, IHD, neurological or psychiatric illness were excluded. The patients were oriented about the Visual Analogue Scale (VAS) and Verbal Rating Score (VRS).The patients were randomly divided into 3 equal groups by card sampling. In Group-A, patients received 0.5mg/kg ketamine I/V 90secs before surgical incision. In Group- B, Patients received 0.5mg/kg ketamine I/V 90secs after surgical incision and Group- C patients were regarded as 'Controlled' and received 0.5ml distilled water 90 sec before incision.

The patients were premedicated with tab. diazepam 5mg with a sip of water 1hr before induction of anaesthesia. Anaesthesia was induced with thiopental sodium 3-5mg/kg. The suxamethonium 1.5mg/kg was given to facilitate endotracheal intubation. Thereafter neuromuscular block was maintained with vecuronium and anaesthesia with nitrous oxide (60-70%) and halothane in oxygen. The halothane was adjusted to maintain the mean arterial pressure and heart rate with in 20% of pre induction value.

At the end of anaesthesia, residural neuromuscular block was antagonized with neostigmine (0.05mg/kg) in atropine (0.02 mg/kg).

Postoperative pain was managed with Pethidine. Upon the first complaint of moderate pain (>5 on VAS), 1.5mg/kg of pethidine was given intra muscularly and then repeated 4 hourly. If the pain intensity remained >5 on VSA scale, rescue analgesic of intravenous Pethidine 10 mg was administered. The pethidine consumption during 0 to 4hr, 4hr to 8hr, and 8hr to 12hr intervals were recorded. In the postoperative period, degree of sedation were assessed with the help of 4 point sedation scoring system. Data was collected in a prescribed form and analyzed by using ANOVA or Chi-Square test as appropriate. Values were regarded as significant if $P< 0.05$ (CL-95%).

RESULT:

Observations of the present study were analyzed in the light of comparison among the groups (Group-A: Pre-incision; Group-B: Post-incision; and Group-C: Placebo Control). All results are expressed as mean ± SD or in frequencies as applicable. The groups were statistically matched for age ($p=0.476$) and weight ($p= 0.465$).

Table-I

Characteristics of the subjects in three groups

Characteristics	Pre-incision group (Group A)	Post-incision group (Group B)	Control (Group C)	p-value
Age in year	43.5±6.0	41.5±4.4	43.4±6.8	0.476
Wight in kg	57.5±10.1	60.6±8.1	57.7±8.1	0.465

Values are expressed as Mean ± SD. Data were analyzed by ANOVA.

Values are regarded as significant if $p <0.05$ (CL- 95%).

Table-II

Time of 1st demand for pethidine and total dose consumed in 24 hours

Background characteristics	Pre-incision (Group-A)	Post-incision (Group-B)	Control (Group-C)	P-value
1st demand (min)	68.4±6.4	37.4±3.3	18.9±2.1	0.001
Pethidine consumption in 24 hrs (mg/kg)	8.6±.11	9.0±.11	9.9±.14	0.001

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if p <0.05 (CL- 95%) and highly significantly if (P<.001)

First demand for pethidine in three groups (Group-A Pre incision: 68.4 ± 6.4min; Group-B Post incision : 37.4 ± 3.3min and Group-C: Control ;18.9 ± 2.1 min; p= <0.001) are significantly different.

The pethidine consumption in 24 hours postoperatively in 3 groups. (Group-A Pre incision; 8.6 ± 0.11mg/kg: Group-B Post incision; 9.0 ± 0.11mg/kg and Group-C Control; 9.9 ± 0.14mg/kg: p= <0.001) are also significantly different (Table-II).

Table-III shows the heart rate at the different times. it differs significantly at 1hr after induction (p=0.01) and after extubation (p=0.000).

Table-III

Heart rate/min of the patients of three groups at different time

Background characteristics	Pre-incision Group A	Post-incision Group B	Control Group C	p-value
Base line	83.6 ±3.3	84.3± 4.2	83.3 ±3.4	0.500
At Induction	100.6± 8.9	104.4± 7.2	103.6± 8.6	0.320
1hr after induction	82.9± 5.3*	87.6 ±4.9*	86.2 ±4.8*	0.010
After extubation	93.7±3.5*	95.85±3.4*	101±3.4*	0.000
4h after extubation	85.7±3.3	86.6±4.2	85.3±3.4	0.518
8h after extubation	86.6±3.1	89.25±4.6	87.1±3.5	0.070
12h after extubation	85.0±4.5	86.6±4.2	85.3±3.4	0.417
24h after extubation	83.7±3.3	84.6±4.2	83.7±3.5	0.641

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if * p <0.05 (CL- 95%).

Table-IV

Mean arterial pressure (MAP) in mm of Hg

Characteristics	Pre-incision (group-A)	Post-incision (group-B)	Control (Group-C)	p-value
Base line	90.3 ± 4.0	90.4 ± 4.8	88.9 ± 4.1	0.450
Induction	96.4 ± 4.3	97.6 ± 4.4	96.9 ± 4.4	0.660
1hr after induction	90.2 ± 3.9	93.4 ± 3.2	91.9 ± 4.4	0.135
At Extubation	96.2±3.4	96.7±4.0	98.4±8.1	0.411
4h after extubation	92.2±3.1	92.8±3.8	91.8±4.8	0.667
8h after extubation	93.3±3.3	94.1±4.3	93.6±3.6	0.815
12h after extubation	90.8±4.1	92.3±4.2	91.7±4.5	0.541
24h after extubation	90.3±4.0	90.41±4.8	89.13±4.6	0.601

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if * p <0.05 (CL- 95%).

Table-IV shows no significant difference in MAP of the patients in three different group at different time.

Pain intensity as measured by VAS was highly significant are at different hour after extubation (Table-V).

The VRS of different groups are significantly different at different hour after extubation (Table-VI).

The sedation Score (SS) are significant different at different hour after extubation Table-VII.

The post operative complications of the different groups are shown in Table-VIII.

Table-V

Visual Analogue Scale (VAS) of the patients of three groups at different hour after extubation

Background characteristics	Pre-incision Group A	Post-incision Group B	Control Group C	p-value
VAS after 4hr	1.2±. 77	2.35±. 93	3.05±. 60	0.000
VAS after 8hr	1.0±. 56	2.2±. 52	2.9±. 55	0.000
VAS after 12hr	1.5±. 69	2.25±. 91	3.55±. 51	0.000
VAS after 24hr	1.25±. 79	2.1±. 31	3.3±. 47	0.000

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if p <0.05 (CL- 95%).

Table-VI

VRS (Visual Rating Score) of the patients of three groups at different hour after extubation

Background characteristics	Pre-incision group A	Post-incision group B	Control Group C	p-value
VRS after 4hr	0.9±. 45	1.1±. 45	1.6±. 50	0.000
VRS after 8hr	0.85±. 37	1.15±. 49	1.65±. 49	0.000
VRS after 12hr	0.95±. 39	1.25±. 44	1.75±. 44	0.000
VRS after 24hr	0.8±. 41	1.15±. 37	1.75±. 44	0.000

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if p <0.05 (CL- 95%).

Table-VII

Sedation Score (SS) of the patients of three groups at different hour after extubation

Period	Pre-incision (Group-A)	Post-incision (Group-B)	Control (Group-C)	p-value
SS after 4hr	2.55±.51	2.25±.44	2.15±.37	0.017
SS after 8hr	2.7±.47	2.3±.47	2.15±.37	0.001
SS after 12hr	1.6±.50	1.6±.50	1.25±.44	0.037
SS after 24hr	1.2±.41	1.1±.31	1.00±00	0.112

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if p <0.05 (CL- 95%) and highly significant if P<0.001.

Table-VIII

Complications (Nausea, Vomiting, Delirium and Hallucination) of the patients of three groups.

Complications	Group	Incidence	F-value	p-value
Nausea	Group-A	8	0.459	0.634
	Group-B	7		
	Group-C	2		
Vomiting	Group-A	2	0.157	0.857
	Group-B	2		
	Group-C	3		
Delirium	Group-A	4	3.595	0.034
	Group-B	6		
	Group-C	1		
Hallucination	Group-A	2	2.280	0.112
	Group-B	4		
	Group-C	0		

Values are expressed as Mean±SD. Data were analyzed by ANOVA.
Values are regarded as significant if $p < 0.05$ (CL-95%)

DISCUSSION:

Preemptive analgesia means - analgesia given before any painful stimulus has effects that outlast the presence of the analgesic in the body[2]. The aim of such treatment is to prevent the spinal cord from reaching a hyper excitable state in which it responds excessively to afferent input[4-5].

In one study, Tverskoy, et al have studied ketamine 2mg/kg as a preemptive analgesic. In their study 95% of the patients were nauseated, hallucination occurred in 89%, and delirium presented in 92%. In our study, the incidence of hallucination and delirium were more in Group A and Group-B, but far less than the study done by Tveskoy. In Group A, four patients (20%) developed delirium, two patient (10%) developed hallucination, eight patients (40%) nauseated and two patient (10%) vomited out of 20 patients. In Group-B, six patients developed delirium (30%), four patients hallucination (20%), seven (35%) patients nauseated and two (10%) patients vomited.

These studies signify, that the side effects like nausea, vomiting, delirium & hallucination were related with ketamine and low dose ketamine is more appropriate for preemptive analgesia.

Our study indicate that the preemptive administration of ketamine markedly decreases the wound hyperalgesia and that this effects outlasts the direct analgesic action of this drug. This results can be regarded as a clinical corroboration of experimental findings of Woolf and Well. who reported that in rat, hyperalgesia produced by electrical stimulation of a c-fibres can be prevented by a relatively low dose of morphine at a time when a much higher dose is required to suppress established hyperalgesia[6]. Our result with ketamine is also compatible with the Woolf and Thompson where preemptive analgesia suppress the NMDA receptors and low dose of analgesic was required for post injury hyperalgesia in rat[7].

Results of this study demonstrated that the addition of low dose ketamine in general anaesthesia delays the first request for analgesic (Group-A, 68.4±6.4 min, Group-B, 37.4±3.3 min and Group-C, 18.9±2.1 min) in the immediate postoperative period. During the first 24 hour total opioid consumption was 9.9±0.14 mg/kg in Group-C where as in Group-A, it was 8.6±0.11 mg/kg and in case of Group-B, it was 9.0±0.11 mg/kg. The difference in consumption is statistically significant ($p < 0.001$). The goals of preemptive analgesia are

at first, to prevent or reduce the development of any "memory" of pain stimulus in the central nervous system and, than to rediced the analgesic requirement[8].

In our study, also indirectly support the goal of preemptive analgesia where first call for analgesic was prolonged and less dose of opioid was required for pain relief.

Considering the findings of our study, it can be concluded that low dose Ketamine (0.5mg/kg) acts as a preemptive analgesia with negligible psychosomatic and cardiovascular side effects.

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