Original Article

Effects of preemptive ketamine on postoperative analgesia after total abdominal hysterectomy (TAH) under general anaesthesia

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Abstract

Background *The concept of 'Pre-emptive analgesia' suggest that the best post operative pain management begins preoperatively. Preemptive low dose ketamine is effective in treating post operative pain after total abdominal hysterectomy.*

Objectives *This study was designed to evaluate the analgesic efficacy of preemptive low dose ketamine in treating moderate to severe acute post operative pain in total abdominal hysterectomy surgery under general anesthesia.*

Methods *Sixty patients aged between 35-50 years, weight between 45-65 kg with ASA physical status I & II underwent elective total abdominal hysterectomy under general anesthesia were randomly divided into two groups. In group A, patients received 10 ml of normal saline I/V over 60-90 second before surgical incision. In group B, patients received 0.15 mg/kg ketamine (mixed with 10 ml normal saline) I/V over 60-90 second before surgical incision. Anesthetic technique was standardized & patients were interviewed regularly. Pain score, analgesic consumption, side effects & quality of recovery score were recorded for 24 hours.*

Results *Patient received preemptive ketamine had a statistically significant lower pain score in first 24 hours after operation compared with placebo group. Mean value of first analgesic demand in group A was 25.67±1.60 & group B was 57.33±2.97 & p = 0.00. Mean value of total opioids consumption in group A was 290.00±9.09 & group B was 210.67±7.01 & p = 0.00. Significant differences were observed between two groups regarding first analgesic demand & total analgesic consumption. There were no significant differences between these two groups in respect to haemodynamic variable or side effects.*

Conclusion *Preemptive low dose intra venous ketamine offer a safe, non opioid, well-tolerated analgesia with efficacy in moderate to severe post operative pain & spare opioid consumption in the post operative pain management.*

Key words *Pre-emptive analgesia, ketamine, abdominal hysterectomy*

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Introduction

Pain is a common experience, frequently encountered in clinical practice that is usually associated with actual or impending tissue damage[1]. Surgical procedure causes local tissue damage with consequent release of pain producing substances like prostaglandins, histamine, serotonin, bradykinin, 5-HT, Substance-P & generation of noxious stimuli. Post operative pain, which is a form of acute pain caused by noxious stimulation due to injury, is typically associated with neuro-endocrine stress response that is proportional to pain intensity[2].

The concept of 'Preemptive analgesia' suggests that the best post operative pain management begins preoperatively[3]. So this concept is based on the

assumption that the administration of an analgesic drug before the occurrence of nociceptive input can prevent sensitization and thus improve post operative analgesia. This can be achieved by infiltration of the wound with local anesthetic, central neuronal blocked, or the administration of effective dose of opioids, ketamine or NSAIDs[3].

Sensory neurons are more sensitive to peripheral inputs after activation of C-fibers by a noxious stimuli, a process called "Central sensitization"[4, 5]. Another mechanism activating spinal sensory neurone, 'Wind-up'[6] is observed after repeated stimulation of C- fibers. These sensitization induce c-fos expression in sensory neurons[7] & are associated with the activation of N-methyl-D-aspartate (NMDA) receptors[5-7]. Ketamine is a NMDA receptor antagonist with analgesic properties that may include intercepting nociceptive input, increasing the threshold for nociception and blocking NMDA receptor activation[7].

Opioids are the potent analgesics but has some complications like sedation, respiratory depression, nausea, vomiting and also its cost limit the widely use. NSAIDs also provide good analgesia with absent of side effects like opioids but have side effects like postoperative G.I.T bleeding, depression of platelet function, increased in bleeding time and decreased in renal perfusion. So we choose the drug ketamine which is readily available and inexpensive , used as a preemptive analgesic agent, administered just before skin incision and may reduce analgesic consumption and at the same time reduces the complication of opioids & NSAIDs.

In the present study, preemptive low dose (0.15mg/kg) I.V. ketamine was used to evaluate patient request for first analgesic demand, total pethidine consumption in 24 hours, pain intensity, haemodynamic status, sedation score, recovery status, any complications like nausea, vomiting, hallucination and delirium etc.

Methods

This clinical study was carried out in the Department of Anaesthesia, Analgesia and Intensive Care Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The purpose of the study were clearly explained to each of the subjects and recruited only after they had given written consent. The approval of the University Ethical Clearance Committee of BSMMU was duly taken before carrying out the study. Sixty patients aged between 35-50 years, weight between 45-65 kg with ASA physical status I & II underwent elective total abdominal hysterectomy under general anesthesia were randomly divided into two groups (30 in each group). Randomizations were done using card sampling.

Patients were excluded if they refuses to take part in the study, history of hypertension (HTN), ischemic heart disease (IHD), valvular heart diseases, neurological & psychiatric disorders, history of hypersensitivity of ketamine, had taken chronic analgesic medication due to chronic pain syndrome, or were active substance abusers.

100mm (10cm) visual analogue scale (VAS) & verbal rating score (VRS) was introduced to every patient to assess the level of postoperative pain. All patients preoperative baseline data like pulse rate, blood pressure, respiratory rate & arterial oxygen saturation (SPO_2) were measured & recorded.

In group A, patients received 10 ml of normal saline I/V over 60-90 second before surgical incision. In group B, patients received 0.15 mg/kg ketamine (mixed with 10 ml normal saline) I/V over 60-90 second before surgical incision.

In the operating room, I/V channel for routine infusion was started & routine monitor attached for measuring pulse, blood pressure and arterial oxygen saturation (SPO_2). All patients received same general anesthesia. After pre oxygenation for 3 min with 100% O_2 induction was done by thiopental sodium 5mg/kg & fentanyl 2μg/kg IV. vecuronium bromide 0.1mg/kg was used to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide , oxygen (70:30) & halothane as required. The lungs were mechanically ventilated. Blood pressure & heart rate was recorded immediately before & every 3 minute during operation. Dosages of vecuronium were repeated as required to maintain muscle relaxation. At the end of surgery, anesthesia was discontinued & residual neuromuscular blockade was antagonized by neostigmine (40μg/kg) &

atropine 20µg/kg. Extubation was done when patient became fully awake.

After complete recovery from anesthesia, the patient was shifted to postoperative ward or recovery room. In postoperative ward, all patients were treated with inj. pethedine 1.5mg/kg IM on demand. As rescue analgesic 10mg IV inj. pethedine was given each time when the pain intensity exceeded the level of 20mm on VAS. The time of first requested analgesic medication (TFA) was recorded. Total pethedine requirements in 24 hours in both groups were also recorded. Postoperatively all patients were interviewed in a standardized fashion by trained nurses who were blind to the study drug. The severity of pain was assessed by VAS at 15 minutes interval for the first hour & then at 2^{nd}, 4^{th}, 6^{th}, 12^{th}, 18^{th} & 24^{th} hours after arrival in the post operative ward. Sedation score as 1-alert, 2-asleep, alert after arousal, 3- asleep, drowsy after arousal, 4-asleep, difficult to arouse & 5-unarousable, was also assessed in same time interval. Respiratory rate, pulse rate, systolic & diastolic blood pressure & arterial oxygen saturation (SPO_2) were recorded in the post operative period in same interval for 24 hours. The incidence of nausea, vomiting, hallucination, bad dream or any other side effects were recorded.All results were expressed as mean ± standard error of mean (SEM) or in frequencies as applicable. The result were compiled and analyzed using Unpaired 't' test, Chi- square (x^2) or ANOVA as appropriate. Results were considered statistically significant if $p < 0.05$ (Confidence Interval CI- 95%).

Results

The studied groups were statistically matched for age (p=0.928) & weight (p=0.477).Mean value of first analgesic demand in group A was 25.67±1.60 and group B was 57.33±2.97 . Mean value of total opioids consumption in group A was 290.00±9.09 & group B was 210.67±7.01. Significant differences were observed between two groups regarding first analgesic demand(p=0.00) & total analgesic consumption(p=0.00). Complication like nausea, vomiting, delirium & hallucination between the studied groups were not significant in post operative period. There was no significant difference of pulse rate (Table IV) at different hours between two groups except at 1 hour after extubation in post operative period; p was 0.008 at that time. Regarding systolic blood pressure (Table V), there was no significant difference at different hours between two groups except during incision where p value was 0.016. There was no significant difference of diastolic blood pressure(Table VI) at different hours between two groups.

There was significantly difference in VAS at different hours(Fig-1) after extubation between two groups ($p < 0.05$), except in the 4^{th} hour after extubation when it was not significant. ($p = 0.375$). Regarding VRS (Fig 2), there was highly significant difference in VRS at different hours after extubation between two groups($p < 0.05$), except in the 12^{th} hour after extubation when it was not significant. ($p = 0.713$). Regarding Sedation score (Table VII), there was no significant difference in sedation score ($p > 0.05$), except in the 18^{th} hour after extubation when it was significant. ($p = 0.018$).

Table I *Demographic data*

Group/ Variable	Group-A (n =30)	Group-B (n =30)	P-value
Age (Years)	41.37±0.84	41.47±0.70	0.928
Weight (Kg)	55.47±1.09	54.30±1.21	0.477

Values are expressed as Mean ± SEM. Between groups analyses were done by t-test. Values are expressed as significant if p<0.05 (CI -95%).

Table II *First analgesic demand & total pethidine consumption*

Background Characteristics	Group-A (n =30)	Group-B (n =30)	P-value
First analgesic demand (min)	25.67±1.60	57.33±2.97	0.000
Total opioids consumption (mg) in 24 hours	290.00± 9.09	210.67± 7.01	0.000

Values are expressed as Mean ± SEM. Between groups analyses were done by t-test. Values are expressed as significant if p<0.05 (CI -95 %).

Table III *Complications (nausea, vomiting, delirium, hallucination) of the studied groups:*

Complication	Group-A	Group-B	P- value
Nausea	3	4	1.00
Vomiting	3	2	1.00
Delirium	0	0	-
Hallucination	0	0	-

Values are expressed as Mean ± SEM. Between groups analyses were done by t-test. Values are Expressed as significant if p<0.05 (CI -95 %).

Table IV *Changes in Pulse rate (beat / min) at different period of the studied groups*

Group	Baseline	During induction	During incision	During incision	1 hr after extubation	4 hrs after extubation	8 hrs after extubation	12 hrs after extubation	18 hrs after extubation	24 hrs after extubation
Group- A	74.47	102.00	100.37	104.70	90.83	82.07	79.40	80.37	79.20	79.07
	±1.24	±1.23	±1.00	±1.30	±0.98	±1.00	±1.23	±1.16	±1.17	±1.10
Group- B	72.83	99.67	99.00	104.37	86.93	83.07	81.63	82.43	78.77	78.33
	±1.13	±1.01	±0.90	±1.06	±1.02	±1.03	±1.34	±0.99	±1.36	±1.04
P value	0.333	0.148	0.313	0.844	0.008	0.489	0.225	0.182	0.810	0.630

Values are expressed as mean ± SEM. Between groups analysis was done by t-test. Analysis between group, time interaction was done by ANOVA. Values are significant when p<0.05 (CI-95%).

Table V *Changes in Systolic blood pressure (mmHg) at different period of the studied groups:*

Group	Baseline	During induction	During incision	During extubation	1 hr after extubation	4 hrs after extubation	8 hrs after extubation	12 hrs after extubation	18 hrs after extubation	24 hrs after extubation
A	120.33	147.00	112.33	143.67	128.83	125.17	124.00	125.00	121.33	123.83
	±1.89	±2.26	±1.85	±1.82	±1.53	±1.54	±1.65	±1.75	±1.90	±1.28
B	120.50	150.00	119.33	148.33	128.50	123.67	122.67	126.00	117.33	124.83
	±1.65	±1.84	±2.11	±2.14	±1.76	±1.40	±1.45	±1.39	±1.22	±1.19
P	0.947	0.307	0.016	0.102	0.887	0.474	0.547	0.655	0.082	0.569

Values are expressed as mean ± SEM. Between groups analysis was done by t-test. Analysis between group, time interaction was done by ANOVA. Values are significant when p<0.05 (CI-95%).

Table VI *Changes in Diastolic Blood pressure (mmHg) at different period of the studied groups:*

Group	Baseline	During induction	During incision	During extubation	1 hr after extubation	4 hrs after extubation	8 hrs after extubation	12 hrs after extubation	18 hrs after extubation	24 hrs after extubation
A	74.67	94.83	72.17	91.50	79.17	75.83	75.33	77.00	74.33	75.50
	±1.20	±1.28	±0.98	±1.27	±0.99	±0.87	±1.42	±1.03	±1.57	±0.84
B	75.67	95.00	75.83	94.33	78.83	74.50	76.00	79.50	72.67	76.17
	±0.95	±1.17	±1.92	±0.95	±1.28	±1.13	±1.36	±0.97	±0.95	±0.89
P	0.516	0.924	0.094	0.080	0.838	0.354	0.736	0.083	0.367	0.588

Values are expressed as mean ± SEM. Between groups analysis was done by t-test. Analysis between group, time interaction was done by ANOVA. Values are significant when p<0.05 (CI-95%).

Table VII *Changes in Sedation score at different period of the studied groups*

Group	After arrival	1 hour after extubation	4 hour after extubation	8 hour after extubation	12 hour after extubation	18 hour after extubation	24 hour after extubation	F	P
A	2.33	1.87	1.40	1.53	1.33	1.53	1.20	15.10	0.000
	±0.11	±0.11	±0.09	±0.09	±0.09	±0.11	±0.07		
B	2.67	1.93	1.60	1.40	1.47	1.20	1.07	31.10	0.000
	±0.13	±0.13	±0.09	±0.09	±0.09	±0.07	±0.05		
t	1.953	0.391	1.555	1.027	1.046	2.438	1.523		
P	0.056	0.697	0.125	0.309	0.300	0.018	0.133		

Values are expressed as mean ± SEM. Between groups analysis was done by t-test. Analysis between group, time interaction was done by ANOVA. Values are significant when p<0.05 (CI-95%).

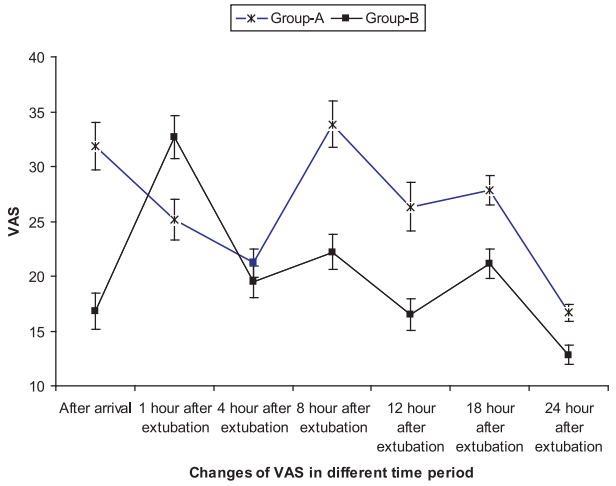

Fig 1 *Changes of VAS in different time period.*
** Statistically significant – (p< 0.05)*

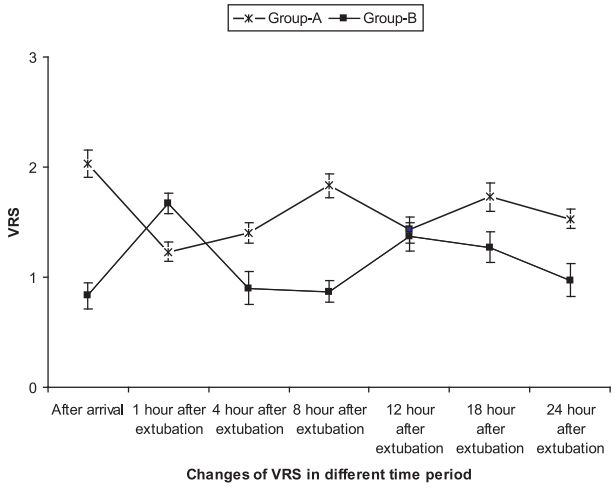

Fig 2 *Change of VRS in different time period.*
** Statistically significant – (p< 0.05)*

Discussion

Pain which is often inadequately treated, accompanies more than 23 million surgical procedures performed each year and may persist long time after tissue heals. Preemptive analgesia an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. Surgery offers the most promising setting for preemptive analgesia because the timing of noxious stimuli is known. When adequate drug doses are administered to appropriately selected patients before surgery, intravenous opiates, local anesthetic infiltration, nerve block, subarachnoid block and epidural block offer benefits that can be observed as long as one year after surgery. The most effective preemptive analgesic regimens are those that are capable of limiting sensitization of the nervous system throughout the entire perioperative period[8].

Low dose preemptive ketamine (0.15mg/kg) when administered I/V just before (60-90 sec) surgical incision as an adjuvant to opioids, have an important role to play in the treatment of acute postoperative pain and this could be explained by prevention of central sensitization prior to tissue injury. The results of the study demonstrate that addition of low dose ketamine to general anaesthesia before surgical incision in total abdominal hysterectomy patients, delays the first request for pethidine (group A 25.67±1.60 min, Group B 57.33±2.97 min) in the immediate postoperative period. P value of first analgesic demand was 0.000.During the first 24hours, total pethidine consumption was 290.00±9.09 mg in group A and 210.67±7.01 mg in group B, which was about 27% lower than group A. It proved that, ketamine acts as preemptive analgesic with also showed significant opioid sparing effects.

Roytblas et al.[9], who used low dose Ketamine (0.15mg/kg) in addition to general anaesthesia in cholecystectomy patients and observed that the cumulative dose of morphine reduced by about 40% in the Ketamine group. Tvers Koy et al.[10] found a decrease in wound hyperalgesia in patient undergoing inguinal herniorraphy with a preemptive ketamine regimen consisting of 20 ìg/kg initial dose followed by a continuous infusion rate of 20 ìg/kg/min. Elia et al. found that with Ketamine giving a clear decrease in 24 hours cumulative morphine consumption with a WMD (weighted mean difference) of -15.7 mg. He also found that Ketamine treatment did not reduce morphine related adverse effect.

Results of pain scores (VAS/VRS) in the post operative room indicated that patient in the control group (group A) had much more pain than in the study group (group B) throughout the 24 hours of assessment. The group B had significantly lower pain score compared with group A (P<0.05). Twenty one of 30 trails found that preemptive Ketamine reduced rescue analgesic requirements or pain intensity, Ketamine was reported to give

a 30-40% reduction of rescue analgesics. Acute pain results in sympathetic over activity which is manifested by increase in heart rate, blood pressure, peripheral resistance and cardiac output[11]. In the present study, heart rate and blood pressure remained stable throughout the study period between two groups and there were no significant different between two groups. Respiratory rate, sedation score, arterial oxygen saturation (SPO_2) in both groups also remained within safe range and were not statistically significant.

Elia 2005 found no decrease in PONV on analysis data from 391 patients treated with Ketamine and 284 patients receiving control. R.F. Bell 5 et al.[12] analyzed on 705 patients treated with Ketamine and 578 patient receiving control, showed a significant reduction of nausea and vomiting in Ketamine treated patient. The observed reduction in PONV may be due to pethedine- sparing effect.In the present study there was no significant difference in the incidence of PONV between two groups.

We also found that no patient in either group had signs or symptoms of psychomimetic phenomenon or incidence of hallucination delirium or bad dream. This findings supports the finding of Roytblat L, et al.[57]. Several investigations have reported a decrease in the incidence of psychomimetic phenomenon when ketamine is used in conjunction with sedative-hypnotic (thiopental), general anaesthetics (halothane, N_2O) and benodiazepines[13] . All factors were observed in this study.

This study demonstrated that low dose Ketamine (0.15mg/kg) given before surgical incision in elective total abdominal hysterectomy patients under general anesthesia, has a preemptive analgesic effect that cause much reduction in the postoperative analgesic requirements.

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