ORIGINAL ARTICLE

Comparison of two analgesic doses of Ketamine on haemodynamic response to surgical incision"

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ABSTRACT

Background: Surgical procedures stimulate patient's haemodynamic system and bring about significant clinical changes in heart rate (H. R) and systolic blood pressure (SBP). These variables can be used to assess depth of anesthesia. Tachycardia is strongly linked to sympathetic stimulation along with concomitant rise in blood pressure and may cause decompensation in patients with heart failure. Various drugs are used to control likelihood of these responses by use of anaelgesics. This study was conducted to compare haemodynamic response with two doses of Ketamine to surgical incision.

Material and Methods: Sixty Patients were randomly divided into two groups using random numbers table. Group A received ketamine 0.25 mg/Kg whereas group B received ketamine 0.5mg/kg. After setting up the monitors, first value of HR and SBP were taken as baseline value. Propofol 1% in a dose of 2 mg/kg and rocuronium in a dose of 0.6 mg/kg were given I/V for induction in both groups and maintained on sevoflurane. Intravenous ketamine was given according to the assigned group.HR and SBP were recorded before induction as the baseline values, before the administration of ketamine, every minute after ketamine till the surgical incision (SI) and the following five minutes; then at ten and twenty minutes after SI. Percentage change in HR and SBP from the baseline will be calculated for all the readings following administration of ketamine.

Results: The results of present study showed that both groups were comparable regarding hemodynamic response after ketamine at 1,2,3,4 and 5 min and their hemodynamic responses were also comparable at 1,2,3,4,5,10 and 20 min after SI. Hemodynamic response to SI was decreased in both groups but there was no statistically significant difference between the two groups.

Conclusion: There is no statistically significant difference in both doses of ketamine (0.25mg/kg and 0.50mg/kg) to blunt the haemodynamic response to surgical incision, so lower dose (0.25mg/kg) of Ketamine can be used to avoid the side effects associated with higher doses of ketamine.

Key words: Ketamine, Haemodynamic Response, Surgical Incision.

INTRODUCTION

Surgical stimulation induces clinically significant changes in haemodynamic variables that can also be used to assess the depth of anaesthesia[1].Tachycardia is strongly linked to the degree of sympathetic stimulation and is also a risk factor for perioperative myocardial ischemia/infarction[2]. Concomitant rise in blood pressure increases wall stress and may cause decompensation in the patients with heart failure [2]. Tachycardia and hypertension are the manifestations of pain on surgical incision, which if not controlled, can cause harmful effects on the body. Suppression of the pain pathways (antinociception) reduces stress responses during surgery[3].

Various pharmacological strategies have been suggested to control haemodynamic responses induced by nociceptive stimuli. Opioids like fentanyl, alfentanil and remifentanil are widely used to attenuate the haemodynamic responses[1, 4] but opioids will, however, increase the chances of post operative nausea and vomiting (PONV)[5]. Increasing depth of anesthesia can also decrease the hemodynamic response to surgical stimuli but on the other hand has its haemodynamic consequences like decrease in heart rate and significant hypotension[6].

N-methyl-d-aspartate (NMDA) receptors which are stimulated by painful stimuli play an important role in the generation and maintenance of pain. NMDA receptor stimulation is not blocked by opioids [7]. Ketamine, a powerful NMDA receptor antagonist and a potent analgesic, is used to provide analgesia and sedation during intraoperative and postoperative periods[8,9].Ketamine in anaesthetic doses cause tachycardia and hypertension. These changes are not apparent in analgesic dose[10]**.** Ketamine has

been shown to provide analgesia without increasing the risk of PONV or hypotension[9].

Assuming that the rise in heart rate and blood pressure in response to skin incision is due to pain, which can be modulated by short acting opioids, an analgesic dose of ketamine which is 0.25-0.5 mg/kg [9],should also obtund this response to skin incision. In an attempt to test the hypothesis that ketamine in this dose prevents tachycardia and hypertension on skin incision, we shall compare 0.25 mg/kg ketamine with a higher dose; that is 0.5 mg/kg. We will also compare the haemodynamic response to the administration of the two doses of ketamine as a secondary outcome measure.

MATERIAL AND METHODS

Study Design: Quasi experimental study.
Setting: Hameed Latif hospital, Lahore, which is a tertiary care hospital, affiliated with The College of Physicians and Surgeons of Pakistan.
Duration of Study: Study was completed in 6 months from – to-------..
Sample Size: Sixty patients fulfilling inclusion criteria; 30 patients in each group were enrolled after obtaining informed consent.
Sampling Technique: Non-probability, convenience sampling.

INCLUSION CRITERIA

- American Society of Anaesthesiologists (ASA) I and II patients undergoing elective surgery under general anaesthesia with Laryngeal Mask Airway (LMA).
- Age between 18-60 years.
- Patients undergoing for elective surgery for gynaecological, general and orthopaedic procedures of more than 30 minutes duration.

EXCLUSION CRITERIA

- Hypertensive patients.
- Patients with psychiatric disorders.
- Patients on beta blockers or any other drug that can interfere with the haemodynamic responses.

DATA COLLECTION PROCEDURE:

After approval from ethical committee of the hospital and a written informed consent, admitted patients fulfilling the inclusion criteria will be enrolled. Patients were randomly divided into two groups using random numbers table. Group A was given ketamine in a dose of 0.25 mg/Kg whereas group B will receive ketamine in a dose of 0.5mg/kg. All patients were pre-medicated with midazolam in a dose of 0.05mg/kg Intravenous (I/V) 15 minutes before shifting to operation theatre.

Intraoperative monitoring included non-invasive blood pressure, heart rate, electrocardiography, pulse-oximetry, capnography and inhalational agent monitor. After setting up the monitors, first value of HR and SBP will be taken as baseline value.

Propofol 1% in a dose of 2 mg/kg and rocuronium in a dose of 0.6 mg/kg was given I/V at induction in both groups. After 1 minute of ventilation with oxygen 2 litre/minute and sevoflurane with dial concentration of 8%, using a face mask, appropriate sized LMA was placed. Anaesthesia was maintained with sevoflurane in 100% oxygen having an end tidal concentration of 2.5%, with intermittent positive pressure ventilation (IPPV).

A period of 5 minutes was given to allow the haemodynamic changes due to LMA insertion to return to baseline. If the change in the parameters was greater than 20% from baseline, the patient would be excluded from the study.

Intravenous ketamine was then given according to the assigned group. A period of 5 minutes was allowed for any change due to ketamine to settle before giving the surgical incision (SI).

HR and SBP were recorded before induction as the baseline values, before the administration of ketamine, every minute after ketamine till the SI and the following five minutes; then at ten and twenty minutes after SI. Percentage change in HR and SBP from the baseline was calculated for all the readings following administration of ketamine. The findings were entered on a specially designed proforma (attached).

RESULTS

The results of present study showed that both groups were comparable regarding haemodynamic response after ketamine at 1,2,3,4 and 5 min and their hemodynamic responses were also comparable at 1,2,3,4,5,10 and 20 min after surgical incision. Haemodynamic response to surgical incision was decreased in both groups but there was no statistically significant difference between the two groups. Hemodynamic response categorized as;
-4= Lowest thru -30.
-3= -29.99 thru -20.

-2= -19.9 thru -10.
-1= -9.99 thru -0.01.
0=0
1= 0.01 thru 10.
2= 10.01 thru 20.
3= 20.01 thru 30.
4= 30.01 thru Highest.

HR 5 min after Induction:
Comparison of HR between two groups (% change from baseline, categorized)

Categories (% change in HR)	Count/%	Study groups		Total
		Group A	Group B	
-4	Count	0	1	1
	%	0%	3.33%	1.66%
-3	Count	0	1	1
	%	0%	3.33%	1.66%
-2	Count	0	4	4
	%	0%	13.33%	6.66%
-1	Count	4	6	10
	%	13.33%	20%	16.66%
0	Count	0	0	0
	%	0%	0%	0%
1	Count	5	4	9
	%	16.66%	13.33%	15%
2	Count	3	6	9
	%	10%	20%	15%
3	Count	8	6	14
	%	26.6%	20%	23.33%
4	Count	10	2	12
	%	33.33%	6.66%	20%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 13.13 P value = 0.07 (> 0.05) No statistically significant difference regarding % change in HR 5 min after induction between two groups				

HR 5 min after Ketamine:
Comparison of HR between two groups (% change from baseline, categorized)

Categories (% change in HR)	Count/%	Study groups		Total
		Group A	Group B	
-4	Count	0	1	1
	%	0%	3.33%	1.66%
-3	Count	2	2	4
	%	6.66%	6.66%	6.66%
-2	Count	2	8	10
	%	6.66%	26.66%	16.66%
-1	Count	0	4	4
	%	0%	13.33%	6.66%

0	Count	0	1	1
	%	0%	3.33%	1.66%
1	Count	8	2	10
	%	26.66%	6.66%	16.66%
2	Count	6	5	11
	%	20%	16.66%	18.3%
3	Count	5	3	8
	%	16.66%	10%	13.33%
4	Count	7	4	11
	%	23.33%	13.33%	18.33%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 14.609 P value = 0.067 (> 0.05) No statistically significant difference regarding % change in HR 5min after ketamine between two groups				

HR5 min after Incision:
Comparison of HR between two groups (% change from baseline, categorized)

Categories (% change in HR)	Count/%	Study groups		Total
		Group A	Group B	
-4	Count	1	1	2
	%	3.33%	3.33%	3.33%
-3	Count	0	3	3
	%	0%	10%	5%
-2	Count	4	4	8
	%	13.33%	13.33%	13.33%
-1	Count	9	5	14
	%	30%	16.66%	23.33%
0	Count	2	0	2
	%	6.66%	0%	3.33%
1	Count	1	6	7
	%	3.33%	20%	11.66%
2	Count	4	3	7
	%	13.33%	10%	11.66%
3	Count	4	5	9
	%	13.33%	16.66%	15%
4	Count	5	3	8
	%	16.66%	10%	13.33%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 10.468 P value = 0.234 (> 0.05) No statistically significant difference regarding % change in HR 5 min after incision between two groups				

SBP 5 min after induction
Comparison of SBP between two groups (% change from baseline, categorized)

Categories (% change in SBP)	Count/%	Study groups		Total
		Group A	Group B	
-4	Count	1	1	2
	%	3.33%	3.33%	3.33%
-3	Count	3	3	6
	%	10%	10%	10%
-2	Count	11	4	15
	%	36.66%	6.66%	25%
-1	Count	5	13	18
	%	16.66%	43.33%	30%
0	Count	0	0	0
	%	0%	0%	0%
1	Count	6	6	12
	%	20%	20%	20%
2	Count	2	2	4
	%	6.66%	6.66%	6.66%
3	Count	2	1	3
	%	6.66%	3.33%	5%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 7.15 P value = 0.30 (> 0.05) No statistically significant difference regarding % change in SBP 5 min after induction between two groups.				

SBP 5 min after Ketamine
Comparison of SBP between two groups (% change from baseline, categorized)

Categories (% change in SBP)	Count/%	Study groups		Total
		Group A	Group B	
-4	Count	1	1	2
	%	3.33%	3.33%	3.33%
-3	Count	7	4	11
	%	23.33%	13.33%	18.33%
-2	Count	5	8	13
	%	16.66%	26.66%	21.66%
-1	Count	7	7	14
	%	23.33%	23.33%	23.33%
0	Count	2	1	3
	%	6.66%	3.33%	5%
1	Count	3	5	8
	%	10%	16.66%	13.33%

2	Count	4	2	6
	%	13.33%	6.66%	10%
3	Count	1	0	1
	%	3.33%	0%	1.66%
4	Count	0	2	2
	%	0%	6.66%	3.33%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 6.010 P value = 0.646 (> 0.05) No statistically significant difference regarding % change in SBP 5 min after ketamine between two groups.				

SBP 5 min after incision
Comparison of SBP between two groups (% change from baseline, categorized)

Categories (% change in SBP)	Count/%	Study groups		Total
		Group A	Group B	
-3	Count	3	3	6
	%	10%	10%	10%
-2	Count	4	5	9
	%	13.33%	16.66%	15%
-1	Count	10	7	17
	%	33.33%	23.33%	28.33%
0	Count	0	1	1
	%	0%	3.33%	1.66%
1	Count	9	6	15
	%	30%	20%	25%
2	Count	4	6	10
	%	13.33%	10%	16.66%
3	Count	0	2	3
	%	0%	6.66%	5%
Total	Count	30	30	60
	%	50%	50%	100%
Statistical analysis Chi-square = 4.641 P value = 0.591 (> 0.05) No statistically significant difference regarding % change in SBP 5 min after incision between two groups.				

DISCUSSION

The present study showed that both groups were comparable regarding hemodynamic response after ketamine at 1,2,3,4 and 5 min and their hemodynamic responses were also comparable at 1,2,3,4,5 10 and 20 min after surgical incision. The study did show a DECREASE in Heart Rate with 0.5 mg/kg ketamine (Group B) at 3 minutes and 5 minutes after ketamine but it was NOT significant statistically (p=0.088 and 0.067 , respectively).

Multiple studies have been performed to blunt hemodynamic response to surgical incision in which inhalational agents, opioids, beta blockers and local anesthetics have been used. We have assessed the efficacy of two doses of ketamine i.e; 0.25mg/kg and 0.5mg/kg for blunting the hemodynamic response after surgical incision. The results of our study were consistent with others.

Kobayashi S et al studied the effect of xenon in combination with sevoflurane anesthesia on the catecholamine and hemodynamic responses to surgical noxious stimulation in humans. They also found that combination anesthesia using xenon and sevoflurane suppressed the plasma Epinephrine concentration and hemodynamic response after surgical incision more effectively than sevoflurane anesthesia alone [12]. In another study Nakata Y, et al, also evaluated the hemodynamic suppressive effects of xenon in combination with sevoflurane at surgical incision in patients undergoing surgery. They concluded that Xenon and nitrous oxide in combination with sevoflurane can reduce hemodynamic responses to surgical incision compared with sevoflurane alone [13]. Nakata Y et al again evaluated suppressive effects of xenon (Xe) and nitrous oxide (N2O) on cardiovascular responses. The authors compared the MAC-BAR values of sevoflurane when administered with Xe or N2O. They concluded that 1 MAC Xe has a more potent suppressive effect on cardiovascular responses to incision than 0.7 MAC Xe or N2O but Xe and N2O have a similar suppressive effect at 0.7 MAC[14]. However Xe being quite expensive[11] cannot be used frequently in our set up. Where as we use ketamine which is not such expensive and is readily available everywhere.

Andrea Albertin et al determined the effect site concentration of remifentanil blunting sympathetic responses to tracheal intubation and skin incision during bispectral index (BIS) guided propofol anesthesia. Their study showed that effect site concentrations of remifentanil of 5ng/mL and 2ng/mL were effective in blunting sympathetic responses to tracheal intubation and skin incision in 50% of patients when combined with a BIS-guided target controlled infusion of propofol[1]. In our study we only used ketamine before incision and not before tracheal intubation and we found ketamine effective in blunting the hemodynamic response to surgical incision.

T. katoh et al studied the effect of fentanyl on minimum alveolar concentration which blocked the adrenergic responses to skin incision (MAC BAR) in 50% of children in the presence of 60% nitrous oxide. The MAC BAR of sevoflurane was 1.45 MAC and this was reduced markedly to 0.63 MAC and 0.38 MAC by addition of fentanyl 2 and 4 ug/kg respectively. They finally came up with the conclusion that fentanyl effectively blocked the hemodynamic response to skin incision and reduced the MAC BAR[15]. Hori K, Nagasaka H also compared the effects of fentanyl injected before and after skin incision on the cardiovascular and plasma catecholamine responses to surgical stimulation. Their results indicated that fentanyl depressed cardiovascular and plasma catecholamine responses irrespective of the time of administration, and that the higher dose of fentanyl produced a greater suppression of MAP and HR responses. In addition, the depressant effects on MAP of high-dose fentanyl administered 5 min before skin incision lasted longer than when injected 5 min after incision. At both doses, the opioids attenuated the rise in plasma Epinephrine, but not more[16]. In our study we observed the decrease in hemodynamic response to surgical incision but no statistically significant difference in both study groups.

Johansen and his co workers designed a study to determine whether esmolol, a short-acting $beta_1$ -receptor antagonist, could reduce the propofol concentration required to prevent movement at skin incision. The propofol Cp_{50} with nitrous oxide was 3.85 micro gram/ml. High-dose esmolol infusions was associated with a significant reduction in the Cp_{50} to 2.80microgram/ml ($P < 0.04$). They concluded that esmolol significantly decreased the anesthetic requirement for skin incision[17]. But beta blockers only attenuate cardiovascular response to surgical stimulus and there is no blockade of pain. Where as ketamine is a potent analgesic as well as it reduces the hemdynamic response to surgical stimulus[8,9].

There are certain limitations in our study that is lack of control group and no pre defind fasting and preload as it affects hemodynamics.

CONCLUSION

We concluded that there is no statistically significant difference in both doses of ketamine (0.25mg/kg and 0.50mg/kg) to blunt the haemodynamic response to surgical incision, so we can use lower dose (0.25mg/kg) to avoid the side effects which can be seen with higher doses of ketamine.

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