Effect of Midazolam on Heart Rate in Pediatric Anesthesia

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ABSTRACT:

BACKGROUND :

Midazolam is one of benzodiazepines. It is most lipid soluble as a result has a rapid onset and short duration of action, used in anesthesia for sedation or intravenous induction according to the dose used.

OBJECTIVE:

Is to notice if there is an effect of midazolam on heart rate in pediatric patients with using ketamine as induction agent under general anesthesia.

PATIENTS AND METHODS:

60 peadiatric patients undergoing surgery randomly allocated in 2 groups(A and B). Aneasthesia was standardized for all patients (except addition of Midazolam in sedative dose (0.03 mg/kg) i.v. preinduction to group(B). Heart rate measured preoperatively as abaseline and 5 and 15 minutes after induction.

RESULTS:

Adding midazolam associated with a reduction in HR by an average of 10 beats/min 5 and 15 minutes after induction of anaesthesia. This effect failed to reach the level of statistical significance although it was clinically significant.

CONCLUSION:

Midazolam have well known sedative effect but have no significant effect on heart rate in paediatric patients.

KEYWORDS: midazolam , heart rate , ketamine.

INTRODUCTION:

Tachycardia is an abnormally rapid heart rate. In adults , this is usually defined as >100 beats per minute (bpm). In paediatrics, the normal heart rate varies with age. Therefore, in children the definition of tachycardia is age dependent(1). There are many medications that can cause tachycardia, either by leading to release of catecholamines or by inducing an arrhythmia[1]. In pediatrics cardiac output is 2 to 3 times that of adult to meet the demand of a higher metabolic rate , and it is rate dependent[2].

Cardiovascular changes following i,v. Injection of ketamine are increase in heart rate, cardiac output and pulmonary artery pressure occur over 3-5 min. and then gradually return to base line over the next 10-20 min,[3]Blood pressure is raised and pulse rate increase by myocardial stimulation and rise in plasma noradrenaline[4] due to blockade of uptake by sympathetic nerve endings and central sympathetic stimulation [5].

Midazolam is one of Benzodiazepines which interact with specific receptors in the CNS this binding enhances the inhibitory effect of various neurotransmitters[6].It is most lipid soluble of benzodiazepines as a result has a rapid onset and a short duration of action[7].Lipid soluble substances diffuse readily into cells and therefore throughout body tissues[8] the elimination half –life is 1.5-2 hours ,its metabolites are inactive[9], used for sedation and i.v. induction of anesthesia[5].It causes a slight fall in systemic vascular resistance and arterial blood pressure with little changes in cardiac output[3].Midazolam had the least side effects at the recovery time when used as the pre-anesthetic medication. They also stated that this medication could reduce the anxiety caused by separation from parents or the induction of anesthesia[10]. Control of pain and stress for children is a vital component of emergency medical care[11].

PATIENTS AND METHODS:

This is a comparative study(not blinded) carried out on 60 pediatric patients undergoing elective surgery divided randomly into 2 groups 30 patients in each group. The criteria required a pediatric patient above 1 year age and below 15 years , from both sexes. Excluding patients with

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congenital heart disease or taking any medication for medical disease (excluding antibiotics and any drugs that affect heart rate in any way direct or indirect).
Parents consent taken for use of general anesthesia as usual (as use of sedation preinduction is part of it).
Aneasthesia was standardized for all patients (except addition of Midazolam in sedative dose (0.03 mg/kg) given i.v. preinduction to group B) as followes :
Induction with ketamine 1.5 mg/kg i.v. , sevoflourane 2% , atracurium 0.5 mg/kg and intubation done and controlled ventilation to all patients.
Monitoring of heart rate done for all patients and started before induction and recorded at 3 different time points as followes:
HR1 heart rate before induction and before midazolam (baseline value)
HR2 5 min. after induction
HR3 15 min. after induction

Statistical Analysis:

Statistical significance of differences in mean of a normally distributed variable between 2 groups was tested by Student's independent samples t-test. The statistical significance of paired differences (mean change) was assessed by paired t-test. We assumed the level of statistical significance at P <0.05. All analyzed statistical tests of significance were bilateral.
Cohen's d is a standardized measure of effect size for difference between 2 means, since it has no unit of measurement. Cohen's d = (mean1-mean2) / Pooled SD of the 2 groups. Cohen's d < 0.3 small effect, 0.3-0.7 (medium effect), while 0.8 and higher is a large effect.

$$Cohen's\ d = \frac{\bar{x}_1 - \bar{x}_2}{S_P}$$

$$S_p = \sqrt{\frac{(n_1 - 1)S_1^{\ 2} + (n_2 - 1)S_2^{\ 2}}{(n_1 + n_2 - 2)}}$$

- Where S_p is the pooled standard deviation
- N is the sample size
- X is the sample mean

RESULTS:

The distribution of sexes and different age groups in both study groups is uniform especially age because heart rate is age dependent in pediatric patients. Effect In group A (ketamine alone)as shown in table 1, the heart rate increased by a mean of 11 beats/min after 5 minutes of using Ketamine . This effect failed to reach the level of statistical significance (but have moderately strong effect on Cohen d measure (Cohen's d=0.67)). The final measurement of heart rate after 15 minutes compared to baseline values. The observed mean increase in HR of 4 beats/min was also not significant statistically.
The effect in group B(midazolam + ketamine) as shown in table 2, although the changes in heart rate after 5 minutes of treatment ranged between an increase of 43 and a reduction of 35 beats/min, the mean of these observed changes was almost equal to zero (1 beat / min), which was not significant statistically. The combined effect of Ketamine and Midazolam resulted in almost no consistent effect on HR. The final measurement of heart rate after 15 minutes showed a weak negative effect (Cohen's d=0.25) on heart rate compared to baseline values. There was an obvious reduction in HR be a mean of 6 beats/min. This effect also failed to reach the level of statistical significance.
Comparing the mean change in HR after 5 and 15 minutes between the 2groups shown in figure1. As shown in table 3, adding midazolam would be associated with a reduction in HR by an average of 10 beats/min after 5 minutes of anaesthesia. This effect failed to reach the level of statistical significance.
Table 4 show that adding midazolam would be associated with a comparable reduction in HR by an average of 10 beats/min after 15 minutes of anaesthesia. Again this effect failed to reach the level of statistical significance .

Table 1: The change in heart rate after 5 and 15 minutes of anaesthesia in group A (Ketamine alone).

	HR (Heart rate)				
Control (Ketamine)	at baseline	After 5 minutes	Changes after 5 minutes compared to baseline	After 15 minutes	Changes after 15 minutes compared to baseline
Range	(110 to 165)	(105 to 170)	(-25 to 53)	(104 to 160)	(-40 to 40)
Mean	126	137	11	130	4
SD	14.7	18.6	26.0	15.6	22.4
SE	3.8	4.8	6.7	4.0	5.8
N	30	30	30	30	30
Effect of Ketamine					
Cohen's d =			0.67		0.25
P (paired t-test)			0.12[NS]		0.53[NS]

Table 2: The change in heart rate after 5 and 15 minutes of anaesthesia in groupB (Ketamine with midazolam).

	HR (Heart rate)				
Intervention (Ketamine+Midazolam)	at baseline	After 5 minutes	Changes after 5 minutes compared to baseline	After 15 minutes	Changes after 15 minutes compared to baseline
Range	(91 to 170)	(84 to 180)	(-35 to 43)	(84 to 158)	(-38 to 35)
Mean	127	129	1	121	-6
SD	24.9	25.7	22.1	26.3	17.6
SE	6.4	6.6	5.7	6.8	4.6
N	30	30	30	30	30
Effect of Ketamine+Midazolam					
Cohen's d =			0.06		-0.25
P (paired t-test)			0.8[NS]		0.19[NS]

Table 3: The difference in mean changes in heart rate after 5 minutes of anaesthesia compared to baseline between the 2 groups.

	mean changes in heart rate after 5 minutes of anaesthesia				
	Range	Mean	SD	SE	N
Control (Ketamine)	(-25 to 53)	11	26	6.7	30
Intervention (Ketamine+Midazolam)	(-35 to 43)	1	22.1	5.7	30
Effect of Midazolam (intervention compared to control)					
Difference in mean=	-10				
Cohen's d =	-0.4				
P (independent samples t-test)	0.28[NS]				

Table 3: The difference in mean changes in heart rate after 15 minutes of anaesthesia compared to baseline between the 2 groups.

	mean changes in heart rate after 15 minutes of anaesthesia				
	Range	Mean	SD	SE	N
Control (Ketamine)	(-40 to 40)	4	22.4	5.8	30
Intervention (Ketamine+Midazolam)	(-38 to 35)	-6	17.6	4.6	30
Effect of Midazolam (intervention compared to control)					
Difference in mean=	-10				
Cohen's d =	-0.5				
P (independent samples t-test)	0.18[NS]				

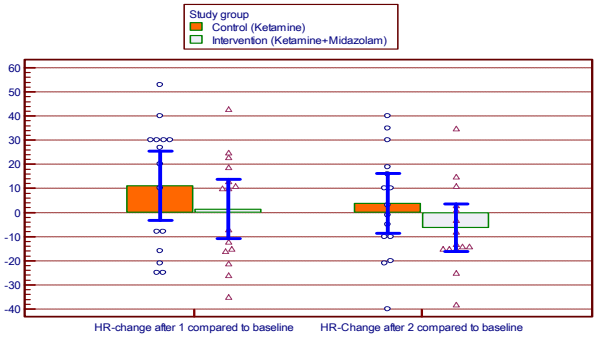

Figure 1: Dot diagram with error bars showing the difference in mean (with 95% confidence interval) change in heart rate after 5 and 15 minutes of anaesthesia between intervention and control groups.

DISCUSSION:

Although basal heart rate is higher than in adults, activation of the parasympathetic nervous system, anesthetic overdose or hypoxia can cause bradycardia and profound reductions in cardiac output [6]. On the other hand tachycardia induced cardiomyopathy which also known as chronotropic cardiomyopathy, is an impairment of the pumping efficiency of the myocardium due to the prolonged periods of a fast heart rate or irregular rhythm [12] it was first descriped by Philips and Levine in 1949 [13] and can occur at any age [14]. If the tachycardia can be abolished the heart muscle can recover after some time [15]). So controlling factors causing tachycardia as important as controlling factors causing bradycardia.

This study show in group A(control group) the heart rate increased by a mean of 11 beat per minute(bpm) after 5 min. and a mean of 4 bpm after 15 min., although both failed to reach the level of ststistical significance but the change after 5 min. evaluated as a moderately strong effect (Cohen's d=0.67).This increase can be attributed to injection of ketamine which cause increase in heart rate occur over 3-5 min. and return gradually to baseline after 10-20 min. [4] and rise in heart rate occur about 14 seconds after the start of laryngoscopy and becomes maximal after 30-45 seconds of direct laryngoscopy[16].

In group B (intervention group) where midazolam added to the control anesthetic management the mean of the observed changes of heart rate after 5 min. was almost equal to zero (1 bpm) which is not significant statistically and after 15 min. reduction of 6 bpm. from baseline.

Comparing the mean change in HR after 5 and 15 minutes between the intervention and control group shown in table 3, adding Midazolam to ketamine would be associated with a reduction in HR by an average of 10 beats/min after 5 minutes of anaesthesia. This effect failed to reach the level of statistical significance(although was evaluated as a moderately strong effect on Cohen d measure).

In the same context, adding Midazolam to ketamine would be associated with a comparable reduction in HR by an average of 10 beats/min after 15 minutes of anaesthesia (table4). Again this effect failed to reach the level of statistical significance .

CONCLUSION:

Midazolam has no statistical significant effect in controlling increased heart rate in peadiatric patients during anesthesia .

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