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Research Article

HIGH DOSES OF KETAMINE INFLICT MYOCARDIAL INJURY AND CAUSE CHANGES IN THE RELATIVE BODY WEIGHT TO HEART OF ADULT ALBINO WISTAR RATS

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ABSTRACT

Objective: Ketamine is widely used as an anesthetic agent in surgery and emergency medicine. It is also used for procedural sedation, treatment of depression, pain management, and sometimes as a recreational drug. These uses, however, have recommended doses to prevent myocardial injury. This study, therefore, was designed to investigate the level of injury on the myocardium following the administration of high doses of ketamine and to determine the relative body weight to heart weight of the experimental animals.

Method: A total of 12 male albino Wistar rats were used and grouped into four including the control group. They were weighed daily and administered 100 mg, 150 mg, and 200 mg/kg/body weight of ketamine intraperitoneally for 2 weeks and weighed again. Experiment was terminated after 14 days and animals were sacrificed and the heart harvested for analysis.

Results: Ketamine caused a significant myocardial injury with increase in the doses in different groups by causing inflammation, hypertrophy, vacuolar degenerative changes, atrophy, and extensive hemorrhage around the myocytes. Weight differentiation was noticed in all experimental groups with heart weight contributing to the total body weight by 1.63%, 1.7%, and 1.2% for the 100 mg, 150 mg, and 200 mg/kg/body weight of ketamine groups, respectively.

Conclusion: Higher doses of ketamine cause significant myocardial injury as well as differential changes in body weight and heart weight in experimental animals.

Keywords: Myocardium, Ketamine, Myocardial injury, Cardiac myocytes, Relative body weight.

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INTRODUCTION

Ketamine has been in clinical use since 1970 and it is widely used as an anesthetic agent in surgery and emergency medicine [1]. It is a unique intravenous (IV) anesthetic that produces a wide spectrum of pharmacological effects including sedation, catalepsy, somatic analgesia, bronchodilation, and sympathetic nervous system stimulation. It is widely used as an anesthetic agent in surgery and emergency medicine [2].

Ketamine is a drug used for procedural sedation, consisting of two tropical enantiomers, (S)- and (R)- ketamine [3]. It acts primarily through blockades of N-methyl-D-aspartates type glutamate receptors to provide sedation [4].

Ketamine is a well-known dissociative anesthetic used medically for induction and maintenance of anesthesia. It is also used as a treatment for depression, pain management tool, and sometimes, as a recreational drug [5].

It has been half a century since ketamine was widely known to medical professionals around the world as a safe anesthetic and sedation drug and since it was used in the first randomized controlled trial (treatment-resistant depression [TRD]), ketamine repeatedly has been shown to be effective in TRD [20]. Despite the growing evidence of its efficacy, a recent consensus statement from the American Psychiatric Association clearly lines out that data are missing for selecting patients who might benefit from this treatment option [19]. Furthermore, the increased use of ketamine as a recreational drug at rave party has raised lots of social concern, severe addictive practices induced by ketamine abuse are very difficult to control and excite abusers to progressively increase ketamine doses [6,7]. Direct negative inotropic effect of ketamine is usually overshadowed by central sympathetic stimulation, which leads to an increase in systemic blood pressure, heart rate, cardiac output, and myocardial oxygen consumption [9]. Other undesired effects reported by illicit users include vertigo, emmetropia, dysarthria, angina pectoris, and so forth [8]. However, some plants that inhibit glutaminergic signaling, such as *Burseraceae* [11], may reduce the adverse effects of ketamine, but it is unclear whether these plants also can diminish the harmful effect of this drug [9].

The internal anatomy of the heart reveals four chambers composed of heart muscle or myocardium [21]. The upper chambers (atria) function mainly as collecting chambers; the two lower chambers (ventricles) are much stronger and function to pump blood [10]. The role of the right atrium and ventricle is to collect blood from the body and pump it to the lungs while that of the left atrium and ventricle is to collect blood from the lungs and pump it throughout the body [12]. There is a one-way flow through the heart; and this flow is maintained by a set of four valves: the atrioventricular valves (tricuspid and bicuspid) allow blood to flow from atria to ventricle and the semilunar valves (pulmonary and semilunar) allow blood flow only from the ventricles out of the heart and through the great vessels. Due to the numerous functions of the heart, the heart is the highest energy-consuming organ of the body, and subtle energetic deficits or induction agents can rapidly induce contractile dysfunction [13].

The heart wall is made up of three layers: the inner endocardium, middle myocardium, and outer epicardium. These are surrounded by a double-membrane sac called the pericardium. The walls of the heart consist mostly of myocardium, especially the ventricles. When the ventricles contract, they produce a wringing motion because of the double-helical orientation of the cardiac muscle fibers [14].

The myocardium, which is the cardiac muscle – a layer of involuntary striated muscle tissue surrounded by a framework of collagen exhibits an elegant and complex pattern, as the muscle cells swirl and spiral around the chambers of the heart, with the outer muscles forming a Fig. 8 pattern around the atria and around the bases of the great vessels and the inner muscles, forming a Fig. 8 around the two ventricles and proceeding toward the apex. This complex swirling pattern allows the heart to pump blood more effectively [15].

Cardiac-related disorders rank high among the major public health concern ailments and their prevalence is increasing at a geometrical rate, especially in developing countries like Nigeria [13]. Commonly used induction and maintenance anesthesia protocols involve agents that are known to affect the sympathetic and parasympathetic nervous systems, vascular tone, and contractile properties of the myocardium [16]. There is current debate about the side effects of induction agents like ketamine, e.g., possible adrenal suppression through etomidate emphasizes the relevance of choosing the correct induction agent in both humans and animals [17]. However, cardiovascular depression is still the most prominent adverse effect of these agents and might be especially hazardous in septic patients presenting with biventricular cardiac dysfunction [3]. Some of heart dysfunctions are attributed to some anesthesia, with ketamine as a case study [18].

In a study conducted by De Carvalho and Thomazini, 2014., they found that the percentage ratio between the relative heart weight to body weight was between 0.5% and 0.7% in the animals with body weight up to 650 g. The maximum and minimum diameters were always statistically lower in females compared to males. The measurements showed that the hearts of the females were shorter, narrower, smaller, and lighter than those of males. Over the life of these females, although the heart weight increases, the heart apparently keeps its shape and size. Furthermore, the hearts of males narrow and stretch along their development. These weight changes may be due to sex variations or caused by ingestion of several products.

Nevertheless, our study will investigate these relative heart weights with regard to the increasing use of high doses of ketamine in adult albino Wistar rats.

METHODS

Experimental design

Twelve male albino Wistar rats were used for the study. The rats weighing 100–250 g were kept for acclimatization within the period of 2 weeks before administration of ketamine. They were divided into four groups; each group consisted of three animals each (n=3).

- Group A (control): Received only distilled water and feeds for the period of 21 days and weighed daily
- Group B (ketamine group 1): Received ketamine at a dose of 100 mg/kg/body weight daily for 2 weeks and weighed daily
- Group C (ketamine group 2): Received ketamine at a dose of 150 mg/kg/body weight daily for 2 weeks and weighed daily
- Group D (ketamine group 3): Received ketamine at a dose of 200 mg/kg/body weight daily for 2 weeks and weighed daily.

Termination and sacrifice of experimental animal

The animals were anesthetized with 0.2 mL of ketamine on day 21 of the experimental period. The heart was harvested carefully with the aid of a sharp surgical blade, by making an incision through to locate the heart on the left side of the thorax just in the midclavicular line horizontally and lateral to the sternum, from the extent of 2nd- 6th ribs vertically. The hearts were weighed immediately and transferred into specimen bottles and labeled with their identification numbers, respectively. The specimen bottles contained a desired quantity of 10% formal saline and

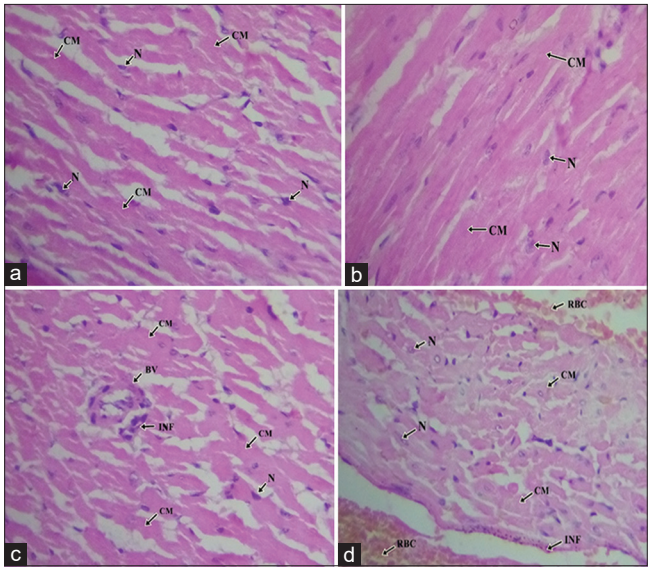

Fig. 1: A micrograph of a section of myocardium; (a) Control group showing the normal histological features of the myocardium. (b) Ketamine group one was administered with 100 mg/kg/ body weight of ketamine showing hypertrophy of cardiac myocytes and sparse inflammatory infiltrate. (c) Ketamine group two was administered with 150 mg/kg/body weight showing swollen cardiac myocytes and vacuolar degenerative changes. (d) Ketamine group three was administered with 150 mg/kg/ body weight showing atrophy of the cardiac myocytes, collection of inflammatory infiltrates, and extensive hemorrhage within the myocardial tissue

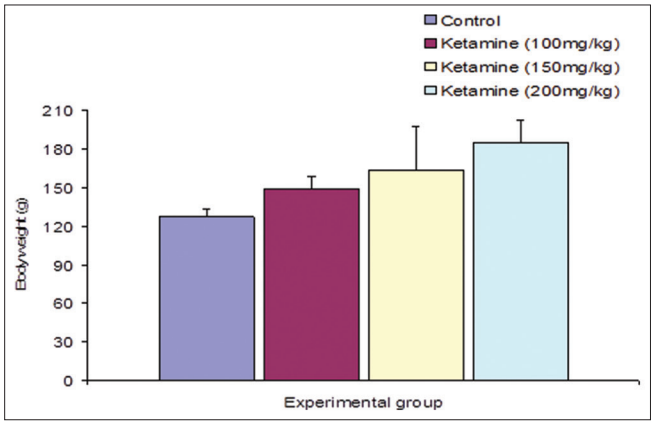

Fig. 2: Body weight of the different experimental groups. Values are expressed as mean±SEM, n=3. No significant differences among groups

cotton wool which were immersed to prevent the floating of the heart for proper fixation to take place.

Histomorphological study

Following fixation, specimen was dehydrated by passing the tissues through ascending grades of alcohol as follows: 70% alcohol 2 changes 1 h each, 95% alcohol 2 changes 1 h each, and 100% absolute alcohol 2 changes 1 h each. Clearing was done with the aid of xylene in two changes 1 h each followed by infiltration by the heart tissue into molten paraffin wax in an oven at a temperature of 60°C 2 changes, hour each. Tissues were embedded in fresh paraffin wax and sectioned accordingly. Staining was done after dewaxing using hematoxylin and eosin (H&E). The different histological slides were obtained and the relative body weight to heart was expressed as mean±SD.

Table 1: The relative body weight to heart of experimental animals in the different groups

Descriptives: One-way								
Groups/ratio	**n**	**Mean**	**Standard deviation**	**Standard error**	**Lower Bound**	**Upper Bound**	**Minimum**	**Maximum**
Group 1 (Control)	3	127.2333	11.29882	6.52338	99.1655	155.3012	119.50	140.20
Group 2 Ket (100 mg)	3	149.4667	15.53459	8.96890	110.8766	188.0567	136.30	166.60
Group 3 Ket (150 mg)	3	163.5000	59.90025	34.58343	14.6995	312.3005	105.70	225.30
Group 4 Ket (200 mg)	3	185.3667	30.51399	17.61726	109.5657	261.1676	155.40	216.40
Total	12	156.3917	37.10059	10.71002	132.8191	179.9643	105.70	225.30
Ht.Wt								
Control	3	2.0867	0.17786	0.10269	1.6448	2.5285	1.93	2.28
Group 2	3	2.5233	0.41968	0.24230	1.4808	3.5659	2.05	2.85
Group 3	3	2.8667	0.98022	0.56593	0.4317	5.3017	1.95	3.90
Group 4	3	2.4833	0.17559	0.10138	2.0471	2.9195	2.30	2.65
Total	12	2.4900	0.54905	0.15850	2.1412	2.8388	1.93	3.90
RHW								
Control	3	0.0164	0.00032	0.00019	0.0156	0.0172	0.02	0.02
Group 2	3	0.0168	0.00172	0.00099	0.0126	0.0211	0.02	0.02
Group 3	3	0.0176	0.00067	0.00038	0.0160	0.0193	0.02	0.02
Group 4	3	0.0135	0.00130	0.00075	0.0103	0.0168	0.01	0.01
Total	12	0.0161	0.00189	0.00054	0.0149	0.0173	0.01	0.02
PRBWR								
Control	3	1.6433	0.03215	0.01856	1.5635	1.7232	1.62	1.68
Group 2	3	1.6833	0.17156	0.09905	1.2572	2.1095	1.50	1.84
Group 3	3	1.7633	0.06658	0.03844	1.5979	1.9287	1.72	1.84
Group 4	3	1.3533	0.13013	0.07513	1.0301	1.6766	1.22	1.48
Total	12	1.6108	0.18861	0.05445	1.4910	1.7307	1.22	1.84
Ket.Dose								
Control	3	0.0000	0.00000	0.00000	0.0000	0.0000	0.00	0.00
Group 2	3	14.9667	1.58219	0.91348	11.0363	18.8971	13.60	16.70
Group 3	3	24.5333	8.96679	5.17698	2.2586	46.8081	15.90	33.80
Group 4	3	37.2667	6.35793	3.67076	21.4727	53.0607	31.10	43.80
Total	12	19.1917	14.98754	4.32653	9.6690	28.7143	0.00	43.80

Table 2: The correlation analysis between ketamine groups and control group using the pearson's correlation

Correlations				
Group/ratio	**Ket.Dose**	**Bw**	**Ht.Wt**	**RHW**
Ket.Dose				
Pearson correlation	1	0.811**	0.546	−0.536
Sig. (2-tailed)		0.001	0.066	0.072
n	12	12	12	12
Bw				
Pearson correlation	0.811**	1	0.826**	−0.463
Sig. (2-tailed)	0.001		0.001	0.129
n	12	12	12	12
Ht.Wt				
Pearson correlation	0.546	0.826**	1	0.104
Sig. (2-tailed)	0.066	0.001		0.747
n	12	12	12	12
RHW				
Pearson correlation	−0.536	−0.463	0.104	1
Sig. (2-tailed)	0.072	0.129	0.747	
n	12	12	12	12

**Correlation is significant at the 0.01 level (2-tailed)

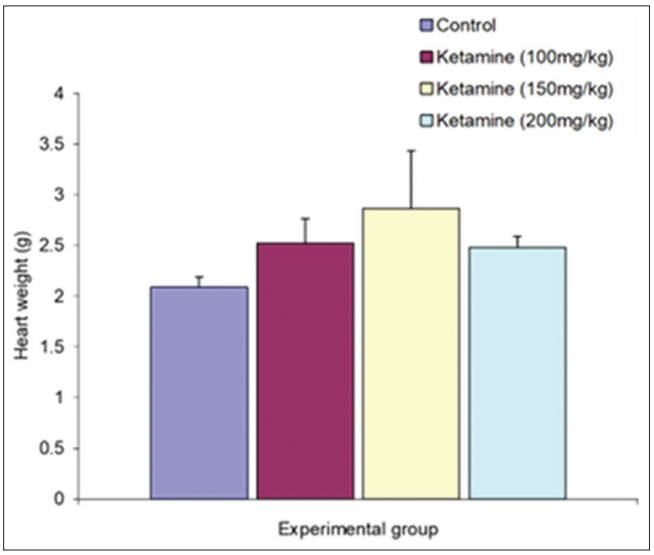

Fig. 3: Absolute heart weight of the different experimental groups. Values are expressed as mean±SEM, n=3. No significant differences among groups

Ethical clearance

According to the International Guidelines for Handling Laboratory Animals, ethical clearance was obtained from the Faculty Animal Research Ethics Committee (FAREC-FBMS), Faculty of Basic Medical Science, University of Calabar.

RESULTS

Histological findings

Micrograph shows of a section of myocardium; representing the Control group, Ketamine group 1 (100 mg/kg/body weight of ketamine), Ketamine group 2 (150 mg/kg/body weight of ketamine) and Ketamine group 3 (200 mg/kg/body weight of ketamine).

Results of relative body weight to heart weight

Result shows body weight of the different experimental groups as well as absolute heart weight of the different experimental groups (Figs. 1-4 and Tables 1 and 2).

DISCUSSION

Ketamine is a unique anesthetic drug that provides profound analgesia, hypnosis, and amnesia. It also causes less respiratory depression than other IV anesthetics at clinically relevant doses and has sympathomimetic properties that make it a useful drug for

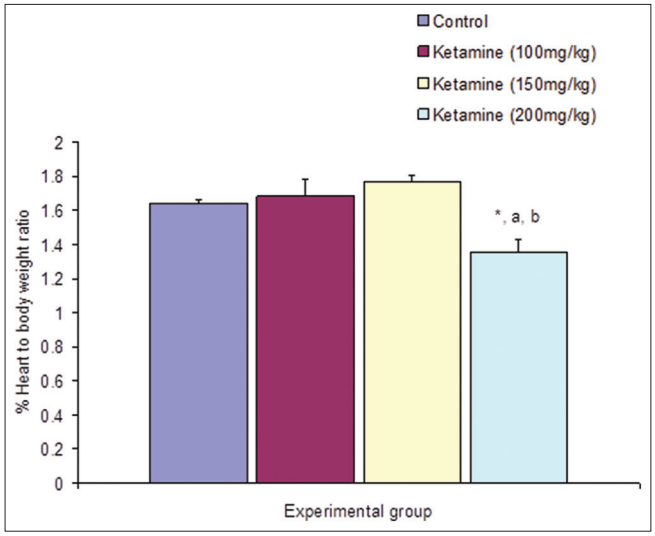

Fig. 4: Percentage heart to body weight of the different experimental groups. Values are expressed as mean±SEM, n=3. *=p<0.05 versus control, a=p<0.05

patients with impaired cardiac function (e.g., cardiac tamponade or systolic heart failure). It also has anti-inflammatory properties that are potentially useful in attenuating the inflammatory response to cardiopulmonary bypass (Loix *et al*., 2012) [23]. The use of ketamine in anesthesia reflects its characteristics as a drug of choice for short-term procedures when muscle relaxation is not required (Rosenbaum *et al*., 2020) [18]. However, these properties of ketamine depend on accurate doses and duration of its administration.

Ketamine infusions are used for acute pain treatment in emergency departments and in the perioperative period in individuals with refractory pain. The doses are lower than those used for anesthesia; they are usually referred to as sub-anesthetic doses. Adjunctive to morphine or on its own, ketamine reduces morphine use, pain level, nausea, and vomiting after surgery. It is well known that clinically, ketamine enhances myocardial contractility by central nervous system-mediated sympathomimetic stimulation [4].

This present work is designed to explore the level of myocardial injury and relative body weight changes to the heart following the administration of different doses of ketamine over time. Myocardial injury induced by high doses of ketamine is due to inflammation and destruction of cardiac myocytes and blood vessels as well as hypertrophy and/or atrophy of the cardiac myocytes. Weight changes of Wistar rats showed weight differentiation in both body weight and heart weight; as normal control animals recorded the lowest mean value of 0.3473±0.0586 while experimental control group of ketamine 1 and 2 recorded the highest mean value of 0.3915±0.841 and 0.7354±0.2058. Heart weight significantly differed in experimental groups at p>0.05 from normal control, except for experimental control group which was higher.

In this study, the control group shows the normal histological features of the myocardium with prominent bundles of interdigitated cardiac muscle fibers. The individual cardiac myocytes are spindle shaped with distinct nuclei. The intervening stromal is scanty with normal distribution of blood vessels. While the heart constitutes 1.6% of the total body weight of experimental animal corroborating a study by De Carvalho *et al*, 2014 [22].

Ketamine group one was administered 100 mg/kg/body weight of ketamine showing prominent bundles of interdigitated cardiac muscle fibers. The individual cardiac myocytes appear hypertrophied with distinct nuclei. The intervening stromal is abundant harboring sparse inflammatory cells while the relative body weight study shows that the heart constitutes 1.63% of the total body weight of animal, a minimal deviation from the control group. This indicates that, at this dose of ketamine administered, there were some mild injuries to the myocardium, most likely an early stage of myocarditis.

On the one hand, the ketamine group two was administered 150 mg/kg/body weight, the myocardium showed features of further injury. It has features of hypertrophied cardiac muscle fibers with individual cardiac myocytes swollen but having distinct nuclei. The intervening stromal is scanty and vacuolar degenerative changes were noted within the myocardial tissue indicating a severe form of myocardial injury. This group presents a heart weight that is 1.7% of the total body weight of experimental animal.

Furthermore, the ketamine group three shows prominent bundles of interdigitated cardiac muscle fibers, and the individual cardiac myocytes are atrophic with distinct nuclei. The intervening stromal is grossly scanty. There are collections of inflammatory infiltrates and extensive hemorrhages around the myocytes. The heart in this group with the highest dose of ketamine administered contributes only 1.2% of the total body weight. This is explained by the atrophy noticed in the cardiac myocytes and further explains that with increasing doses of ketamine administration, more damage may ensue.

From these findings, morphological changes were dose dependent in the heart sections from ketamine administration compared to the control rats suggesting myocardial injury with increasing and chronic use of ketamine.

CONCLUSION

Higher doses of ketamine cause significant myocardial injury which is worsened at every increase in the dose as well as differential changes in body weight and heart weight in experimental animals.

CONFLICT OF INTEREST

This study was carried out accordingly without any conflict of interest.

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