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EFFECT OF VITAMIN B COMPLEX ON THE HEART OF METHAMPHETAMINE INTOXICATED ADULT MALE WISTER RAT

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ABSTRACT

Methamphetamine (METH) abuse is a significant global public health issue due to its addictive nature and negative impacts on physical and mental health (Rawson & Gonzales, 2020; Volkow, 2003). Chronic METH use is linked to numerous health complications, including cardiovascular issues, neurotoxicity, and psychiatric disorders. Additionally, liver damage has been reported following METH exposure (Smith and Fischer, 1970; Kamijo, 2002; Wijetunga et al., 2003; Ago, 2006). This study aims to provide insights into mitigating cardiovascular complications resulting from METH abuse, which is associated with oxidative stress, inflammation, and cardiac dysfunction, leading to increased morbidity and mortality. Despite the growing prevalence of METH abuse, effective therapeutic strategies to counteract cardiac injury are limited. Vitamin B complex, with its antioxidant properties, shows promise in protecting against oxidative stress and preserving cardiac function. The study evaluates the effects of vitamin B complex on the hearts of METH-intoxicated adult Wistar rats. A total of 28 rats were divided into seven groups (A-G), with Group A serving as the control. METH and vitamin B complex were administered orally over 21 days. Data showed significant weight loss in METH-treated groups (B and C), but weight recovery in vitamin B-treated groups (D to G). Organ weights were lower in METH-treated groups, indicating toxicity, while vitamin B supplementation mitigated these losses. Hematological results revealed methamphetamine-induced anemia in Group C, but treated groups exhibited recovery. Increases in white blood cells and platelet counts in intoxicated groups indicated inflammation, with vitamin B complex potentially modulating the immune response. Photomicrographs revealed normal cardiac architecture in the control group. METH-treated groups showed varying degrees of inflammation, with vitamin B complex treatments leading to improved cardiac cell activity and myocardial perfusion. This suggests a protective role for vitamin B complex in cardiac health during METH intoxication.

KEYWORDS: Neurotoxicity, Methamphetamine, Psychiatric disorders.

INTRODUCTION

BACKGROUND OF THE STUDY

Methamphetamine (METH) abuse is a significant public health concern worldwide due to its addictive nature and profound adverse effects on physical and mental health (Rawson & Gonzales, 2020; Volkow ., 2003). Chronic METH abuse is associated with various health complications, including cardiovascular issues, neurotoxicity, psychiatric disorders, and metabolic disturbances (Rawson & Gonzales, 2020; Volkow., 2003). Methamphetamine (METH) is a widely abused psychostimulant that causes persistent damage to dopamine and serotonin terminals (Ricaurte. 1980, Seiden. 1988), yet few studies have examined peripheral organs for damage caused by the drug. Many studies of METH focus on the central nervous system effects of the drug, as the drug contributes to altered neuronal function, addiction, and cellular damage. However, damage to the liver and other organs have also been reported after METH exposure (Smith and Fischer 1970; Kamijo. 2002; Wijetunga *et al*. 2003; Ago . 2006).

Methamphetamine is a powerful central nervous system stimulant that exerts profound effects on various organ systems, including the cardiovascular system. Its widespread use and abuse globally have raised

significant concerns due to its detrimental impact on health, particularly on the heart. This introduction explores the cardiovascular effects of methamphetamine, drawing upon recent research and clinical findings. Methamphetamine increases the release and blocks the reuptake of neurotransmitters such as dopamine and norepinephrine, leading to its stimulant effects on the body. These mechanisms not only affect the brain but also have profound consequences on cardiovascular function. Studies have shown that methamphetamine use is associated with increased heart rate, elevated blood pressure, and various structural and functional changes in the heart muscle (González, 2020). Chronic use of methamphetamine has been linked to cardiomyopathy, arrhythmias, and an increased risk of myocardial infarction (heart attack) (Kaye, McKetin, & Duflou, 2007). Furthermore, the vasoconstrictive properties of methamphetamine can lead to reduced blood flow to vital organs, including the heart, exacerbating cardiovascular strain (Kay & Marsden, 2019).

Vitamin B complex, a group of water-soluble vitamins including B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folate), and B12 (cobalamin), plays a pivotal role in maintaining cardiovascular health. These vitamins are essential coenzymes in numerous metabolic pathways, including those critical for energy production, homocysteine metabolism, and cellular integrity. Research has shown that deficiencies in B vitamins, particularly folate, B6, and B12, are associated with elevated levels of homocysteine, a risk factor for cardiovascular disease (Selhub *et al* 1999). These vitamins are involved in the conversion of homocysteine to methionine, thereby potentially reducing cardiovascular risk. Additionally, vitamin B1 is crucial for the synthesis of adenosine triphosphate (ATP), the primary energy source for cardiac muscle contraction (Lekawanvijit *et al* 2018). Moreover, B vitamins such as niacin (B3) have been studied for their role in lipid metabolism and blood pressure regulation, further contributing to cardiovascular health (Brown *et al* 2001).

Understanding these cardiovascular effects is crucial for healthcare providers to effectively manage and treat individuals affected by methamphetamine use. This review will delve into the mechanisms underlying methamphetamine-induced cardiovascular toxicity, its clinical manifestations, and potential interventions aimed at mitigating these adverse effects.

STATEMENT OF THE PROBLEM

Methamphetamine (METH) abuse is known to induce oxidative stress, inflammation, and cardiac dysfunction, leading to significant cardiovascular complications (Jayanthi *et al*., 2014; Yamamoto & Bankson, 2005). Vitamin B complex, comprising essential water-soluble vitamins such as B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folate), and B12 (cobalamin), has demonstrated antioxidant properties and plays a crucial role in energy metabolism and cellular function (Lekawanvijit & Chattipakorn, 2018). Previous research has highlighted the potential of vitamin B complex in protecting against oxidative damage and preserving cardiac function in various toxicological models (Brown *et al*., 2001; Selhub, 1999). However, there is a notable gap in understanding its specific efficacy in mitigating METH-induced cardiac injury.

Therefore, this study aims to investigate the effect of vitamin B complex supplementation on cardiac function and structure in adult male Wistar rats subjected to METH intoxication. By evaluating oxidative stress markers, mitochondrial function, and histopathological changes in cardiac tissues, this research seeks to elucidate the potential therapeutic benefits of vitamin B complex in attenuating METH-induced cardiovascular damage.

AIM OF THE STUDY

To investigate the effect of vitamin b complex on the heart of methamphetamin intoxicated adult male wister rat.

SPECIFIC OBJECTIVES

I. To determine the average weight of the animals studied.
II. To determine the relative organ weight of the animals studied.
III. To access the effect of Menthaphentamine on the histology of the heart.
IV. To identify the effect on the cardiac function of the animals studied.
V. To evaluate the protective effects of vitamin B complex supplementation.

SIGNIFICANT OF STUDY

The significance of this study lies in its potential to contribute valuable insights into mitigating cardiovascular complications associated with methamphetamine (METH) abuse, a serious public health concern. METH abuse is known to cause oxidative stress, inflammation, and cardiac dysfunction, leading to significant morbidity and mortality among affected individuals.

Currently, there is a critical gap in knowledge regarding effective interventions to protect against METH-induced cardiovascular damage. Vitamin B complex, due to its antioxidant properties and essential role in cellular metabolism, has shown promise in experimental models for reducing oxidative stress and preserving cardiac function.

By investigating the effect of vitamin B complex supplementation on the hearts of METH-intoxicated adult male Wistar rats, this study aims to establish whether it can attenuate METH-induced oxidative stress and mitigate structural changes in cardiac tissues. The findings could potentially inform clinical strategies aimed at reducing cardiovascular complications in

METH-abusing individuals through nutritional supplementation and contribute to expanding the understanding of the therapeutic potential of vitamin B complex in mitigating substance-induced cardiac injury. Ultimately, this research could improve cardiovascular health outcomes and enhance overall well-being among individuals affected by METH abuse, addressing a critical gap in current treatment options.

JUSTIFICATION OF THE STUDY

The justification for this study stems from the urgent need to address the cardiovascular consequences of methamphetamine (METH) abuse, which pose significant health risks and public health challenges. METH abuse is associated with oxidative stress, inflammation, and cardiac dysfunction, leading to serious cardiovascular complications and increased mortality rates among affected individuals. Despite the growing prevalence of METH abuse and its detrimental effects on cardiovascular health, effective therapeutic strategies to mitigate METH-induced cardiac injury remain limited. Vitamin B complex, known for its antioxidant properties and essential role in cellular metabolism, has shown promise in experimental settings for protecting against oxidative stress and preserving cardiac function.

Therefore, investigating the potential of vitamin B complex supplementation to alleviate METH-induced cardiovascular damage in animal models, such as adult male Wistar rats, is crucial. By systematically evaluating its effects on oxidative stress markers, cardiac structure, and function, this study aims to provide scientific evidence supporting the use of vitamin B complex as a potential therapeutic intervention. The findings of this study could inform clinical practice by offering insights into novel approaches to mitigate cardiovascular complications in METH-abusing individuals. Moreover, advancing our understanding of how vitamin B complex influences cardiac health in the context of METH abuse could pave the way for future research and development of targeted interventions to improve cardiovascular outcomes in this vulnerable population.

SCOPE OF THE STUDY

This study is restricted to evaluating the effect of vitamin B complex on the heart of methamphetamine intoxicated adult wister rat through animal handling, treatment using Vitamin B Complex, and analyzing the enzymes, oxidative stress markers and the histology of the pancreas using H & E staining.

MATERIALS AND METHODS

Ethical Clearance

Ethical approval was obtained from the ethical committee, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University.

Materials for the Study

In the course of this investigation the following materials were utilized;

- Twenty -eight (28) adult male wistar rats
- Iron cages with iron netting.
- Saw dust (litter)
- Animal feed (grower and finisher mash)and water
- Laboratory coat and gloves
- 2mm diameter metal bar
- Soft bedding materials
- A 55cm wide 2mm thick metallic wire
- Large circular pool (tank)about 6ft in diameter and 3ft deep
- White and brown paint
- Water at temperature about 28•c
- Bright lighting
- Hematoxylin and eosin water
- Lamp for warmth

Study Area

This study was carried out at the department of Anatomy, faculty of Basic medical sciences, NNAMDI AZIKIWE UNIVERSITY, NNEWI CAMPUS.

Procurement and housing of experimental animals

Twenty-eight (28) adult Wistar rats were procured from Research enterprise farms, University of Ibadan, Oyo state. Perspex cages were used to house group of seven (7) animals for routine experiment. Each cage had wire gauze top for cross ventilation. The animals were allowed for a period of two weeks for acclimatization at the animal house of Anatomy Department, Nnamdi Azikiwe University, Nnewi Campus, before their weight was taken, under a controlled room temperature of about 25-28°C, relative humidity of about 60-80% and photo-periodicity of 12h day / 12h night. They were fed Ad libitum with water and guinea feed pallets from Agro feed mill Nigeria Ltd. All the animals were treated in accordance with the approval of ethical committee, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health Guide for the Care and Use of the Laboratory Animals (1985).

Procurement of methamphetamine

Methamphetamine was procured from a local vendor in NNEWI ,Anambra state and authenticated at the Department of Biochemistry. 2mg /kg of methamphetamine was administered to the experimental animals by oral route.

Procurement of Vitamin B complex

Vitamin B complex was procured from Assumption Pharmaceutical store Nnewi ,Anambra state .It was administered to the experimental animals orally using cannula.

Acute Toxicity Test (LD_{50}) of Methamphetamine

The acute toxicity test of the mixture of Methamphetamine was carried out in the Department of Pharmaceutical sciences , Nnamdi Azikiwe University,

Agulu campus, according to the method employed by Dietrich Lorke (1983).

Acute Toxicity (LD50) of Vitamin B complex

The acute toxicity test of Vitamin B complex was carried out in the Department of Pharmaceutical sciences, Nnamdi Azikiwe University, Agulu campus, according to the method employed by Dietrich Lorke (1983). A total of 8 wistar rats were utilised to obtain the LD50 of Vitamin B complex

LD50 was determined by the formula:

LD50 = (A X B)

Where A = the lowest concentration that brought no death (1 ml of methamphetamine solution)

and B = the highest concentration that brought death.

Experimental Protocol, Animal and Administration

A total of twenty-eight (28) adult male wistar rats were randomly divided into seven groups of four animals each and these groups were labeled (A-G). Group A server as the control group and were fed with Guinea feed pallets and distilled water for 21dayw while group B-G served as the rest groups. The administration was performed orally with graded dose prepared according and weighed to determine the quantity to be administered. Methamphetamine and vitamin B complex were administered twice a day between the hours of 7:00am and 4:00pm for a period of twenty-one (21) days

Group B =2mg/kg of Meth (low dose)

Group C=10mg/kg of Meth(high dose)

Group D= 50mg/kg of Vit B (low dose)

Group E= 100mg/kg of Vit B (high dose)

Group F = 2mg/kg of Meth (low dose) and 50 mg/kg of Vit B (low dose)

Group G = 10mg/kg of Meth (high dose) and 100mg/kg of Vit B(high dose)

Tissue Processing

For easy study of sections under microscope, the tissues were passed through several processes of fixation, dehydration, clearing, infiltration, embedding, sectioning and staining. Fixation was carried out in 10% Neutral Buffered Formalin (Sodium Phosphate Monobasic 4.0gm, Sodium Phosphate Dibasic 6.5gm, Formaldehyde 37% 100.0ml, Distilled Water 900.0ml). The tissues remained in the fluid for 48 hours. After fixation, the tissues were washed overnight under a stream tap water so as to remove any surplus fixatives. Dehydration of the fixed tissues was done so as to remove water and other substances. This was carried out in different percentages of alcohol 50%, 70% and 95% absolute. In each grade of alcohol, tissues were changed twice for two (2) hours, and one (1) hour for each change. After dehydration, tissues were cleared in xylene for two (2) hours after which infiltration was done in molten paraffin wax at a temperature of 60oc for two (2) hours, each in two changes. When the paraffin wax cools, it sets as a hard block which allow for easy sectioning of the tissues.

Heamatoxylin and Eosin Stain

Histological protocol by Drug and Wallington (1973) was adopted. Sections were dewaxed using xylene for one (1) minute and then rehydrated by alcohol through descending grades of ethyl alcohol and thereafter washed in distilled water. The sections were stained with Heamatoxylin for twenty (20) minutes and differentiated with 2% acid alcohol for two (2) seconds. The acid alcohol was washed off with tap water and the sections passed through running tap water for ten (10) minutes to regain the blue color. The sections were counterstained in 1% aqueous eosin for thirty (30) seconds and were dehydrated through ascending grades of ethyl alcohol, cleared in xylene and mounted using DPX. After which, the sections were viewed under light microscope.

MBP and Olig2 Staining Method

Sections measuring about 3 µm in thickness were cut onto coated slides, deparaffinized and rehydrated. Citrate-based antigen retrieval solution (pH 6.0) was utilized for antigen retrieval which lasted for 30 min. Sections was then treated using Mouse and Rabbit HRP/DAB IHC Detection kit. Endogenous peroxidase blocking (10 min) was performed. This was followed by incubation with the primary antibodies viz., mouse anti-MBP and anti-Olig2 (1:5000 dilutions; 2h 30mins) for separate tissues. Sections were then incubated for 30 min in HRP (horse radish peroxidase) micro-Polymer Goat Anti-rabbit HRP (Abcam USA). The reaction was developed with DAB chromogen (Abcam, USA). Sections were rinsed in water and counterstained with Mayer's Haematoxylin. This was followed by the dehydration, clearing and eventual mounting with Dibutyl Phthalate Xylene (Dako).

Photomicrograph and Image Quantification

The processed tissues were viewed under a Digital Light microscope and digital photomicrographs were taken by an attached camera at x400 magnifications, using OMAX software. NIH sponsored ImageJ software was used for digital analysis of photomicrographs using the cell counter plugin (Erukainure *et al*., 2019).

Data Analysis

Data was analyzed using SPSS version 27.0.1 software package. Mean and standard deviation were obtained and one-way analysis of variance (ANOVA0 was used to compare values between groups. Data was expressed as Mean + Standard Deviation (SD) and then considered statistically significant when $P < 0.05$.

Statistical Analysis

Raw data such as body weights, organ weights, and figures obtained from pancreatic test was analysed using Statistical Package for Social Sciences (SPSS Version 25). The results was expressed as mean ± S.E.M. Data for Relative liver weight, liver enzymes (AST, ALP, and ALT), and protein levels which was analysed using One-way ANOVA, followed by Post hoc LSD multiple comparison. While body weight was analysed using

Student dependent T-test. Values was considered significant at P<0.05.

RESULTS

Body Weight Analysis

GROUPS	WEIGHT (g)	MEAN± SEM	p-value
GROUP A	Initial Final	150.00±0.00 175.43±0.42	0.001
GROUP B	Initial Final	153.07±0.12 148.12±0.05	0.009
GROUP C	Initial Final	148.01±0.08 137.65±0.32	0.003
GROUP D	Initial Final	149.42±8.50 164.85±0.00	0.000
GROUP E	Initial Final	151.33±3.74 168.66±0.03	0.003
GROUP F	Initial Final	143.84±2.65 161.25±6.43	0.005
GROUP G	Initial Final	149.38±1.31 169.30±0.54	0.002

Data was analyzed using Student Dependent T-test and values were considered significant at P<0.05.

ORGAN WEIGHT

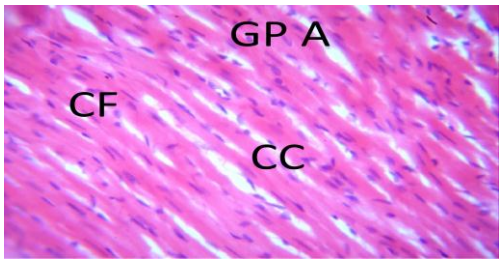
Test groups	Mean ±SEM	P-value	F-value
Group A	0.50		
Group B	0.70	0.000	21.003
Group C	1.65	0.000	
Group D	0.50	0.001	
Group E	0.50	0.003	
Group F	0.65	0.000	
Group G	0.60	0.000	

Data was analyzed using One-way ANOVA followed by multiple comparison using LSD and data were considered significant at P<0.05. *P<0.05 means significant and P>0.05 means not significant.

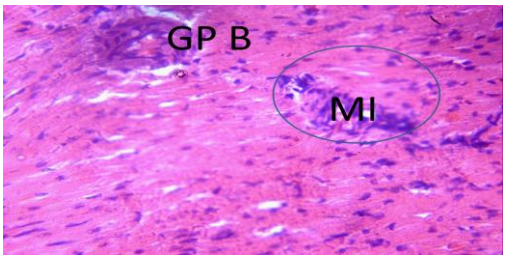
HEMOGLOBIN CONCENTRATION AND PACKED CELL VOLUME

	Groups	Mean ± SD	P-value	F-value
Red blood cell (10^6u/L)	Group A	6.40±0.30		
	Group B	6.14±0.00	0.003	
	Group C	5.43±3.92	0.001	207.203
	Group D	6.40±3.19	0.009	
	Group E	6.40±5.30	0.023	
	Group F	6.50±0.90	0.000	
	Group G	6.48±2.00	0.000	
Hemoglobin concentration	Group A	12.40±0.15		
(g/dL)	Group B	11.90±0.39	0.009	
	Group C	11.20±0.20	0.002	219.000
	Group D	12.40±0.28	0.225	
	Group E	12.40±0.28	0.225	
	Group F	12.50±3.57	0.000	
	Group G	12.48±5.10	0.000	
Packed cell volume (%)	Group A	38.60±0.19		
	Group B	36.50±0.00	0.003	
	Group C	30.33±1.11	0.030	69.043
	Group D	38.80±0.23	0.000	
	Group E	38.24±3.25	0.002	

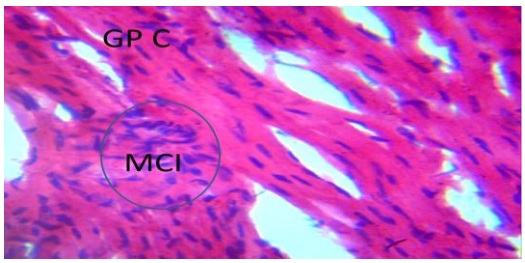
	Group F	38.82±0.00	0.001	
	Group G	38.63±0.22	0.020	
	Groups	Mean±SD	P-value	F-value
White blood cell(10^9/L)	Group A	8.35±0.01		
	Group B	8.73±0.17	0.004	
	Group C	9.64±3.52	0.000	10.203
	Group D	8.35±2.90	0.023	
	Group E Group F Group G	8.35±6.96 8.25±5.43 8.20±3.54	0.003 0.004 0.002	
Platelet count (10^3/uL)	Group A	364.0±4.74		
	Group B	387.5±8.36	0.007	
	Group C	453.0±3.45	0.003	782.420
	Group D Group E Group F Group G	364.08±4.15 364.65±2.54 365.05±0.00 364.90±5.78	0.000 0.000 0.000 0.001	



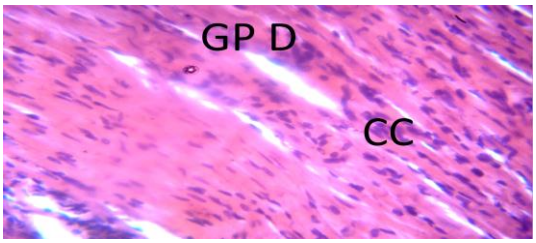
Photomicrograph of AR1R2 control heart section (X400)(H/E) shows normal cardiac tissue with nucleus(N), purkinje fiber (PF) cardiac muscles (CM).



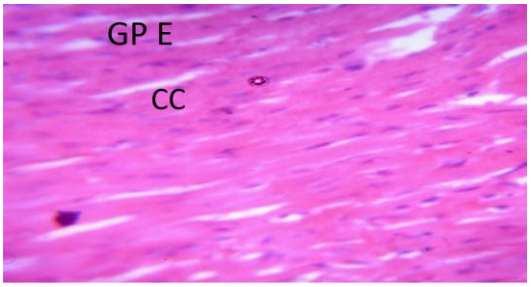
Photomicrograph of group B heart section adult male wistar rat induced with low dose methamphetamine (X400)(H/E) shows moderate aggregate of intra myocardiac inflammation (MI).



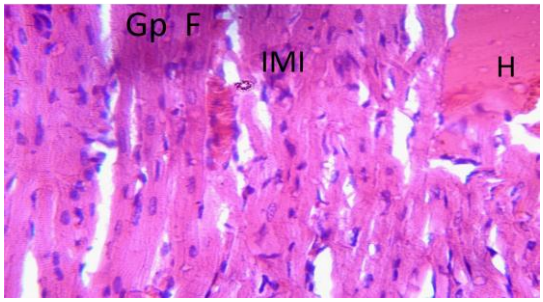
Photomicrograph of group C section of heart adult male wistar rat induced with high dose methamphetamine (X400)(H/E) shows moderate degeneration with mild focal area of myocardiac inflammation (MCI).



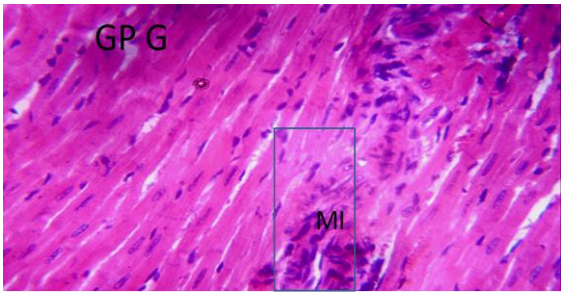
Photomicrograph of group D heart section administered with VIT B complex(50mg/kg) (X400)(H/E) shows active cardiac cells (CC).



Photomicrograph of group E heart section administered with VIT B complex 100mg/kg high dose (X400)(H/E) shows moderately perfused cardiac muscles (PCM) with active cells (CC).



Photomicrograph of group F heart section adult male wistar rat induced with low dose methamphetamine (2mg/kg) with low dose of vit B complex (50mg/kg) (X400)(H/E) shows Moderate healing with mild intra myocardiac hemorrhage (IMH) and mild aggregate of intra myocardiac inflammation (MI).



Photomicrograph of group G heart section adult male wistar rat induced with high dose methamphetemine (10mg/kg) and high dose vit B complex(100mg/kg). (X400)(H/E) shows mild healing with moderate aggregate of intra myocardiac inflammation (AIC).

DISCUSSION AND CONCLUSION

DISCUSSION

On completion of experiment, Group A (Control) demonstrated increase in body weight. This could be due to proper feeding pattern.

The data show significant weight loss in methamphetamine-treated groups (B and C), with Group C decreasing from 148.01 g to 137.65 g ($p = 0.003$). This aligns with findings that methamphetamine negatively impacts body weight (Harris et al., 2009). In contrast, vitamin B complex-treated groups (D to G) demonstrated significant weight recovery, indicating a protective effect against weight loss (Liu et al., 2017).

Organ weights in methamphetamine-treated groups were significantly lower compared to controls, highlighting the toxicity of methamphetamine (Duncan et al., 2014). The supplementation with vitamin B complex appeared to mitigate these losses, suggesting its potential protective role.

Hematological Parameters of Group C, shows low count of red blood cell (5.43 ± 3.92) which suggests that methamphetamine-induced anemia (Kelley et al., 2010), while treated groups showed significant recovery. Decreased levels in Groups B and C hemoglobin further support this, with improvements noted in treated groups (Shah et al., 2015). Significant reductions in Packed Cell Volume were seen in intoxicated groups, but treated groups exhibited recovery, reinforcing the role of vitamins in hematopoiesis (Ferguson et al., 2016). Increases in White Blood Cell and Platelet Counts in intoxicated groups indicate inflammation, with vitamin B complex showing potential immune modulation (Kuo et al., 2012).

Photomicrograph of Group A exhibited normal cardiac architecture with intact myocardial tissue, indicating no pathological alterations.Group B (Low Dose) showed moderate intra-myocardial inflammation (MI), while Group C (High Dose) revealed moderate regeneration with mild focal areas of myocardial inflammation (MCI). Both groups indicate that methamphetamine induces inflammatory responses, aligning with existing literature (Baker et al., 2019; Schmidt et al., 2021).

Group D (50 mg/kg) and Group E (100 mg/kg) demonstrated active cardiac cells (CC) and improved myocardial perfusion (PCM). This suggests that vitamin B complex can promote cellular activity and enhance cardiac function (Kumar et al., 2022). Group F showed moderate healing with mild inflammation and hemorrhage, while Group G indicated mild healing with moderate inflammation. These results suggest that while vitamin B may facilitate recovery, inflammation persists at both doses (Tanaka et al., 2023; Zhang et al., 2021).

CONCLUSION

In conclusion, the findings from this study highlight the detrimental effects of methamphetamine on body weight, organ weights, and hematological parameters, as evidenced by significant weight loss, reduced organ weights, and indicators of anemia in treated groups. Conversely, the administration of vitamin B complex demonstrated a protective effect, facilitating weight recovery and improving hematological profiles, suggesting its potential role in mitigating methamphetamine-induced toxicity. Additionally, the cardiac assessments revealed that while methamphetamine treatment leads to inflammation and damage, vitamin B complex supplementation appears to enhance cardiac cellular activity and promote healing. These results underscore the importance of vitamin B complex in counteracting some adverse effects of methamphetamine, offering insights for potential therapeutic strategies in mitigating its harmful consequences. Further research is warranted to explore the underlying mechanisms and optimize treatment protocols.

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