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HISTOARCHITECTURAL AND BIOCHEMICAL EVALUATION OF ISOPROTERENOL-INDUCED MYOCARDIAL ISCHEMIA IN HEART & LUNGS – AN EXPERIMENTAL DOSE-DEPENDENT STUDY

Subbulakshmi Packirisamy * [1], Valli Gunam [1], Jaideep Mahendra [2], Parimala Kathirvelu [1] and Deepa Rajendiran [3]

Department of Pharmacology [1], Department of Periodontology [2], Meenakshi Ammal Dental College, Meenakshi Academy of Higher Education & Research, Chennai - 600095, Tamil Nadu, India.
Department of Biochemistry [3], Madha Dental College & Hospital, Chennai - 600069, Tamil Nadu, India.

Keywords:

Myocardial ischemia, Isoproterenol, Dose determination, Cardioprotection, Cardiovascular disease, Experimental animals

Correspondence to Author:
Mrs. P. Subbulakshmi

Lecturer,
Department of Pharmacology,
Meenakshi Ammal Dental College,
Meenakshi Academy of Higher Education & Research, Chennai - 600095, Tamil Nadu, India.

E-mail: subbu.buvi@gmail.com

ABSTRACT: Background: Numerous methods have been used to induce myocardial ischemia (MI) in Experimental animals. MI induction using chemicals like isoproterenol in animal models is a simple and standardized method with fewer complications. Various doses of Isoproterenol were used extensively as an inducing agent. **Aim:** The present research aimed to evaluate the effect of Isoproterenol on the heart and lungs of male Wistar albino rats at different doses. **Methods:** Wistar albino rats were categorized as five groups with six animals each and administered with ISO for two days. Serum and histopathological studies were done. **Results:** Biochemical alterations and Microscopic features of the tissues showed pathological changes such as focal areas of inflammation, edema and vacuolar changes, and necrosis according to the dose administered, confirming myocardial injury and related necrotic lesions. **Conclusion:** These findings provide an idea and support fixing the dose for the inducing agent ISO for further cardioprotective studies.

INTRODUCTION: Catecholamines are naturally synthesized amines that can act both as neurotransmitters and hormones. Its synthesis occurs primarily at the sympathetic nerve endings which is vital in stress responses and acts as a regulator in myocardial contractility and metabolism [1]. The cellular functions are modulated by activating the adrenoceptors termed α and β.

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If catecholamines are produced more, they cause cellular damage, thus altering the cardiovascular and metabolic actions, including myocardial contractility, increasing heart rate, blood pressure, and cardiac conduction velocity. In many disease processes, contractile dysfunction is the common etiology, including systemic hypertension, angina, valvular heart disease, and transient myocardial hypoxia.

Myocardial Ischemia is ischemic heart disease (IHD), with multifactorial pathophysiological conditions. It occurs when there is an imbalance between oxygen supply and demand, involving the myocardium and coronary vessels. Clinical manifestations are due to narrowing of epicardial

coronary arteries, atherosclerotic plaque, and microvascular dysfunction, which may seriously damage the myocardium and result in severe ischemia. Once ischemia is triggered, a hypoxic condition prevails in the myocytes. Anaerobic glycolysis begins, followed by tissue acidosis from the lactate production, coronary sinus oxygen desaturation, ion pump disturbances causing an increase in Na^+ and Ca^{2+}, pH decrease, and adenosine reduction triphosphate (ATP) availability are some of the important validates of myocardial ischemia [2].

Isoproterenol [1-(3, 4dihydroxyphenyl 2-isopropylamino ethanol) hydrochloride] (ISO) is one of the widely used tools to induce myocardial infarction in experimental animals. It can be induced chemically and non-invasively to see the development of myocardial necrosis and ischemia. ISO is the synthetic catecholamine with beta-adrenergic activity, in large doses, causes myocardial changes, as seen in humans. The various mechanisms proposed to explain the underlying mechanism of ISO-induced cardiotoxicity in experimental models. Catecholamines are known to form highly toxic free radicals through autooxidation from quinoid compounds, which stimulate lipid peroxidation, and may be the causative factor for irreversible damage to the myocardial membrane [3].

In addition, ISO administration also causes coronary hypotension, which triggers reflex tachycardia [4], calcium overload, hypoxia, and inflammation, thereby increasing myocardial oxygen demand. Persistent β-adrenergic receptor activation with ISO causes inotropic and chronotropic actions. The degree of pathomorphological changes depends on the dose used for ISO administration [5]. Depending on the dose and duration of ISO administration, the ISO-induced effects on the heart could be divided into 3 categories such as low, moderate, and high, and the changes can be seen accordingly. Experimental rats administered with a low dose of ISO, such as 0.3–6 mg/kg for 1–3 weeks, were seen with myocardial necrosis and fibrosis [6]. 5 mg/kg for 10 days were seen with spontaneous regression of the left ventricular hypertrophy [7]. 6 mg/kg, 21 days were seen with cardiac hypertrophy, which, however, exhibited preserved t-tubule system [8]. As per the literature, ISO medium dose were used in animal studies such as 65 mg/kg for 2 days were noted with left ventricles myocardial damages mainly near the apex similar to infarct-like lesions [9]. 10–85 mg/kg for 2 days showed Mitochondrial swelling, decreased amount cristae and increased presence of the homogenized matrix in mitochondrial population [10]. 2 days administration of high dose ISO 85–300 mg/kg were seen with myocardial necrosis, left ventricular dilatation and myocardial hypertrophy [11].

A single dose (24 hrs) administration of ISO 150 mg/kg was reported with necrotic changes in cardiomyocytes, a meshwork of thick and thin collagen fibers, and diastolic dysfunction[12]. Two days of administration of ISO 200 mg/kg was seen with an apical aneurysm of the left ventricle; multifocal disseminated microscopic cardiac lesions [13]. Based on the previous research, Very low doses of ISO, 0.3 mg/kg, applied for 7 days did not affect the blood pressure in rats [14]. But however, a minimal dose ISO produces cardiac lesions [15]. Low dose administration (12.5 mg/kg) showed [16] Significant elevations in the serum and troponin levels [17]. Most of the ISO-induced cardioprotective studies used the moderate dose (85mg/kg) which expressed notable histopathological and biochemical changes with moderate necrosis [18]. Myocardial damage becomes more substantial with a higher dose of ISO [19]. This study was performed to determine the ISO dose showing the myocardial necrosis damage and investigate the effect of ISO on the lungs.

MATERIALS & METHODS:

Chemicals & Reagents: All the chemicals, including Isoproterenol hydrochloride(ISO) procured from Sigma-Aldrich (St. Louis, Missouri, USA) were of analytical grade. ISO dissolved in normal saline (0.9% NaCl) and used within 10 minutes of its preparation [4].

Experimental Animals: The study was carried out with Wistar male albino mature rats (150-180 g body weight; 10-12 weeks old) obtained from Mass Biotech (Chengelpet, Tamil Nadu, India.) Rats were housed in polypropylene cages (47 cm x 34 cm x 20cm) and acclimatized to the laboratory conditions before randomization. Rats were marked for proper identification with cage cards. The

study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Meenakshi Medical College and Research Institute (MMCH&RI), Kanchipuram, Tamil Nadu, India, by the Indian National Law on Animal Care (765/Po/Re/S/03/CPCSEA dated 20.07.2021, Pro. No.003). The animals were housed in an air-conditioned room and were kept in standard laboratory conditions under a 12:12 h light-dark cycle. They were maintained in plastic cages with paddy husk for bedding at 50±10% RH and an ambient temperature of 25±2°C with free access to pellet diet (Krishna Valley agrotech, Pune, Maharashtra) and water *ad libitum*. All animals were handled with humane care. The pellet diet consisted of crude protein 16.58%, ether extract 4.11%, crude fiber 4.25%, moisture 8.90%, calcium 0.81%, phosphorus 0.65%, and 8.92% ash. The diet provided metabolizable 3000 Kcal.

ISO Dose Determination: Wistar albino rats were used to induce myocardial ischemia. After acclimatization, the animals were examined carefully and administered doses (65, 75, 85, and 95 mg/Kg body weight) of Isoproterenol hydrochloride (ISO).

Preparation of ISO Solutions: ISO was dissolved in physiological saline (1 mL) and used immediately for subcutaneous administration to rats at 24 hrs for two consecutive days [20].

Experimental Plan: Animals were randomly grouped into five groups of six animals each and received a Normal laboratory diet with drinking water *ad libidum* for two days, and one group served as control.

Group I: Severed as Normal control and received water (1ml/Kg p.o) for two days (48 hrs).

Group II: ISO induced (65 mg/Kg bw, s.c.) for two days (48 hrs).

Group III: ISO induced (75 mg/Kg bw, s.c.) for two days (48 hrs).

Group IV: ISO induced (85mg/Kg bw, s.c.) for two days (48 hrs)

Group V: ISO induced (95 mg/Kg bw, s.c.) for two days (48hrs)

The rats were anesthetized with pentobarbital sodium (35 mg/Kg, i.p.,) 24 h after the last dose, and euthanized by cervical dislocation. The blood samples were obtained from the left jugular vein (3 mL) in a tube, centrifuged at 2000r/min for 10 minutes, and the separated serum was used for the biochemical estimations. Immediately after sacrifice, hearts were excised, rinsed in ice-cold isotonic saline, blotted with filter paper, and homogenized in 0.05 M ice-cold phosphate buffer (pH 7.4) for biochemical assays. A small portion of the tissues was stored in 10% formalin for histological analysis.

Biochemical Determination of Troponin T, CK-MB, LDH in the Serum: Various markers have been used for detecting myocardial ischemia, such as CK-MB, the MB isoenzyme of Creatine kinase, lactate Dehydrogenate (LDH), myoglobins and cardiac troponins (cTn). Enzyme immunoassay analyzers were employed for the *in-vitro* quantitative determination of cTnI in serum samples by ECLIA method (Electro Chemiluminescence Immunoassay, Roche Diagnostics, Switzerland). The activities of LDH and CK-MB were analyzed quantitatively in serum using Kinetic UV analyzers purchased from Beckman Coulter, US. All measurements were performed according to the kit manufacturer's instructions [21].

Histological Examination: Immediately after the sacrifice of the rats, the hearts were dissected and washed thoroughly with saline. The extracted segment was stored in 10% formalin solution. Heart samples were embedded in paraffin, and five micron-thick sections were sliced. Standard histological methods were used to remove paraffin, and the samples were passed through a gradual alcohol series (50, 70,80,90,95 and 100) and hydrated. Tissue was processed for sectioning and staining by standard histological methods. Sections (5 mm, Leica RM 2125, Germany) from the left ventricle were stained with Hematoxylin and Eosin (H&E) and examined by light microscopy (Nikon, Tokyo, Japan) at 200 x magnifications [22].

The slides were observed for evidence of inflammatory cell infiltration, necrosis, and edema.

Statistical Analysis: All the Data were expressed as the mean ± *S.D.* and analyzed using SPSS (SPSS Inc., Chicago, standard version 16.0) statistical software with a significance level of 0.05.

RESULTS & DISCUSSION: In this study, no animal deaths occurred. Evaluations were carried out after 24hrs of the 2nd day of ISO administration. The results of hematologic examinations and histopathological slides of the heart and lungs were shown. **Fig. 1** illustrates the Graphical abstract of the study. **Table 1** and **Fig. 2** represent the effect of Isoproterenol on the levels of specific marker enzymes and the activities of serum CnTn, CK-MB, and LDH in normal and ISO-induced experimental rats. During MI, cardiac-specific cytosolic marker enzymes are released from the damaged heart tissue into the bloodstream when the cell membrane becomes more permeable and ruptures, which helps in monitoring the myocardial damage [23]. Troponins are highly sensitive and specific biomarkers of cardiac cell injury [24]. It rapidly increases after acute myocardial infarction (AMI) and may persist up to 2 weeks after that. Troponin T (cTnT) is an independent prognostic marker that can predict the mild and long-term outcomes of patients with acute coronary syndrome (ACS) [25, 26] and [27].

Isoforms of Troponins such as C, I and T are proteins that form the muscle fibers' thin filaments, and help regulate the contractile protein and its movement in the cardiac tissue [28]. Creatine Phosphokinase is a cytosolic enzyme, that acts as a standard marker enzyme during myocyte injury or death releases due to increased sarcoplasmic permeability and disintegration of contractile apparatus [29]. In our study, the ISO-treated group of animals showed a significant increase in the serum levels and activities of these marker enzymes compared to the normal control rats.

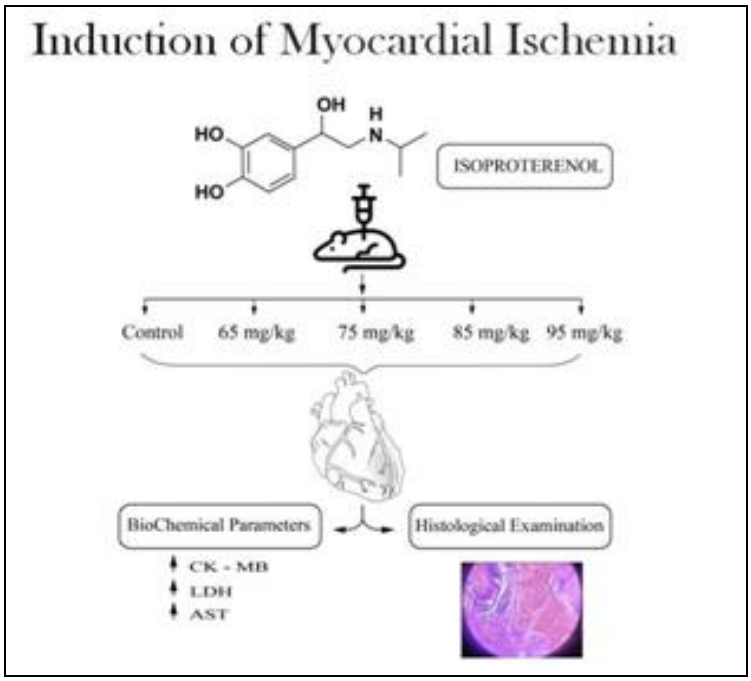
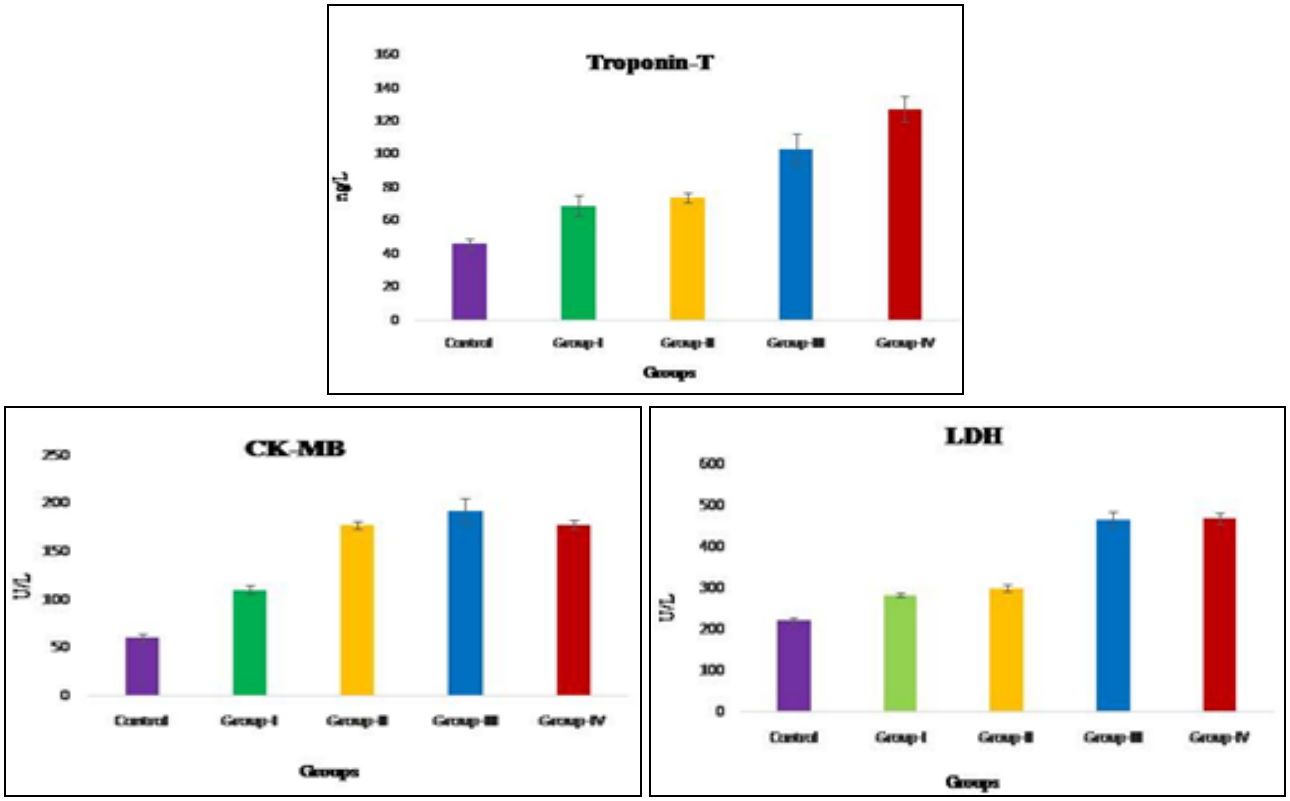


FIG. 1: GRAPHICAL ABSTRACT OF THE STUDY

TABLE 1: DOSE DETERMINATION OF ISO IN SERUM

Iso Treatment Dose mg/kg(sc)	Parameters		
	Troponin T (ng/L)	CK-MB (U/L)	LDH (U/L)
CONTROL	46 ± 3.28	60.8± 3.71	221± 6.63
65 mg/kg	69 .3 ± 6.53	110.6±4.27	283.8 ± 4.53
75 mg/kg	74±2.82	177.5 ± 4.13	300.8± 8.86
85 mg/kg	103.3±9.45	192.6± 13.5	467.8 ± 17.97
95 mg/kg	127.6±7.91	178.0± 4.85	470.6 ± 13.54

Mean (SD) levels of cardiac troponin t (CTNT) in the serum of male wistar rats treated with isoproterenol (ISO) at 0 (control), 65, 75, 85,95mg/kg. results are expressed mean ± SD, n=6.



EFFECT ON SERUM CARDIAC TROPONIN-I CK-MB, LDH IN DIFFENT DOSE OF ISOPROTERENOL

FIG. 2: SHOWING THE EFFECT *PICRORHIZA KURROA* ROOT EXTRACT ON SERUM CARDIAC TROPONIN-I, CK-MB, LDH IN DIFFERENT DOSE OF ISOPROTERENOL

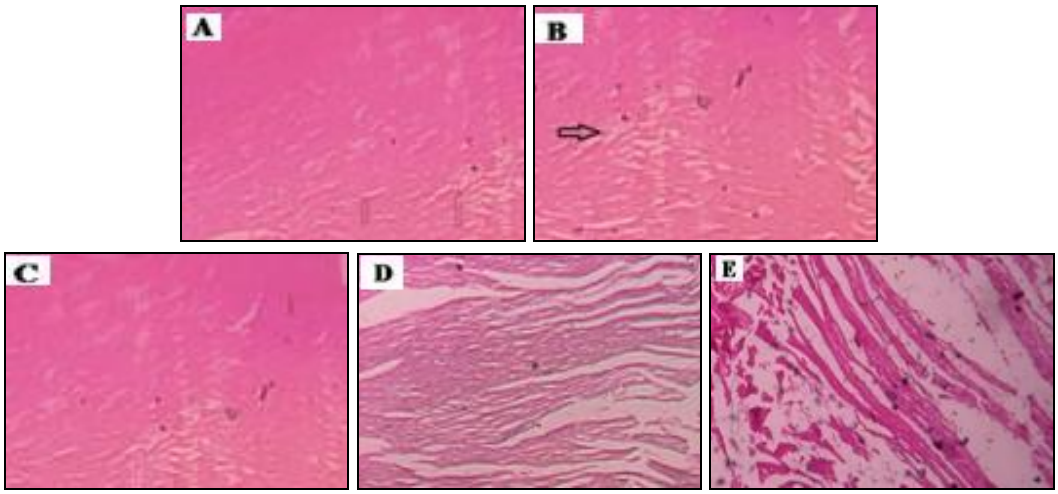


FIG. 3: HISTOPATHOLOGICAL ALTERATIONS OF MYOCARDIAL TISSUE (H&E); MAGNIFICATION ×400. (A) CONTROL ANIMAL SHOWING NORMAL MYOCARDIAL STRUCTURE; (B) ISO (65MG/KG) SHOWING MILD INFLAMMATORY CHANGES;(C) ISO (75MG/KG) SHOWING FOCAL AREAS OF INFLAMMATION AND EDEMATOUS PATCHES ; (D) ISO (85MG/KG) SHOWING PATCHY AREAS OF INFLAMMATORY CELLS WITH MUSCLE STRIATIONS;((E) ISO (95MG/KG) SHOWING MASSIVE INFLAMMATORY AND EDEMATOUS PATCHES WITH AREAS OF NECROSIS.

Dose-dependent changes were observed in the four different doses of ISO induced model, which produced extensive enzymatic and histological variations in the heart, indicating the development of ischemic changes **Fig. 3**. Control rats showed the normal linear architecture of the myocardium with nuclei, coronary veins, and more mitochondria without any alterations. Rats treated with 65mg/kg ISO showed mild inflammatory changes and disruptions of myofibrils.75mg/kg administered rats showed focal areas of necrosis, irregular mitochondria, and interstitial edematous patches. Rats treated with 85mg/kg showed loss of membrane integrity, enlarged myofibrils, myocytic

necrosis, lymphocytic infiltration, and patchy areas of inflammatory cells with muscle striations. Massive inflammation and edematous patches with more focal necrosis were seen in the 95mg/kg dose. The heart and lungs constitute an inseparable anatomic and functional unit. Change in one may affect the other and vice versa [30]. In myocardial ischemia, hypoxia is one of the important characterizations which indicate the direct or indirect influence on functional disturbance of the lungs. In the present study, along with dose determination, the effect of ISO on lungs was also studied through histopathological examination. In **Fig. 4**, Control rats showed normal lung architecture with dense alveoli, and alveolar sacs. In 65mg/kg, dense inflammatory infiltrations and 75mg/kg interstitial thickening with irregular air spaces were seen. Intense chronic inflammation with lymphoid follicles and extensive inflammation with congestion and interstitial thickening was seen at 85 mg/kg and 95mg/kg, respectively.

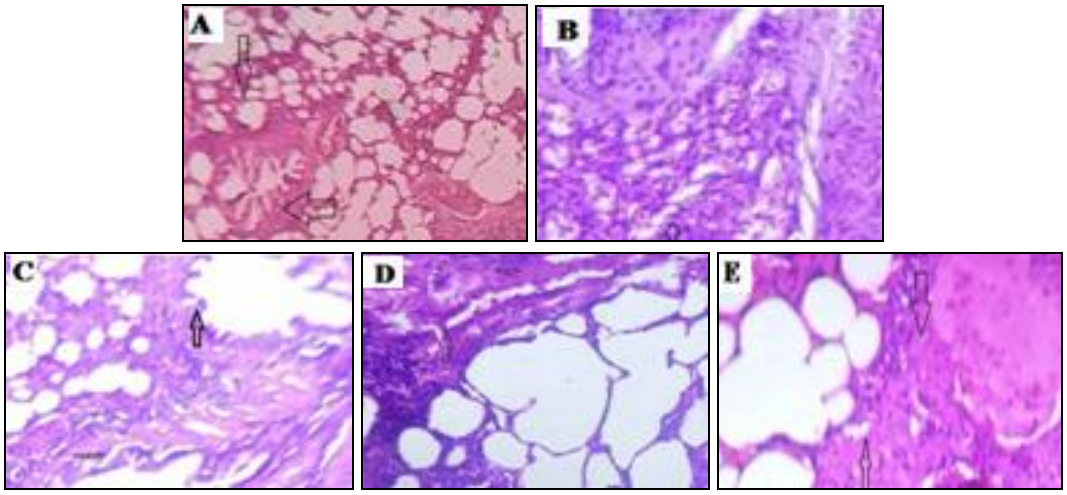


FIG. 4: REPRESENTATIONS OF H&E STAINED LUNG TISSUE WITH DIFFERENT ISOPROTERENOL DOSES TO NORMAL AND INTOXICATED RATS SHOWING MORPHOLOGICAL CHANGES. (A) CONTROL RATS SHOWING NORMAL LUNG ARCHITECTURE WITH DENSE ALVEOLI, ALVEOLAR SAC. (B) ISO (65MG/KG) SHOWING DENSE INFLAMMATORY INFILTRATIONS; (C) ISO (75MG/KG) SHOWING INTERSTITIAL THICKENING WITH IRREGULAR AIR SPACES; (D) ISO (85MG/KG) SHOWING INTENSE CHRONIC INFLAMMATION WITH THE PRESENCE OF LYMPHOID FOLLICLES;((E) ISO (95MG/KG) SHOWING EXTENSIVE INFLAMMATION WITH CONGESTION AND INTERSTITIAL THICKENING

CONCLUSION: Animal models were employed to mimic clinical conditions similar to those found in humans. ISO-induced myocardial ischemia is a simple and less complicated method. As per the review of the literature, single-dose administration of ISO is enough to produce myocardial injury, but infarct-like lesions will be more extensive in repeated doses. In the present investigation, histopathology and biochemical findings confirm that myocardial injury and related necrotic lesions are dose-dependent manners. As the dose increases, the clinical patterns vary, producing severity in myocardial necrosis. Also, evidence of the ISO effect in lungs histologically.

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