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# Pharmacological Study of Dopamine Receptors Agonist and Antagonist on Mouse Model of Myocardial Injury

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Author MFS designed the study, wrote the protocol, wrote the first draft of the manuscript. Author AAZ managed the literature searches, analyses of the study and managed the experimental process. Both authors read and approved the final manuscript.*

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## ABSTRACT

**Objective:** The present study was designed to evaluate the potential protective effect of using mix of bromocriptine 7 mg/kg & metoclopromide 3 mg/kg on the inflammatory biomarkers AST, ALT and LDH1 against isoprotrenol-induced myocardial injury (MI) in mice model.
**Methodology:** Study the effect of dopamine, bromocriptine and metoclopramide on the blood pressure, myocardial inflammatory biomarkers and histological structure of the myocardial tissue. 35 adult male mice were divided into seven groups (5 mice each): group I, control group; group II, isoprotrenol treated group. Group III, Mice with MI were treated with dopamine (0.5/kg/day. IP) for 30 days. Group IV, Mice with MI were treated with bromocriptine (10 mg/kg/day, IP) for 30 days. Group V, Mice with MI were treated with metoclopromide (10 mg/kg. IP) for 30 days. Group VI, Mice with MI were treated with bromocriptine (3 mg/kg) & metoclopromide (7 mg/kg) for 30 days. Group VII, Mice with MI were treated with bromocriptine (7 mg/kg) & metoclopromide (3 mg/kg) for 30 days.

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**Results:** Isoprotrenol induced MI was confirmed by disturbance in serum and heart tissue markers enzymes such lactate dehydrodenase, aspartate transaminase, alanin tranaminase and histopathological changes in the heart of Isoprotrenol administered mice. Mice with MI were treated with bromocriptine (7 mg/kg) & metoclopromide (3 mg/kg) for 30 days was found to ameliorate the effect of isoprotrenol induced histopathological changes, retained myocardial marker enzymes activities at near normal level.
**Conclusion:** The above results indicate the cardioprotective effect of mix of bromocriptine 7 mg/kg & metoclopromide 3 mg/kg aganist isoprotrenol-induced myocardial injury in mice.

*Keywords: Isoprotrenol; myocardial injury; bromocriptine; metoclopramide; lactate dehydrodenase; aspartate transaminase; alanin tranaminase; mice.*

## 1. INTRODUCTION

Myocardial injury is the major cause of morbidity and mortality for cardiovascular diseases [1,2]. Injury may induce deleterious changes, such as decreased myocardial contraction. The mechanisms of injury include the production of reactive oxygen species and calcium overload [3,4]. The resulting alteration in cellular metabolism and generation of toxic molecules contribute to tissue damage in injury, which is characterized by the presence of necrotic areas in the affected organ [5,6].

Dopamine receptors belong to the family of G-protein coupled receptors. The diverse physiological actions of dopamine are mediated by at least five distinct G protein-coupled receptor subtypes. Two $D_1$-like receptor subtypes ($D_1$ and $D_5$) activate adenylyl cyclase. The other receptor subtypes belong to the $D_2$-like subfamily ($D_2$, $D_3$, and $D_4$), inhibit adenylyl cyclase, and activate $K^+$ channels [7]. The activation of $D_2$-like receptors decreases intracellular calcium levels. The underlying mechanisms for this effect may be related to $D_2$-like receptor-induced activation of potassium currents and the subsequent alterations in membrane potential and activation of G proteins. The latter directly inhibits some calcium channels [8]. The activation of $D_2$-like receptors decreases intracellular calcium levels [8]. Dopamine plays an important role in elevation of blood pressure by regulating epithelial sodium transport, vasoconstriction and production of reactive oxygen species and by interacting with the RAS [9]. In rats, $D_1$-like receptors are present on the smooth muscle of the blood vessels in most major organs [10]. $D_2$ receptors have been identified in the atria of rat hearts [11,12]. Dopamine increases myocardial contractility without changing heart rate, by signaling through dopamine receptors. The activation of $D_2$ receptors decreased heart rate, arterial blood pressure [12]. The expression of $D_2$ receptors was reduced in myocardial hypertrophy [13]. $D_2$ receptors also had the protective effect on cerebral injury [14]. However, the role of $D_2$ receptors on myocardial injury has not been clear. In this study, myocardial injury was applied in mice cardiomyocytes and explored the effects of $D_2$ receptors agonist and antagonist on cell apoptosis progression.

## 2. MATERIALS AND METHODS

### 2.1 Animals

The experimental animals used in this study were male albino mice, each weighing 20-30gm. The study was conducted according to the National Institutes of Health guidelines for the care and use of laboratory animals. All animal care and experimental procedures were carried out with the ethics approval of the local regulatory authority. The animals were kept at room temperature with a 12 h/12 h dark /light cycle, which allowed us to perform experiments in the active phase of the animals. Rats were habituated to laboratory conditions. Rats received a standard diet and water.

### 2.2 Chemicals and Drugs

The drugs used were: bromocriptine, dopamine, metoclopramide and isoproterenol. All drugs were purchased from Sigma Chemical Company U.S.A. AST kit, ALT kit and LDH1 kit were purchased from the local market. All other chemicals used in the study were of analytical grade.

### 2.3 Induction of Myocardial Injury

Catecholamines at low concentrations are considered to be beneficial in regulating heart function by exerting a positive inotropic effect. Catecholamines administration at high doses or excess release of it from the endogenous stores may deplete the energy reserve of cardiomyocytes and thus may result in

biochemical and structural changes which are responsible for the development of irreversible damage. Isoproterenol, a sympathomimetic beta-adrenergic receptor agonist, causes severe stress to the myocardium resulting in an infarct like necrosis of heart muscle [15].

The induction of MI was performed in the mice, through IP administration of isoproterenol at a dose of 150 mg/kg/day diluted in 2 ml of saline on two consecutive days with an interval of 24 hours between applications. The false induction of MI in the mice was performed by IP administration of 2 ml of saline on two consecutive days, also with an interval of 24 hours between applications [16,17].

## 2.4 Experimental Design

All the mice were divided into seven groups, each of 5 mice. Group 1: Normal control mice injected with normal saline 10 ml/kg IP for 5 weeks. Group 2: MI mice injected with normal saline 10 ml/kg IP.for 5 weeks. Group 3: MI mice treated with dopamine 0.5 mg/kg IP for 5 weeks. Group 4: MI mice treated with bromocriptine 10 mg/kg IP for 5 weeks. Group 5: MI mice treated with metoclopromide 10 mg/kg IP for 5 weeks. Group 6: MI mice treated with bromocriptine 7 mg/kg + metoclopromide 3 mg/kg IP for 5 weeks. Group 7: MI mice treated with bromocriptine 3 mg/kg + metoclopromide 7 mg/kg IP for 5 weeks.

At the end of the experimental period, the animals were sacrificed by cervical decapitation, blood was collected using heparin as an anticoagulant and plasma was separated for the determination of cardiac marker enzymes (AST, ALT & LDH 1). The heart was dissected out and immediately washed with ice-cold saline. A portion of heart tissue (100 mg) was homogenized in 5 ml of (0.1 N Tris HCl buffer, pH 7.4) and used for the biochemical studies. The homogenate was centrifuged at 2500 rpm and the clear supernatant solution was taken for the assay of biomarker enzyme (AST, ALT & LDH1). Another portion of the heart tissue was stored in formal saline for histological studies.

## 2.5 Blood Pressure Recording

Basal blood pressure and heart rates were measured using non-invasive blood pressure recorder apparatus (Ugo basile instruments, Varese, Italy). Each rat was placed in restrainer and appropriate cuff with sensor was mounted on its tail and warmed to about 33- 35℃. The tail cuff was inflated to a pressure above 200 mmHg, systolic blood pressure; diastolic blood pressure and heart rate were measured directly by the tail cuff and pulse sensor [18,19].

## 2.6 Biochemical Estimation

LDH-Lactate dehydrogenase was assayed according to the methods of Nieland, 1955 [20] & King, 1959 [21]. Alanine aminotransferase (ALT) & Aspartate aminotranseferase (AST) were assayed by the method of King, 1965 [22] using a spectrophotometer (Shimadzu, model AA200, Tokyo, Japan).

## 2.7 Histopathology

Histological evaluation was performed on lower portion of the heart tissue. The heart was then washed with saline solution apical region of the left ventricle was put into a bottle, properly identified, containing a 10% buffered formalin solution. The fixed organs were dehydrated in ascending series of alcohol, cleared in xylene and embedded in paraffin wax, then 4 – 5 µm thick sections were obtained by rotary microtome and stained with Hematoxylin and Eosin [23] and observed microscopically. The severity and extent of MI were observed for each case. The findings were classified into the following degrees, to compose a range of histologic myocardial injury: (0) No change: (1) Mild - focal myocyte damage or small multifocal degeneration with slight degree of inflammation, (2) Moderate - extensive myofibrillar degeneration and/or diffuse inflammatory process, (3) Severe - necrosis with diffuse inflammatory process [24].

## 2.8 Statistical Analysis

All data were expressed as mean ± standard deviation for four animals in every group. Mean values were obtained by one-way analysis of variance (ANOVA), followed by t student's test using 7.5 version of SPSS computer software. The significance of difference between and within various groups was determined. The values were considered significant when $p< 0.05$.

# 3. RESULTS

## 3.1 Hemodynamic Parameter

It was observed that the systolic blood pressure significantly ($p < 0.001$) decreased from 106 ± 5.6 mmHg in the control group to 68 ± 6 mmHg in the isoproterenol treated group (Fig. 1). MI

groups treated with dopamine, bomocriptine and mix of bromocriptine metoclopromide (7:3) induced a significant ($p < 0.001$) increase in SBP as compared to MI control group.

MI groups treated with metoclopromide or mix of bromocriptine & metoclopromide (3:7) showed no change in SBP as compared to MI control group (Fig. 1).

### 3.2 Myocardial Inflammatory Markers

Isoprotrenol-induced MI group produced a significant ($p < 0.001$) decrease of some inflammatory markers inside the myocardial tissue as AST, ALT and LDH 1 (Table 1).

MI groups treated with dopamine, bomocriptine, metoclopromide and mix of bromocriptine metoclopromide 3:7 showed no change in level of all inflammatory markers AST, ALT & LDH1 as compared to MI control group.

MI groups treated with mix of bromocriptine & metoclopromide 7:3 produced a significant ($p < 0.001$) increase in level of AST, ALT & LDH1 in the myocardial tissue as compared to MI control group (Table 1).

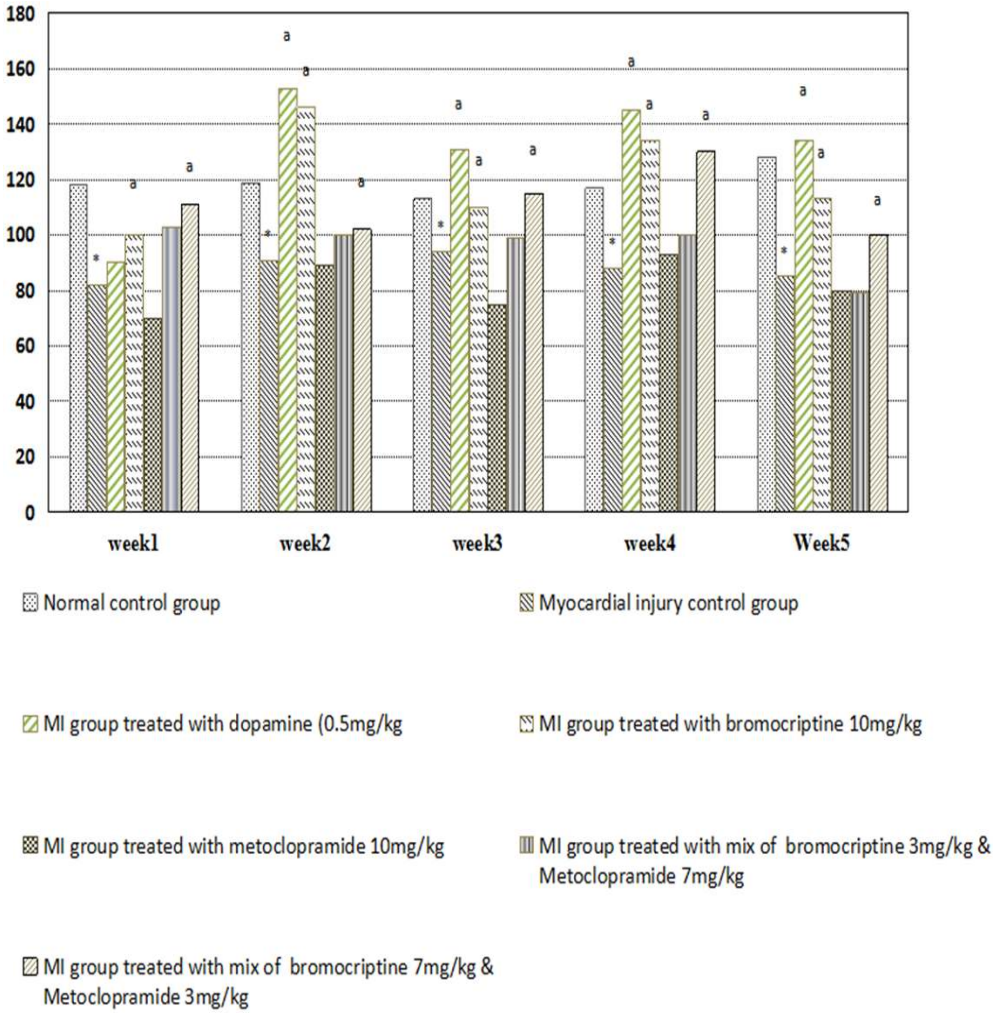


**Fig. 1. The effect of dopamine, bromocriptine, metoclopromide, mix of bromocriptine & metoclopramide (3:7) and mix of bromocriptine & metoclopramide (7:3) on the systolic blood pressure in isoproterenol-induced myocardial injury in mice**

*[Results are expressed as mean ± SD for 6 mice in each group*
** p< 0.05 statistically significant when compared to normal control. [a] p< 0.05 statistically significant when compared to isoproterenol induced myocardial injury control group]*

**Table 1. The effect of dopamine, bromocriptine, metoclopromide, mix of bromocriptine & metoclopramide (3:7) and mix of bromocriptine & metoclopramide (7:3) on AST, ALT and LDH1 contents in heart tissue of isoproterenol induced MI in mice**

| Groups | AST (IU/mg protein) | ALT ( IU/mg protein) | LDH (IU/mg protein) |
|---|---|---|---|
| Normal control group | 51.08±4.93 | 33.72±2.75 | 242.5±25.46 |
| MI control group | 33.44±3.78* | 16.21±1.1* | 134.26±12.55* |
| MI group treated with dopamine (0.5 mg/kg) | 37.41±2.60 | 20.21±1.59 | 163.30±11.46 |
| MI group treated with bromocriptine (10 mg/kg) | 32.81±2.80 | 20.2±1.60 | 156.42±17.47 |
| MI group treated with metoclopromide (10 mg/kg) | 31.81±3.70 | 18.64±1.96 | 129.91±12.55 |
| MI group treated with mix of bromocriptine 7 mg/kg & Metoclopramide 3 mg/kg | 48.79±5.62 [a] | 20.70±2.50 [a] | 194.7±13.54 [a] |
| MI group treated with mix of bromocriptine 3 mg/kg & Metoclopramide 7 mg/kg | 29.58±2.51 | 15.46±1.30 | 139.32±14.43 |

** P< 0.05 statistically significant when compared to normal control. [a] P< 0.05 statistically significant when compared to isoproterenol induced myocardial injury control group*

### 3.3 Histopathology Study

Isoproterenol induced MI group showed edema, area of necrosis and increase in number of inflammatoy cells in the myocardial tissue (class 3), (Fig. 3).

MI groups treated with bromocriptine, metoclopramide and mix of bromocriptine metoclopramide 3:7 showed no changes in the myocardial tissue as compared to MI control group (class 3), (Figs. 5, 6 and 7).

MI group treated with dopamine showed a moderate change in myocardial tissue (class 2). Only mix of bromocriptine & metoclopromide 7:3 showed marked decreases in necrotic area, edema and inflammatory cells (class 1), (Figs. 4 and 8).

## 4. DISCUSSION

Cardiomyocyte apoptosis is a major pathogenic mechanism underlying myocardial injury [25]. However, very little is known about the effect of dopamine $D_2$ receptors activation or suppression on cardiac apoptosis-induced by ischemia/reperfusion injury. In this study, we examined whether bromocriptine (a selective agonist of dopamine $D_2$ receptors) or haloperidol (dopamine $D_2$ receptors antagonist) play a role in cardiomyocyte apoptosis induced by simulated ischemia/ reperfusion injury.

It has been proposed that ISO-induced metabolic and morphologic aberrations in the heart tissue of the experimental animals have been reported to be similar to those observed in human myocardial infarction [26]. Myocardium contains an abundant concentration of diagnostic marker enzymes of myocardial injury, LDH1 and transaminases and once metabolically damaged, releases its contents into the extra cellular fluid [27]. In isoproterenol induced myocardial injury group, the increased activities of the serum marker enzymes accompanied by their concomitant reduction in the heart homogenate confirm the onset of myocardial necrosis. The increased levels of malondialdehyde indicate excessive formation of free radicals by auto-oxidation of ISO and activation of the lipid peroxidation process, resulting in irreversible damage to heart in animals subjected to ISO stress [28]. Using mix of bromocriptine 7 mg/kg and metoclopromide 3 mg/kg shows a marked decrease in the inflammation of the myocardial injury by decreasing the inflammatory markers AST, ALT and LDH1 in the heart tissue. The protective effect could be due to reducing the cardiac damage, thereby restricting the leakage of these enzymes into the circulation. The small dose of the metoclopromide induced a partial stimulation of bromocriptine on D2 receptors in the myocardial tissue because of its D2 antagonism effect. The role of the metoclopromide in the mix is protection of the cardiac tissue and decrease the adverse effect of the bromocriptine.

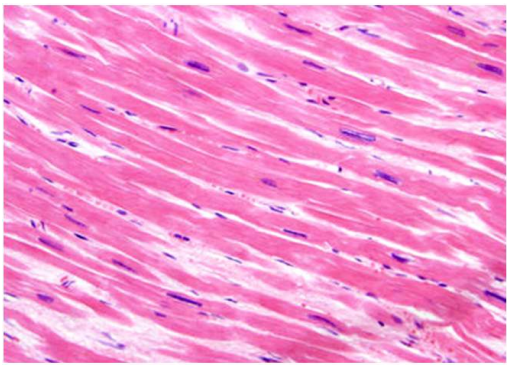

**Fig. 2. Normal control group received saline showing normal architecture of myocardium**

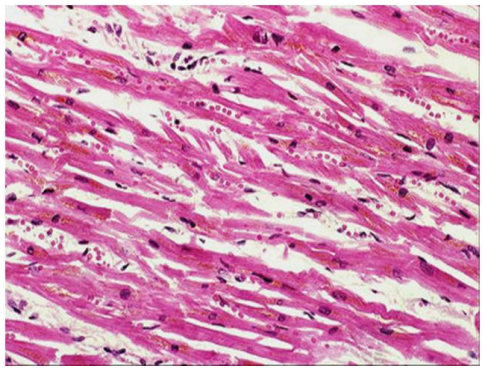

**Fig. 3. MI control group received two IP injections of ISO showing necrosis of myofibrils and edema through penetration of inflammatory cells and extravasations of red blood cells**

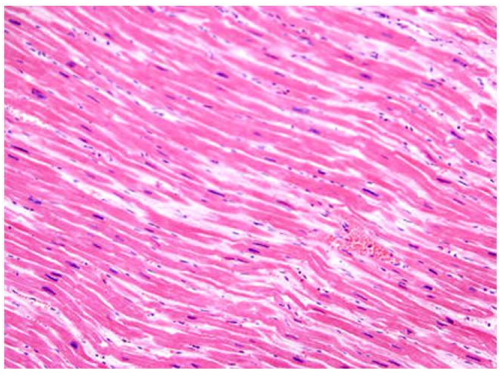

**Fig. 4. MI gp treated with dopamine showed a moderate change in the myocardial tissue**

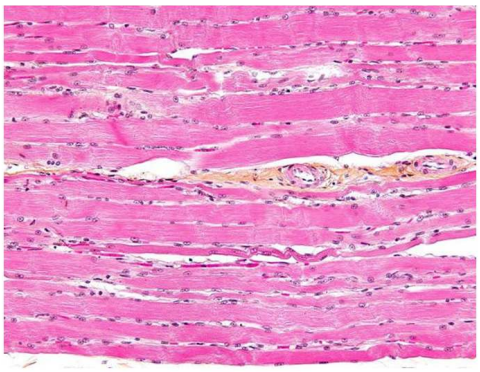

**Fig. 5. MI Group treated with Bromocriptine showed a small area of necrosis of muscle fibers with cell infiltration, edema, increased connective tissue among myocardial fibers**

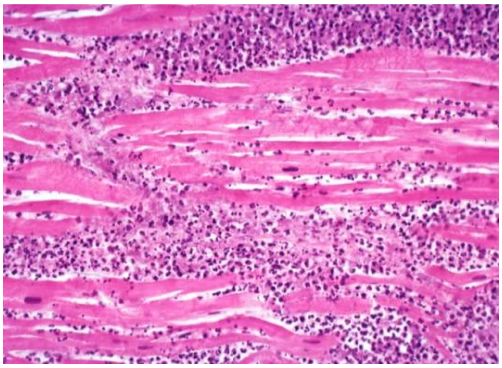

**Fig. 6. MI group treated with metoclopromide showed edema through penetration of inflammatory cells and extravasations of red blood cells**

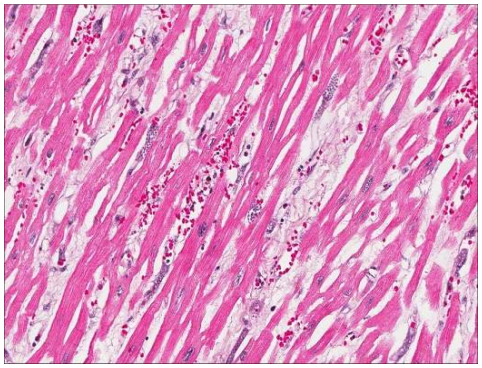

**Fig. 7. MI group treated with mix of bromocriptine & metoclopromide (3:7) showed a necrosis of muscle fibers with cell infiltration, edema, increased connective tissue among myocardial fibers**

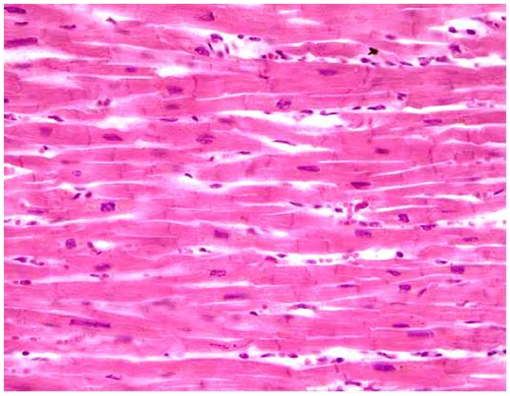

**Fig. 8. MI group treated with mix of bromocriptine & metoclopromide (7:3) showed protection from myocardial injury evidenced by decreased myonecrosis as well as edema and extravasations of the RBCs with minimal inflammation (magnification 200x)**

According to the obtained results, Stimulation of D2 receptors by dopamine or bromocriptine (D2 agonist) show increasing in BP in the myocardial injury mice model. Over the past 25 years, bromocriptine has been studied in the treatment of clinical indications such as acromegaly, hyperprolactinemia, postpartum lactation suppression, cocaine craving, and diabetes mellitus, in addition to Parkinson disease. Rather than a cardioprotective effect, bromocriptine shares with other ergot alkaloids the property of vasoconstriction, with the potential for serious tissue injury. Hypertension [29] and cardiac injury [30] have been reported in association with bromocriptine use in lactation suppression. Seizures and myocardial infarction were reported in association with bromocriptine use in the treatment of cocaine craving, which led the Italian Health Ministry to request the withdrawal of bromocriptine for use in cocaine craving [31]. Finally, in clinical trials of bromocriptine for the treatment of Type 2 diabetes presented to the Food and Drug Administration, a relative risk of myocardial infarction after bromocriptine treatment was found.

## 5. CONCLUSION

In the present study, using of metoclopromide (selective D2 antagonist) in high dose antagonize the effect of bromocriptine on the BP. The effect of bromocriptine alone didn't show any protection on the myocardial injury after treatment for 5 weeks. The histopathology study reveals the cardioprotection effect of mix bromocriptine, metoclopramide (7:3) as compared to using bromocriptine alone. Using metoclopromide in high dose produced complete blocking of D2 receptors and antagonizes the effect of bromocriptine on the myocardial tissue but using metoclopramide in small dose induced partial antagonism on D2 receptors and may block the risk of bromocriptine on the myocardial tissue. This study needs more methods to study the effect of bromocriptine alone and in combination with metoclopramide on isolated heart perfusion to reveal the effect of the drugs on the force of contraction of the heart and rate of heart beating.

## CONSENT

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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