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The Potential Renoprotective Effects of Ticagrelor in Rhabdomyolysis-Induced Acute Kidney Injury in Rat

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ORIGINAL STUDY

The Potential Renoprotective Effects of Ticagrelor in Rhabdomyolysis-induced Acute Kidney Injury in Rat

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Abstract

Background: **Rhabdomyolysis is a potentially lethal range of symptoms results from muscle cell destruction. It is recognized by the escape of cell contents such as myoglobin, creatine kinase, and electrolyte into the bloodstream then undergo glomeruli filtering. Therefore, among the most dangerous complication of rhabdomyolysis is acute renal injury. The complex and interrelated processes underlying rhabdomyolysis that ends with acute kidney injury include obstruction and damage of tubules, inflammation, and intrarenal vasoconstriction (activation of the sympathetic, renin-angiotensin). Glycerol is frequently used to inflict this kind of harm when used as a single dose injection that given intramuscularly to an animal model.**

Aim of study: **This study aims to evaluate the reno protective effect of ticagrelor in rat model of rhabdomyolysis condition (caused by glycerol injection) that leads to acute kidney injury.**

Methods: **Sprague Dawley adult male rats (thirty-five) were classified into (A) group of control (B) group of vehicles (C) induction group (glycerol) (D) vehicle with induction group (E) ticagrelor with induction group. The markers used in this study which include renal function tests (blood urea nitrogen and serum creatine) were measured by chemical analysis while interleukin one beta and caspase3 were measured by enzyme-linked immunosorbent assay.**

Results: **When comparing the induction group (glycerol) to the group of control there is a significant increase in the serum creatine as well as blood urea nitrogen and renal tissue interleukin one beta in addition to renal tissue caspase3, on other hand all these markers reduced in the group of ticagrelor in contrast to induction group.**

Conclusion: **Ticagrelor reduced renal dysfunction in rhabdomyolysis caused by glycerol via reducing the potential for apoptosis and the body's response to inflammation in addition to its antiplatelets impact.**

Keywords: Acute kidney injury, Caspase 3, IL-1β, Renal function, Rhabdomyolysis

1. Introduction

Acute kidney damage occurs when there is a swift (within a few of hours) drop in functions of the renal system, encompassing decline in function in addition to structural deterioration [1]. Acute kidney injury (AKI) has an affiliation to greater rates of hospitalization and death rate making it a major worldwide health concern [2]. It affects approximately 13.3 million individuals annually resulting in about 1.7 million death [2]. It was considered a syndrome within a simplified frame including the pre, post and intra-renal disorders associated with numerous variables [3]. Acute kidney injury in hospital acquired cases, which account for 20% of patient cases appears to be caused by renal ischemia, sepsis, and nephrotoxic drugs such aminoglycosides, vancomycin, amphotericin, non-steroidal anti-inflammatory drugs, cisplatin, and ciclosporin [4]. Acute kidney damage can have a variety of effects the most prevalent ones being metabolic abnormalities such as swelling in the peripheral regions, high levels of phosphate and potassium, besides the problems that could affect the heart's function and the nervous systems of the body [5]. Acute kidney injury consider one of the

Abbreviations: NF-KB, Nuclear factor kappa B; MDA, Malondialdehyde; Mb, Myoglobin; IL-1β, Interleukin one beta; DMSO, dimethyl sulfoxide; ELISA, Enzyme linked immunosorbent assay.

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most frequent negative outcomes of rhabdomyolysis which is a disease that arises after muscle destruction due to injury or damage [6]. In as many as 7–10% of cases of rhabdomyolysis is thought to be AKI [7].

Rhabdomyolysis describes injury to skeletal muscle cells brought on by drugs, toxins, ischemia, trauma, metabolic processes, or infections that impair the function of the plasma membrane (sarcolemma) [8]. Its distinguishing features include the release of myoglobin, sarcoplasmic proteins (alanine, aspartate aminotransferase, aldolase, and lactate dehydrogenase) and electrolyte from muscle cells [9]. These compounds can trigger (AKI) through multiple pathways including tubular injury brought on by the generation of oxygen-reactive compounds beside the vasoconstriction that caused by myoglobin and renin angiotensin aldosterone system activation as a result of fluid released from the cells to interstitial. Vasoconstriction negatively affect renal blood flow and exacerbate renal injury due to ischemia, in addition to intratubular obstruction caused by precipitation of proteins [10]. Rhabdomyolysis etiology can be classified into physical causes (trauma, fever, immobilization, ischemia, exercise) and no physical causes (infection electrolyte disturbance, genetic disorder, drug and toxin) [11].

Among the frequent animal model used to evaluate AKI as a side effect of RM is rat when given just one injection of glycerol 50% intramuscularly 10 mL per kilogram [12].

Ticagrelor, which works as an analog of adenosine triphosphate (ATP), is the first direct inhibitor of the platelet P2Y12 receptor. Compared to other adenosine receptors, ticagrelor is highly selective and lipophilic for this particular adenosine receptor [13]. Ticagrelor is the first oral P2Y12 receptor reversible antagonist that binds reversibly and inhibits platelet activity in individuals with coronary artery disease (CAD) [14]. It has been demonstrated in previous studies [15,16] that ticagrelor lowers the death rate from infections and sepsis which are two inflammatory diseases. Therefor aim of current study to evaluate ticagrelor role in rhabdomyolysis condition based on its anti-inflammatory, antiapoptotic and antiplatelets impact. The best of our knowledge there is no previous research about ticagrelor role in rhabdomyolysis condition.

2. Materials and methods

This study was carried out in compliance to the Kufa University pharmacy college research ethical standards committee. The University of Kufa's Animal Care and Research Committee had to approve the study before rats could be included.

2.1. Animals

Rats of Sprague-Dawley species were purchased (200–250) gram from the animal house of Kufa University in Iraq, which is home to the scientific staff. Animals had been placed in carefully regulated environments with a cycle of 12 h of light and darkness 24 ± 1 °C constant temperature, and 60 ± 10% humidity. Before any experimental techniques, a week was spent acclimating.

2.2. Drug and chemical used

Ticagrelor has been brought from Med. Chem-Express in the United States and formulated to clear solution by using dimethyl sulfoxide (10% DMSO and 90% normal saline). It has been administered at a dose of 30 mg/kg intraperitoneally, in addition to glycerol that also brought from Med. Chem-Express and diluted with 90% normal saline to get 50% concentration, glycerol was given at dose of 10 mg/kg.

2.3. Experimental design

Thirty-five adult male Sprague-Dawley rats were divided into five groups, each consisting of seven rats at random.

1-Group of control: Rats of this group didn't undergo any intervention.

2-Group of Vehicle: Rats of this group were given a solvent consisting of dimethyl sulfoxide (DMSO) 10% diluted with normal saline 90% serving as a vehicle for ticagrelor (following manufacturing direction Med chem express/USA) given via intraperitoneal (IP) injection.

3-Induction group (glycerol): Rats were given injectable intramuscular (10 ml/kg) glycerol with 50% concentration (glycerol was injected deeply into each of the rear legs).

4-Ticagrelor group: Rats were injected with ticagrelor 30 mg/kg intraperitoneally then after half hour rats were given 10 ml/kg glycerol 50% intramuscular injection.

5-Vehicle with induction group: Rats were administered dimethyl sulfoxide (DMSO) 10% with normal saline 90% via intraperitoneal (IP) injection followed by 10 ml/kg glycerol intramuscular injection 50%.

Following 24 h of procedure rats were anesthesia by ketamine (100 mg/kg) and xylazine (10 mg/kg) [17] an inner abdominal opening was made and an

intracardiac needle was used to drain the blood. Samples of blood were put in a simple tube and kept at 37 °C devoid of the use of an anticoagulant. The serum was then extracted from the tubes by centrifuging them for 10 min at 3000 rpm. Serum creatinine and urea were determined from the recovered serum in accordance with the manufacturer's instructions (using chemical analysis test Backman Coulter fully automatic AU400 apparatus). Ahigh-intensity ultrasonic liquid processor was used to homogenize the frozen kidney tissue (1:10 wt/volume) in phosphate-buffered saline. The left kidney was frozen at −80 °C. Protease inhibitor cocktail and 1% Triton X-100 were used in this process. The homogenate was centrifuged for 20 min at 4 °C at 3000 rpm. Then the supernatant was collected. Using the enzyme-linked immunosorbent assay (ELISA) technique the levels of and interleukin one beta (IL-1β) and caspase 3 were detected in accordance with the manufacturer's instructions.

2.4. The statistical analysis

GraphPad Prism 8.0.1 was used for the analysis of the data in this study. The results were evaluated using One-Way Analysis of Variance (ANOVA). A significant value of $P < 0.05$ was used to evaluate statistical significance for each test.

3. Results

After collection of data from a total of 35 samples (7 rats in each group) which undergo many measures such as measurement of inflammatory markers (IL-1β) and Caspase3 for apoptosis. In addition to evaluate renal function serum creatine and blood urea nitrogen all undergo appropriate statistical analysis to evaluate the goals of the study. The serum concentration of urea was increased significantly in the induced (glycerol) group the mean of urea in the induction group was (88.29) mg/dl when compared with group of control the mean of urea in the control group was (22.57) mg/dl. While the level of blood urea of glycerol group was not changed significantly in comparison with glycerol with vehicle group in which the mean of urea was (89.00) mg/dl, rats with ticagrelor group significantly lowered blood urea level when compared with glycerol induced group with mean of serum urea in ticagrelor group was (38.14) mg/dl as shown in Fig. 1 and Table 1. Serum creatine mean of glycerol group was (3.366) mg/dl and for ticagrelor group (1.294) mg/dl. While the control group and vehicle were (0.6100) and (0.6000) mg/dl

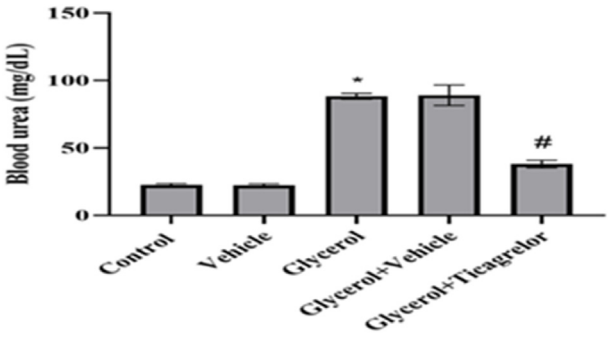

Fig. 1. Serum concentration of urea in the experimental groups. Data are presented as mean ± standard error mean (SEM) (n = 7) #: Significant differences when compared to glycerol (p value less than 0.05): Significant differences when compared to control (p value less than 0.05).*

Table 1. Serum blood urea nitrogen levels means and standard error mean in experimental study.

Groups	Mean	SEM (standard error mean)
Control	22.57	1.172
Vehicle	22.14	1.335
Glycerol	88.29	2.168
Glycerol + vehicle	89.00	7.515
Glycerol + ticagrelor	38.14	2.849

respectively as shown in Fig. 2 and Table 2. The tissue concentration of IL-1β was increased significantly in the induced group (5069) pg/ml, in contrast to control group (2036) pg/ml. The level of

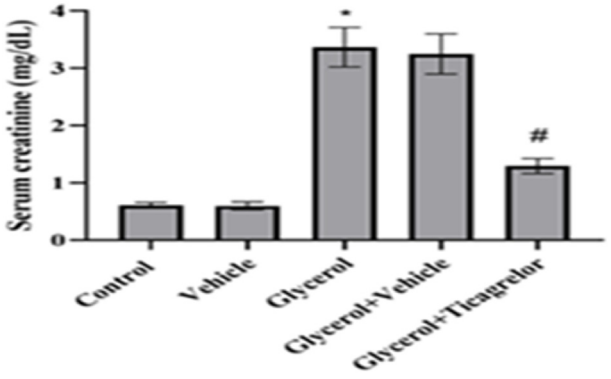

Fig. 2. Serum concentration of creatinine in the experimental groups. Data are presented as mean ± standard error mean (SEM) (n = 7) #: Significantly different in contrast to glycerol (p < 0.05): Significant differences when compared to control (p value less than 0.05).*

Table 2. Serum creatine means and standard error means in experimental groups.

Group	Mean	SEM
Control	0.6100	0.04865
Vehicle	0.6000	0.06782
Glycerol	3.366	0.3448
Glycerol + vehicle	3.249	0.3500
Glycerol + ticagrelor	1.294	0.1310

IL-1β of glycerol with vehicle was (4883) pg/ml not changed significantly in comparison with induced group glycerol only. Rats with ticagrelor group significantly lowered IL-1β level (3081) pg/ml when compared with induced group as shown in Fig. 3 and Table 3. The tissue level of caspase-3 was significant elevated in the induced group the mean of caspace3 was (2442.86) ng/ml when compared to control group the mean was (304.429) ng/ml while the vehicle group mean was (317.286) ng/ml. The level of caspase-3 mean of glycerol with vehicle group was (2444.57) ng/ml was not changed significantly in comparison with induced group. Rats with ticagrelor group (1366.71) ng/ml significantly lowered caspase-3 level when compared with induced as in Fig. 4 and Table 4.

4. Discussion

A quickly drop in function of the kidneys consider an indicative of acute kidney injury which is linked to more complicated pathophysiological events and may have several fundamental causes [18]. Rhabdomyolysis is a very serious set of signs that arises

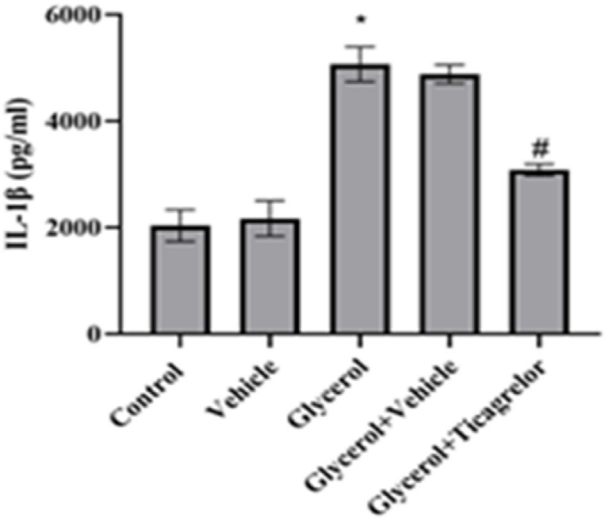

Fig. 3. Tissue concentration of IL-1 Beta in the experimental groups. Data are presented as mean ± standard error mean (SEM) (n = 7) #: Significant difference in comparison with glycerol (p value less than 0.05) Significant differences in contrast to control (p value less than 0.05).*

Table 3. Renal tissue IL-1 beta means and standard error means in experimental groups.

Group	Mean	SEM
Control	2036	297.2
Vehicle	2169	331.9
Glycerol	5069	328.6
Glycerol + vehicle	4883	174.7
Glycerol + ticagrelor	3081	110.2

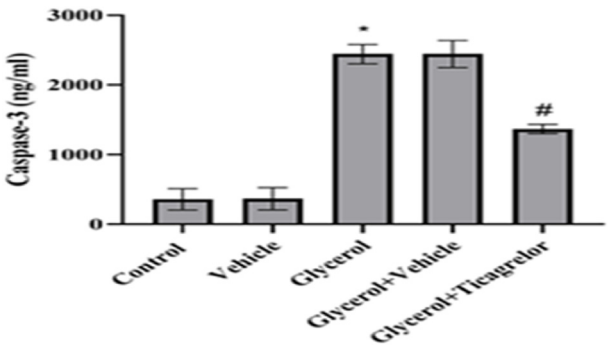

Fig. 4. Tissue renal concentration of caspase 3in the experimental groups. Data are presented as mean ± standard error mean (SEM) (n = 7) #: Significant differences when compared to glycerol (p < 0.05) Significant differences when compared to control (p value less than 0.05).*

Table 4. Renal tissue caspase 3 means and standard error means in five groups.

Group	Mean	SEM
Control	304.429	34.1996
Vehicle	317.286	57.9962
Glycerol	2442.86	139.039
Glycerol + vehicle	2444.57	194.891
Glycerol + ticagrelor	1366.71	66.2814

from the breakdown of muscles and excessive release of intracellular components such as potassium, creatine kinase and myoglobin in the bloodstream's [19]. The mechanisms behind AKI caused by rhabdomyolysis include vasoconstriction, tubular obstruction, direct tubule injury and inflammation are all induced by free myoglobin [20].

4.1. The rhabdomyolysis effects on renal function (blood urea nitrogen and serum creatine) and the role of ticagrelor in such case

Intracellular fluid leaks initially and later get trapped in extracellular gaps during muscle breakdown. Depleting the intravascular volume causes the renin-angiotensin-aldosterone system to be activated, which reduces renal blood flow and causes vasoconstriction. Myoglobin nephrotoxicity also contributes to this reduction in renal blood flow by obstructing it [10]. Following rhabdomyolysis, the structural damage in kidney tissue such as absence of brush boundaries, tubular casts, and damaged tubes were viewed this resulted in deteriorate in renal function. Loss of kidney excretory function suggests problems with the kidneys' primary job of maintaining homeostasis like the elimination of waste materials from the metabolic process. Urea and serum creatinine levels frequently serve as

markers of reduced kidney function [21]. Also, serum creatine level rise after rhabdomyolysis as the damaged muscle produces creatinine [22].

In present study serum creatine and nitrogen blood urea significantly elevated in induction group (rats were injected with glycerol only) compared to control group this agree with other study in rat model injected with intramuscular glycerol that also elevated serum creatine and nitrogen blood urea [23], in addition to other study with equivalent effect on rat model [24] and group that injected with glycerol and vehicle showed absence of significant change when compared with induction group this may be due to lack any benefit from intraperitoneal vehicle injected to rat. In other hand vehicle and control group have no significant differences this because the vehicle doesn't make any change and rats were injected with vehicle to exclude any response that may related to vehicle and the result showed no response to the vehicle. While group of ticagrelor results in significant reduction in serum creatine this agree with the impact of ticagrelor on immediate damage to the renal system in rats with sepsis [25], same result of ticagrelor in other research on rapid renal damage triggered by sepsis in a mice species [26]. There is no previous research on the impact of ticagrelor on nitrogen blood urea to be compared with current study. Since platelets are largely involved in the coagulation synthesis of substances that promote inflammation and stimulation of immune system pathways, so ticagrelor's ability to improve renal function may be connected to its antiplatelet properties [27]. Platelets have a critical role in controlling leukocyte activity and consequently inflammatory immunological responses [27,28]. Platelet activity is inhibited by ticagrelor [14]. According to the findings, ticagrelor may be able to preserve renal function by reducing inflammation and the neutrophil inflow into the kidney as a consequence of activating platelets. Therefore, the results protect renal tissue and improve renal function.

4.2. The rhabdomyolysis and ticagrelor effects on apoptotic pathway in renal tissue

Apoptosis in rhabdomyolysis is associated with myoglobulin nephrotoxicity through enhancing oxidative damage. Myoglobin (Mb), an iron and oxygen-carrying protein primarily found in skeletal muscle, releases free ions to catalyze the Mb redox cycle-induced lipid peroxidation and the Fenton reaction, both of which injure the kidney through oxidative stress [29]. In comparison to the control and vehicle groups caspase 3, which is thought of as a marker for the apoptotic pathway, increased dramatically in the induction (glycerol) group and the glycerol with vehicle group this agree with other study [30] that showed elevated caspase3 in case of glycerol injection in mice model in addition to another research on rat model produced same effect in glycerol group when compared to control group [27]. While in ticagrelor group results showed significant reduction in caspase3 compared to induction (glycerol) group and (glycerol with vehicle) group this result exactly agree with previous study that validate ticagrelor's anti-apoptotic characteristics in an in vitro manner using oxygen deprivation endothelial cells in a cell culture setting [31], the explanation for ticagrelor ability in reduce caspase3 may due to reduces oxidative damage and lipid peroxidation, which is a sequence of myoglobin nephrotoxicity on tubules. This idea is consistent with other rats' study of ticagrelor that reduced lung and cardiac apoptosis (cell death) by minimizing Malondialdehyde (MDA) an index of lipid peroxidation mediated by oxidative stress [32]. Previous study has shown that MDA is typically high in rhabdomyolysis condition that are generated by glycerol [24].

4.3. The rhabdomyolysis and ticagrelor effect of on IL-1β

Apart from myoglobin and other substances produced by damaged cells during rhabdomyolysis, these can also result in oxidative stress and trigger the induction of the Nuclear Factor Kappa B (NF-kB) signaling cascade [33], subsequently releasing inflammatory agents including IL-1β.This can trigger inflammatory process and damage to renal tissue in rhabdomyolysis [34]. The results of present study glycerol group and glycerol with vehicle group showed high level of IL-1 β that is significant when compared with control and vehicle groups this totally agree with previous study of glycerol injected intramuscularly to mice and level of IL-1β was significantly elevated when compared with control group of same study [35] while ticagrelor group appeared with low level of IL-1 β and is significant when compared to glycerol and glycerol with vehicle groups this agree with past study on mice with sepsis [25] additionally ticagrelor markedly reduced the development of caspase-1 and the release of IL-1β and compatible with other research in macrophage in vitro experiment [36]. It is also possible that the Platelet p-selectin (CD62P) which is a classic platelet activation protein that directly stimulate the production of IL-1β and additional cytokines [37]. CD62p usually activated during

platelet activation [35]. Since platelet activated in rhabdomyolysis syndrome [38] so antiplatelet effect of ticagrelor may be responsible for attenuating the release of IL-1 β.Other possible explanation about ticagrelor ability to decline IL-1B may related to ticagrelor ability to suppress NFKB pathway [39], therefore NFKB suppression by ticagrelor may leads to reduce IL-1B release [23].

5. Conclusion

Ticagrelor demonstrates significant renoprotective property in rat model with rhabdomyolysis triggered by glycerol through minimizing renal dysfunction and attenuating kidney tissue damage via its anti-apoptotic, anti-inflammatory effect in addition to its antiplatelet role suggesting potential therapeutic benefit in acute kidney injury induced by rhabdomyolysis.

Ethics Information

The research ethics committee of Kufa University confirmed the ethical rules and steps that were followed in completing this work with document number 13076 in 25/12/2023.

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