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The effect of prostaglandin E2 on gentamicin- induced nephrotoxicity in rats

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ABSTRACT

Introduction: Gentamicin (GM) is a widely used aminoglycoside antibiotic. The nephrotoxicity of gentamicin causes reducing renal blood flow via vasoconstriction. Given PGE2's vasodilatory effects and the mechanisms of tissue damage in GM-induced nephrotoxicity, such as vasoconstriction, the aim of this study was to investigate the protective role of PGE2 in GM-induced nephrotoxicity. The diclofenac sodium was used to assess the direct effects of exogenous PGE2 by blocking endogenous production.

Materials and methods: The experiment was conducted on 56 male Wistar rats (200–250 g). Renal nephrotoxicity was induced by intraperitoneal (i.p.) injection of gentamicin (100 mg/kg). The therapeutic effects of PGE2 (0.2 µg/kg) and diclofenac (0.5 mg/kg) were assessed. The rats were placed in individual metabolic cages to collect urine. The systolic blood pressure and renal blood flow were measured. Levels of urea, creatinine, sodium, potassium, magnesium, and osmolarity were analyzed in plasma and urine samples. The left kidney was used for histological analysis.

Results: Administration of gentamicin for eight consecutive days resulted in a significant increase ($p<0.001$) in serum creatinine, blood urea nitrogen (BUN), absolute sodium excretion (UNaV), and fractional excretion of sodium and potassium (FENa and FEK), while creatinine clearance, urine osmolarity, and renal blood flow significantly decreased ($p<0.001$) compared to the control group.

Treatment with PGE2 significantly reducing serum creatinine, UNaV, FENa, FEK ($p<0.001$), and BUN ($p<0.05$), while significantly increasing creatinine clearance, urine osmolarity, and renal blood flow ($p<0.001$).

Conclusion: Prostaglandin E2 provided substantial protective effects against gentamicin induced acute nephrotoxicity in rats.

Keywords: Gentamicin, Nephrotoxicity, Prostaglandin E2, Diclofenac, Rat.

INTRODUCTION

Gentamicin (GM) is an aminoglycoside antibiotic widely used to treat infections caused by Gram-negative bacteria. However, its use is limited due to side effects such as nephrotoxicity. Gentamicin-induced nephrotoxicity (GIN) occurs in 10 to 20 percent of treatment cases (1). GIN typically presents as non-oliguric acute renal failure, characterized by reduced renal blood flow and impaired ability to concentrate urine (2). The pathological mechanism of GIN involves oxidative stress, lysosomal phospholipidosis, increased endothelin-1 levels, and enhanced macrophage infiltration, leading to inflammation (3-5). These processes ultimately result in tubular dysfunction, a reduction in glomerular filtration rate (GFR), and dynamic intraglomerular changes (6).

Prostaglandins, derivative of arachidonic acid, are involved in various physiological and pathological functions within the kidneys, intestines, cardiovascular, and reproductive

systems (8). Among them, PGE_2 plays a crucial role in kidney function, including transmembrane and transepithelial transport of water and solutes. (9). Furthermore, PGE_2 plays a vital role in regulating glomerular blood flow, exhibiting both vasodilatory and vasoconstrictory effects, and influencing GFR through its impact on the renal vascular system. (10-12). PGE_2 exerts its effects through four main receptors, known as EP receptors: EP1, EP2, EP3, and EP4. These receptors are G protein-coupled receptors that activate various intracellular signaling pathways upon binding to PGE_2. Among these receptors, EP2 and EP4 are more closely associated with promoting vasodilation, inflammation, and renal functions, including the regulation of GFR (12-14).

Endogenously, PGs are produced by cyclooxygenases (COXs). Cyclooxygenase consists of COX-1 and COX-2, which convert arachidonic acid into PGs (15-17). (18, 19). Nonsteroidal anti-inflammatory drugs (NSAIDs) are inhibitors of COXs and can block their functions either selectively or non-selectively. Diclofenac is a non-selective NSAID that possesses anti-inflammatory, antipyretic, and analgesic properties.(20, 21). It has been shown that diclofenac exerts a strong, dose-dependent inhibitory effect on the production of PGE_2 among PGs (22). Given vital role of PGE_2 in normal kidney function such as supporting renal blood flow, GFR, and electrolyte balance its inhibition by diclofenac can have detrimental effects on kidney function, especially in individuals with existing renal conditions.

In this study, we aimed to explore whether exogenous administration of PGE_2 could counteract the adverse effects of GM on renal function. We hypothesized that PGE_2 would provide a protective effect by maintaining renal perfusion, promoting GFR, and reducing tubular damage. By focusing on the role of PGE_2, we aimed to enhance our understanding of its potential therapeutic applications in preventing or alleviating nephrotoxicity associated with GM treatment.

Additionally, diclofenac sodium was utilized in this study to inhibit the production of endogenous prostaglandins, including PGE_2. By administering diclofenac, we could effectively block the natural synthesis of PGE_2 in the body. This approach allowed us to assess the direct effects of exogenous PGE_2 administration, isolating its protective role from any contributions made by the body's own prostaglandins. This comparative analysis was crucial for understanding how PGE_2 functions in the context of GM-induced renal injury and for evaluating its therapeutic potential.

In this study, we demonstrated that PGE2 enhances renal blood flow and restores electrolyte balance, disrupted by gentamicin-induced nephrotoxicity.

MATERIALS AND METHOD

Animal

Animal care, surgery and recording procedures were in accordance with the guidelines laid down by the animal care and ethics committee of Arak university of medical science. The experiments were conducted on56 male Wistar rats weighing between 200 and 250 grams. The animals were kept at a controlled temperature of 23 ± 2°C and subjected to a 12-hour light/dark cycle. All rats were housed in plastic cages under standardized conditions and had free access to standard food and water. All the ethical codes established by Committee of Monitoring Laboratory Animals of Arak University of Medical Sciences

considered for all experiments on animals (Ethical code: IR.ARAKMU.REC.1394.248).

Experiments protocol:

GM (100mg/kg/d, Alborz daruo Co.Iran), Diclofenac (5mg/kg/d, sigma, USA) and PGE_2 (2µg/kg/d, Cayman, USA) were intrapritoneally injected for 8 consecutive days (23). Experimental groups consist of 1. control group (received saline injection for 8 days), 2. GM group (received GM injection for 8 day), 3. Diclofenac (DIC) group (received diclofenac injection for 8 days), 4. GM+DIC group (received GM+DIC injection for 8 days), 5. PGE_2 group (received PGE_2 injection for 8 days), 6. GM+PGE_2 group (received GM+PGE_2 injection for 8 days), 7. GM+DIC+PGE_2 group (received GM+DIC+PGE_2 injection for 8 days).

Urine collection and blood pressure measurement

After completing the 8-day treatment period, the rats were placed in metabolic cagesfor 6 hours to collect urine. Once the urine was collected and weighed, the animals were anesthetized using sodium pentobarbital (60 mg/kg, intraperitoneally, Sigma-USA)(26). Then, Systolic blood pressure was measured using LabChart and PowerLab (AD Instruments, Australia) paired with a non-invasive blood pressure system with a specialized tail transducers/cuff which measured blood pressure based on the periodic occlusion of tail blood flow.

Renal blood flow measurement

A longitudinal incision was made in the shaved abdominal area to expose the left kidney's artery and vein. Renal blood flow was assessed with a flowmeter with a specialized probe (T402, USA), the probe was placed around the kidney artery to measure renal blood following a 30-minute stabilization period, the renal blood flow was measured for 1 hour.

Collecting blood sample

Blood samples were collected from the abdomial aorta using a heparinized syringe, and plasma was obtained by centrifugation (Eppendorf AG22331, Germany). Both urine and plasma samples were analyzed for concentrations of sodium, potassium, magnesium, creatinine, blood urea nitrogen (BUN), and osmolarity.

Histology

The left kidney was preserved in 10% buffered formaldehyde for subsequent histological examinations. After the dehydration process, the kidney tissues were embedded in paraffin, and 5µm sections were prepared. These sections were then mounted onto glass slides and stained with hematoxylin and eosin. A pathologist examined the morphological changes in the tubular and glomerular regions. The analysis focused on several parameters, including an increase in Bowman's capsule space, the presence of casts in the tubular lumen, tubular cell necrosis, and glomerular congestion.

The severity of impairments was graded as follows:

1. Glomerular Injury (percentage of renal parenchyma involvement): none = 0, <25% = +1, 25–50% = +2, 50–75% = +3, and >75% = +4.
2. Acute Tubular Injury (percentage of renal parenchyma involvement): none = 0, <25% = +1, 25–50% = +2, 50–75% = +3, and >75% = +4.

Statistical analysis

All data were presented as means ± standard error of the mean (S.E.M.). The results were analyzed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. To compare the pathological damage scores between groups, the Kruskal–Wallis test and Dunnett's post-hoc test were used. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Effects of PGE_2 and DIC on systolic blood pressure and renal blood flow (RBF):

Blood pressure did not show significant changes in any of the groups (Fig. 1A). Gentamicin (GM) caused a significant reduction in renal blood flow (RBF) compared to the control group (7.85 ± 0.36 ml/min vs. 4.94 ± 0.23 ml/min, $p<0.001$). However, in the GM + PGE_2 group, PGE_2 prevented the GM-induced reduction in RBF (6.5 ± 0.2 ml/min, $p<0.001$). In the GM + DIC group, there was no significant change in RBF compared to the GM group. Although RBF increased in the GM + DIC + PGE_2 group, the increase was not statistically significant compared to the GM group (Fig. 1B).

Effects of PGE_2 and DIC on plasma creatinine, BUN, urine osmolarity levels, FE_{Na}, FE_K, $U_{Na}V^{\circ}$,U_KV°,C_{Cr}:

Serum creatinine (0.52 ± 0.05 in control vs 2.25 ± 0.2in GM), BUN (21.3 ± 1.06 in control vs 74.25 ± 4.9 in GM), absolute excretion of sodium (UNaV) (0.924 ± 0.01 in control vs 2.2 ± 0.6 in GM), as well as fractional excretion of sodium (0.39 ± 0.002 in control vs 2.4 ± 0.3 in GM) and potassium (43.9 ± 3.23 in control vs 458.00 ± 39.7 in GM) (FENa and FEK), were significantly elevated following gentamicin administration compared to the control group ($p<0.001$) [Table 1]. Gentamicin-treated animals also had a

significantly lower creatinine clearance (1.4±0.08 in control vs 0.732±.01 in GM) and urine osmolality (1502±54.1 in control vs 709±24 in GM) than control rats ($p<0.001$). PGE_2 treatment demonstrated a significant protective effect, resulting in decreased levels of serum creatinine (0.90 ± 0.03), BUN (23.6 ± 1), and absolute sodium excretion (1.03 ± 0.07) (UNaV). It also led to a reduction in fractional excretion of sodium (0.93 ± 0.10) and potassium (124 ± 4.8) (FENa and FEK) ($p<0.001$). Additionally, PGE_2 treatment significantly increased creatinine clearance (1.27 ± 0.118) and urine osmolarity (1367 ± 63.1, $p<0.001$).

Co-treatment with diclofenac sodium and gentamicin resulted in a decrease in the fractional excretion of sodium (0.855 ± 0.005) and potassium (328 ± 17.6, $p<0.001$). However, it led to an increase in plasma creatinine (2.9 ± 0.03) and BUN (93.9 ± 2.7, $p<0.001$), along with a reduction in creatinine clearance (0.427 ± 0.01). Co-treatment with prostaglandin E2, diclofenac sodium, and gentamicin resulted in a decrease in the fractional excretion of sodium (0.6 ± 0.006) and potassium (86.3 ± 4.25, $p<0.001$), as well as a reduction in plasma creatinine (1.61 ± 0.18, $p<0.01$) and BUN (70.5 ± 3.9, not significant). However, there was a significant increase in creatinine clearance (1.12 ± 0.09) ($p<0.01$). The absolute excretion of potassium (UKV) did not show significant changes in any of the groups((Table 1).

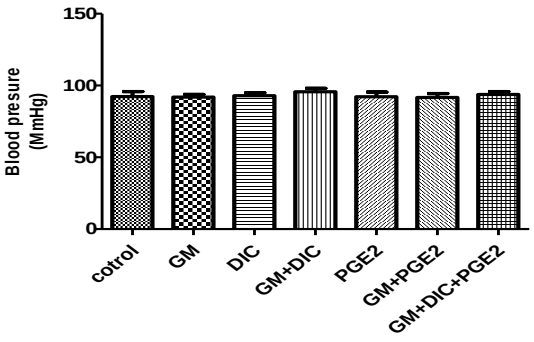

Fig1.A (Mean arterial pressure)

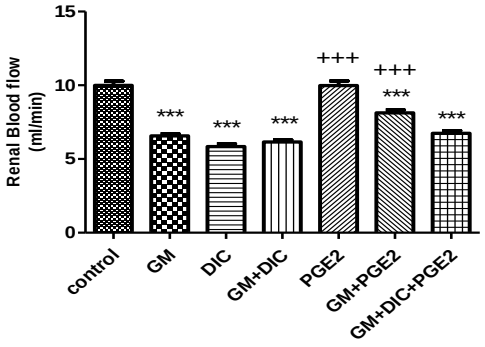

Fig1.B (Renal blood flow)

Fig. 1: PGE_2 improved the gentamicin-induced decrease in RBF while MAP remained unchanged. (A) Mean arterial pressure (MAP) showed no significant changes across the groups. (B) Renal blood flow (RBF) was significantly reduced in gentamicin-treated rats, while PGE_2 attenuated the gentamicin-induced decrease in RBF. Values are expressed as means ± S.E.M. for eight animals per group. *P<0.05, **P<0.01, ***P<0.001 vs. control; +P<0.05, ++P<0.01, +++P<0.001 vs. gentamicin. Gentamicin(GM), Diclofenac(DIC), Prostaglandin E2(PGE2)

Table1: Changes in Fractional excretion of potassium, sodium, absolute excretion of potassium sodium, creatinine clearance, Serum creatinine, BUN, and urine osmolarity levels across different groups. $^{*}P<0.05$ $^{**}p<0.01$ $^{***}p<0.001$ *vs* control; $^{+}P<0.05$ $^{++}p<0.01$ $^{+++}p<0.001$ *vs* gentamicin . Data are means ± S.E.M., n=8

Groups	FE_K%	FE_{Na}%	$U_KV°$ (mmol/min/kg)	$U_{NaV}°$ (mmol/min/ kg)	C_{Cr} (ml/min/kg)	$[Cr]_p$ (mg/dl)	$[BUN]_P$ (mg/dl)	$[Osmol]_u$ (mOsm/kg H_2O)
control	43.9±3.23	.039±0.002	2.23±0.1	0.924±.01	1.4±0.8	0.52±0.05	21.3±0.06	1502±54.1
GM	*** 458±39.7	*** 2.4±0.3	2.2±0.4	*** 2.2±0.6	*** 0.732±0.01	*** 2.25±0.02	*** 74.25±4.9	*** 709±24
DIC	+++ 29.6±3.01	+++ 0.231±.004	2.15±0.3	*+++ 0.723±0.01	+++ 0.727±0.007	*** 1.4±0.1	***++ 57.4±1.7	*** 702±26.7
GM+DIC	***+++ 328±17.6	+++ 0.885±0.005	2.14±0.7	*+++ 0.424±0.01	+++ 0.427±0.01	*** 2.9±0.1	***+++ 93.9±2.7	***+++ 439±14.3
PGE2	+++ 40.6±6.04	+++ 0.4±0.006	2.22±0.1	+++ 1.47±0.09	1.47±0.09	+++ 0.58±0.08	+++ 21.7±1	+++ 1488±58.3
GM+PGE2	+++ 124±4.8	+++ 0.93±0.1	2.26±0.4	+++ 1.27±0.118	1.27±0.118	+++ 0.9±0.03	+++ 23.6±1	+++ 1367±63.1
GM+DIC+PGE2	+++ 86.3±4.25	+++ 0.6±0.006	2.15±0.2	+++ 1.12±0.09	1.12±0.9	***++ 1.61±0.18	*** 70.5±3.9	***++ 936±37.7

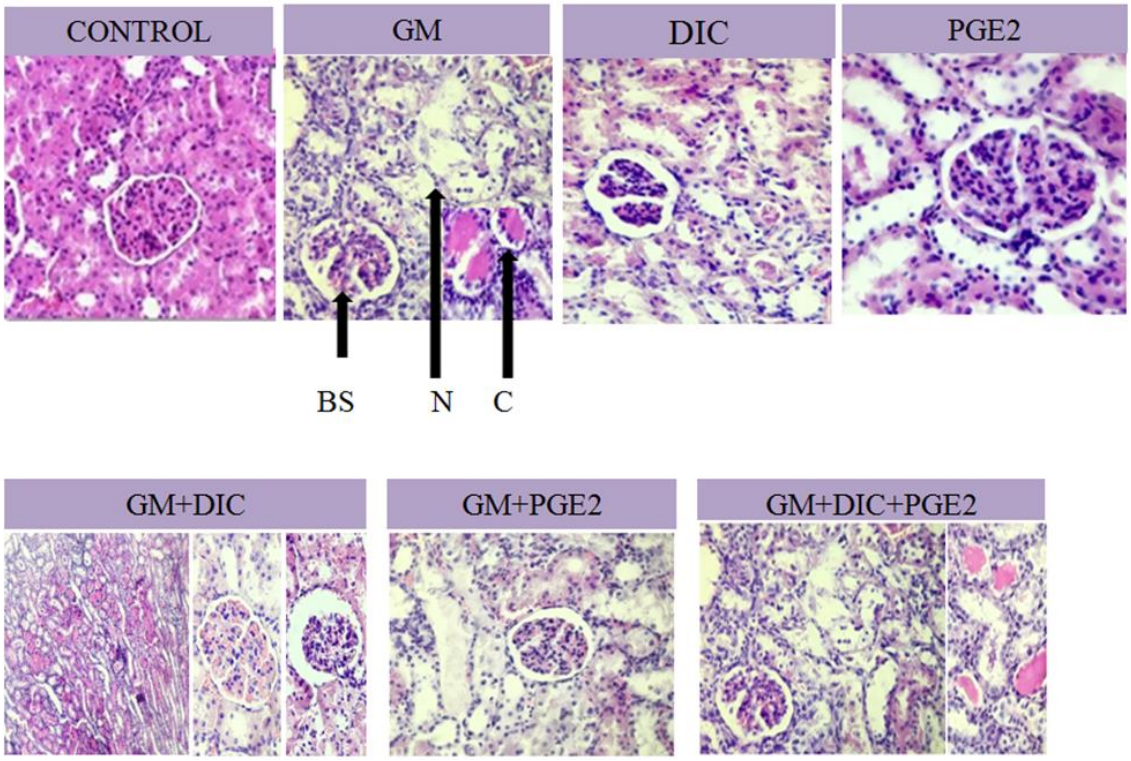

Fig2; PGE_2 reverses histological alteration induced by GM. Control group showed normal glomerular and tubular structures. GM group, showed a moderate increase in Bowman's capsule space, tubular necrosis, and the formation of intraluminal casts. The DIC group showed a slight increase in Bowman's capsule space and tubular necrosis. The PGE_2 group maintained normal glomerular and tubular structures. In the GM+DIC group, there was a slight increase in glomerular congestion, Bowman's capsule space, and a significant formation of casts. The GM+PGE_2 group demonstrated a decrease in Bowman's capsule space and tubular necrosis. Lastly, the GM+DIC+PGE_2 group exhibited slight tubular necrosis, moderate intraluminal casts, and a slight increase in Bowman's capsule space. Gentamicin (GM), Diclofenac (DIC), Prostaglandin E2(PGE2)

Table2: Changes in necrosis, cast formation, vacuolization, increased Bowman's capsule space and glomerular congestion across different groups. $^{*}P<0.05$ $^{**}p<0.01$ $^{***}p<0.001$ *vs* control; $^{+}P<0.05$ $^{++}p<0.01$ $^{+++}p<0.001$ *vs* gentamicin . Data are means ± S.E.M. n=8.

Groups	Necrosis	Cast formation	vacuolization	Increased Bowman's capsule space	Glomerular congestion
control	0±0	0±0	0±0	0±0	0±0
GM	** 1.25±0.164	*** 2.25±0.164	*** 2.75±0.164	** 2±0	*** 2.25±0.164
DIC	** 1.25±164	1.25±0.164	+ 2.63±0.138	** 2±0	1.25±0.164
GM+DIC	** 1.38±0.183	*** 2.38±0.183	3.75±0.164	*** 3±0	*** 2.38±0.183
PGE2	++ 0±0	+++ 0±0	0±0	++ 0±0	+++ 0±0
GM+PGE2	+ 0±0	0.875±0.125	0.625±0.183	1±0	0.883±.0125
GM+DIC+PGE2	0±0	1.13±0.125	2.5±0.267	** 2±0	1.13±0.125

Effects of PGE_2 and diclofenac on changes in kidney histopathology

Histological examination revealed increased tubular necrosis (0 in control vs 1.25 ± 0.164 in GM), intraluminal casts (in control vs 2.25 ± 0.164 in GM), tubular vacuolization (in control vs 2.75 ± 0.164 in GM), an increase in Bowman's capsule space (in control vs 2 ± 0 in GM), and glomerular congestion (in control vs 2.25 ± 0.164 in GM) in gentamicin-treated rats compared to the control group ($p<0.001$). Treatment with PGE_2 significantly reduced gentamicin-induced tubular necrosis (0 ± 0, $p<0.05$), cast formation (0.875 ± 0.125), tubular vacuolization (0.625 ± 0.183), and glomerular congestion (0.887 ± 0.125); however, the latter three changes were not statistically significant (Table 2 and Fig 2).

DISCUSSION

In this study, we demonstrated that gentamicin induces nephrotoxicity is accompanied by increasing plasma concentrations of urea and creatinine while decreasing their clearance. Co-treatment with diclofenac also resulted in elevated plasma creatinine levels, whereas co-treatment with PGE_2 reduced plasma creatinine concentrations in both the PGE_2 + GM and PGE_2 + GM + DIC groups. Additionally, PGE_2 significantly decreased plasma urea concentrations, which had been increased following gentamicin administration.

Effect of GM and PGE_2 on GFR

Previous studies have reported that GM accumulates in proximal tubule cells via the cubilin-megalin transporter, resulting in tubular dysfunction (28). Additionally, GM induces tubular cell necrosis, leading to a reduced number of functional nephrons and a consequent decrease in hydraulic conductivity (kf) and GFR (29, 30). On the other hand, diclofenac administration has been shown to cause necrosis, tissue fibrosis, and tubular atrophy, ultimately resulting in kidney dysfunction (31). In contrary, PGE_2 has been shown to enhances GFR by increasing cAMP levels through activation of the EP4 receptor, leading to the vasodilation of afferent arterioles (32). Considering the positive impact of PGE2 on GFR, it may enhance tubular dysfunction caused by GM by elevating GFR levels (Table1).

Effect of GM and PGE_2 on sodium and potassium levels

It has also been observed that GM elevates sodium and potassium levels, contributing to an increase in fractional excretion of potassium (FE_K) and fractional excretion of sodium (FE_{Na}) (33). GM reduces Na/K pump activity, inhibits the Na/Pi transporter, and blocks the NHE1 exchanger in renal tubular cells (33, 34). The Na/K pump creates the chemical and electrical gradients necessary for sodium and potassium transport; thus, its inhibition or decreased activity leads to sodium and water accumulation within cells, resulting in cell necrosis and increased sodium and potassium excretion (35). We showed that administration of diclofenac, PGE_2, or their combination reduced sodium and potassium excretion as well as FE_K and FE_{Na}. Indeed, it has been demonstrated that diclofenac enhances the expression of the NKCC co-transporter in the ascending loop of Henle, promoting the reabsorption of sodium and potassium, as well as the NHE_1 exchanger, which can further decrease sodium and potassium excretion in the diclofenac group. Therefore, diclofenac might have reduced the sodium and potassium excretion through this mechanism. The ameliorative effects of PGE_2 on sodium and potassium excretion might have occurred through either direct or indirect pathways. In the direct pathway, PGE_2 activates EP_2 and EP_4 receptors, which increases cAMP levels and subsequently enhances sodium absorption (36). In the indirect pathway, PGE_2 influences renin secretion via the same receptors, leading to increased aldosterone secretion from adrenal glomerular cells and, consequently, enhanced sodium absorption (37). Our data did not explore the underlying mechanisms behind the observed effects; however, here we are discussing potential mechanisms that could explain how these effects occurred (Table1).

Effect of GM and PGE2 on MAP and RBF

In this study we demonstrated that hemodynamic parameters, such as mean arterial pressure (MAP), did not significantly change among the experimental groups, although a notable reduction in RBF was observed in the GM and DIC groups. Co-treatment with PGE2 increased RBF. Previous studies have indicated that GM

reduces RBF by increasing renal vascular resistance (38). In fact, PGs, including PGE2, play a critical role in renal vasodilation, while DIC decreases RBF by inhibiting PG production (39). As it has been explained previously, PGE_2 acts through the EP_2 and EP_4 receptors to increase cAMP, leading to vasodilation of the renal afferent arteriole. Furthermore, it has been demonstrated that PGE_2 reduces the vasoconstrictive effects of endothelin through a feedback mechanism, which in turn increases RBF (40, 41). Therefore, the observed increase in renal blood flow (RBF) in this study may be attributed to the vasodilation caused by PGE_2 (Fig1A and B).

Effect of GM and PGE2 on histological parameters

Our histological examination demonstrated that GM leads to increased necrosis, expanded Bowman's capsule space, cast formation, and glomerular congestion. However, co-treatment with PGE_2 improved all measured parameters. Previous studies have shown that PGE_2 protects gastric mucus cells from necrosis, although the underlying mechanism remains unclear (42). It appears that the nephrotoxic effects of GM are mediated by a reduction in RBF. Perhaps, it is by improving RBF that PGE_2 helps to prevent renal cell necrosis and enhances renal function.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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