Effects of Nitroglycerine on Renal Ischemia-Reperfusion Injury in Adult Male Rats

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Key words
nitrroglycerine, renal ischemia-reperfusion injury, rat

Introduction

AKI has been defined as a sudden reduction (for a few hours) in kidney function with structural damage and loss of function [1]. AKI is manifested by a significant increase in serum Cr and reduction of urine output [2]. The pathophysiology of AKI is divided into tubular and vascular causes. In the AKI induced by vascular damage, renal medullary blood flow decreases, leading to a reduction in total renal perfusion. The AKI is associated with damage to the endothelium of arterioles, characterized by the increased vascular contraction in response to elevated tissue levels of endothelin I and II, thromboxane A2, and leukotrienes C4 and D4. Moreover, vasodilation decreases in response to acetylcholine, bradykinin, and nitric oxide [3]. The renal injury initiates from the onset of ischemia and continues after the reperfusion, the tissues undergo subsequent damage. Generation of cytokine and oxygen free radicals also neutrophil accumulation occurs in renal ischemia and reperfusion injury. During ischemia the tubular cells and their residues are separated from the basement membrane that reacts with proteins like fibronectin and forms protein casts that causes a tubular obstruction and, therefore, increased intratubular pressure [4]. In renal ischemia and reperfusion injury, the tubular disruption activates the tubuloglomerular feedback mechanism that reduces glomerular filtration rate (GFR) to prevent water and electrolytes loss [5]. The animal ischemia-reperfusion model is used in fundamental and treatment studies on AKI [6].
Nitric oxide (NO) is an effector molecule and a lipophilic free radical, the physiological effects of which are exerted by cGMP [7]. NO has a half-life of 6–30 s [8] and in the kidney is produced by three isoforms of NOS: endothelial NOS (eNOS or NOS3) in renal vessels, neuronal NOS (nNOS or NOS1) in the macula densa, and inducible NOS (iNOS or NOS2) in renal tubular segments, in the glomerulus, and intertubular and renal arcuate arteries [9].

The molecular and chemical effects of NO are administered by preventing neutrophil filtration, reducing the pro-inflammatory cytokines, inhibiting platelet aggregation and therefore reducing vascular inflammation and improving perfusion to ischemic tissue [10–12]. The role of NO in the regulation of endothelium vasomotor tone decreases the effect of vascular contraction and promotes endothelial-dependent vasodilatation, which improves perfusion to ischemic tissue [8, 10].

Nitroglycerin (NG) is a potent vasodilator and has been used in the treatment of angina pectoris heart failure and high blood pressure acts through the liberation of nitric oxide (NO). NG is an organic nitrate that reacts with thiols and other reducing substrates [11]. It is converted into 1, 2- glyceryl dinitrate and nitrite in the vascular smooth muscle cells, which is then metabolized by mitochondrial aldehyde dehydrogenase 2 with a half-life of 1–4 min [13, 14].

Regarding the NO characteristics and the ability of nitroglycerin to release exogenous nitric oxide (NO donor) in our present study, we aim to evaluate the effects of treatment with nitroglycerin after renal ischemic reperfusion injury.

Materials and Methods

This study was conducted on 24 Wistar rats weighing 250–300 g and kept in separate cages under a photoperiod of 12 h light/12 h dark at room temperature (about 23 ± 2 °C) and with ad libitum access to food and water. All ethical codes created by the Monitoring Committee for Laboratory Animals of Arak University of Medical Sciences were complied with for all of the studied rats. The study groups included: (1) the control group that did not receive any drugs, (2) the sham group that were anesthetized without any ischemia (the kidneys were only touched), (3) the I-R group that experienced bilateral ischemia of the renal arteries and veins for 20 min and then reperfusion for 24 h, and (4) the post-treatment group that were injected with intra peritoneal (IP) NG (Caspian Tamin, Iran) at 50 μg/kg, 24 h after reperfusion started [15].

To induce AKI, the rats were weighed first and then injected with IP sodium thiopental (Sandoz, GmbH, Estonia) at 25 μg/kg [16]. After shaving the hair on the back of the rats, 1.5 cm incisions were made on either side of the midline using scissors and forceps. When the kidneys became visible, a special clamp was employed to block renal arteries and veins for 20 min., after which the clamps were removed immediately. The surgery sites were then closed and the animal’s recovered.

After recovery, the rats were placed in metabolic cages and the 12-h urine volume was measured using the gravimetric method. The rats were anesthetized 24 h after reperfusion. Systolic blood pressure was measured using a Power Lab instrument (AD Instruments, Australia) [17, 18] and employing the tail-cuff method. A longitudinal incision was then made on the surface of the abdo-

Both kidneys were removed and weighing them, they were divided into two halves. The right kidney was placed in liquid nitrogen for the ferric reducing antioxidant power (FRAP) and malondialdehyde (MDA) biochemical analyses and then immediately placed in a freezer at −20 °C. The amount of lipid peroxidation was determined by Okawa’s MDA method. Benzie and Strain’s method was used to measure FRAP [25, 26].

The capsule of the left kidney was separated and placed in 10 % buffered formalin. It was then fixed, dehydrated, and clarified before being embedded in melted paraffin. Following that, 5-micron-thick sections were prepared and stained with hematoxylin and eosin. Examination of tissue from prepared slides was performed by an expert pathologist.

Bowman’s capsule space, reduction in the number of glomerular red blood cells (RBC), shedding of tubular epithelial cells into the lumen, formation of protein casts inside the lumen, and vacuolation and necrosis of tubular cells were evaluated. The amount of inflicted damage was graded based on calculated percentages as follows: no damage: grade 0, 1–25 % damage: grade 1, 25–50 % damage: grade 2, 50–75 % damage: grade 3 and 75–100 % damage: grade 4 [27].

In addition, all data were analyzed with SPSS version 25 (Chicago, II., USA), one-way variance (ANOVA), the Tukey test, Kruskal-Wallis multiple comparison test, and Dunnett’s test at P < 0.05 as the significance level for statistical analysis [28].
Result

The effects of post-treatment NG on RBF and systolic blood pressure

In compared to the control group, RBF showed a significant decrease in the NG group (7.36 ± 0.02 ml/min., P < 0.001), in the I-R group (6.42 ± 0.31 ml/min., P < 0.001), and in the sham group (8.5 ± 0.2 ml/min., P < 0.01). The NG group showed a significant increase compared to the I-R group (P < 0.01). There were no significant differences between the groups in systolic blood pressure (Fig. 1).

Post-treatment effects of NG on Creatinine clearance (C_cr), absolute (U_NaV) and relative (FENa) excretions of sodium, and absolute (U_KV) and relative (FE_k) excretions of potassium

Results indicated that creatinine clearance declined significantly in the I-R group (0.008 ± 0.005 µl/min.gkw, P < 0.01) and in the NG group (0.02 ± 0.006 µl/min.gkw) compared to the control and sham groups (0.05 ± 0.01 µl/min.gkw). There was a significant increase of C_cr in the NG group (P < 0.001).

There was a non-significant increase in the fractional excretion of Na⁺ (FeNa) of the I-R group compared to the control group (0.42 ± 0.2 % vs. 0.39 ± 0.3 %). The FeNa in the NG group (0.001 ± 0.0008 %) declined significantly compared to the I-R group at P < 0.01 and the control group at P < 0.05, but was not significantly different from that of the sham group. The absolute excretion of Na⁺ (U_NaV) did not differ significantly among the groups. The fractional excretion of potassium (FE_k) in the I-R group showed a significant increase compared to the control group (47.28 ± 13.3 % vs. 28.6 ± 9.8 %, P < 0.05). Moreover, the FE_k declined significantly in the NG group (21.73 ± 7.7 %) compared to the sham group (47.74 ± 13.8 %, P < 0.05) and the I-R group (47.28 ± 13.3 %), but had no significant difference with that of the control group. The absolute excretion of K⁺ (U_KV) in the I-R group decreased significantly compared to the sham group (2.68 ± 0.3 and 2.16 ± 0.2 µmol/min.gkw, respectively), whereas there were no significant differences between the NG and the I-R groups (Table 1).

Post-treatment effects of NG on urinary levels of sodium ([Na]u), potassium ([K]u), creatinine ([Cr]u), and osmolality (Osmol_u)

Urinary sodium concentration in the I-R group was significantly higher than the control group (28.7 ± 8.4 µmol/mL vs. 65.7 ± 6.9 µmol/mL, P < 0.001). The urinary concentration of sodium in the NG group (32.1 ± 5.3 µmol/mL) did not differ significantly from those in the sham (32.3 ± 3.9 µmol/mL) and control groups. The urinary concentration of sodium in the NG group declined significantly compared to the I-R group (P < 0.001).

Urinary potassium concentration in the I-R group exhibited a significant decrease compared to the control group (133.6 ± 13.6 µmol/mL vs. 122.9 ± 2.7 µmol/mL, P < 0.01). The urinary concentration of potassium in the NG group (88.7 ± 5.8 µmol/mL) was significantly lower than those in the sham (120.8 ± 9.3 µmol/mL, P < 0.001) and control groups (P < 0.001) and in the I-R group (P < 0.01). Although urinary potassium concentration in the I-R group was lower than that in the sham group, this difference was not significant. The groups did not exhibit any significant differences in urinary concentration of creatinine.

Urine osmolality in the I-R group decreased significantly compared to the control group (133.6 ± 13.6 mOsm/KgH_2O vs. 151.5 ± 70.5 mOsm/KgH_2O, P < 0.001). Urine osmolality in the NG group (103.1 ± 58.23 mOsm/KgH_2O, P < 0.001) declined significantly compared to the sham (149.3 ± 80.85 mOsm/KgH_2O) and control groups (P < 0.001), but did not differ significantly compared to the I-R group (Table 2).

Post-treatment effects of NG on plasma concentrations of sodium ([Na]p), potassium ([K]p), creatinine ([Cr]p), urea ([BUN]p), and osmolality (Osmol_p)

Results indicated that plasma creatinine concentration in the I-R group (1.24 ± 0.35 mg/dL) significantly increased (P < 0.001) compared to the control group (0.55 ± 0.09 mg/dL) and the sham group (0.64 ± 0.08 mg/dL), whereas in the NG group plasma creatinine concentration (0.77 ± 0.13 mg/dL, P < 0.01) exhibited a significant
reduction compared to the I-R group, but did not significantly differ from those of the control and sham groups.

Plasma concentration of BUN in the I-R group (41.11 ± 6.5 mg/dL) significantly increased compared to the control group (18.76 ± 2.4 mg/dL, P < 0.001) and the sham group (24.9 ± 3.1 mg/dL, P < 0.01). There were no significant differences between the NG and the I-R groups.

Compared to the control group, plasma concentration of sodium in the I-R group experienced a decline, which was not significant (149.23 ± 6.2 μmol/mL vs. 152.1 ± 6.1 μmol/mL, P > 0.01). The plasma concentration of sodium in the NG group (141.46 ± 2.6 μmol/mL, P < 0.01) decreased significantly compared to the control group but did not differ significantly from those of the sham (144.45 ± 6.7 μmol/mL) and I/R groups.

▶ Table 1 Comparison of creatinine clearance (CCr), absolute (UNaV°) and relative (FENa) excretions of sodium and absolute (UKV°) and relative (FEK) excretions of potassium.

<table>
<thead>
<tr>
<th>Ccr µl/min. gkw</th>
<th>UNaV° µmol/min. gkw</th>
<th>UKV° µmol/min. gkw</th>
<th>FENa %</th>
<th>FEK %</th>
<th>Parameters</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 ± 0.01</td>
<td>0.56 ± 0.1</td>
<td>2.68 ± 0.3</td>
<td>0.39 ± 0.3</td>
<td>28.6 ± 9.8</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>0.05 ± 0.01</td>
<td>0.58 ± 0.1</td>
<td>2.16 ± 0.2</td>
<td>0.28 ± 0.05</td>
<td>42.7 ± 13.8</td>
<td>Sham</td>
<td></td>
</tr>
<tr>
<td>0.008 ± 0.005</td>
<td>0.47 ± 0.1</td>
<td>0.82 ± 0.2</td>
<td>0.42 ± 0.2</td>
<td>42.7 ± 13.3</td>
<td>I/R</td>
<td></td>
</tr>
<tr>
<td>0.02 ± 0.006</td>
<td>0.49 ± 0.1</td>
<td>1.33 ± 0.2</td>
<td>0.001 ± 0.008</td>
<td>21.7 ± 7.7</td>
<td>TNG + I/R</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001 * * *, P < 0.01 * *, P < 0.05 * compared to the control group. P < 0.001 ++ +, P < 0.01 ++, P < 0.05 + compared to the sham group. P < 0.001□□□, P < 0.01□□, P < 0.05□ compared to the I-R group. Results expressed in mean ± standard deviation (SD) for 6 rats in each group.

▶ Table 2 Comparison of urinary concentrations of sodium ([Na]u), potassium ([K]u), creatinine ([Cr]u) and osmolality (Osmol_u) among the groups.

<table>
<thead>
<tr>
<th>Osmol_u mosm/KgH2O</th>
<th>[Cr]u mg/dl</th>
<th>[K]u µmol/ml</th>
<th>[Na]u µmol/ml</th>
<th>Parameters</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1515 ± 70.5</td>
<td>1.38 ± 0.2</td>
<td>133.63 ± 13.6</td>
<td>28.72 ± 8.4</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>1493.83 ± 80.8</td>
<td>1.33 ± 0.3</td>
<td>120.28 ± 9.1</td>
<td>32.33 ± 3.9</td>
<td>Sham</td>
<td></td>
</tr>
<tr>
<td>908.33 ± 48.1</td>
<td>1.25 ± 0.2</td>
<td>112.9 ± 2.7</td>
<td>65.73 ± 6.9</td>
<td>I/R</td>
<td></td>
</tr>
<tr>
<td>1031.5 ± 58.2</td>
<td>1.32 ± 0.2</td>
<td>88.76 ± 5.8</td>
<td>32.11 ± 5.3</td>
<td>TNG + I/R</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001 * * *, P < 0.01 * *, P < 0.05 * compared to the control group. P < 0.001 ++ +, P < 0.01 ++, P < 0.05 + compared to the sham group. P < 0.001□□□, P < 0.01□□, P < 0.05□ compared to the I-R group. Results expressed in mean ± standard deviation (SD) for 6 rats in each group.

▶ Table 3 Comparison of plasma concentrations of sodium ([Na]p), potassium ([K]p), creatinine ([Cr]p) and osmolality (Osmol_p) among the groups.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>309.16 ± 30.2</td>
<td>18.76 ± 2.4</td>
<td>0.55 ± 0.09</td>
<td>3.66 ± 0.4</td>
<td>152.1 ± 6.1</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>305.66 ± 6.1</td>
<td>24.9 ± 3.1</td>
<td>0.64 ± 0.08</td>
<td>3.79 ± 0.4</td>
<td>144.45 ± 6.7</td>
<td>Sham</td>
<td></td>
</tr>
<tr>
<td>318.83 ± 10.06</td>
<td>41.11 ± 6.5</td>
<td>1.24 ± 0.3</td>
<td>4.02 ± 0.5</td>
<td>149.23 ± 6.2</td>
<td>I/R</td>
<td></td>
</tr>
<tr>
<td>332.16 ± 19.7</td>
<td>38.18 ± 4.3</td>
<td>0.77 ± 0.1</td>
<td>3.91 ± 0.5</td>
<td>141.46 ± 2.6</td>
<td>TNG + I/R</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001 * * *, P < 0.01 * *, P < 0.05 * compared to the control group. P < 0.001 ++ +, P < 0.01 ++, P < 0.05 + compared to the sham group. P < 0.001□□□, P < 0.01□□, P < 0.05□ compared to the I-R group. Results expressed in mean ± standard deviation (SD) for 6 rats in each group.
The plasma concentration of potassium and osmolality did not show any significant differences between groups (▶ Table 3).

Post-treatment effects of NG on MDA and FRAP levels in renal tissue

Results showed that the MDA level per gram kidney weight (gkw) significantly increased in the I-R group (35.68 ± 6.41 μmol/gkw) compared to the control group (15.33 ± 4.21 μmol/gkw) and the sham group (20.41 ± 3.3 μmol/gkw) (P < 0.001). The MDA levels did not differ significantly in the sham and control groups. The MDA level in the NG group (24.66 ± 2.4 μmol/gkw) exhibited a significant increase compared to the control and sham groups (P < 0.01) and a significant reduction compared to the I-R group (P < 0.01; ▶ Fig. 2a).

In the I-R group the kidney tissue level of FRAP (5.69 ± 0.5 mmol/gkw) declined significantly compared to the control group (8.61 ± 1.06 mmol/gkw) and the sham group (7.59 ± 0.3 mmol/gkw). The tissue level of FRAP were not significantly different in the control and sham groups. The FRAP level in the NG group (8.69 ± 1.4 mmol/gkw) increased significantly compared to the I-R group (P < 0.001), but did not differ significantly from that of the control group (▶ Fig. 2b).

Post-treatment effects of NG on histological changes (▶ Fig. 3)

Results demonstrated that necrosis of tubular cells (grade 3), vacuolation of tubular cells (grade 2), increased Bowman’s capsule space (grade 1), formation of protein casts within the tubular lumen (grade 2), scattering of cells into the tubule lumen (grade 3), reduction in the number of glomerular red blood cells (grade 1), and glomerular injury (grade 2) in the I-R group were significantly different compared to the control group (grade 0) (P < 0.05). Increased Bowman’s capsule space and cell necrosis in the sham group (grade 1) were significantly different compared to the control group (P < 0.05). Moreover, necrosis of tubular cells (grade 1), vacuolation of tubular cells (grade 0), formation of protein casts within the tubular lumen (grade 0), scattering of cells inside the tubular lumen (grade 0), reduction in the number of glomerular red blood cells (grade 0), and glomerular injury (grade 0) were significantly different compared to the I-R group (P < 0.05), whereas the increase in Bowman’s capsule space (grade 1) was not significantly different compared to the I-R group (▶ Fig. 3).

In the NG group, necrosis of tubular cells (grade 2) significantly increased compared to the control and sham groups (P < 0.05), but declined significantly compared to I-R group (P < 0.05). In the NG group, increased Bowman’s capsule space (grade 2), formation of protein casts (grade 2), vacuolation (grade 2), glomerular injury (grade 2), cell scattering (grade 2) and reduction in the number of glomerular red blood cells (grade 1) were not significantly different compared to the I-R group (▶ Table 4).

Discussion

The results of the present study indicated that renal ischemia-reperfusion injury accompanied by increased plasma creatinine and BUN and by reduced creatinine clearance [29]. These results could be due to back-leak of filtrate and impaired ion re-absorption that leads to renal tubular obstruction with the decrease in GFR in the reperfusion stage. Furthermore, sodium is not appropriately re-absorbed by the injured proximal tubules (which activates tubuloglomerular feedback). This feedback probably participates in constriction of pre glomerular arteries that further decreases GFR [30]. The creatinine clearance level in the NG group increased significantly compared to the I-R group. Previous research has shown that NG increases NO and cGMP levels [31]. Increased intracellular cGMP levels dilate the afferent and efferent arteries, thus increasing clearance of creatinine [32]. There was a plasma electrolyte disorder in the I-R group compared to the control group. The FE Na in the I-R group increased compared to the control group, but this increase was not significant. The FE K was also higher in the I-R group. This increase indicates that epithelial tubular cells, especially proximal tubular cells, are damaged during ischemia-reperfusion injury [26]. In addition, ischemia-reperfusion injury causes brush border destruction with reduced re-absorption of sodium by proximal tubules, impaired expression of tubular sodium transporters, and unsuitable regulation of Na+/K+-ATPase expression in the basal-lat-

![Fig. 2](comparison of MDA and FRAP levels among the groups. P < 0.001 * * * compared to the control group, P < 0.001 + + + + compared to the sham group, P < 0.001 + + + compared to the I-R group. Results expressed in mean ± standard deviation (SD) for 6 rats in each group.)
Fig. 3  Comparison of renal histological between different groups. a - Control group with glomerular and normal tubular structure(×40); b - I-R group with tubular cell necrosis, formation of protein casts inside the tubule lumen, cells scattering into the tubule lumen, vacuolation of tubular cells, increased Bowman’s space and reduced number of red blood cells in glomerulus(×40); c - sham group with tubular cell necrosis(×40); d – Nitroglycerin group with increased Bowman’s space, vacuolation of tubular cells and reduced tubular cell necrosis(×40). RBC: Red Blood Cell, N: Necrosis, C: Intratubular cast, D: Downfall, V: Vacuolization, BS: Bowman’s space.

Table 4  Comparison of necrosis level, protein casts, cell scattering, vacuolation, the reduced number of red blood cells, increased Bowman’s capsule space, and glomerular injury.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cell necrosis</th>
<th>Vacuolation</th>
<th>Increased Bowman’s capsular space</th>
<th>Formation of protein casts</th>
<th>Cell scattering</th>
<th>Reduced number of red blood cells</th>
<th>Glomerular injury</th>
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<td>0</td>
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<td>0</td>
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<td>TNG + I/R</td>
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</table>

P<0.05 * compared to the control group. P<0.05 + compared to the sham group. P<0.05 □ compared to the I-R group. Results expressed in mean ± standard deviation (SD) for 6 rats in each group.
Thieme


Original Article

Thieme

indicated that NG inhibited contraction of vascular smooth muscles tend to decrease RBF [43]. The RBF rates in the NG group might have been influenced by the effects of anesthesia and surgery stress. Research by Mercatello showed that anesthesia drugs influenced renal function not only directly, but also through changes in cardiovascular function and endocrine activity. Many barbiturates tend to decrease RBF [43]. The RBF rates in the NG group increased significantly compared to the I-R group. Previous studies indicated that NG inhibited contraction of vascular smooth muscles through increasing cGMP and reduced effect of exogenous endothelin-1 on heart and kidney function. NG also neutralizes increases in EP, NE, and aldosterone caused by Endothelin [31]. Histological studies in the present research revealed that, contrary to the control group, necrosis of tubular cells, vacuolation of tubular cells, increased Bowman’s capsule space, formation of protein casts within the tubular lumen, cell scattering into the tubular lumen, decreased number of glomerular red blood cells, and glomerular injury happened in the I-R group. The pathological analysis did not show the improvement effect in the group that received the drug. Imbalance between expression and activity of eNOS and iNOS (reduction in eNOS activity and increase in iNOS expression level) is responsible for the pathology results during I-R injury [9]. Previous research also did not show any improvement in the pathological changes during I-R injury by the NG [44]. The authors believe that the time of using NG also plays a very important role in pathological changes.

Conclusions

Results of the present study indicated that post-treatment intraperitoneal injection of Nitroglycerin reduces renal ischemia-reperfusion injury. Nitroglycerin improved the renal tissue antioxidant defense system by increasing level of FRAP and also reducing lipid peroxidation. Nitroglycerin improved hemodynamic parameters the same as plasma creatinine, creatinine clearance, and renal blood flow through generation of nitric oxide (NO).

Further investigation requires determining the protective effect of nitroglycerin against renal ischemia-reperfusion injury in human kidneys. Additional examinations need to determine the incidence of renal ischemia-reperfusion injury in nitroglycerin-treated patients with acute heart failure.

IRB Ethical Approval Number

The Research Ethics Committee of Arak University of Medical Sciences approved this research under registration number IR.ARAKMU.REC. 1396.287.

Informed Consent

This was not a research on humans. All ethical codes developed by the Monitoring Committee for Laboratory Animals at Arak University of Medical Sciences were complied within the experiments conducted in the present research.

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