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Oral Melatonin for Colistin-induced Nephrotoxicity Reduction in Intensive Care Unit: A Randomized Placebo Controlled Clinical Trial

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Abstract

Background: Colistin is a drug of choice against multidrug-resistance (MDR) bacteria. The most important side effect of colistin is nephrotoxicity, observed in 20 - 54% of patients. According to the studies that examined its antioxidant effect, it can reduce the kidney toxicity of various drugs, including colistin.
Objectives: This study aimed to investigate melatonin's effect on reducing colistin-induced kidney toxicity to use this drug with fewer complications.
Methods: This double-blind, randomized clinical trials with two groups involved 56 critically ill adults infected by MDR bacteria. The intervention group received 3 mg of oral melatonin simultaneously with intravenous colistin, which continued until the end of the treatment. The control group received placebo orally with IV colistin. We measured urine volume, blood creatinine, and blood urea nitrogen (BUN) daily and determined the patients with renal failure using the KDIGO guideline. STATA software analyzed data with a P-value of less than 0.05 as the significance level.
Results: Data obtained from recipients were analyzed for age (P-value = 0.357), gender (P-value = 0.945), weight (P-value = 0.438), APACHE score (P-value = 0.162). We did not observe significant difference in acute kidney injury (AKI) criteria between the two groups. Compared to the control group, melatonin did not decrease blood creatinine (P-value = 0.110) and BUN (P-value = 0.567) and, made no change of urinary volume (P-value = 0.913). There was no decrease in kidney failure in the intervention group compared to the control group. As a result, we did not find a significant difference in outcome of the two groups.
Conclusions: We did not reveal any significant difference in the AKI criteria including blood creatinine, BUN, and daily urine volume with the addition of melatonin in participants receiving colistin; However, no complication was observed in the intervention group who received melatonin.

Keywords: Colistin, Melatonin, Nephrotoxicity, Renal Injury, Randomized Clinical Trial

1. Background

Acute kidney injury (AKI) is a heterogeneous syndrome. AKI can be caused by reduced cardiac output, toxins, drugs, major surgeries, and sepsis or pathologic reasons such as inflammation or hypoperfusion. Acute kidney injury in critical care may lead to water and electrolyte metabolism disturbance and increases morbidity, mortality, and a worsening of the patient's long-term prognosis (1). The length of stay in ICU for AKI patients was significantly longer than for non-AK patients. The average was 4.2 days higher than the average of 2.9 days. Mortality rate is twice in patients with AKI that without renal failure (2).

Colistin is a polycationic peptide antimicrobial agent used in critical care and causes an increase in AKI in high prevalence (3, 4). This antibiotic belongs to the polymixin class. Physicians use two polymixins clinically: Polymixin B and polymixin E or colistin. Colistin is the antibiotic of choice for multidrug- resistant (MDR) bacteria (5). The lipopolysaccharides (LPS) bilayer in gram- negative bacteria prevents the penetration of antibiotics into the

cells (6).

Colistin L-diaminobutric acid binds to the phosphate groups of Lipid A. Lipid A plays a vital role in bacterial permeability. It then inserts its hydrophobic terminal fatty acid chain and expands the outer layer of the membrane (OM). It disrupts the membrane integrity of gram negative bacteria by interfering with the transport of calcium and magnesium ions and increasing membrane leakage: Hence, colistin can overcome MDR bacteria (5).

Kidney injury from antibiotics increases morbidity, mortality, and treatment costs (7-10). It causes kidney damage by different mechanisms, including glomerular hemodynamic dysfunction, cytotoxicity, inflammation, crystalline renal toxicity, rhabdomyolysis, and capillary microangiopathy. An initial kidney injury after consumption is necrosis in proximal tubular cells (11).

All organisms contain melatonin. It regulates circadian rhythm (12, 13). In critical care, melatonin is used to prevent delirium (14). In laboratory studies, this substance also has anti-inflammatory and antioxidant effects, preventing acute and chronic inflammation of tubular-glomerular cells due to the nephrotoxic effects of drugs (15-17). The mechanism of this action is to inhibit free radicals. The inhibition of NF-B transmission and binding causes the anti-inflammatory effect of melatonin. The antioxidant effect of melatonin is receptor-dependent and non-receptor-dependent in two respects increasing glutathione peroxidase and accelerating the removal of H2O2 and its conversion to water and oxygen (16, 18). Glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) have antioxidant enzymes augmented by melatonin. Glutathione disulfide (GSSH) is converted to glutathione (GSH) with the help of the glutathione reductase (GRd) enzyme, melatonin activates the glutathione reductase enzyme by increasing the production of glutathione (GSH), and glutathione plays a role in removing H2O2. In this process, glutathione reductase uses NADPH as the cofactor, which will be recovered by G6PD. Again, melatonin plays a role in protecting cells by inducing the activity of the G6PD enzyme via inhibiting oxidative activity.

Melatonin directly scavenges free radicals ($ONOO^-$) and NO molecules. Also, OH is the most toxic for the cell that is converted into OMH 3-hydroxymelatonin (3-OHM), which is non-toxic (19) (Figure 1).

Thus, melatonin has a significant role in protecting the cell against oxidative stress. We used melatonin's ability to protect cell against oxidative stress to reduce colistin nephrotoxicity.

2. Methods

A double-blind, permuted block randomized, placebo-controlled trial of colistin-treated acute infections was conducted at Imam Hossein (AS) Hospital, affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. Cases of acute infection were treated with colistin and admitted to the intensive care unit in the two intervention groups that used colistin and melatonin and a control group of colistin and placebo from February 20, 2021, to April 20, 2022. The Iranian Registry of Clinical Trials (IRCT) has assigned the research protocol with a code 20210110049990N1.

We selected patients admitted to the intensive care unit with severe infection with MDR bacteria treated with colistin. The inclusion criteria included ICU patients aged twelve years and above who were treated with colistin at a 4.5 million unit every twelve hours, and Creatinine levels were $<$ 1.5 mg/dL in males and $<$ 1.3 mg/dL in the females, creatinine clearance (CrCL) $>$ 60 mg/min with mortality or discharge after 48 hours.

Exclusion criteria were dissatisfaction, death, leaving the group within 48 hours or melatonin sensitivity or intolerance, history of AKI, and use of nephrotoxic drugs such as vancomycin, aminoglycoside, NSAIDs, Etc.

All participants were interviewed to become familiar with the project before entering the study. Written consent was obtained from all cases. If the participants could not provide informed consent, a family member or the attending physician fills out the form. The research ethics committee of SBMU approved the ethical code of IR.SBMU.RETECH.REC.1399.1372.

According to the 54% prevalence of kidney disease caused by colistin in patients, a 50% reduction in nephrotoxicity, a 5% error, and an 80% power, a sample of 56 participants was selected, considering the duration of the study.

In all cases admitted to the intensive care unit with severe infection (due to MDR and colistin-sensitive organisms), IV colistin was prescribed by an infectious disease specialist or intensivist as follows: A loading dose of 300 mg followed by a amount of 300 to 360 mg daily in divided doses twice daily (20) in cases with reduced creatinine clearance. Afterward, we adjusted the dosage of colistin based on creatinine clearance and then randomized the patients into two groups. Melatonin was produced by the Nature Made Company at a dose of 3 mg daily for ten days in the intervention group and a placebo for the control group corresponding to the same drug received. The melatonin or placebo was administrated until the patient received colistin. The group pharmacotherapist prepared melatonin and

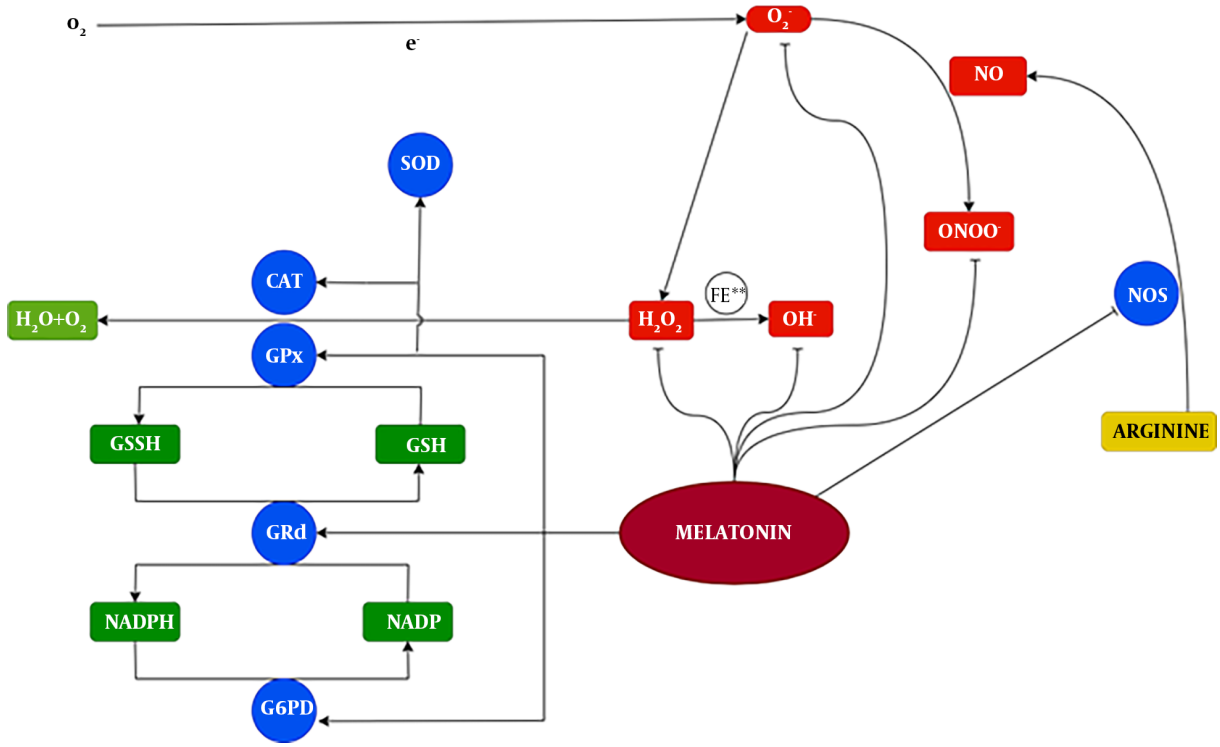

Figure 1. Melatonin has an antioxidant process in kidney protection. Melatonin directly induces endogenous antioxidant enzyme (left) and inhibits the pro-oxidation pathway of nitric oxide synthesis (NOS) through direct neutralization of active (right) species.

placebo pills in packages for the patients to consume and then labeled them with random numbers selected by the computer. The Project Executive and the patients did not know the type of medicine. Urine volume, blood creatinine, and blood urea nitrogen (BUN) were monitored daily for all participants, and kidney function was evaluated according to the KIDIGO tool every 48 hours. Several tools can investigate acute drug nephrotoxicity, and we used KIDGO, as it is more recent and preferable to investigate AKI. It is divided into three stages based on increased serum creatinine and decreased urine output. The KDIGO guideline defines AKI as increased serum creatinine by $\geq$0.3 mg/dL within 48 hours, increased serum creatinine to $\geq$ 1.5 times baseline, or decreased urine volume $<$ 0.5 mL/kg/for six hours. This study selected males with serum Cr $<$ 1.5 mg/dL and females with Cr $<$ 1.3 mg/dL. An increase in blood creatinine above 0.3 mg in 48 hours, either a 1.5-fold increase in serum creatinine in seven days or a decrease in urine output below 0.5 cc kg/h in six hours, is a sign of renal dysfunction (21). AKI classification was used as follows: Stage 1, an serum creatinine (SCr) increase of 0.3 mg/dL or more within 48 hours or an SCr increase of 1.5 - 2 times the baseline value within seven days. Stage 2, an increase in SCr $\geq$ 2 - 3 times the baseline value within seven days, and stage 3, an increase in SCr $\geq$ 3 times the baseline value within seven days.

The Apache score was measured to match the results obtained, and the reason for admission was registered. The participant's demographics were recorded, and at the end of the study, two intervention and control groups were determined using the key. Collected data were analyzed using the STATA software.

2.1. Statistical Analysis

We collected all data in a standard format in STATA version 17 for further analysis. Frequency (percentage) was employed for categorical variables, and Mean ± SD for continuous variables.

The variables obtained were compared using an independent samples *t*-test, and variance analysis was performed using repeated measurements ANOVA of parameters in each group. The compression of quantitative parameters between two groups was made using chi-square and Fisher's exact tests. Binary logistic regression was used to analyze the association between

melatonin intake and the incidence of renal failure, considering possible covariates. Simple linear regression assessed the possible relationship between oral melatonin and AKI reduction. P-value less than 0.05 is considered as significance level.

3. Results

We had enrolled 110 critical ill adults with acute infection with MDR bacteria, 56 of them were eligible. (27 cases in the intervention group and 29 in the control group), with a mean age of 48.2 ± 19.3 years. Of the patients, 35 (62.5%) were male (Figure 2). The mean age of patients (17 (62.96%) males and 10 (37.04%) females) in the intervention group was 49.22 ± 18.90 years. In the control group, there were 18 (62.07%) males.

The body mass index was 26.9 ± 3 in the intervention group. Additionally, 18.52% of patients in the intervention group and 37.9% in the control group were opium users (Table 1).

The second table compares the cases treated with melatonin and Colistin and those treated with Colistin and placebo based on demographic characteristics and test results. In the comparison of the variables obtained from the patients, including; gender (P-value = 0.945), age (P-value = 0357), in patients addicted to opium compared to patients who did not use (P-value = 0.108), BMI (P-value = 0.438), source of infection (P-value = 0.516), comparison Severity of the disease in the Apache (P-value = 0.162), plasma creatinine (P-value = 0.110), plasma BUN level (P-value = 0.567), serum bilirubin level (P-value = 0362) albumin blood level (P-value = 0.456), same-time use of nephrotoxic drugs (P-value = 0.269).

In all cases, the differences were statistically insignificant, and we did not see a difference in the outcome of the two groups.

After controlling for the effect of independent variables, logistic regression analysis of the dependent variable (kidney injury) showed that melatonin had no significant impact on nephrotoxicity (Table 2). This means that the simultaneous administration of melatonin with a dose of 3 mg daily does not prevent colistin-induced nephrotoxicity.

Serum creatinine, BUN, and CrCl levels were compared in two drug-treated and control groups. An increase in SCr and BUN was observed in both groups along with a decrease in CrCl. There was no significant difference between the two groups in any of the three indicators at any time. The changes between the two were insignificant for all three parameters (Table 3).

Acute kidney injury is a common occurrence in both groups. The intervention group had 18 cases of AKI (66.67%) and the control group had 13 cases (44.83%). The majority of them have mild renal failure, and the 2nd and 3rd stages of AKI are less frequent. The statistical difference between the two groups was insignificant (P = 0.1) (Table 4).

4. Discussion

This double-blind RCT trial of colistin administration with melatonin, melatonin did not reduce colistin-induced AKI, and we did not find any other differences between the groups at the follow-up. Similar findings were present when several variables were considered, such as age, sex, BMI, and site of infection. As mentioned above, nephrotoxicity remains colistin's most crucial side effect, and oral melatonin can help reduce renal failure in laboratory studies (22, 23). However, due to the difference in some parameters, contradictory results were observed and led to the different results.

We enrolled patients who were acutely infected with colistin – sensitive (MDR) bacteria, and then Melatonin or placebo was used until they received colistin. concerning the source of infection, most participants had pneumonia, 25 (86%) in the intervention group and 21 (78%) in the control group, 3% had a urinary tract infection, 11% positive blood culture, and 3% wound infection.

In this study more nephrotoxicity was observed in comparison to the data, the rate of (48 - 62%) compared to (20 - 54%) of the reference (24). According to the results, the most renal function disturbance is increased blood BUN (intervention group38.61 ± 20.87 and control group 39.62 ± 23.34), and the least is a decrease in urinary output (intervention group four patients and control group four patient). The causes include the high APACHE score of the participants, 14.96 ± in the intervention group and 13.83 ± 4.00 in the control group. Serum albumin is a significant effect on the outcome of many disease process. Low serum albumin (SAL) $<$ 3 g/dL is the level of hypoalbuminemia in the clinical practice, suggesting the higher mortality rate in critically ill patient (25). In the studied patients, serum albumin concentration was $<$ 3 g/dL, which is consistence with their high APACHE score. Additionally, because of (MDR) bacteria, some cases (15%) had sepsis and septic shock. As a result, the renal failure rate was high.

Melatonin has been used safely in critically ill patients (26). The authors observed minor side effect in the intervention group after taking melatonin.

Some patients had risk factors for drug nephrotoxicity, such as COPD in 12 (21%), abdominal surgery in 3 (5%), and age $>$ 65 in years 11 (20%) (27).

This trial is the first study of the combined effect of melatonin and colistin on human, so it has several limitations. The duration of the study was limited, only

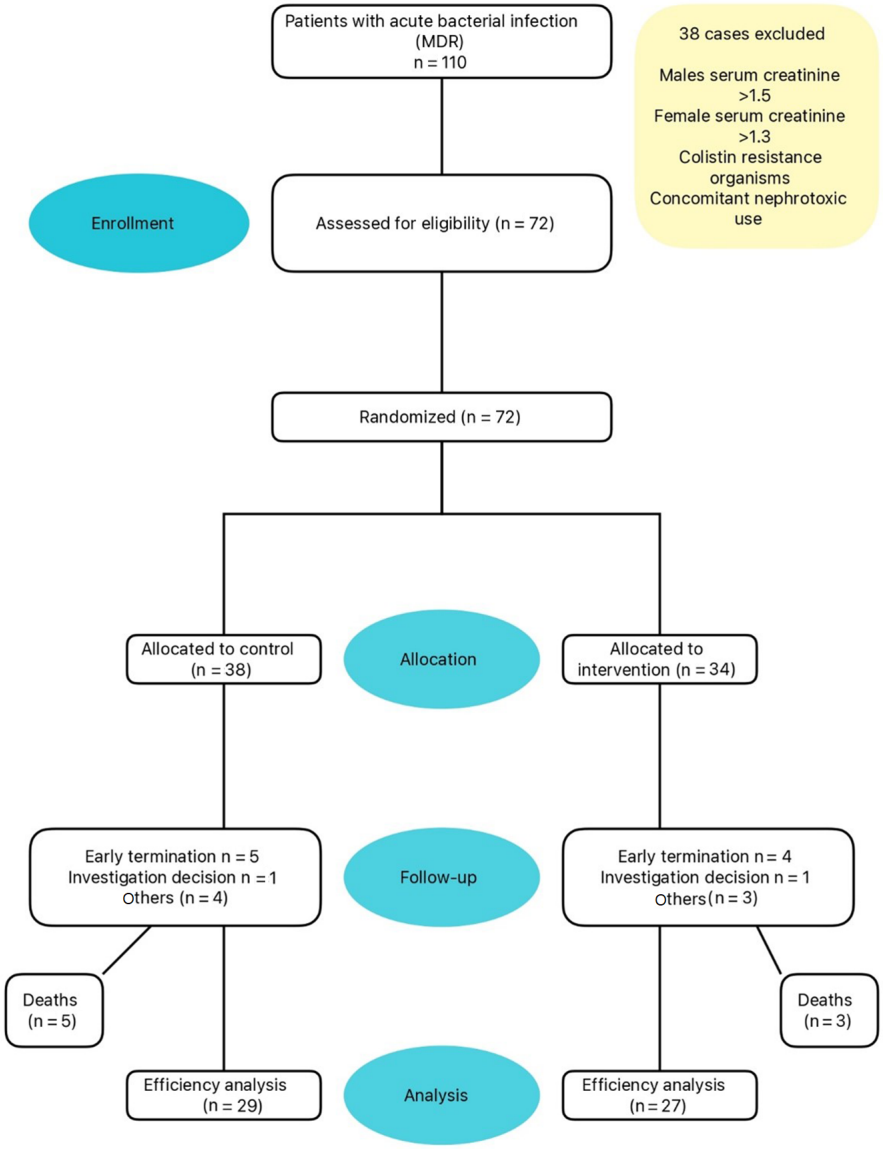

Figure 2. Participant flow diagram of randomized control trial

56 participants were examined, which was not enough. We could not reach the target number of cases. Due to insufficient study participants, no difference in the reduction of colistin- induced nephrotoxicity or change in outcome was observed. Little information is available on the dosage and duration of melatonin to prevent AKI. For this reason, the lowest amount of melatonin has been applied. In future investigations, it is recommended to use a higher dose of melatonin or a loner period to obtain the desired results

This study has several vital points, such as the small number of cases and the significant differences in certain basic features between the groups. The strength of our study is its randomized, double-blind, placebo-controlled nature. In addition, we used a reliable tool (KDIGO) to diagnose and measure renal failure.

Further analysis provides new insights into the different roles of melatonin in critical care patients. We conducted this clinical trial on a limited number of patients; thus, we cannot certainly conclude that patients can prevent renal nephrotoxicity by taking melatonin. More research is needed to investigate the effect of

Table 1. Demographic Characteristics and Laboratory Parameters of the Patients at Baseline

Characteristic	Patients Receiving Colistin (n = 29)	Patients Receiving Melatonin + Colistin (n = 27)	P-Value
Age, y	47.31 ± 20.02	49.22 ± 18.90	0.357
Gender			0.945
Male	18 (62.07)	17 (62.96)	
Female	11 (37.93)	10 (37.04)	
Opium			0.108
No	18 (62.07)	22 (81.48)	
Yes	11 (37.93)	5 (18.52)	
BMI	26.28 ± 2.90	26.90 ± 3.01	0.438
Specimen site			0.516
Sputum	25 (86.21)	21 (77.78)	
Urine	1 (3.45)	1 (3.70)	
Blood	3 (10.34)	3 (11.11)	
Wound culture	0 (0.00)	2 (7.41)	
APACHE II	13.83 ± 4.00	14.96 ± 4.53	0.162
BUN	38.61 ± 20.87	39.62 ± 23.34	0.567
Alb	2.75 ± 0.42	2.73 ± 0.56	0.456
Bilirubin	0.33 ± 0.18	0.35 ± 0.20	0.362
Cr toxicity			0.110
No	18 (62.07)	11 (40.74)	
Yes	11 (37.93)	16 (59.26)	
low urinary output			0.913
No	25 (86.21)	23 (85.19)	
Yes	4 (13.79)	4 (14.81)	
Nephrotoxicity			0.269
No	15 (51.71)	10 (37.04)	
Yes	14 (48.28)	17 (62.96)	

Table 2. Regression Analysis for the Effect of Multiple Variables on Nephrotoxicity Occurrence After Administering Melatonin

Variables	OR (95% CI)	P-Value
Gender (Ref. male)	1.938 (0.480 - 7.826)	0.353
Age	1.017 (0.985 - 1.051)	0.302
Opium (Ref. no)	2.609 (0.643 - 10.585)	0.179
BMI	1.008 (0.797 - 1.276)	0.944
APACHE II	1.072 (0.930 - 1.236)	0.337
Group (Ref. placebo)	2.073 (0.631 - 6.809)	0.229

melatonin on reducing nephrotoxicity.

4.1. Conclusions

We conducted this double-blind trial to study the effect of melatonin on colistin-induced kidney toxicity reduction The results showed no significant difference between melatonin and the placebo in reducing colistin-induced AKI. Currently, there is no practical way to minimize colistin-induced AKI. We recommend careful monitoring of renal function and appropriate dosage adjustment during treatment in high-risk populations because they are essential to reducing the risk of drug-induced AKI in critically ill patients.

Table 3. Comparison of Value of the Parameters Between Two Groups [a]

Parameter and Study Stage	Intervention Group (n = 27)	Control Group (n = 29)	P-Value [b]
SCr, mg/dL			
Day 1	0.90 ± 0.27	0.84 ± 0.27	0.42
Day 2	0.94 ± 0.31	0.85 ± 0.39	0.36
Day 3	1.09 ± 0.47	0.90 ± 0.35	0.10
Day 4	1.17 ± 0.63	0.92 ± 0.33	0.10
Day 5	1.39 ± 0.84	0.87 ± 0.33	0.01
Day 6	1.36 ± 0.93	0.98 ± 0.36	0.08
Day 7	1.46 ± 1.01	1.04 ± 0.49	0.15
Day 8	1.34 ± 1.07	1.09 ± 0.59	0.42
Day 9	1.43 ± 0.97	1.06 ± 0.56	0.24
Day 10	1.50 ± 1.15	0.82 ± 0.28	0.07
P-value [c]	0.0874	0.3220	0.0428
BUN, mg/dL			
Day 1	34.60 ± 17.98	36.36 ± 19.94	0.73
Day 2	37.11 ± 19.30	38.13 ± 26.20	0.87
Day 3	37.15 ± 18.42	40.87 ± 28.59	0.57
Day 4	37.46 ± 22.18	40.37 ± 26.77	0.68
Day 5	42.36 ± 25.79	42.01 ± 23.83	0.96
Day 6	43.70 ± 34.28	39.47 ± 21.85	0.63
Day 7	45.53 ± 42.07	43.45 ± 30.71	0.86
Day 8	41.97 ± 39.09	43.48 ± 31.04	0.90
Day 9	50.02 ± 43.51	42.16 ± 22.40	0.56
Day 10	47.38 ± 47.28	37.21 ± 19.60	0.52
P-value [c]	0.86	0.99	0.85
CrCl, mg/dL			
Day 1	100.65 ± 47.97	109.08 ± 44.35	0.50
Day 2	98.73 ± 50.71	112.52 ± 49.65	0.32
Day 3	89.31 ± 51.56	103.43 ± 84.30	0.30
Day 4	90.54 ± 53.51	99.07 ± 40.51	0.53
Day 5	83.97 ± 58.40	111.56 ± 52.27	0.10
Day 6	90.32 ± 62.56	96.59 ± 43.93	0.70
Day 7	87.09 ± 63.54	94.57 ± 44.24	0.68
Day 8	98.83 ± 68.12	93.56 ± 48.89	0.80
Day 9	92.95 ± 74.65	92.70 ± 42.61	0.99
Day 10	95.89 ± 82.38	111.59 ± 41.10	0.58
P-value [c]	0.99	0.88	0.53
Urine, mg/dL			
Day 1	3633.33 ± 1798.66	3323.79 ± 1660.39	0.51
Day 2	3336.48 ± 1547.57	3458.62 ± 1702.21	0.78
Day 3	3712.96 ± 1529.24	3417.59 ± 2122.42	0.56
Day 4	3733.46 ± 1580.59	3198.80 ± 1736.11	0.26
Day 5	3650 ± 1342.94	3244 ± 1303.95	0.29
Day 6	3575 ± 1507.34	3194.78 ± 1412.43	0.39
Day 7	3594.74 ± 1699.09	3740 ± 1839.59	0.8
Day 8	4361.54 ± 1742.50	3447.22 ± 1947.66	0.19
Day 9	4354.17 ± 1397.67	3413.33 ± 1349.67	0.09
Day 10	3920 ± 1510.56	3363.64 ± 1549.53	0.42
P-value [c]	0.71	0.99	0.19

[a] Values are expressed as Mean ± SD.
[b] Independent sample *t*-test.
[c] Repeated measures ANOVA.

Table 4. Comparison of the Frequency of AKI Between Two Groups

Parameter	Drug (n = 27), No. (%)	Control (n = 29), No. (%)	P-Value [a]
Number of AKI cases	18 (66.67)	13 (44.83)	0.1
AKI stage			0.24
Stage 1	13 (48.15)	10 (34.48)	
Stage 2	2 (7.41)	3 (10.34)	
Stage 3	3 (11.11)	0	

[a] Independent sample *t*-test

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Footnotes

Authors' Contribution: Conceptualization: Mohammad Torabi; Data curation: Mohammad Torabi; Formal analysis: Mohammad Torabi, Hashemi; Funding acquisition: Mohammad Sistanizad, Mohammad Torabi; Project administration: Seyedpouzhia Shojaei, Mohammad Sistanizad; Software: Mohammad Torabi; Visualization: Mohammad Torabi; Writing-original draft: Mohammad Torabi and Editing: All authors.

Clinical Trial Registration Code: IRCT20210110049990N1.

Conflict of Interests: The authors declare no conflict of interests.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study is approved under the ethical approval code of IR.SBMU.MSP.REC.1399.581 by Shahid Beheshti Medical University.

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