Original Article

Effects of Different Dosage of Calcium on Gentamicin-Induced Nephrotoxicity in Rabbits

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ABSTRACT

Objective: To Study the Effects of Different Dosages of calcium on Gentamicin-Induced Nephrotoxicity in Rabbits.
Study Design: Experimental Study
Place and Duration of Study: This study was conducted at the Idris Teaching Hospital Sialkot and DHQ Teaching Hospital Faisalabad during Feb 2020 to April 2020.
Materials and Methods: Fifty-four Rabbits were included in this experimental study. Different doses of Calcium and Gentamicin were given to rabbits and Blood urea nitrogen (BUN), Serum Creatinine, Urine Protein, Kidney SOD and histopathology of kidney were recorded. The Ethical Committee Permission was taken before start of the study and data published in Medical Journal. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 14.0 package. The data were expressed as mean ± standard deviation (SD). Student's unpaired t-test, analysis of variance (ANOVA), and Wilcoxon Rank Sum test were used for parametric and non-parametric data, respectively. P <0.05 was considered significant.
Results: Rabbits: Effect on BUN, serum Creatinine, urinary proteins and kidney SOD: The levels of BUN, serum creatinine, urinary proteins, and kidney SOD were compared between the five groups, on day 7, after six days of consecutive treatment with respective drugs. The baseline values were similar in all groups on day 0. Results showed that BUN, serum creatinine, and urinary proteins were significantly elevated ($P < 0.05$) and kidney SOD levels were significantly reduced ($P < 0.05$) in group II (Gentamicin-treated group). While calcium 0.5 g/kg/day and calcium 1.0 g/kg/day significantly reduced ($P < 0.05$) the elevated BUN, serum creatinine, urinary proteins, and significantly elevated ($P < 0.05$) the SOD levels when administered with gentamicin in group V, respectively. There was a significant dose-dependent relationship between group 4 with group 5 (calcium 1.0 g/kg/day) showing more significant effect on above parameters when compared to group V.
Histopathological effects: The histopathological picture of animals in group I, III, and IV revealed normal architecture of glomeruli and mesangium. Basement membrane of the tubules was found to be intact. However, animals in group II (gentamicin only) showed numerous patches of focal and diffuse necrosis of tubular cells. Basement membrane breaks were found in tubule sections. Glomerular changes of grade 4 were seen with occasional infiltration. The renal histopathology picture in group V (calcium 0.5 g/kg/day) revealed normal architecture of glomeruli and mesangium with few areas of focal necrosis while group V (calcium 1.0 g/kg/day) revealed normal architecture of glomeruli and mesangium. Basement membrane of the tubules was found to be intact in both groups Basement membrane breaks were found in tubule sections. Glomerular changes of grade 4 were seen with occasional infiltration
Conclusion: The administration of calcium 1.0 g/kg/day is more efficacious than calcium 0.5 g/kg/day in preventing Gentamicin-induced Nephrotoxicity in rabbits. Further, there is no species sensitive variation in results that could be extrapolated to humans.

Key Words: Rabbits, Gentamicin, Calcium, Nephrotoxicity.

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INTRODUCTION

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Aminoglycosides are utilized in the administration of genuine and hazardous gram-negative bacterial contaminations in light of their synergism with beta-lactam anti-toxins, their stamped post-anti-toxin impact, and their quick fixation subordinate murdering impact. Be that as it may, nephrotoxicity especially on delayed organization is seen in 10–20% of hospitalized patients who create intense harmful renal failure.[1] Various investigations completed so far have demonstrated that in 39% of instances of intense renal disappointment, earlier organization of medications was the reason for failure.[2] More disturbing was the way that gentamicin organization was answerable for the same number of as 89% of these cases. Nephrotoxicity is answerable for

more and all the more exorbitant hospitalizations and potentiates the poison levels of other drugs.[3]

An expanding assemblage of proof shows that the systems engaged with gentamicin-initiated nephrotoxicity are multifaceted. The atomic and pathophysiological instruments of gentamicin-instigated nephrotoxicity are all around described. Gentamicin is disguised through the mammoth endocytic complex that is specially communicated in renal proximal cylindrical fragments S1 and S2.[4] In these cells, gentamicinis for the most part amassed in lysosomes, the Golgi contraption and endoplasmic reticulum, delivering lysosomal phospholipidosis, unfurled protein reaction and different impacts, in this way turning on apoptotic and necrotic passing pathways.[5]

Past decade has seen a colossal examination on operators altering gentamicin-initiated nephrotoxicity, for example, utilization of different cell reinforcements like nutrient E and nutrient C,[6], S-allylcysteine,[8] diallysulfide,[9] home grown medications, for example, Withania somnifera, Crocus Sativus, Nigella sativa and utilization of adjusted aminoglycosides, for example, astromicin and dactimicin which tie less firmly to phospholipid bilayers and are more fragile inhibitors of lysosomal phospholipases.[10] None of the above specialists has genuinely settled itself in clinical practice. Past examinations utilizing calcium channel blockers, for example, verapamil have demonstrated opposing outcomes in gentamicin-prompted nephrotoxicity with some indicating an advantageous impact. while others have demonstrated a nephrotoxicity upgrading potential.[10] An ongoing report has indicated a useful impact of oral calcium (Ca+2) organization in gentamicin-actuated nephrotoxicity in rodents. Likewise, it has been discovered that oral calcium stacking ensures against gentamicin-prompted intense renal excretory failure.[10] Ca2+ is a serious inhibitor of 125I-gentamicin authoritative to disengaged renal storm cellar layers, the underlying film site of association among gentamicin and renal proximal tubule cells, accordingly forestalling basic cell confusions initiated by gentamicin inside the renal cylindrical cell instead of on its cell surface. In any case, there are not many investigations contrasting the organization of various measurements of calcium and verapamil in gentamicin-instigated nephrotoxicity in rodents and bunnies all the while to perceive any species delicate variety in results.

MATERIALS AND METHODS

Fifty-four Rabbits were included in this experimental study. Different doses of Calcium and Gentamicin were given to rabbits and Blood urea nitrogen (BUN), Serum Creatinine, Urine Protein, Kidney SOD and histopathology of kidney were recorded. The Ethical Committee Permission was taken before start of the study and data published in Medical Journal.

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 14.0 package. The data were expressed as mean ± standard deviation (SD). Student's unpaired t-test, analysis of variance (ANOVA), and Wilcoxon Rank Sum test were used for parametric and non-parametric data, respectively. $P < 0.05$ was considered significant.

RESULTS

Rabbits

Effect on BUN, serum creatinine, urinary proteins and kidney SOD

The levels of BUN, serum creatinine, urinary proteins, and kidney SOD were compared between the seven groups, on day 7, after six days of consecutive treatment with respective drugs. The baseline values were similar in all groups on day 0. Results showed that BUN, serum creatinine, and urinary proteins were significantly elevated ($P < 0.05$) and kidney SOD levels were significantly reduced ($P < 0.05$) in group II (Gentamicin-treated group). Calcium 1.0 g/kg/day and verapamil 7.0 mg/kg/day had no significant effect on above parameters when administered alone in group III and group IV, respectively (Table 1) while calcium 0.5 g/kg/day and calcium 1.0 g/kg/day significantly reduced ($P < 0.05$) the elevated BUN, serum creatinine, urinary proteins, and significantly elevated ($P < 0.05$) the SOD levels when administered with gentamicin in group V and group VI, respectively. [Table 2] There was a significant dose-dependent relationship between group V and group VI with group VI (calcium 1.0 g/kg/day) showing more significant effect on above parameters when compared to group V. Table 2

Table No.1: Effect of normal saline, gentamicin, calcium, on blood urea nitrogen (BUN), serum creatinine, urinary proteins, and kidney SOD in rabbits

Parameters	Mean +_ SD		
	Group 1 (Control, normal saline (2ml/kg)	Group 2 (Gentamicin 80 mg/kg/ day, i.m.)	Group 3 (Calcium 0.5 g/kg/ day, p.o.)
Blood urea nitrogen (BUN)(mg/dl)	17.95 +_ 1.2390	127.01 +_ 4.25	18.97 +_ 1.140
Serum Creatinine (mg/dl)	0.5 +_ 0.083	4.58 +_ 0.59	0.49 +_ 0.10
Urinary proteins(mg/dl)	0.24 +_ 0.43	2.07 +_ 0.91	0.28 +_ 0.061
Kidney superoxide dismutase (SOD) (U/ml)	0.161 +_ 0.162	0.57 +_ 0.04	0.76 +_ 0.021

$P<0.05$ as compared to group 1. SOD= Superoxide dismutase level, BUN= Blood urea nitrogen, SD= Standard deviation.

Table No. 2: Effect of gentamicin, gentamicin+calcium (0.5 g/kg/day), gentamicin+calcium (1.0 g/kg/day), on blood urea nitrogen (BUN), serum creatinine, urinary proteins, and kidney SOD in rabbits

Parameters	Mean +_ SD		
	Group 2 (Gentamicin 80 mg/kg/ day, i.m.)	Group 5 (Gentamicin 80 mg/kg/ day, i.m. + calcium 0.5 g/kg/day, p.o.)	Group 5 (Gentamicin 80 mg/kg/ day, i.m. + calcium 1.0 g/kg/day, p.o.)
BUN (mg/dl)	125.95 +_ 3.97	92.95 +_ 4.97	20.96 +_ 1.72
Serum Creatinine (mg/dl)	4.58 +_ 0.60	2.20 +_ 0.47	0.47 +_ 0.060
Urinary proteins (mg/dl)	2.07 +_ 0.093	1.12 +_ 0.028	0.24 +_ 0.035
Tissue superoxide dismutase (SOD) (U/ml)	0.56 +_ 0.04	0.39 +_ 0.01	0.17 +_ 0.015

P<0.05 as compared to group 2.'P< 0.05 compared group 5. SOD= Superoxide dismutase level, BUN= Blood urea nitrogen, SD= Standard deviation.

Table No.3: Effect of normal saline, gentamicin, calcium, on histopathology in rabbit kidney

Histopathology scores	0	1	2	3	4	Mean rank
Group 1 (n=16) normal saline 2.0 ml/kg	6	0	0	0	0	6.5
Group 2 (n=16) Gentamicin 80 mg/ kg, i.m.	0	0	0	0	6	9.5
Group 3 (n=16) Calcium 1.0 g/kg, p.o.	6	0	0	0	0	6.5

P<0.05 as compared to group 1

Table No.4: Effect of gentamicin, gentamicin+calcium (0.5 g/kg/day), gentamicin+calcium (1.0 g/kg/day) on histopathology in rabbit kidney

Histopathology scores	0	1	2	3	4	Mean rank
Group 2 (n=16) Gentamicin 80 mg/kg, i.m.	0	0	0	0	5.95	9.4
Group 4 (n=16) Gentamicin 80 mg/kg, i.m. + calcium 0.5 g/kg, p.o.	1.98	3.98	0	0	0	4.2
Group 5 (n=16) Gentamicin 80 mg/kg/day, i.m.+ calcium 1.0 g/kg/day, p.o.	4.96	1	0	0	0	4.0

P<0.05 as compared to group 2

Table No.5: Effect of normal saline, gentamicin, calcium, on blood urea nitrogen (BUN), serum creatinine, urinary proteins, and kidney superoxide dismutase (SOD) in rabbits

Parameters	Mean +_ SD		
	Group 1 (Control, normal saline, 2.0 ml/kg)	Group 2 (Gentamicin 80 mg/kg/day, i.m.)	Group 3 (Calcium 1.0 g/kg/ day, p.o.)
BUN (mg/dl)	18.95 +_ 1.50	130.07 +_ 3.80	19.80 +_ 2.01
Serum Creatinine (mg/dl)	0.34 +_ 0.04	3.90 +_ 0.15	0.29 +_ 0.32
Urinary proteins (mg/dl)	0.17 +_ 0.65	1.25 +_ 0.21	0.15 +_ 0.092
Kidney SOD (U/ml)	0.20 +_ 0.018	0.52 +_ 0.42	0.21 +_ 0.021

P<0.05 as compared to group 1 SOD=Superoxide dismutase levels, BUN=Blood urea nitrogen, SD= standard deviation

Histopathological effects: The histopathological picture of animals in group I, III, and IV revealed normal architecture of glomeruli and mesangium. Basement membrane of the tubules was found to be intact. However, animals in group II (gentamicin only) showed numerous patches of focal and diffuse necrosis of tubular cells. Basement membrane breaks were found in tubule sections. Glomerular changes of grade 4 were seen with occasional infiltration. (Table 3) The renal histopathology picture in group V (calcium 0.5 g/kg/day) revealed normal architecture of glomeruli and mesangium with few areas of focal necrosis while group VI (calcium 1.0 g/kg/day) revealed normal architecture of glomeruli and mesangium. Basement membrane of the tubules was found to be intact in both groups (Table 4). However, the animals in group VII (gentamicin + verapamil) showed patches of focal and diffuse necrosis of tubular cells. Basement membrane breaks were found in tubule sections. Glomerular changes of grade 4 were seen with occasional infiltration (Table 5).

Rabbits

Effect on BUN, serum creatinine, urinary proteins, and kidney SOD: The levels of BUN, serum creatinine, urinary proteins, and kidney SOD were compared between the five groups on day 7 after 6 days of consecutive treatment with respective drugs in a manner similar to those in rabbits. The baseline values were similar in all groups on day 0. The results were identical to results obtained in rabbits with group II (gentamicin only) showing a significant elevation ($P < 0.05$) of BUN, serum creatinine, urinary proteins, and significant reduction ($P < 0.05$) of kidney SOD when compared to control group [Table 5].

Table No.6: Effect of gentamicin, gentamicin+calcium (0.5 g/kg/day), gentamicin+calcium (1.0 g/kg/day), and gentamicin+verapamil (7 mg/kg/day) on blood urea nitrogen (BUN), serum creatinine, urinary proteins, and kidney superoxide dismutase (SOD) in rabbits

Parameters	Mean +_ SD		
	Group 2 (Gentamicin 80 mg/kg/ day, i.m.)	Group 5 (Gentamicin 80 mg/kg/ day, i.m. + calcium 0.5 g/kg/day, p.o.)	Group 6 (Gentamicin 80 mg/kg/ day, i.m. + calcium 1.0 g/kg/day, p.o.)
BUN (mg/dl)	130.08 +_ 3.75	95.41 +_ 4.40	21.49 +_ 1.75
Serum Creatinine (mg/dl)	3.90 +_ 0.14	1.43 +_ 0.35	0.29 +_ 0.027
Urinary proteins (mg/dl)	1.29 +_ 0.21	0.75 +_ 0.07	0.13 +_ 0.045
Kidney SOD (U/ml)	0.50 +_ 0.039	0.40 +_ 0.018	0.23 +_ 0.013

P< as compared to group 2, P<0.05 as compared to group 5.SOD=Superoxide dismutase levels, BUN Blood urea nitrogen, SD=Standard deviation

Groups III and IV showed no significant change in above parameters when compared to control group (Table 5) while groups V showed a dose dependent effect on above parameters with group V (calcium 1.0 g/kg/day) showing a more significant reduction (P < 0.05) of BUN, serum creatinine, and urinary proteins when compared to group V (calcium 0.5 g/kg/day) [Table 5]. The levels of kidney SOD were also raised significantly by calcium 1.0 g/kg/day (group V) when compared to calcium 0.5 g/kg/day (group V).

Histopathological effects: The renal histopathological picture results were also identical to that observed in rabbits with groups V showing a significant reversal of tubular necrosis and intact basement membrane when compared to group II [Table 6] which showed a histopathological score of 4 suggestive of tubular necrosis and glomerular basement membrane damage.

Table No.7: Effect of normal saline, gentamicin, calcium, on histopathology in rabbit kidney

Histopathology scores	0	1	2	3	4	Mean rank
Group 1 (n=16) Normal saline 2.0 ml/kg/day	5.95	0	0	0	0	6.4
Group 2 (n=16) Gentamicin 80 mg/kg, i.m.	0	0	0	0	5.93	9.3
Group 3 (n=16) Calcium 1.0 g/kg/day, p.o.	6	0	0	0	0	6.3

P<0.05 as compared to group 1

Table No.8: Effect of gentamicin, gentamicin+calcium (0.5 g/kg/day), gentamicin+calcium (1.0 g/kg/day), on histopathology in rabbits kidney

Histopathology scores	0	1	2	3	4	Mean rank
Group 2 (n=16) Gentamicin 80 mg/kg/day, i.m.	0	0	0	0	4.95	9.3
Group 4 (n=16) Gentamicin 80 mg/kg, i.m. + calcium 0.5 g/kg/day, p.o.	2.95	2.95	0	0	0	4.95
Group 5 (n=16) Gentamicin 80 mg/kg/day, i.m.+ calcium 1.0 g/kg/day, p.o.	4.96	1	0	0	0	4.0

P<0.05 as compared to group 2

DISCUSSION

This investigation was directed to think about the impacts of various doses of calcium on Gentamicin-prompted Nephrotoxicity in hares.

Gentamicin 80 mg/kg/day i.e. for six days in hares is known to deliver morphological and biochemical adjustments in kidneys like the signs in human kidney.[11] Hence, Gentamicin was utilized in our investigation for acceptance of Nephrotoxicity in hares in comparative portion and term. In clinical settings, intense renal disappointment is analyzed based on BUN and serum Creatinine. They are considered as the most solid and practical markers of renal capacity among some other renal parameters.[12] Therefore BUN, serum Creatinine, and urinary proteins were evaluated for estimation of kidney work in our investigation. Different lysosomal compounds like decreased glutathione, SOD, malondialdehyde, and histopathological changes. Thus, we additionally evaluated superoxide dismutase levels and histopathological changes as boundaries for estimating renal poisonousness. These boundaries have been effectively utilized by different analysts in past studies.[13]

The outcomes showed in hares, calcium when regulated alone for six days in bunches III and IV, individually, didn't build the BUN, serum creatinine, urinary proteins, or decreased kidney SOD levels, demonstrating that these medications are not nephrotoxic without anyone else. Then again, gentamicin particularly expanded the BUN, serum creatinine, urinary proteins, and diminished the kidney SOD levels when directed for six days in bunch II in hares. These outcomes were steady with recently directed examinations in which gentamicin has been demonstrated to be exceptionally nephrotoxic.[14] Gentamicin extraordinarily upgrades the age of receptive oxygen metabolites in the mitochondria. Histopathological changes of evaluation 4 reminiscent

of cylindrical rot and glomerular harm were likewise found in Gentamicin-rewarded hares in bunch II affirming the nephrotoxic capability of Gentamicin saw in before examines.[15]

In our examination we found that low portions of calcium, for example 0.5 g/kg/day had the option to forestall nephrotoxicity actuated by gentamicin in a huge way when contrasted with bunch II creatures regulated gentamicin alone. There was a noteworthy decrease in BUN, serum creatinine, urinary proteins, and rise of kidney SOD levels when contrasted with hares given Gentamicin alone. Histopathological assessment likewise demonstrated less rounded and glomerular harm when contrasted with hares given gentamicin alone.[16]

Calcium in a high portion of 1.0 g/kg/day alongside Gentamicin demonstrated huge decrease in BUN, serum creatinine, urinary proteins, and rise of kidney SOD in bunch V when contrasted with Gentamicin alone The histopathological assessment additionally indicated typical engineering in creatures co-rewarded with calcium 1.0 g/kg/day and gentamicin. The portion of calcium 1.0 g/kg/day was altogether more useful than calcium 0.5 g/kg/day in normalizing the disturbed biochemical boundaries and forestalling the morphological modifications in tubules and glomerulus of kidney. These outcomes were like a previous investigation directed indicating a portion subordinate defensive impact of calcium.[15] Some laborers have shown that oral Ca2+ load notably decreases the gentamicin-prompted renal disappointment in people and rabits. Others anyway have neglected to record a Ca2+-incited enhancement in gentamicin nephrotoxicity in bunnies. While still others have detailed Ca2+ to potentiate intense renal disappointment in people rewarded with gentamicin. Calcium has nephroprotective activity by either reducing practical hemodynamic modifications at the glomerular level or forestalling basic cell harm at the rounded level. Others propose that the defensive activity of Ca2+ might be intervened either (a) by initiating metabolic changes during oral Ca2+ loading,[18] (b) by easing back renal cortical collection, or (c) by upgrading the discharge of gentamicin.[18]

In this investigation, we didn't discover any adjustment in the BUN, serum creatinine, urinary proteins, and SOD levels in bunnies regulated with gentamicin. Further histopathology indicated numerous regions of extreme central corruption and rounded harm in gentamicin gathering. . Likewise, there was no huge increment in the harmfulness on attending gentamicin[18] yet not at all like the examination did by Ali et al., 2002[15] which indicated improve the impacts of gentamicin.

CONCLUSION

The administration of calcium 1.0 g/kg/day is more efficacious than calcium 0.5 g/kg/day in preventing Gentamicin-induced Nephrotoxicity in rabbits. Further, there is no species sensitive variation in results that could be extrapolated to humans.

Author's Contribution:

Concept & Design of Study:	Nauman Idris Butt
Drafting:	Mohammad Rafique, Umra Imran
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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