IN VIVO EVALUATION OF PROTECTIVE EFFECT OF HYDRATION WITH SODIUM CHLORIDE VERSUS URINE ALKALINISATION ON COLISTIN INDUCED NEPHROTOXICITY IN RATS

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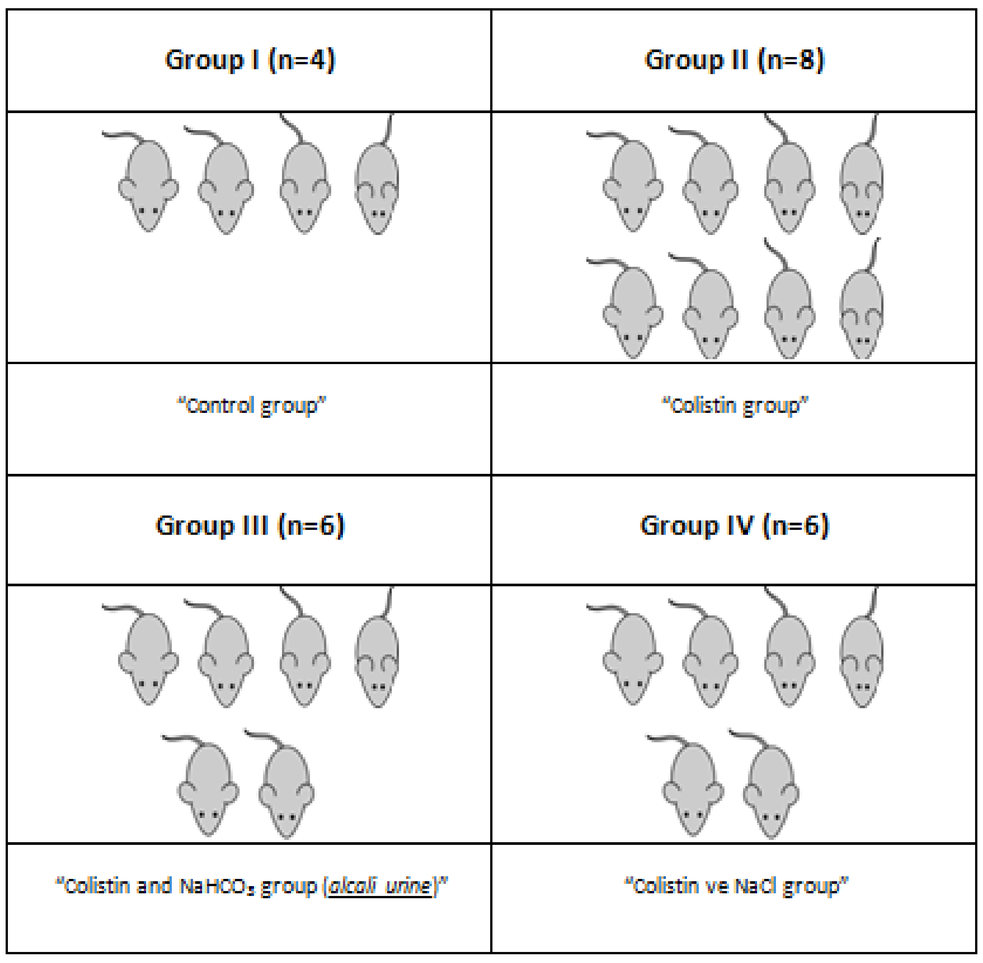
OBJECTIVES

Colistin is a vital antibiotic that is used in drug-resistant nosocomial infections. The most important side effect that causes severe morbidity and mortality is nephrotoxicity.
Nephrotoxicity of colistin is due to its direct exposure to renal tubules causing acute tubular necrosis. Colistin is a weak acid. In this study, it is aimed to evauate the possible protection of urine alkalinisation that is used in toxicities of weak acids.

METHODS

Sprauge Dawley rats were divided into four groups. Group I (control) were injected intramuscular distilated water. Group II (colistin) were injected 750000 IU/kg/day of colistin. Group III (colistin-bicarbonate) were injected same dose of colistin, after they reach urinary pH>7 by addition of bicarbonate in their drinking water.Group IV (colistin-NaCl) were injected the same dose of colistin after reaching GroupIII's urine density by adding NaCl in their drinking water. Urine and blood samples were collected and necropsy was performed.



RESULTS

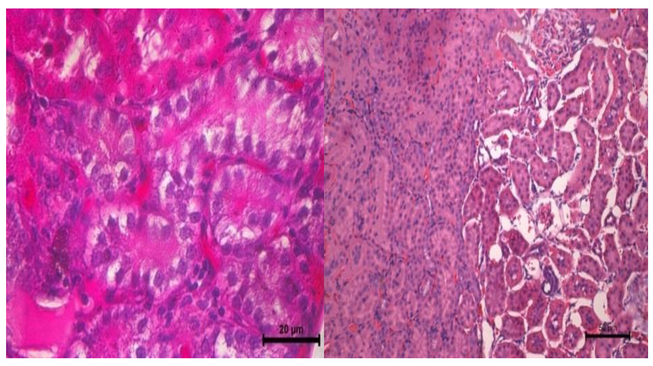
Table-1. The histopathological grading scheme for tubular degeneration, *Keirstead et all*.

Score	Tubular Degenaration Grade	Histopathological Findings
0	Normal	Normal renal tubular epitelial cells
1	Minimal	Tubular cells with brightly eosinophilic cytoplasm and pyknotic nuclei
2	Slight	Occasional degenerate cells with pyknotic to karyorrhectic nuclei and sloughed cells within tubular lumina (protein casts)
3	Mild	Small clusters of 2–4 degenerate cells with pyknotic nuclei and protein casts
4	Moderate	Larger clusters and chains of degenerate cells, some with complete loss of chromatin, affecting numerous tubules
5	Marked	Majority of tubules affected by chains of degenerate cells, or entire tubular segments affected by degeneration

Table-2. Correlation of urine density and tubular degeneration scores

	Urine density <1010	Urine density >1010	
Tubular Degeneration Score (0-5)	n (%)	n (%)	*p* value
1,00	6 (50)	-	*0,001*
2,00	4 (33,3)	-	
3,00	1 (8,3)	2 (25)	
4,00	1 (8,3)	2 (25)	
5,00	-	4 (50)	

Picture-1 and 2. Renalcortex. × 63 objective H&E ; renal cortex × 20 objective H&E



Serum urea levels showed borderline statistical difference (*p*=0,046) but, it was not clinically correlated when compared histopathologically. Serum creatinine values showed no statistical difference (*p*=0,131). According to histological tubular degeneration average scores (scored 0-5,Table-1); protection was achieved against nephrotoxic agent (*p*<0,001). In control group normal renal tubul epitelial cells were seen and; in colistin-treated rats,mild-marked tubular degeneration detected, pyknotic nuclei and sloughed cells within tubular lumina(protein casts) and vacuolation of the cytoplasm seen(pictures 1 and 2). In colistin-bicarbonate group, less tubules were affected, loss of epithelial cells, basal membrane separation, in some areas pale basophilic accumulation in tubule lumen, a small number of protein casts, vacuolization and necrosis were detected (Grade1-4 degeneration). Incolistin-NaCl group dilatation seen in few tubules, separation between epithelial cells, in some tubule lumen pyknotic nuclei of the cells and interstitial edema were observed in some areas. Bicarbonate group was not superior to NaCl group(*p=0,601*). Urine densities and tubular degeneration scores were statistically correlated independent of the groups. The lower the urine density was, the lower the tubular score (*p=0.001*).

CONCLUSIONS

Colistin is a very effective and unprecedented agent in drug-resistant nasocomial infections. The most common and mortality-morbidity related side effect of this drug is nephrotoxicity. Colistin is a weak acid and excreted in urine unmetabolised and is toxic to tubules directly. The protection is alcali urine is studied in rats. Bicarbonate group was not superior to NaCl group (*p=0,601*). Urine densities and tubular degeneration scores were statistically correlated independent of the groups. The lower the urine density was, the lower the tubular score(*p=0.001*). Bicarbonate hydration is not superior to NaCl hydration, and both are effective similarly. Decrease in urine density is correlated with tubular protection.
Since diluated urine is protective, further studies with diuretics could be benefical for protection; most importatntly fot patients that cannot be hydrated massively.

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