International Journal of Innovative Studies in Sciences and Engineering Technology (IJISSET)

ISSN 2455-4863 (Online) www.ijisset.org *Volume: 3 Issue: 11 | November 2017*

Assessment of Aminoglycosoid Nephrotoxicity in Egyptian Full Term Neonates with Sepsis

Mohamed Abdelaziz El-Gamasy[1*],MD,Akram Elshafei Elsadek,MD[2], Mohammed Abd Ellatif Nassar,MD[1]

[1]From Department of Pediatrics and Neonatology, Faculty of Medicine , Tanta University, Egypt.
[2]From Department of Pediatrics and Neonatology, Faculty of Medicine , Benha University, Egypt.

Corresponding Author: Dr.Mohamed A.El-Gamasy

Assistant Professor of Pediatrics & Neonatology,Tanta Faculty of Medicine, Egypt

Abstract:

Introduction: *Infections and their treatments as common problems in neonates may cause different complications. Ampicillin and Aminoglycosides, as of choice drugs for this condition may have many dangerous side effects, such as nephrotoxic effect. Therefore, aim of this study was evaluation of nephrotoxic effects of Gentamicin and Amikacin in neonates with infection.*

Materials and Methods: *This clinical trial, doubl blind study was conducted on 80 full term neonates with neonatal sepsis (NS)selected fron Neontal Intensive Care Units(NICU) of Tanta and Benha University Hospitals .They were treated by aminoglycosides addministration. As a first step, on hospital admission at NICU, we have taken serum and urine samples for diagnosis of infection. Subjects based on their treatment were divided into two groups, 40 patients were treated by ampicillin and amikacin and 40 patients were treated by ampicillin and gentamicin, in 7 days period. At the end of treatment period serum and urine samples were taken for measurment of laboratory variables, and GFR, for evaluation of kidney founction.*

Results: *BUN, serum creatinine and glomerular filteration rate (GFR) before and after treatment in the two groups had not statistically significant difference in two groups ($p > 0.05$). In addition age at diagnosis, gender, birth age, infection type, occupation and education of parents and milk type were equal in two groups.* ***Conclusion*****:** *Based on our study there were no differences between nephrotoxic effect of gentamicin and amikacin in the two studied groups.*

Keywords: *Nephrotoxic, Gentamicin, Amikacin, neonates, Infection.*

1. INTRODUCTION

Infections in neonatal population and their treatment are common problems in pediatrics (1). Combination of ampicillin and aminoglycosides is an approved of choice treatment which have been used since decades for nenatal infections, but both of them have many important side effects and previous studies not evaluated these effects widely (2, 3). Due to high concentration of aminoglycosides in the renal cortex, these drugs may be having side effects on kidney. Nephrotoxic effect, namely nephrotoxic acute tubular necrosis (ATN) is presented as acute kidney injury(AKI) that is defined as increase of serum creatinine, from its baseline, in range of 0.5 or more than 0.5 milligrams per deciliter. Contrary to the therapeutic effects of aminoglycoside, this toxicity is not dose-dependent (4). So high or low concentration of aminoglycosides in cortex of kidney induce nephrotoxic effect as a common and important side effect (5). Also increasing duration of treatment with aminoglycosides increase the risk of nephrotoxic effect, so that more than 14 days period of treatment increase the risk of nephrotoxic effect to 50% (6, 7). Aminoglycosides induce damage of proximal convoluted tubule, and rarely induce dysfunction of glomeruli. Then, acute tubular necrosis , reduced GFR and anuria can be occurring at the end as a life threatening complication and in most cases. The induced nephrotoxic effect by these drugs is irreversible (8). Based on this context we found infectionous diseases in neonatal population and their treatment are common problems. **Aim of this study** : was evaluation of nephrotoxic effect of Gentamicin and Amikacin in neonatal population to make better use of medications for neonatal infection, with less nephrotoxic effects.

2. ETHICAL CONSIDERATIONS

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. In addition, the research ethical committee of Tanta and Benha University Hospitals approved the study protocol and informed parental written or verbal consents from all subjects involved in the study.

3. METHODS AND DESIGN OF THE STUDY AND SETTING

This double blind, clinical trial ,hospital-based study was conducted.upon 80 neonatal patients who were hospitalized at NICUs of Tanta Universality hospital in the period from September 2016 to September 2017. Their gestational ages ranged from 38.4± 1.2 weeks. They were 33 males and 27 females,

Inclusion Criteria: The patients were diagnosed with different forms of infections and indicated for treatment with aminoglycosides. Based on synchronization we divide them into two groups. 40 patients were treated by ampicillin and amikacin and 40 patients were treated by ampicillin and gentamicin, in 7 days period.

4. EXCLUSION CRITERIA

Neonates with perinatal history of maternal azotemia ,neonates with underlying congenital renal and urinary tract disorders such as Bartter, RTA and any proximal tubular dysfunction, recent history of use of nephrotoxic medications especially gentamicin and amikacin, ABG acid-base disorders, disrupted tests before start of treatment.

and those neonates who died during the research. During the study, parents of patients, who wish not to continue working or were not available to complete the study were excluded from study

5. MEASUREMENTS

After selection of neonates, basic information including age (in days) and gender (male or female) to be recorded in the question list and first serum and urine samples were taken from patients. The neonates were divided into two groups and treated in 7 days of period, 40 neonates treated by ampicillin and amikacin and 40 neonates treated by ampicillin and gentamicin. Antibiotics were injected intravenously by micro infusion set and within a 30 minutes period. Ampicillin were used for Listeria and group B of Streptococcus, and aminoglycosides were used for enteric gram negativities. Registerations of laboratory variables were done by secondary serum and urine samples. Studied variables were including bicarbonate, BUN,serum creatinine, sodium, potassium, calcium, urine analysis and GFR and nephrotoxic effects were define as increase of serum creatinine, from its baseline, in range of 0.5 or more than 0.5 milligrams per deciliter.

6. ANTIBIOTICS PROTOCOL

Antibiotics doses of two groups were used based on gestational age and weight, as mentioned in Table (1).

Table 1: *Doses of Administered Antibiotics*

Antibiotics [a]	Postnatal Age	
	≤ Seven Days	> Seven Days
	1200 to >2000 (g)	1200 to >2000 (g)
	2000 (g)	2000 (g)
Amikacin	7.5 (Per 12-18 hr)	10 (Per 12 hr)	7.5 (Per 8-12 hr)	10 (Per 8 hr)
Gentamicin	2.5 (Per 12-18 hr)	2.5 (Per 12 hr)	2.5 (Per 8-12 hr)	2.5 (Per 8 hr)
Ampicillin [b,c]	50 (Per 24 hr)	75 (Per 24 hr)	75 (Per 24 hr)	100 (Per 24 hr)

[a] *mg/kg/hr, IM or IV.*

[b] *In meningitis dose of Antibiotics will doubled.*

[c] *Doses of Ampicillin were equal in two groups.*

7. STATISTICAL ANALYSIS

Data analysis was conducted by frequency, mean, standard deviation, and standard error, for quantitative variables in SPSS program. In addition, covariance analysis, chi-square test, independent T-test, or equivalent non-parametric tests were used to compare the mean of parameters in groups and after these tests significance level of difference ($p < 0.05$) were considered.

8. RESULTS

We did not find any statistically significant difference between studied patients as regard evaluated variables, so nephrotoxic effects of Gentamicin and Amikacin were not different in our study. Based on table (2) reported demographic information in the two studied groups which were not different. In total of 80 children who have been evaluated, 45 neonates of them were males (56.3 %) and 35(43.7 %) neonates were females ($P = 0.652$). Mean age of our studied neonates was 3.51 ± 2.76 days in Gentamicin group and 3.22 ± 2.5 days in Amikacin group and 3.36 ± 2.63 days in total ($P = 1$). Other evaluated factors including educational status of

fathers of included patients (P = 0.864) and educational status of mothers of included patients (P = 0.407), There was no significant difference between the studied patients groups as regard fathers occupational status (P = 0.338), mothers occupational status (P = 0.603), and living area (P = 1). Table (3) indicated that as regard renal function tests ,the two used antimicrobial drugs did not have difference in their possible nephrotoxic effects on treated neonates. Mean value of BUN before treatment with antibiotics in Gentamicin group was 29.85±14.38 mg % and in Amikacin group was 29.81±16.33 mg % so they showed no statistically significant difference (P = 0.670) and after treatment with antibiotics in Gentamicin group,BUN mean value was 23.45±14.53 mg % and in Amikacin group was 24.87±15.25 mg % so they showed also no statistically significant difference (P = 0.992). As regard GFR before treatment with antibiotics in Gentamicin group,its mean value was 26.73±7.47 ml/min/1.73 m^2 and in Amikacin group, it was 29.11±16.24 ml/min/1.73 m^2 so they showed also no statistically significant difference (P = 0.402) and after treatment with antibiotics .mean value of GFR in Gentamicin group was 41.81±18.28 ml/min/1.73 m^2 and in Amikacin group was 38.21±13.85 ml/min/1.73 m^2 so they showed also no statistically significant difference (P = 0.324).Serum Creatinie mean value before treatment with antibiotics in Gentamicin group was 0.85±0.21 mg% and in Amikacin group was 0.84±0.26 mg % so they showed also no statistically significant difference (P = 0.896) and after treatment with antibiotics ,its mean value in Gentamicin group was 0.56±0.16 mg% and in Amikacin group was 0.60±0.16 mg % (P =0.34). Serum Calcium in Gentamicin group was 8.68±0.7 and in Amikacin group was 9.11±1.2 (P = 0.813). Mean serum Sodium level in Gentamicin group was 138.87±5.71 mg% and in Amikacin group was 139.98 ± 6.8 mg % so they showed also no statistically significant difference (P = 0.431). Mean serum Potassium level in Gentamicin group was 4.42 ± 0.62 mg % and in Amikacin group was 4.61 ± 0.54 mg % so they showed also no statistically significant difference (P = 0.158). Mean serum Bicarbonate level in Gentamicin group was 17.74 ± 2.39 and in Amikacin group was 18.13 ± 3.47 mg % so they showed also no statistically significant difference (P = 0.558). As showed in table (4), there were no statistically significant differences between two studied groups of Gentamicin and Amikacin as regarding delivery status of patients, gestational age, birth weight, infection source, birth height, head circumference at birth, type of consumed milk and maternal diseases during pregnancy(P > 0.05).

Table 2; *Demographic Status of neonates in Gentamicin and Amikacin Groups*

Variables	Groups		Total	P Value
	Gentamicin	Amikacin		
Gender				0.652
Male : No(%)	21(52.5)	24(60)	45(56.2)	
Female: No(%)	19(47.5)	16(40)	35(43.8)	
Age (days)				1
Mean±SD	3.51±2.76	3.22±2.50	3.36±2.63	
Fathers Education Level				0.864
Under Diploma No(%)	20(50)	21(52.5)	41(51.3)	
Diploma and Associate	17(42.5)	15(37.5)	32(40)	
Bachelor and Higher No(%)	3(7.5)	4(10)	7(8.7)	
Mothers Education Level				0.407
Under Diploma No(%)	24(60)	19(47.5)	43(53.8)	
Diploma and Associate No(%)	14(35)	15(37.5)	29(36.2)	
Bachelor and Higher No(%)	2(5)	6(15)	8(10)	
Fathers Occupation				0.338
Self-Employed :No(%)	20(50)	26(65)	46(57.5)	
Employer No(%)	16(40)	10(25)	26(32.5)	
Employee No(%)	4(10)	4(10)	8(10)	
Mothers Occupation				0.603
Housewife No(%)	39(97.5)	38(95)	77(96.3)	
Employer No(%)	1(2.5)	1(2.5)	2(2.5)	
Employee No(%)	0(0)	1(2.5)	1(1.2)	
Living Area				1
Urban No(%)	25(62.5)	24(60)	49(61.3)	
Rural No(%)	15(37.5)	16(40)	31(38.7)	

Table 3: *Kidney Function Tests and Electrolytes in Gentamicin and Amikacin Goups*

Variables	Groups		Total	P Value
	Gentamicin	Amikacin		
Bicarbonate				0.558
Mean±SD	17.74±2.39	18.13±3.47	17.94±2.84	
BUN (mg/dl) Before Treatment				0.992
Mean±SD	29.85±14.38	29.81±16.33	29.83±15.35	
BUN (mg/dl) After Treatment				0.670
Mean±SD	23.45±14.53	24.87±15.25		
GFR (ml/min) Before Treatment				0.402
Mean±SD	26.73±7.47	29.11±16.24	28.41±11.85	
GFR (ml/min) After Treatment				0.324

Mean±SD	41.81±18.28	38.21±13.85	40.01±16.05	
Cr (mg/dl) Before Treatment				0.896
Mean±SD	0.85±0.21	0.84±0.26	0.85±0.23	
Cr (mg/dl) After Treatment				0.340
Mean±SD	0.56±0.16	0.60±0.16	0.58±0.16	
Calcium (mg/dl)				0.813
Mean±SD	8.68±0.7	9.11±1.2	8.89±.0.95	
Sodium (mEq/l)				0.431
Mean±SD	138.87±5.71	139.98±6.8	139.58±6.25	
Potassium (mEq/l)				0.158
Mean±SD	4.42±0.62	4.61±0.54	4.51±0.58	

Table 4: *Delivery and Medical Status of neonates in Gentamicin and Amikacin Goups*

Variables	Groups		Total	P Value
	Gentamicin	Amikacin		
Gestational age (Week)				1
Mean±SD	35.4±3.08	35.4±5.39	35.4±4.23	
Birth Weight (g)				0.965
Mean±SD	2477.25±624.55	2470.37±780.19	2473.31±702.35	
Infection Source				0.619
Sepsis	33(82.5)	35(87.5)	68(85)	
Pneumonia No(%)	5(12.5)	4(10)	9(11.3)	
UTI No(%)	2(5)	1(2.5)	3(3.7)	
Birth Height (cm)				0.237
Mean±SD	47.52±2.59	46.71 ±3.44	47.11±3.01	
Birth Head Circumference (cm)				0.652
Mean±SD	33.3±2.08	32.77±3.02	33.03±2.49	
Type of Milk				0.346
Formulas No(%)	0(0)	1(2.5)	1(1.2)	
Breast Milk No(%)	39(97.5)	36(90)	75(93.8)	
Both No(%)	1(2.5)	3(7.5)	4(5)	
Multiple Pregnancies				0.317
Singleton No(%)	34(85)	35(87.5)	69(86.3)	
Twins No(%)	4(10)	4(10)	8(10)	
Triplets No(%)	2(5)	1(2.5)	3(3.7)	
Gestational Diabetes				1
Yes No(%)	5(12.5)	5(12.5)	10(12.5)	
No No(%)	35(87.5)	35(87.5)	70(87.5)	
Number of Pregnancy				0.009
1 No(%)	13(32.5)	23(57.5)	36(45)	
2 No(%)	12(30)	14(35)	26(32.5)	
3 No(%)	12(30)	1(2.5)	13(16.3)	
> 3 No(%)	3(7.5)	2(5)	5(6.2)	
Gestational HTN				1
Yes No(%)	1(2.5)	1(2.5)	2(2.5)	
No No(%)	39(97.5)	39(97.5)	78(97.5)	
Delivery Maternal Age (yrs)				0.235
Mean±SD	30.30±5.74	28.77±5.65	29.5±5.70	

9. DISCUSSION

In our study, we have compared nephrotoxic effects of gentamicin and amikacin. We concluded that based on our srudy no nephrotoxic effect for either gentamicin or amikacin provided adjustment of therapeutic doses of them and so there was no aesthetic preference for one drug over the other. Most aminoglycosoid related articles were comparable with our study results. Bajracharya et al. in atheir study compared nephrotoxic effect of amikacin and gentamicin throughout creatinine clearance testing, in post-operative patients with normal renal function. They found that although the dose of administered Gentamicin was much lower than that of Amikacin, Gentamicin had more nephrotoxic effects on kidney(9).In our study ,we found that nephrotoxic effects of these drugs were not different in both groups. Sweileh et al in their study investigated nephrotoxic effects of gentamicin and amikacin. They evaluated 94 patients in two groups of gentamicin (45 neonates) and amikacin (49 neonates). They found that amikacin had significantly lower nephrotoxic effects than gentamicin and that multiple dosing of gentamicin was more nephrotoxic than single dosing, but nephrotoxic effects of amikacin was not significantly dependent on frequency of dosing (10), but we have not found similar results. Also Dayan et al. in their study found that nephrotoxic effect were reduced by reduction in frequency of aminoglycosides consumption (11), but we have not evaluate this factor in our study thus it was considered on of limitations in our study. Sassen et al. in their study, evaluate effects of gentamicin on dysregulation of renal sodium transporters in rates. They found that the fraction excretion of electrolytes significantly were increased in day 7 of treatment with gentamicin (12). Takamoto et al. in their work studied the effects of antibiotics on glucose absorption in kidney, and they found that glucose absorption in proximal tubule of kidney were reduced in children with consumption of gentamicin (13). Akbari et al. in their study investigated effects of antibiotherapy on the renal function. They evaluate

142 patients and found that GFR as contributing renal function, were reduced in children that treated by antibiotics (14), These results were similar to our finding. Also Wolf et al. in their study found that impaired renal function were more in infections of diabetic foot (15). Pannell et al. in their study evaluate nephrotoxic effects of gentamicin and found that gentamicin had some complications on kidney(16). Roger et al. in their study, evaluated impacts of amikacin and gentamicin on the serum creatinine concentrations. They conducted their study on 63 pdiatric critically ill patients with severe sepsis. Also that these drugs increase peak serum concentrations in 59% of patients (17). Sonia et al. conducted a study on neonates and evaluates fractional excretion of Magnesium (Fe Mg), as a marker of nephrotoxicity that induced by aminoglycoside, and found that Fe Mg can be considered as a biomarker of tubular damage and nephrotoxicity effect of aminoglycoside therapy can be detected by this marker(18). Therefore, all of previously mentioned studies found nephrotoxicity effects for gentamicin and amikacin and a difference between their complication, but we have not found this difference in nephrotoxicity effect of drugsin our study. Limitation of our study was small size of population of the study which may be attributed to the non cooperation of some parents of involved patients in study. After explanations of importance of study of effects of antibiotherapy on renal function to them, some of them were convinced. However based on few clinical studies that have been carried out regarding the nephrotoxic effects of aminoglycoside in pediatric patients. Further studies are still required with greater groups of cases on larger scale for evaluation of common antibiotic side effects.

10. CONCLUSIONS

Based on our study there was no difference between Gentamicin and Amikacin about nephrotoxic effects on the studied neonates. Therefore, there were no aesthetic preferences about side effects, between Gentamicin and Amikacin for use in neonatal population.

Conflicts of interest:

The authors declared no competing interests.

REFERENCES

[1] Gallardo-Godoy A, Muldoon C, Becker B, Elliott AG, Lash LH, Huang JX, et al. Activity and predicted nephrotoxicity of synthetic antibiotics based on polymyxin B. Journal of medicinal chemistry. 2016;59(3):1068-77.

[2] Rezagholi-Zamnjany M, Yousefichaijan P. An overview on peritoneal dialysis. Annals of Research in Dialysis. 2016;1(1).

[3] Saban JA, Pizzi M, Caldwell J, Palijan A, Zappitelli M. Previous aminoglycoside use and acute kidney injury risk in non-critically ill children. Pediatric Nephrology. 2017;32(1):173-9.

[4] Picard W, Bazin F, Clouzeau B, Bui H-N, Soulat M, Guilhon E, et al. Propensity-based study of aminoglycoside nephrotoxicity in patients with severe sepsis or septic shock. Antimicrobial agents and chemotherapy. 2014;58(12):7468-74.

[5] Lau L, Al-Ismaili Z, Harel-Sterling M, Pizzi M, Caldwell JS, Piccioni M, et al. Serum cystatin C for acute kidney injury evaluation in children treated with aminoglycosides. Pediatric Nephrology. 2017;32(1):163-71.

[6] Mingeot-Leclercq M-P, Décout J-L. Bacterial lipid membranes as promising targets to fight antimicrobial resistance, molecular foundations and illustration through the renewal of aminoglycoside antibiotics and emergence of amphiphilic aminoglycosides. MedChemComm. 2016;7(4):586-611.

[7] Denamur S, Boland L, Beyaert M, Verstraeten SL, Fillet M, Tulkens PM, et al. Subcellular mechanisms involved in apoptosis induced by aminoglycoside antibiotics: Insights on p53, proteasome and endoplasmic reticulum. Toxicology and applied pharmacology. 2016;309:24-36.

[8] Downes KJ, Patil NR, Rao MB, Koralkar R, Harris WT, Clancy JP, et al. Risk factors for acute kidney injury during aminoglycoside therapy in patients with cystic fibrosis. Pediatric Nephrology. 2015;30(10):1879-88.

[9] Bajracharya S, Pandey K, Haque A. To evaluate the creatinine clearance and compare nephrotoxic potential of amikacin and gentamicin, in post-operative patients with normal baseline renal function. International Journal of Basic & Clinical Pharmacology. 2017;5(5):1942-8.

[10] Sweileh WM. A prospective comparative study of gentamicin-and amikacin-induced nephrotoxicity in patients with normal baseline renal function.

Fundamental & clinical pharmacology. 2009; 23(4): 515-20.

[11] Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing and nonproducing bacteria: a comparative study. The Journal of pediatrics. 2013;163(5):1417-21.

[12] Sassen MC, Kim S, Kwon T-H, Knepper MA, Miller RT, Frøkiær J, et al. Dysregulation of renal sodium transporters in gentamicin-treated rats. Kidney international. 2006;70(6):1026-37.

[13] Takamoto K, Kawada M, Usui T, Ishizuka M, Ikeda D. Aminoglycoside antibiotics reduce glucose reabsorption in kidney through down-regulation of SGLT1. Biochemical and biophysical research communications. 2003; 308(4):866-71.

[14] Akbari R, Javaniyan M, Fahimi A, Sadeghi M. Renal function in patients with diabetic foot infection; does antibiotherapy affect it? Journal of Renal Injury Prevention. 2017;6(2).

[15] Wolf G, Ritz E. Diabetic nephropathy in type 2 diabetes prevention and patient management. Journal of the American society of nephrology. 2003;14(5):1396-405.

[16] Pannell WC, Banks K, Hahn J, Inaba K, Marecek GS. Antibiotic related acute kidney injury in patients treated for open fractures. Injury. 2016; 47(3): 653-7.

[17] Roger C, Nucci B, Louart B, Friggeri A, Knani H, Evrard A, et al. Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. Journal of Antimicrobial Chemotherapy. 2015:dkv291.

[18] Sonia SF, Hassan MS, Ara F, Hanif M. Fractional excretion of magnesium, a marker of aminoglycoside induced nephrotoxicity in neonates. Saudi Journal of Kidney Diseases and Transplantation. 2016;27(5):902.