

Original Article**Effect of Gentamicin on urinary Calcium Creatinine Ratio and Serum Calcium in Neonates****Ahmed M. Ezzat¹, Asmaa A. EL Fallah², Marwa T. Zaghoul³ and Wesam E. Afify¹**

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Abstract**Introduction:** Gentamicin was associated with an apparent increase in the number of neonates with symptoms of hypocalcemia, including seizures.**Aim of the study:** This study aimed to assess the effect of gentamicin on calcium /creatinine ratio in urine and serum calcium in neonates.**Methods:** This case-control study included 100 children, divided into two groups. Group I: Fifty neonates received gentamicin. Group II: Fifty neonates did not receive antibiotics at all (control group), Serum calcium and urinary calcium/creatinine ratio, were done at 1st day of admission, and at day 3 and 6 of aminoglycosides therapy.**Results:** On admission, serum calcium showed a non-significant difference between both groups, P-value was 0.453. On the 3rd day, serum calcium was significantly lower in cases compared to controls with P-value was <0.001. Also, on the 6th day, serum calcium was significantly lower in cases compared to controls, with P-value was <0.001. Regarding calcium/creatinine ratio on admission showed a non-significant difference between both groups, P-value was 0.184. On the 3rd day, the median calcium/creatinine ratio was significantly higher in cases compared to controls, P-value was <0.001. Also, on the 6th day, calcium/creatinine ratio was significantly higher in cases compared to controls, with P-value was <0.001.**Conclusion:** Gentamicin was associated with decreased serum calcium and increased urinary calcium excretion on 3rd day and 6th day of treatment, so cautious and proper monitoring of serum calcium is mandatory in neonates treated with gentamycin.**Keywords:** Gentamicin; Calcium Creatinine Ratio; Calcium; Neonates**Running title:** Effect of Gentamicin on Calcium in Neonates**Corresponding author:** Marwa Tarek Zaghoul

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Introduction

Gentamicin is an important antibiotic for the treatment of many serious gram-negative aerobic bacillary infections. It kills bacteria by inhibiting protein synthesis and to some extent by lysing the cell envelope. It is the aminoglycoside of first choice because of its reliable activity against most resistance gram-negative aerobes and because of the long experience with its use [11].

Combination of injection ampicillin and injection gentamicin is the first choice in the neonatal age-group for the management of sepsis [2]; and used as prophylaxis when cannulation is indicated for other purposes [2]. The major indications for gentamicin are in combination with other antibiotics (e.g., β -lactams) to treat serious aerobic bacterial infections. Gentamicin in combination with a β -lactam antibiotic is recommended for the treatment of pneumonia or sepsis, where multi-drug-resistant gram-negative organisms such as *P. aeruginosa*, *Enterobacter*, *Klebsiella* and *Serratia* may be the causative pathogen and/or the consequences of failing to provide initially active therapy [3].

Serious toxicity is predominantly seen with treatment longer than 7-10 days where there are sustained high trough serum levels and/or co-exposure to other ototoxic drugs [4]. Although nephrotoxicity secondary to gentamicin has been described extensively, this complication appears to be uncommon in neonates when serum drug levels are monitored closely [5].

However, after implementation of every 24 h gentamicin dosing,

Chirovolu et al., [6] noted an apparent increase in the number of neonates with symptoms of hypocalcemia, including seizures. Almost 70% of calcium filtered by the glomerulus is reabsorbed at the proximal tubule and 30% reabsorbed at other sites. Gentamicin can alter kidney and tubular function. One type of tubular dysfunction is electrolyte wasting. Electrolyte balance is very important for newborns, especially those with illness. Electrolyte disorders can further worsen the condition of a sick newborn. One of these important electrolytes is calcium [7].

The most accepted method of evaluating normal calcium excretion is by collecting urine for 24 hours. Urinary calcium excretion of <200 mg calcium/L is considered normal [8]. However, 24-hour urine collection in children and adolescents is cumbersome and inadequate, compared to estimating by spot Calcium/Creatinine ratio, which is easier and more practical. Hypercalciuria is defined as Calcium/Creatinine ratio values above the 95th percentile [9].

This study aimed to assess the effect of gentamicin on calcium /creatinine ratio in urine and serum calcium in neonates.

Methods

This prospective case-control study was conducted on one hundred newborns admitted to NICU of our hospital, and received gentamicin on dose of 4mg/kg per dose every 24h, during the period from April 2020 to September 2020. The neonates were grouped as following: Group I: Fifty

neonates received gentamicin on a dose of 4mg/kg per dose every 24h. Group II: Fifty neonates did not receive antibiotics at all (control group).

Neonates were excluded if they are preterm, weight < 2500 gm, had other causes of hypocalcemia in neonates as small for gestational age, maternal diabetes, perinatal asphyxia, or patients received diuretics or steroids. Approval of the study protocol by an Ethical Scientific Committee of Benha University was obtained and informed consent was obtained from the parents before enrollment in the study.

All studied cases was subjected to full history taking, complete clinical examination including general examination , cardio-pulmonary and gastrointestinal examination and laboratory investigations including routine investigations as complete blood count, kidney and liver function tests, and investigations for monitoring of serum calcium and urinary calcium/creatinine ratio .

Sample collection:

- Serum samples: whole blood was collected on plain vacationer tubes, left to clot then centrifuged for 15 minutes at 3000 rpm. Serum samples were separated and serum calcium was measured.
- Urine samples: urine samples were collected using urine bags and used for estimation of urinary calcium / creatinine ratio.

Serum calcium was measured by cobas 6000 by kits supplied by cobas 6000 (Germany). Test method: quantitative photometric method. Test principle: Calcium reacts with 5-nitro 5'-methyl-BAPTA (NM-BAPTA) under alkaline conditions to form

a complex. This complex reacts in the second step with EDTA to form a colored product whose intensity is directly proportional to the concentration of calcium in the specimen. It is measured photometrically.

Urine calcium was measured on cobas 6000 instrument. Test principle for urine calcium is the same as in the methodology as serum calcium. Urinary creatinine: Test method: Jaffe's modified method. Test principle: creatinine reacts with alkaline picrate to produce a red colored complex. The rate of red colored complex formation is directly proportional to creatinine concentration in the specimen and is measured photometrically.

Statistical methods

Data management and statistical analysis were done using SPSS version 25. (IBM, Armonk, New York, United States). The normality of numerical data was assessed using the Kolmogorov-Smirnov test and direct visualization methods. Then, numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Comparisons between both groups were done using independent t-test or Mann-Whitney U test for normally and non-normally distributed numerical data, respectively. Categorical data were compared using Chi-square test or Fisher's exact test if appropriate. Correlation analyses were done between serum ca and other maternal and neonatal characteristics using Parsons's correlation. Spearman's correlation was used for testing the

correlation between the Ca/Cr ratio and other parameters. “r” is the correlation coefficient. It ranges from -1 to +1. -1 indicates a perfect negative correlation, +1 indicates a perfect positive correlation, and 0 indicates no correlation. All P values were two-sided. P values less than 0.05 were considered significant [10].

Results

There were no significant differences between both groups regarding all maternal and neonatal characteristics, including neonatal, gestational age, neonatal gender, maternal age, mode of delivery, maternal co-morbidity, and birth weight (Table 1). The control group comprises all neonates with jaundice. The most frequent cause of admission in cases was respiratory distress, followed by tracheoesophageal fistula and the least frequent cause of admission was diaphragmatic hernia (Figure 1).

White cell count was significantly higher in cases compared to controls. No significant differences were noted regarding red cell count, hemoglobin, hematocrit, platelets and CRP. All liver and kidney functions, including urea,

creatinine, AST, ALT and random blood sugar, showed non-statistically significant differences between both groups (Table 2).

On admission, serum calcium showed a non-significant difference between both groups. On the 3rd day, serum calcium was significantly lower in cases compared to controls. Also, on the 6th day, serum calcium was significantly lower in cases compared to controls (Table 3).

On admission, calcium/creatinine ratio showed a non-significant difference between both groups. On the 3rd day, the median calcium/creatinine ratio was significantly higher in cases compared to controls. Also, on the 6th day, calcium/creatinine ratio was significantly higher in cases compared to controls (Table 4).

Serum calcium on admission, 3rd day, and 6th day showed no significant correlations with neonatal age, gestational age, maternal age, and birth weight (Table 5). Calcium/creatinine ratio on the 6th day showed significant positive correlation with maternal age. No other parameters showed a significant correlation with the calcium/creatinine ratio on admission, 3rd day, and 6th day (Table 6)

Table 1: Maternal & neonatal characteristics in both groups

			Cases (N= 50)	Controls (N = 50)	P value
Neonatal age (days)	Mean ±SD		4 ±2	4 ±1	0.667
Gestational age (weeks)	Mean ±SD		38 ±1	38 ±1	0.363
Neonatal gender	Males	N (%)	24 (48.0)	21 (42.0)	0.546
	Females	N (%)	26 (52.0)	29 (58.0)	
Maternal age (years)	Mean ±SD		33 ±7	31 ±7	0.251
Mode of delivery	Vaginal	N (%)	4 (8.0)	6 (12.0)	0.505
	Cesarean	N (%)	46 (92.0)	44 (88.0)	
Maternal co-morbidity	DM	N (%)	6 (12.0)	2 (4.0)	0.207
	HTN	N (%)	6 (12.0)	10 (20.0)	
	Negative	N (%)	38 (76.0)	38 (76.0)	
Birth weight (gm)	Mean ±SD	N (%)	3414 ±688	3430 ±594	0.9

Independent t-test was used for numerical data. Categorical data were compared using Chi-square test

Table 2: Complete blood count & CRP in both groups

		Cases (N = 50)	Controls (N = 50)	P value
Red cell count	Mean \pm SD	4.7 \pm 0.6	4.5 \pm 0.6	0.102
White cell count	Mean \pm SD	15 \pm 6.9	9.3 \pm 4.4	<0.001
Hemoglobin (g/dl)	Mean \pm SD	14 \pm 1.8	13.5 \pm 1.8	0.171
Hematocrit (%)	Mean \pm SD	42 \pm 5.3	40.4 \pm 5.5	0.137
Platelets	Mean \pm SD	247 \pm 69	238 \pm 46	0.444
CRP	Median (range)	6 (0 - 65)	6 (0 - 12)	0.147
Urea (mg/dl)	Mean \pm SD	20.5 \pm 2.3	21 \pm 2.8	0.352
Creatinine (mg/dl)	Mean \pm SD	1.1 \pm 0.4	1.1 \pm 0.3	1.0
AST	Mean \pm SD	31 \pm 7	30 \pm 8	0.832
ALT	Mean \pm SD	36 \pm 10	39 \pm 7	0.098
RBS (mg/dl)	Mean \pm SD	107 \pm 26	109 \pm 23	0.646

Independent t-test was used for numerical data. Only CRP was compared using Mann Whitney U test

Table 3: Serum calcium on admission, 3rd day, and 6th day in both groups

		Cases (N = 50)	Controls (N = 50)	P value
On admission	Mean \pm SD	8.3 \pm 0.6	8.4 \pm 0.7	0.453
On 3 rd day	Mean \pm SD	8 \pm 0.5	9 \pm 0.5	<0.001
On 6 th day	Mean \pm SD	7.6 \pm 0.4	9.4 \pm 0.5	<0.001

Independent t-test was used

Table 4: Calcium creatinine ratio on admission, 3rd day, and 6th day in both groups

		Cases (N = 50)	Controls (N = 50)	P value
On admission	Median (range)	0.043 (0.015 - 0.167)	0.04 (0.031 - 0.047)	0.184
On 3 rd day	Median (range)	0.058 (0.026 - 0.24)	0.045 (0.031 - 0.05)	<0.001
On 6 th day	Median (range)	0.079 (0.045 - 0.244)	0.047 (0.032 - 0.051)	<0.001

Mann Whitney U test was used

Table 5: Correlation between serum calcium on admission, 3rd day, and 6th day and other maternal and neonatal characteristics

	Serum calcium					
	On admission		3 rd day		6 th day	
	R	P value	r	P value	r	P value
Neonatal age (days)	-0.161	0.265	-0.179	0.213	-0.097	0.503
Gestational age (weeks)	-0.027	0.85	0.086	0.555	0.037	0.796
Maternal age (years)	0.01	0.946	0.148	0.305	0.196	0.172
Birth weight (gm)	-0.216	0.132	-0.194	0.178	-0.101	0.485

Pearson's correlation was used, r = Correlation coefficient

Table 6: Correlation between calcium-creatinine ratio on admission, 3rd day, 6th day and other maternal and neonatal characteristics.

	Ca/Cr ratio					
	On admission		On 3 rd day		On 6 th day	
	r	P value	r	P value	r	P value
Neonatal age (days)	-0.126	0.382	0.081	0.578	-0.216	0.132
Gestational age (weeks)	0.255	0.074	0.177	0.218	-0.074	0.609
Maternal age (years)	-0.129	0.371	0.114	0.429	.308*	0.029
Birth weight (gm)	0.144	0.317	-0.275	0.054	-0.005	0.975

Spearman's correlation was used, r = Correlation coefficient, * Significant

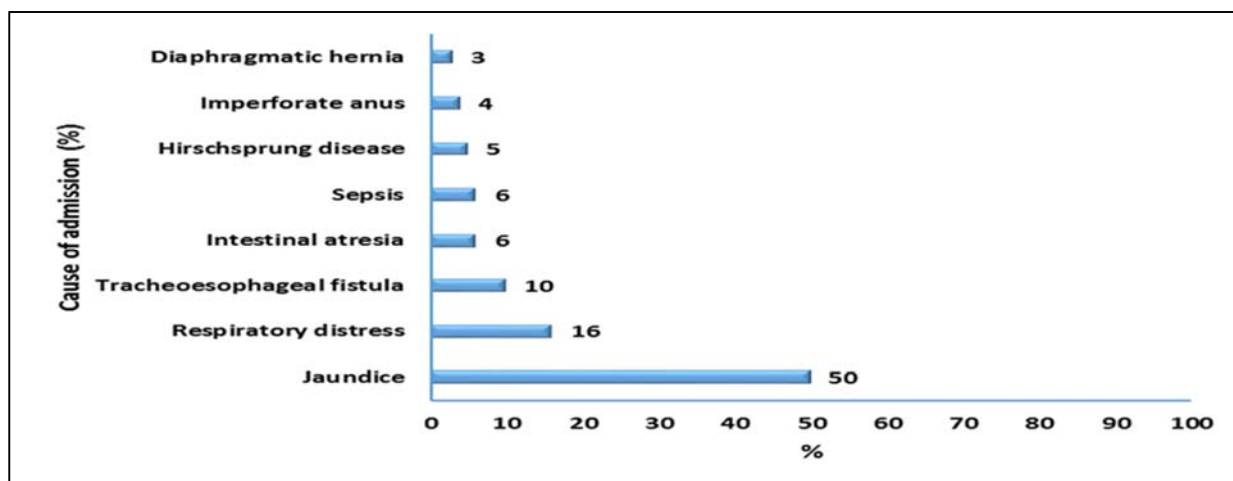


Figure 1: Causes of admission in the whole study participants

Discussion

Gentamicin was associated with an apparent increase in the number of neonates with symptoms of hypocalcemia, including seizures [6]. The aim of our study was to assess the effect of gentamicin on calcium/creatinine ratio in urine and serum calcium in neonates.

Our study showed that there were no significant differences between both groups regarding all neonatal characteristics, including neonatal age (the mean was 4 ± 2 days in cases and 4 ± 1 days in controls, P value = 0.667), gestational age (the mean was 38 ± 1 weeks in cases and 38 ± 1 weeks in controls, P value = 0.363), Our results are in agreement with the study by Chiruvolu et al., [6], gestational age (GA) was 39.4 ± 1.7 weeks. In the study by Tan et al., [11], the mean gestational age was 38.6 ± 0.9 weeks.

Routine investigations showed non-statistically significant differences between both groups except white cell count was significantly higher in cases (15 ± 6.9) compared to controls (9.3 ± 4.4), P -value was <0.001 . This can

be explained by the fact that, in our study, the cause of admission in 32% of cases was respiratory distress, and 12% had tracheoesophageal fistula, and 12% had sepsis, while all cases in control group had jaundice, with no septic conditions.

On admission, serum calcium showed a non-significant difference between both groups, (mean was 8.3 ± 0.6 mg/dl in cases and 8.4 ± 0.7 mg/dl in controls, P -value was 0.453). On the 3rd day, serum calcium was significantly lower in cases (8 ± 0.5 mg/dl) compared to controls (9 ± 0.5 mg/dl), P -value was <0.001 . Also, on the 6th day, serum calcium was significantly lower in cases (7.6 ± 0.4 mg/dl) compared to controls (9.4 ± 0.5 mg/dl), P -value was <0.001 .

Our results are in agreement with Giapros et al., [12], who observed increased incidence of hypocalcemia after starting single daily dose of gentamicin infusions, which peaked on third day of treatment, and increase in fraction excretion of calcium after gentamicin infusion in term and preterm newborns, and this effect continued even after gentamicin infusion stopped. They suggest that kidney does not adapt

by decreasing urine calcium excretion. Indeed, a cumulative effect of gentamicin was observed.

Our results also agreed with Jackson et al., [13] In their study; they observed that the lowest serum calcium occurred relatively early in the course of gentamicin treatment suggests that a possible effect of gentamicin on serum calcium in neonates is not a reflection of the total or cumulative amount of gentamicin administered. Aminoglycosides have been shown to mimic the effect of calcium and magnesium on parathyroid cells, which would reduce parathyroid hormone secretion.

In contrast to, Dehkordi et al., [14] observed that blood calcium increased significantly ($P < 0.05$) at 72, 84, 96, 120, 108, 168, and 216 h after gentamycin injection in sheep, and they explained these results by increasing the parathormone into the blood, increasing levels of calcium in the blood and subsequently hypercalciuria occurs.

In our study, on admission, calcium/creatinine ratio showed a non-significant difference between both groups, P-value was 0.184. On the 3rd day, the median calcium/creatinine ratio was significantly higher in cases (0.058) compared to controls (0.045), P-value was < 0.001 . In addition, on the 6th day, calcium/creatinine ratio was significantly higher in cases (0.079) compared to controls (0.047), P-value was < 0.001 .

This was in agreement with Tan et al., [11] who observed that after the first dose of intravenous gentamicin, urinary calcium excretion increase, with median 0.043 (range 0.009 to 0.156) mg/mg, compared to that before intravenous

gentamicin was given [median 0.021 (range 0.004 to 0.071) mg/mg ; $P=0.001$]. Similar results were also observed after the second dose of intravenous gentamicin [median 0.144 (range 0.015 to 1.160) mg/mg] compared to before intravenous gentamicin, and after the first dose of intravenous gentamicin ($P=0.001$).

Also our results are in agreement with the study by Lee et al., [15] on rats, who found that single-dose gentamicin administration induced significant calciuria and magnesiuria (urine calcium/creatinine: 0.11 ± 0.02 vs. 1.50 ± 0.44 , magnesium/creatinine: 0.12 ± 0.05 vs. 1.17 ± 0.23 , both $p < 0.05$). They found that gentamicin caused a profound calcium wasting within 6 h after injection: urine calcium excretion was 14- fold normal.

The mechanism of gentamicin-mediated changes in urinary calcium excretion remains unexplained. Gentamicin filters freely through the glomerulus without being metabolized, and around 10% of it accumulates in the kidney cortex, especially at the proximal tubules [16].

Ward et al., [17] hypothesized that sodium-potassium-chloride co-transporter (NKCC2) level decreases after injection of gentamicin into mice, hence, decreasing the lumen positive voltage and increasing urinary calcium excretion, even in the therapeutic range of gentamicin. Gentamicin accumulates in the kidney cortex through a specific transport mechanism that involves megalin binding to gentamicin. Gentamicin increases cytosolic calcium concentrations through an inositol triphosphate-mediated mechanism and activates the calcium-sensing receptor

(CaR). This receptor (CaR) is found on the basolateral membrane of tubules. Activation of CaR inhibits reabsorption of calcium in the tubules.

In our study, there were no significant correlations between serum calcium on admission, 3rd day, and 6th day with neonatal age, gestational age, maternal age, and birth weight. Our results are in agreement with Elsayry et al., [18] who found that there was no statistically significance association between hypocalcemia and neonatal factors (sex, gestational age, type of feeding, perinatal complication, and vitamin D level). However, they observed a statistically significant positive correlation between total and ionized serum calcium level and the age of neonates; ($r=0.24$, $p=0.01$). They concluded that hypocalcemia improves with age. There was also a statistically significant positive correlation between serum vitamin D level and birth weight ($r=0.23$, $p=0.02$).

The result of a Korean study was different from ours as it reported a high prevalence of neonatal hypocalcemia among formula-fed neonates [19]. It also disagrees with Indian and Iranian studies which concluded that early and late hypocalcemia were more frequent among mothers with diabetes [20, 21]

In our study, the calcium/creatinine ratio on admission, 3rd day, and 6th day excretion with gentamycin, and proper ways to decrease these losses.

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showed no significant associations according to neonatal gender and maternalco-morbidity.

Calcium/creatinine ratio on the 6th day showed significant positive correlation with maternal age ($r = 0.308$ & P value = 0.029). No other parameters showed a significant correlation with the calcium/creatinine ratio on admission, 3rd day, and 6th day.

This study provided a new evidence urinary calcium excretion increase after gentamicin infusion, so cautious and proper monitoring of serum calcium is mandatory.

Conclusion

In our study; gentamicin was associated with decreased serum calcium and increased urinary calcium excretion on 3rd day of treatment, A cumulative effect of gentamicin treatment on serum calcium and urinary calcium excretion is also observed on 6th day of treatment, so cautious and proper monitoring of serum calcium is mandatory in neonated treated with gentamycin.

Further studies should be conducted to assess the effect of calcium intake during treatment with gentamycin.

Further studies should be conducted to assess the cause of increased calcium

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Statements

Ethics approval and consent to participate:

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Benha university hospital and informed written consent was obtained in every case from their legal guardians.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material
“Not applicable”

Conflict of interest

The authors declare no conflict of interest

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