ORIGINAL ARTICLE

Monitoring Serum Gentamicin Concentration among Newborns in the Neonatal Ward of Hospital Sultan Ismail Petra (HSIP), Malaysia

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Abstract

Background: Gentamicin is the empirical therapy of choice for sepsis in newborns, with dosing of 4mg/kg every 24 – 36 hours, depending on premenstrual age. ***Objective:*** To investigate the therapeutic drug monitoring (TDM) outcomes (within therapeutic ranges or toxic) of the current IV Gentamicin regimen in treating infections among neonates. ***Methods:*** This retrospective cohort study was conducted in Hospital Sultan Ismail Petra (HSIP), between January 2020 and December 2022. Data were abstracted and collected for neonates treated with gentamicin during the study period. Trough and peak levels were measured on the third dose where the therapeutic ranges were <1.0 mg/L and >5.0 mg/L, respectively. Elevated serum creatinine was defined as serum creatinine level (SCr) >71 µmol/L. Multivariable logistic regression was performed to identify the risk factors of acquiring toxic trough levels. ***Results:*** A total of 227 patients were included. The total number of patients achieving the targeted peak level was 74.90%. More than half of the patients (52.0%) experienced toxic trough levels. The mean serum trough and peak levels (standard deviation) were 1.23 (1.11) mg/L and 7.31 (3.93) mg/L respectively. The risk factor associated with toxic trough level was elevated SCr (odd ratio 2.55, 95% confidence interval [1.19,5.46], p=0.016). ***Conclusion:*** The current gentamicin regimen resulted in an alarming proportion of patients having toxic trough levels, particularly with elevated SCr. The study findings underscore the need to refine the dosing regimen to optimise efficacy and minimise toxicity in neonates.

Keywords: gentamicin, neonate, creatinine, gestational age, therapeutic drug monitoring

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INTRODUCTION

As widely known, Gentamicin is an aminoglycoside that binds to 30S ribosomal resulting in inhibition of synthesis of bacterial cell walls. One of the main drawbacks of Gentamicin is its nephrotoxicity as it is predominantly excreted in the urine due to its water solubility characteristic. This nephrotoxin will bind to the proximal tubular brush border membrane and high concentrations of the drug may lead to proximal tubular damage and cause renal injury[1]. Over decades, gentamicin has been the mainstay empirical therapy of sepsis in newborns, frequently used in combination with beta lactam antibiotics such as ampicillin or penicillin[2,3]. Sepsis in the newborns can cause chronic illnesses and mortality rate can reach up to 50% without proper management[4]. Gentamicin is a narrow therapeutic drug that requires therapeutic drug monitoring (TDM) during the treatment period in order to ensure the efficacy of the drug while avoiding toxicity due to the use of gentamicin.

International guidelines differ in dosing regimens for gentamicin, ranging from 4-5mg/kg every 24–36 hour. Current World Health Organization

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(WHO) guidelines recommend a once-daily dosing regimen, from 3-7.5 mg/kg/day according to age and birth weight[5]. According to currently available knowledge, term infants should receive IV gentamicin 4.0-4.5mg/kg every 24 hour[6]. Kidney function is reduced in preterm neonates owing to incomplete nephrogenesis, hence a longer dosing interval of 36 to 48 hourly is recommended for preterm neonates[6].

In Hospital Sultan Ismail Petra (HSIP), neonates who are at risk for neonatal sepsis such as being premature, have very low birth weight and maternal factors such as Group B Streptococcus status, presence of chorioamnionitis, or prolonged rupture of membranes will be treated in the neonatal ward. Gentamicin will be prescribed as the empirical treatment at dose of 4mg/kg, either 24 or 36 hourly depending on the premenstrual age in combination with beta lactam antibiotics commonly benzylpenicillin at dose of 100,000u/kg 12 hourly or 100,000u/kg 6 hourly based on indication. Peak and trough levels were measured on the third dose of therapy. The therapeutic ranges for trough and peak levels were <1.0 µg/mL and >5.0 µg/mL, respectively.

The standard gentamicin dosing regimens may not be able to produce intended therapeutic peak and trough serum concentrations in all patient populations. Hence, determining factors correlated with undesirably high or low peak or trough values could be useful to neonatal practitioners in predicting which patients are most likely to have serum drug levels outside the therapeutic range[7].

METHODS

This study was conducted in the neonatal ward of Hospital Sultan Ismail Petra (HSIP), Kuala Krai, Kelantan State of Malaysia, between January 2020 and December 2022. Newborns who received gentamicin treatment for more than 3 days were monitored by taking trough and peak levels. Data collection was done by using data collections form extracted from TDM request form and electronic lab systems. Newborns who met the inclusion criteria were included in this study. The criteria include term and premature babies treated with IV gentamicin, where data on pre and post serum concentration of gentamicin were available. Patients were excluded if the sample was rejected due to sampling error (sample lysed, inadequate blood volume), the sampling was gentamicin random level for toxicity monitoring only. Any invalid results were excluded together with patients with incomplete data that is required for this research (such as missing data for urea and serum creatinine level). Our data collection form included patients' demographic data, total daily dose of gentamicin, serum creatinine level, diagnosis, urea level, dosing interval of gentamicin and total dose per body weight of gentamicin.

Descriptive statistics were performed using Statistical Package for the Social Science (SPSS) version 26.0 for Windows. Data was expressed as frequency and percentage as well as mean and standard deviation (SD), as applicable. Chi-square test was used to analyse the data. A p-value <0.05 indicates statistical significance. Multivariable logistic regression was also performed to identify the risk factors of acquiring toxic trough levels.

RESULTS

A total of 286 samples were reviewed and samples that met the inclusion criteria were analysed. Only 59 samples were not included in the analysis due to random sampling time (n=5), blood lysed (n=18), sampling error including wrong sampling time and inadequate blood volume (n=4), lack of SCr or Urea baseline (n=20) and invalid result (n=12). The majority of the neonates (73.57%) were categorized as term where their gestational age was more than 37 weeks. The dosing interval of 24 hourly was vastly used in more than 90% of the neonates (Table 1). Common clinical diagnoses were congenital pneumonia 171(75.33%) and presumed sepsis 37(16.30%) (Table 2). Gentamicin was started in the majority of neonates on first day of life. A trough level above 1mg/L is considered toxic whereas a peak level of 5mg/L and above is considered effective. Majority of neonates treated with a dose of 4mg/kg/dose achieved effective peak levels of more than 5mg/L (74.9%), hence we can conclude a dose of 4mg/kg is effective in achieving its desired effect. However, more than half of the neonates (52%) had toxic trough levels with current dosing regimen (Table 3). Only a small percentage of neonates with effective peak level had supra-therapeutic levels (8.8%) where the concentration was more than 12mg/L (Table 4). No statistically significant difference was observed through comparison of neonatal demographic data with trough and peak serum gentamicin concentrations

(p>0.05) (Table 5). Preterm neonates had a higher percentage of having toxic trough levels (58.33%) as compared to term neonates (49.70%). Nevertheless, dose and body weight played no significance in having a toxic trough level or sub- therapeutic peak level as shown in Table 6 and Table 7. Furthermore, for the most common diagnosis in neonatal ward, more than 50% of the newborns who were diagnosed with congenital pneumonia (n=171) and presumed sepsis (n=37) experienced toxic trough levels. No statistically significant difference was observed in mean serum urea levels between the non-toxic and toxic groups for gentamicin trough and peak concentration (p=0.685). On the other hand, the mean serum creatinine levels differ significantly between the non-toxic and toxic groups for gentamicin trough concentration (p=0.008). There is also a significant difference in mean serum creatinine levels between the effective and sub-therapeutic groups for gentamicin peak concentration (p=0.001) (Table 8). Those results suggest that serum creatinine levels might be a more sensitive indicator of toxicity and effectiveness of gentamicin concentrations compared to serum urea levels in this context. We further analyzed the factor of serum creatinine by categorizing the data into normal and elevated serum creatinine levels. It was observed that toxic levels were significantly associated with elevated serum creatinine levels (>71 µmol/L) (Table 9). Multivariate analysis of factors associated with elevated gentamicin trough concentration was found associated with only serum creatinine levels (p<0.05) (Table 10).

Table 1: Demographic and clinical Characteristics (N= 227)

Premature, n (%)	**60 (26.43%)**
Term, n (%)	167 (73.57%)
Body weight, kg, mean ± SD	3.03 ± 0.57
Total daily dose, mg, mean ± SD	12.0 ± 2.32
Dosing interval 24 hourly, n (%)	205 (90.31%)
Dosing interval 36 hourly, n (%)	22 (9.69%)
Total dosage, mg/kg body weight, mean±SD	3.92 ± 0.27
Premature, n (%)	**60 (26.43%)**
Serum creatinine (SCr), µmol/L, mean±SD	57.64 ± 15.00
Serum urea, mmol/L, mean ± SD	3.99 ± 6.33
Through level, mg/L, mean±SD	1.23 ± 1.11
Peak level, mg/L, mean±SD	7.31 ± 3.93

Table 2: Initial diagnoses before starting empirical gentamicin therapy in neonates

Clinical Sepsis, n (%)	**5 (2.20%)**
Congenital pneumonia, n (%)	171 (75.33%)
Congenital sepsis, n (%)	1 (0.44%)
Presumed sepsis, n (%)	37 (16.30%)
GBS sepsis, n (%)	1 (0.44%)
Hypoxic Ischemic Encephalopathy (HIE), n (%)	2 (0.88%)
Meconium Aspiration Syndrome (MAS), n (%)	5 (2.20%)
Neonatal Jaundice secondary to Sepsis, n (%)	2 (0.88%)
Prematurity with Respiratory Distress Syndrome (RDS), n (%)	1 (0.44%)
Presumed Meningitis, n (%)	2 (0.88%)

Table 3: Percentage of target peak and trough at 4mg/kg/dose (N=227)

Trough, n (%)	
Non-toxic <1mg/L	109 (48.00%)
Toxic ≥ 1mg/L	118 (52.00%)
Peak, n (%)	
Effective, ≥5mg/L	170 (74.90%)
Sub-therapeutic <5mg/L	57 (25.10%)

Table 4: Normal and supra-therapeutic effective peak level at 4mg/kg/dose (n=170)

Effective Peak Level	
Normal ≥ 5 – 12 mg/L, n (%)	150 (66.10%)
Supratherapeutic > 12mg/L, n (%)	20 (8.8%)

Table 5: Comparison of neonatal demographic data with trough and peak serum gentamicin concentrations

Variables	Gentamicin Trough Concentration			Gentamicin Peak Concentration		
	Non toxic	Toxic	p-value	Effective	Sub- therapeutic	p-value
All	109 (48.00%)	118 (52.00%)	0.251	170 (74.90%)	57 (25.10%)	0.711
PMA Age, n (%)						
Premature	25 (41.67%)	35 (58.33%)		46 (76.67%)	14 (23.33%)	
Term	84 (50.30%)	83 (49.70%)		124 (74.25%)	43 (25.75%)	
Mean body weight (SD), kg	3.03 (0.60)	3.09 (0.54)	0.47	3.06 (0.56)	3.04 (0.59)	0.78
Mean actual dose (SD), mg	11.88 (2.48)	12.19 (2.17)	0.308	12.10 (2.32)	11.94 (2.34)	0.718
Mean dose per body weight (SD), mg/kg	3.90 (0.33)	3.95 (0.2)	0.165	3.92 (0.254)	3.93 (0.328)	0.724

Table 6: Association between dose and body weight with gentamicin concentration

Diagnosis	Gentamicin Trough Concentration			Gentamicin Peak Concentration		
	Non toxic	Toxic	p-value	Effective	Sub- therapeutic	p-value
Clinical sepsis	4 (80%)	1 (20%)	0.197	2 (40%)	3 (60%)	0.102
Congenital pneumonia	82 (48%)	89 (52%)	0.973	131 (76.6%)	40 (23.4%)	0.297
Congenital sepsis	-	1 (100%)	1.000	1 (100%)	0 (0%)	1.000
Presumed sepsis	16 (43.2%)	21 (56.8%)	0.525	29 (78.4%)	8 (21.6%)	0.593
GBS sepsis	1 (100%)	-	0.480	-	1 (100%)	0.251
HIE	-	2 (100%)	0.499	2 (100%)	-	1.000
Meconium aspiration syndrome	2 (40%)	3 (60%)	1.000	3 (60%)	2 (40%)	0.602
NNJ secondary to sepsis	2 (100%)	-	0.229	-	2 (100%)	0.062
Prematurity with RDS	1 (100%)	-	0.480	-	1 (100%)	0.251
Presumed meningitis	1 (50%)	1 (50%)	1.000	2 (100%)	-	1.000

Table 7: Comparison of mean trough and peak levels gentamicin concentration

Variables		Gentamicin Trough Concentration			Gentamicin Peak Concentration		
	All	Non toxic	Toxic	p-value	Effective	Sub-therapeutic	p-value
Mean trough level (SD), mg/L	1.23 (1.11)	0.59 (0.26)	1.83 (1.26)	<0.001			
Mean peak level (SD), mg/L	7.31 (3.93)				8.52 (3.81)	3.69 (0.89)	<0.001

Table 8: Comparison of mean serum urea and creatinine levels with peak and trough serum gentamicin concentrations

Variables	Gentamicin Trough Concentration			Gentamicin Peak Concentration		
	Non toxic	Toxic	p-value	Effective	Sub-therapeutic	p-value
Mean serum urea (SD), mmol/L	3.56 (4.12)	4.39 (7.83)	0.326	3.86 (4.6)	4.29 (9.81)	0.685
Mean serum creatinine (SD), µmol/L	54.72 (15.19)	60.34 (14.35)	0.008	59.61 (14.29)	51.77 (15.62)	0.001

Table 9: Relationship between serum creatinine level and percentage of non-toxic and toxic trough level (N=227)

Variables	Non toxic	Toxic	Total	p-value
Normal SCr (<71 µmol/L) n (%)	98 (51.85)	91 (48.15)	189	0.010
Elevated SCr (>71 µmol/L) n (%)	11 (28.94%)	27 (71.05%)	38	

Table 10: Multivariate analysis of factors associated with elevated gentamicin trough concentration (N=227)

Neonatal variables	Odd Ratio (95% CI)	p-value
Serum creatinine (umol/L)*	2.55 (1.19 - 5.64)	0.016
Serum urea (mmol/L)	1.028 (0.983 - 1.074)	0.231
Gestational Age	0.767 (0.416 - 1.413)	0.394

*Normal SCr (<71 µmol/L); elevated SCr (>71 µmol/L)

DISCUSSION

Among 286 TDM forms for IV Gentamicin received in 2020-2022, only 227 patients were included in this study. Another 59 patients were excluded as rejected sample due to sampling error such as sample lysed (n=18), inadequate blood volume (n=4), gentamicin TDM form was requested for random level to monitor for toxicity only (n=5), invalid result such as pre level was

higher than post level (n=12) and incomplete patient important data required for this study such as missing data for SCr (n=20). In this study, we found that 74% (n=170) of those receiving IV gentamicin 4mg/kg achieved effective peak levels of more than 5mg/L as shown in Table 3 (mean peak level=7.31±3.93 mg/L, p<0.001). This finding corresponds with a previous study where 82.3% neonates receiving intravenous Gentamicin at the same dose of 4mg/kg achieved effective peak levels[8].

From the findings, we ascertained that from the 170 samples that achieved effective peak levels, only 8.8% (n=20) had supratherapeutic levels with peak levels of more than 12mg/L. On the other hand, there were at most 25.10% (n=57) that experienced subtherapeutic peak levels of less than 5mg/L. This outcome suggested that 4mg/kg dose is considered effective in neonatal population at our hospital.

Previous study identified that only 30% of neonates treated with gentamicin exhibited potential toxicity as the trough levels exceeded 1.0 µg/mL[5]. Contrary to our finding, most neonates treated with intravenous gentamicin had experienced toxic trough in at least 52% of them who had trough level more above 1.0µg/mL (mean trough level=1.23±1.11 mg/L, p<0.001). Similar with a study by Mulhall et al. reported similar findings where 63% of the neonates treated with IV gentamicin were reported to have potential toxic level of gentamicin with most babies being premature with low gestational age, low birth weight and in the first week of life[9].

Considering the regimen adjustment was based on neonates' birth weight and gestational age (GA), it was anticipated that there would be no significant statistical differences in the mean peak and trough concentrations among all neonates categorized by GA and BW in this study as shown in Table 5.

In the neonatal ward, the predominant diagnoses included congenital pneumonia (n=171) and presumed sepsis (n=37), as reflected in our sample. Both diagnoses showed high efficacy rates (>70%) with the current treatment regimen of 4mg/kg: congenital pneumonia at 76.61% (n=131) and presumed sepsis at 78.38% (n=29). However, more than half of the cases exhibited toxic trough levels, with congenital pneumonia at 52% (n=89) and presumed sepsis at 56.8% (n=21).

Even though the standard dose 4mg/kg demonstrates high efficacy rate, aminoglycoside is commonly known to exhibit nephrotoxicity. Therefore, elevated serum creatine levels in newborns can be influenced by gentamicin trough levels. A study conducted in Iowa, USA, revealed that neonates with mildly elevated serum creatinine levels (71.6–87.5 µmol/L) and elevated serum creatinine levels (≥88.4 µmol/L) were significantly associated with a 2-fold and 4.5-fold increase in gentamicin trough levels respectively, compared to neonates with normal baseline serum creatinine levels (≤70.7µmol/L)[10].

In our NICU, among babies with elevated serum creatine (≥71µmol/L, n=38), it is revealed that the majority of neonates from this group (71.05%, n=27) experienced toxic trough levels (p=0.01) as shown in Table 9. Thus, a multivariable logistic regression was performed to identify the risk factors of acquiring toxic trough levels (Urea level and SCr) and it is found that SCr significantly affects the toxic trough level of neonates (odd ratio 2.55, 95% confidence interval [1.19, 5.46], p=0.016). This finding was known to correspond with the study by Antolik et al.[10].

We used serum creatinine level ≥71µmol/L as the cut off point for elevated creatinine level as our ward avoids the use of gentamicin for neonates with SCr levels ≥88.4µmol/L. Instead the use of third generation cephalosporins such as cefotaxime will be added as an alternative due to its lower nephrotoxicity effect while still offering spectrum coverage against gram negative bacteria. However, caution is highly necessary to prevent overuse of third-generation cephalosporins to mitigate the emergence of resistant gram-negative bacteria[11].

In our study the trough level was toxic in more than half of the babies probably due to sepsis and renal immaturity. As mentioned by previous study, in full-term neonates, factors such as renal immaturity, dehydration, birth asphyxia, sepsis, and maternal condition for instance preeclampsia and genetic factors will impact babies' kidney development[12]. Medications such as gentamicin especially may increase the likelihood of high serum creatinine. Fortunately, gentamicin induced kidney injury is often reversible upon discontinuation of the medication[12].

Consequently, a study also revealed that 8.3% of the study participants with high baseline serum

creatinine experienced 10-fold (83%) increase in SCr within 7 days of initiating gentamicin treatment[12]. Therefore, it is very crucial to take into account serum creatinine levels when determining the initial dose of intravenous gentamicin for neonates, aiming for an effective and safe treatment regimen.

By conducting this study, we finally discovered that the current gentamicin regimen 4mg/kg 24 hourly in term neonate and 4mg/kg 36 hourly in preterm neonate used in our neonatal ward resulted in an alarming proportion of patients having toxic trough levels, particularly with elevated SCr. The study findings underscore the need to refine the dosing regimen to optimise efficacy and minimise toxicity in neonates. In patients with serum creatinine ≥71µmol/L, dosing interval of gentamicin may be prolonged by 12 hours to prevent toxic trough levels. Additionally, as discussed by Murphy et al. (2019), adequate hydration by clinicians also may reduce or prevent nephrotoxicity, and early signs of fluid overload must be closely monitored for example by doing daily weights and observing intake/output of babies with risk[1]. Early monitoring of gentamicin in patients with elevated SCr, (i.e TDM on second dose of IV Gentamicin) can be proposed as 25% of all patients from a previous study that received gentamicin therapy for more than 48 hours without monitoring of gentamicin concentration and renal function will develop acute kidney injury (AKI) that may progress to chronic kidney disease (CKD)[12].

We acknowledge that there are several limitations to our study. Firstly, the sample size for preterm neonates was relatively small, which prevents us from determining whether post-menstrual age significantly impacts toxic trough levels. Additionally, we observed that some TDM request forms were incomplete. For instance, the length of the babies and details of concomitant drugs were not consistently provided in the forms, which are crucial data points needed to enhance the value of our research. We also acknowledge other constraints. For instance, some samples had human error in sending them to the lab after more than 4 hours, resulting in deterioration and lysis of the sample. Furthermore, the TDM forms are entirely handwritten, leading to potential errors such as incorrect ID and registration numbers, which can hinder the traceability of patients' medical profiles and lab values which is known as human error in writing. However, with technological advancements, we now see that laboratory information systems are fully computerized, thereby preventing such errors in the future.

CONCLUSION

In summary, elevated SCr levels in neonates indicate reduced kidney function, which can lead to prolonged half-life, altered clearance, and delayed attainment of steady-state concentrations of gentamicin, necessitating adjustments in dosing and careful monitoring to ensure effective and safe therapy. The current gentamicin regimen resulted in an alarming proportion of patients having toxic trough levels, particularly with elevated SCr. The study findings underscore the need to refine the dosing regimen to optimise efficacy and minimise toxicity in neonates.

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