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Is fat-free mass-based gentamicin dosing regimen preferable than whole-body weight in neonates?

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ABSTRACT

Importance: Body fluid dynamics and renal maturation status vary during the neonatal period. We hypothesized that differences in peak and trough gentamicin concentrations could be expected.

Objective: To predict the peak and trough gentamicin concentrations in critically ill neonates and to predict the changes in the predicted peak plasma concentrations of gentamicin following fat-free mass dosing.

Methods: Critically ill neonates that received gentamicin and have gentamicin concentration measured were recruited. Fat mass was estimated using skinfold thicknesses. Changes in the peak plasma concentrations (C_{max}) using whole-body weight (estimated using the current dosing regimen) and predicted concentrations following the fat-free mass-based dosing were the outcome measures.

Results: Eighty-nine critically ill neonates were recruited. Sub-therapeutic C_{max} was estimated using the current dosing regimen in 32.6%, and 22.5% neonates following the first and second doses of gentamicin. Preterm neonates had significantly higher fat mass compared to term neonates. All except one had C_{max} above 12 μg/ml after the first dose and all had after the second gentamicin dose following the predicted fat-free mass-based gentamicin dosing. The recommended doses are as follows: extreme preterm: 7.95 mg/kg every 48 h; very preterm: 7.30 mg/kg every 36–48 h; late preterm: 5.90 mg/kg every 36–48 h; and term neonates at 5.10 mg/kg every 24 h.

Interpretation: Fat-free mass dosing may be considered for obtaining optimal therapeutic effects in the neonatal population.

KEYWORDS

Aminoglycosides, Body weight, Fat, Fat-free mass, Gentamicin

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INTRODUCTION

Gentamicin is a commonly administered antimicrobial drug in critically ill neonates. Gentamicin is less distributed in adipose tissue, so it is recommended to adjust body weight to calculate the appropriate dose for adults.[1] The total body water content can vary substantially between preterm and term neonates, and during postnatal days of life.[2] Neonatal fat is an indicator of maternal-fetal intra-uterine milieu and plays a crucial role in metabolic health.[3] Fat and fat-free mass have been shown to determine the cerebellar volume at birth, and amongst those admitted to the hospital, they also determine neurological outcomes at the end of one year old of age.[4] Gender and ethnic differences were observed in the neonatal fat mass.[5] Lipophilicity is a principal determinant of the volume of distribution of drugs.[6] The fact that gentamicin is water-soluble and is predominantly eliminated by the kidneys indicates that there could be differences in the volume of distribution of this drug in neonates. Hence, our hypothesis was that the dosage of gentamicin shall need adjustment for the fat mass which is inversely proportional to the total body water. Additionally, renal function is altered in neonates particularly in preterm as the required numbers are achieved only around 36 weeks of life.[7] Prenatal events such as exposure to nephrotoxic drugs and intra-uterine growth retardation may have a negative impact on kidney functions and renal maturation.[8] Renal maturation changes are also expected during the initial few weeks of neonatal life.[9] Also, considering the immaturity of nephrons in preterm neonates and the rapid development during the post-natal period, the pharmacokinetics of gentamicin is likely to differ in these subpopulations. Due to the differences in fat mass content and immature renal functions, gentamicin pharmacokinetics vary considerably in preterm neonates with a longer elimination half-life.[10] The differences in the pharmacokinetics may determine the optimal dose of gentamicin that can reduce the risk of possible nephrotoxicity and ototoxicity which is crucial in the neonatal population. Hence, we carried out the present study to predict the peak and trough gentamicin concentrations in critically ill neonates and then to predict the changes in the predicted peak plasma concentrations of gentamicin following fat-free mass dosing.

METHODS

Ethical approval

The present study is a cross-sectional study carried out in the neonatal intensive care unit of Salmaniya Medical Complex, Ministry of Health, the largest tertiary care hospital in the Kingdom of Bahrain, from November 2019 to October 2020. Institutional Ethics Committee approval was obtained prior to study initiation (Secondary Healthcare Research Subcommittee during the meeting 14/19 held on 19/11/2019) and we adhered to the latest Declaration of Helsinki guidelines. Written consent was obtained from either of the parents of the recruited neonates.

Study design

The inclusion criteria were neonates admitted to the intensive care unit that have received at least two doses of gentamicin and had their trough gentamicin concentrations measured just before the third dose. The exclusion criteria were those neonates for whom the gentamicin concentrations were unavailable. Their demographic details, diagnoses, birth weight, length, Apgar scores, gentamicin dosing regimen, and plasma concentrations were captured. Skinfold thicknesses were estimated at the triceps, subscapular, and thigh regions on the right side of the body using Lange calipers by a validated method.[9] A single rater measured the skinfold thicknesses, and two measurements were taken at each anatomical landmark. In case the differences in the measurements exceed 0.5 mm, a third measurement was obtained. The average of the measurements was used for the analysis. The triceps skinfolds were measured at the mid-point between acromial process of scapula and olecranon process of ulna. The lower angle of scapula was used for measuring subscapular skinfold thickness; and thigh skinfold was measured at the mid-point between the patella and inguinal groove on the anterior surface. Fat mass (kg) was measured using the Deierlein equation *et al.*[11] as follows: $-0.012 - 0.064 \times$ sex (1 = male; 0 = female) $+ 0.0024 \times$ post-natal age (days) $- 0.150 \times$ body weight (kg) $+ 0.055 \times$ body weight $(kg)^2 + 0.046 \times$ ethnicity (1 = Hispanic; 0 = not Hispanic) $+ 0.020 \times$ sum of 3 skinfolds (triceps, subscapular and thigh). Gentamicin dosing regimen in our critical care unit was according to Micromedex NeoFax recommendations (Table S1). Neonates were classified based on their gestational age as follows: extremely preterm (< 28 weeks); very preterm (28 to < 32 weeks); and late preterm (32 to < 37 completed weeks of gestation) and term (≥ 37 weeks).[12] Birth weights were classified as follows: ≥ 2.5 kg–normal; 1.5 to < 2.5 kg–low; 1 to < 1.5 kg–very low; and < 1 kg–extremely low birth weights. We considered the following therapeutic targets for gentamicin: concentrations (C_{max}) > 12 μg/ml; and trough concentrations (C_{min}) < 0.5 μg/ml.[13]

Pharmacokinetic analysis

Plasma samples were used for analyzing gentamicin concentrations using the latex-enhanced immunoturbidimetric method. BestDose software was used for estimating mean C_{max}, and C_{min}. C_{max} was also predicted based on the fat-free mass. BestDose® 1.126 software uses

a multiple-model Bayesian adaptive control through a one-compartment model with the summary of population pharmacokinetic parameters mentioned in Table S2.

Statistical analysis

Descriptive statistics were used for representing the demographic variables. Kruskal-Wallis test was used for the comparison of numerical variables and the Jonchkheere-Terpstra test was used for evaluating trends in the numerical variables across different categories of gestational age and birth weight. Pearson correlation tests were carried out for assessing the significance of the association between the numerical variables. Linear regression was used for evaluating the relationship between the predicted concentrations and the body weight (continuous variable). Bootstrapping simulations in 1000 samples were used for confirming the regression coefficient and *P*-values. Mann-Whitney *U* test was used for comparing the transformed values following linear regression with the original values for the predicted concentrations. Bonferroni corrected *P*-values were used for evaluating the statistical significance. A *P*-value of ≤ 0.05 was considered significant. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) was used for statistical analysis.

RESULTS

Demographics

Eighty-nine neonates were recruited, and their demographic details are listed in Table 1. Most of the neonates were term (33, 37.1%), followed by the late pre-term (27, 30.3%) category. Similarly, most of the preterm neonates were observed to have normal birthweight followed by the low birthweight category. A similar distribution of gender was observed amongst the study participants. The following diagnoses were observed amongst the study participants: suspected neonatal sepsis ($n = 53$); respiratory distress syndrome ($n = 40$); patent ductus arteriosus ($n = 11$); hypoxic-ischemic encephalopathy ($n = 11$); neonatal jaundice ($n = 10$); pneumonia ($n = 6$); transient tachypnea of the newborn ($n = 5$); metabolic acidosis ($n = 5$); intrauterine growth retardation ($n = 4$); congenital heart disorder ($n = 3$); birth asphyxia ($n = 3$); cleft palate ($n = 2$); intestinal obstruction ($n = 2$); and one each with chronic lung disorder, diaphragmatic hernia, hydrops fetalis, pneumothorax, and metabolic storage disorder. A high correlation was observed between the gestational age and birthweights ($r = 0.8$; $P < 0.001$).

TABLE 1 Summary of demographic details of the study participants ($n = 89$)

Variables	Parameter values
Gestational age (weeks)[†]	35 (26–40)
Category of gestational age (*n*)[‡]	
Term	33
Late pre-term	27
Very pre-term	19
Extreme pre-term	10
Chronological age (days)[†]	1 (1–2)
Birthweight (kg)[†]	1.99 (0.71–4.58)
Category of birthweight (*n*)[§]	
Normal	32
Low	29
Very low	16
Extremely low	12
Length (cm)[†]	44 (29–57)
Apgar score[†]	
1 minute	8 (0–10)
5 minutes	10 (2–10)
10 minutes	10 (4–10)
Male: Female (*n*)	48: 41
Duration of ICU stay (days)[†]	16 (1–95)

Abbreviation: ICU, intensive care unit.
[†]Represented in median (Range).
[‡]Gestational age was classified as follows: extremely preterm (<28 weeks); very preterm (28 to <32 weeks); late preterm (32 to <37 weeks); and term (≥37 weeks of gestation).
[§]Birth weights were classified as follows: ≥ 2.5 kg–normal; 1.5 to < 2.5 kg–low; 1 to < 1.5 kg–very low; and < 1 kg–extremely low birth weights.

Gentamicin dosing regimen and concentrations

Each neonate had one gentamicin concentration estimated (just before the third gentamicin dose) with the overall median (range) plasma gentamicin concentrations amongst the study participants as 0.7 (0 to 8.9) μg/ml. The median (range) dose of gentamicin administered was 4.4 (3.7 to 5.2) mg/kg. Gentamicin was administered once daily for 46 neonates; every 36 h in 23; and every 48 h in 20 neonates. No significant differences ($P = 0.800$) were observed in the gentamicin trough concentrations in various categories of study participants (Figure 1). Few neonates had trough concentrations above 2.0 μg/ml and none of them were observed with nephrotoxicity.

Estimated gentamicin concentrations

The median (range) estimated C_{max} following the first dose was 13.3 (4.0–21.1) μg/ml; and after the second dose, it was 13.5 (5.1–32.4) μg/ml. The estimated C_{min} was 0 (0–0.73) and 0.42 (0.01–6.45) μg/ml following the first and second doses of gentamicin, respectively.

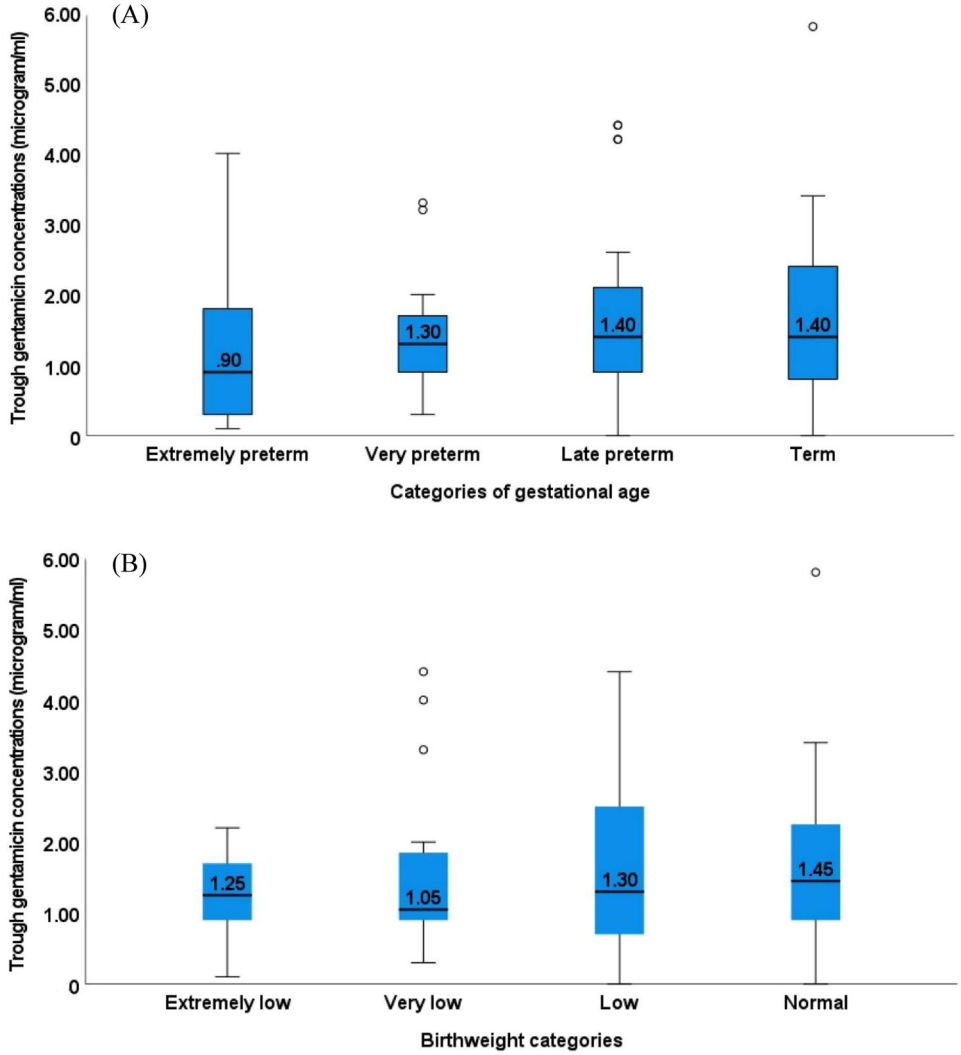

FIGURE 1 Measured gentamicin trough concentrations amongst the study participants. The box plots represent the comparison of median plasma gentamicin concentrations (depicted by the horizontal line in the middle of the box) with upper and lower horizontal lines in the box representing the first and third quartiles, respectively, observed in various categories of gestational age (A) and birthweight (B). The circles represent the outliers. There were 33 terms, 27 late pre-term, 19 very pre-term, and 10 extreme pre-term neonates. Also, there were 32 with normal birthweight, 29 with low, 16 with very low, and 12 extremely low birthweight neonates. No statistically significant differences were observed between the groups.

Distributions of C_{max} following the first and second doses based on gestational age and birthweight categories are depicted in Figure 2. Extremely preterm neonates had significantly ($P = 0.001$) higher C_{max} compared to the term following the first and the second doses. Additionally, a statistically significant ($P = 0.050$) higher C_{max} was observed in late preterm compared to term neonates. A significant trend ($P = 0.001$) of decrease in the C_{max} values was observed following the first and second doses of gentamicin from extreme preterm to term categories of neonates. Comparisons across the birthweight categories revealed a significantly ($P = 0.001$) higher C_{max} in extremely low and low birthweight categories compared to normal following the first and second doses. Sub-therapeutic C_{max} was observed in 29 (32.6%), and 20 (22.5%) neonates following the first (term – 15/33, 45.5%; late preterm – 7/27, 25.9%; very preterm – 6/19, 31.6%, and extremely preterm – 1/10, 10%) and second doses (term – 10/33, 30.3%; late preterm – 5/27, 18.5%; very preterm – 5/19, 26.3%) of gentamicin.

Estimation of body fat and fat-free mass

The median (range) of skinfold-thickness in the triceps, subscapular, and thigh regions amongst the study participants are 10 (8–14), 10 (6–16), and 10 (6–16), respectively. The estimated body fat was 0.5 (0.2–1.2) kg. The proportion of body fat was 24.9% (16.4%–54.1%). Figure 3

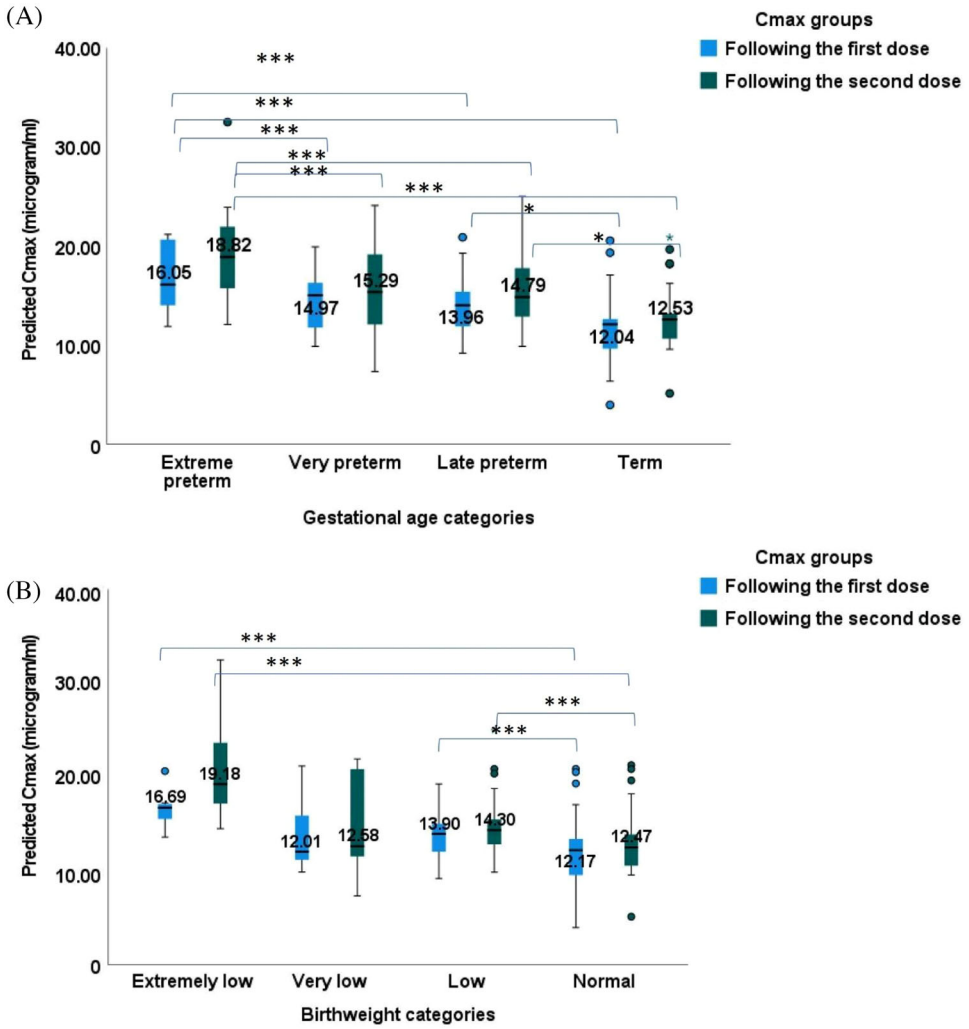

FIGURE 2 Distributions of estimated C_{max} in various gestational age groups. The box plots represent the predicted C_{max} gentamicin concentrations (the median is depicted by the horizontal line in the middle of the box) with upper and lower horizontal lines in the box representing the first and third quartiles, respectively, in various categories of gestational age (A) and birthweight (B). The circles represent the outliers. Statistical significance: $^{*}P < 0.05$; $^{***}P < 0.001$.

depicts the proportions of body fat distributions based on various gestational age and birthweight categories. A significant ($P = 0.001$) trend of higher proportions of fat mass in the neonates was observed from extreme preterm to term as well as from extremely low to normal birthweight. Fat mass and fat-free mass correlated significantly with gestational age ($r = 0.7$, $P = 0.001$; and $r = 0.9$, $P = 0.001$, respectively) and body weight ($r = 0.9$, $P = 0.001$; and $r = 1.0$; $P = 0.001$, respectively) (Figure 4).

A weak negative correlation was observed between fat mass and fat-free mass with C_{max} following the first gentamicin dose ($r = -0.3$, $P = 0.014$; and $r = -0.3$, $P = 0.002$, respectively), and following the second gentamicin dose ($r = -0.3$, $P = 0.004$; and $r = -0.4$, $P = 0.001$, respectively) (Figure 4). The proportion of body fat was positively correlated with C_{max} following the first and second doses ($r = 0.3$, $P = 0.002$; and $r = 0.4$, $P = 0.001$, respectively).

Differences in the estimated C_{max} following the whole-body weight and predicted C_{max} following fat-free mass dosing of gentamicin

Linear regression tests revealed a significant relationship between body weight and the predicted concentrations as follows: C_{max} following the first gentamicin dose = 16.061–1.183 × (body weight), and C_{max} following the second gentamicin dose = 19.045–1.949 × (body weight). The regression coefficient and the *P*-values of all the above concentrations were observed to be within the 95% confidence

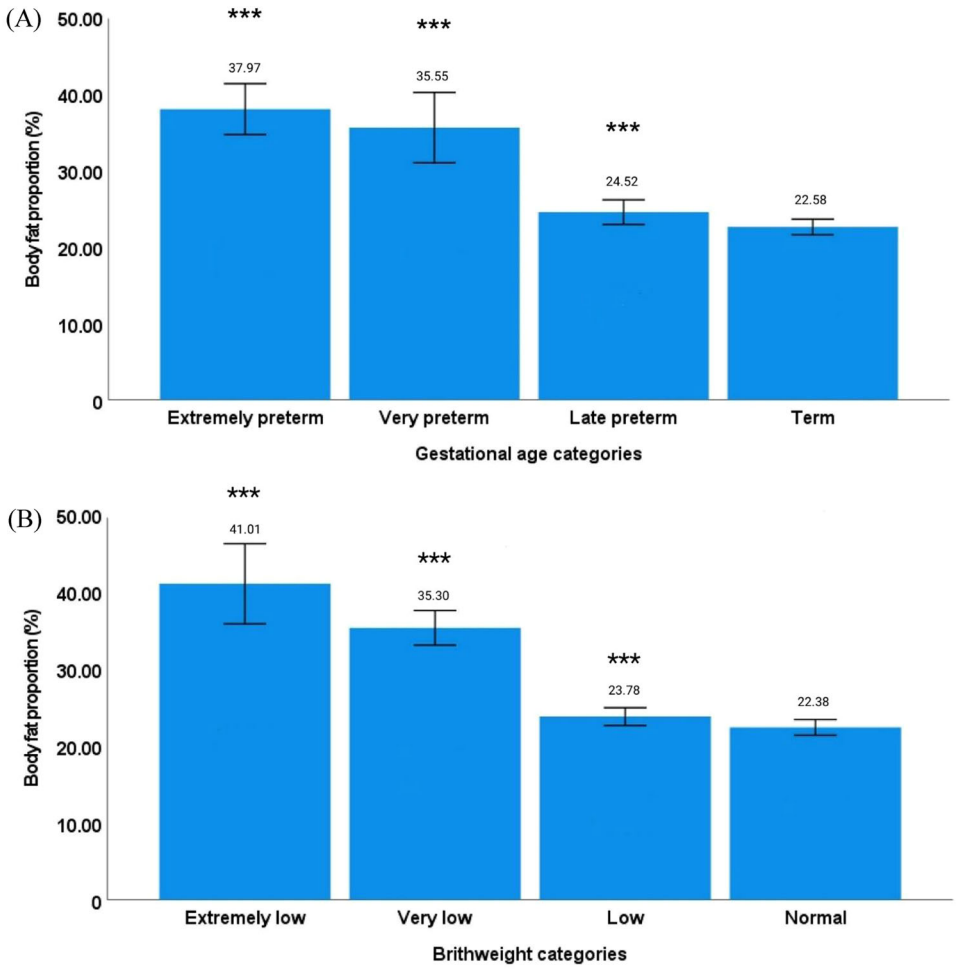

FIGURE 3 Comparison of fat proportions of body weight in various categories of the study participants. The bar charts represent the distributions of proportions of body fat in different categories of study participants as grouped by gestational age (A) and birthweight (B). A trend of higher fat mass was observed as we moved from term to extreme preterm categories. The values on the bars represented the average of each group. *** $P < 0.001$ compared with the term or the normal group.

intervals generated by the bootstrap method. The transformed C_{max} values (at both first and second doses) using regression equations were not significantly ($P > 0.05$) different from the predicted values confirming the validity of the above-mentioned regression equations.

Differences in the predicted C_{max} between the whole-body weight and fat-free mass dosing of gentamicin are depicted in Figure 5 and their absolute values following the first and second doses are mentioned in Figure S1. The estimated C_{max} from whole-body weight was higher than the ones estimated from fat-free mass-based dosing both following the first and the second doses. Similarly, a weak positive correlation was observed between the C_{max} concentrations predicted based on whole body weight and fat-free mass. The median (range) predicted C_{max} was 14.3 (12.1–15.6) and 16.1 (12.5–18.3) μg/ml following the first and second gentamicin doses. All except one of the neonates had their C_{max} above 12 μg/ml after the first dose and all had after the second gentamicin dose following the fat-free mass-based gentamicin dosing. Following are the dosing recommendations based on gestational age category following the median dose observed following fat-free mass: extreme preterm: 7.95 mg/kg every 48 h; very preterm: 7.30 mg/kg every 36–48 h; late preterm: 5.90 mg/kg every 36–48 h; and term neonates at 5.10 mg/kg every 24 hours.

DISCUSSION

We evaluated the changes in the gentamicin concentrations following the fat-free mass-based dosing strategy in 89 critically ill neonates. Bayesian pharmacokinetic approach was used for estimating C_{max} values following the first and second gentamicin doses. Sub-therapeutic C_{max} was observed in 32.6%, and 22.5% neonates following the first and second doses of gentamicin. Preterm

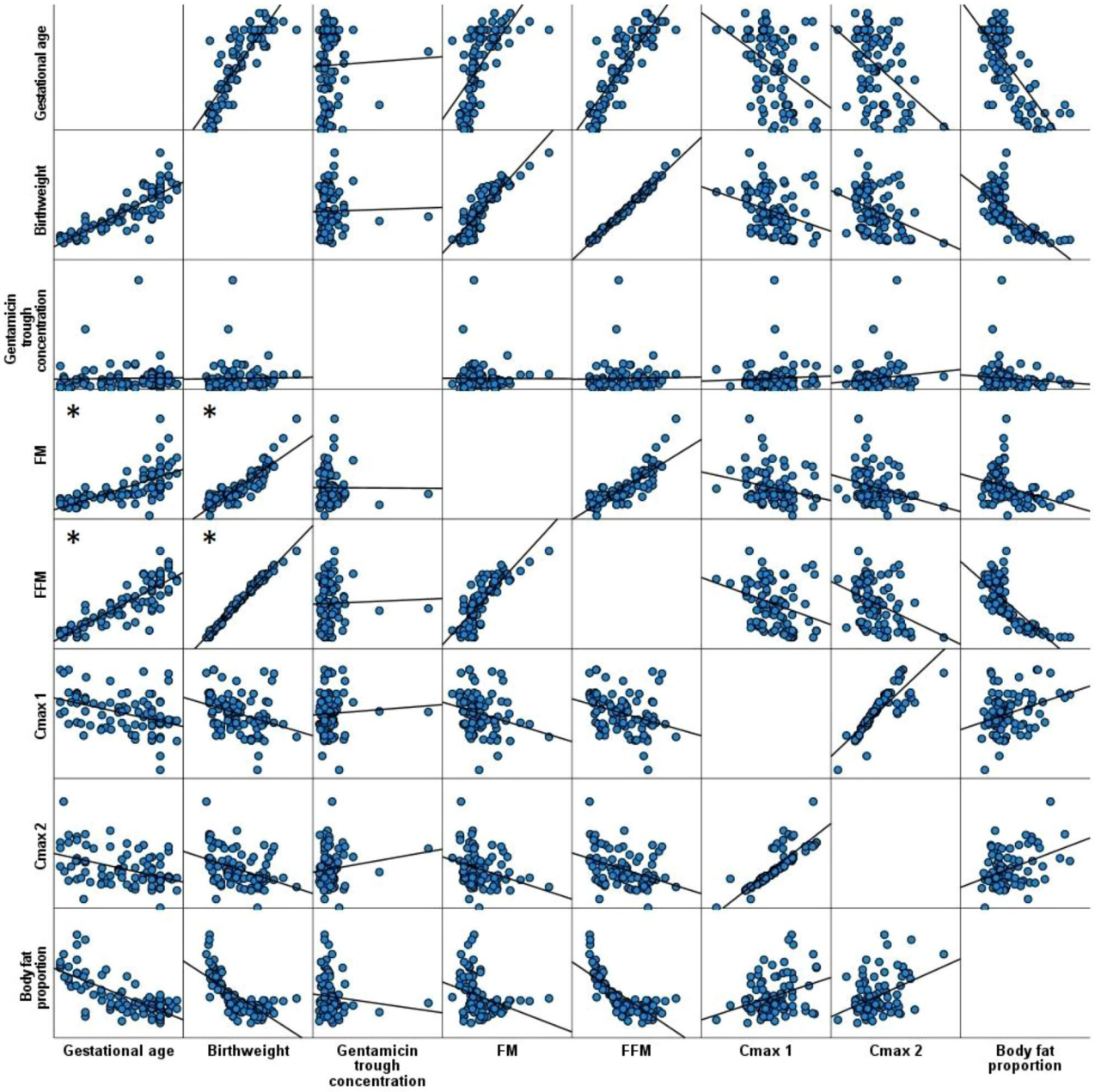

FIGURE 4 Correlations between various indices of weight, gentamicin trough concentrations, and the predicted C_{max} values of gentamicin. Correlation matrix depicting the relationships between various indices. FM, fat mass; FFM, fat-free mass; C_{max} 1, Peak concentrations following first gentamicin dose; C_{max} 2, Peak concentrations following second gentamicin dose. Fat mass and fat-free mass correlated significantly with gestational age and body weight and are represented using asterisks.

neonates had significantly higher fat mass compared to term neonates. Fat-free mass dosing of neonates is likely to achieve optimal predicted C_{max} compared to a whole-body weight-based dosing regimen and the recommended doses are as follows: extreme preterm: 7.95 mg/kg every 48 h; very preterm: 7.30 mg/kg every 36–48 h; late preterm: 5.90 mg/kg every 36–48 h; and term neonates at 5.10 mg/kg every 24 h.

The dosing regimen of gentamicin in critically ill neonates requires a revisit as recent studies have debated and recommended higher gentamicin doses.[10] Neonates were observed to be more prone to achieving supra- or sub-therapeutic concentrations of gentamicin compared to other age groups in children.[14] Due to the rapid changes in the body fluid dynamics as well as renal maturation, significant changes are expected in the volume of distribution

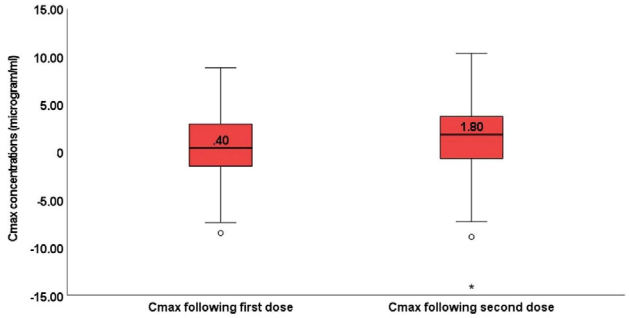

FIGURE 5 Plot of the absolute differences in the estimated C_{max} following whole-body weight and predicted C_{max} following fat-free mass dosing. The boxplots represent the median and first and third quartiles for the differences in the estimated C_{max} values following whole-body weight and the predicted C_{max} fat-free mass-based dosing of gentamicin.

and clearance that impacts the C_{max} and AUC.[15,16] The estimated C_{max} in the present study was like the previous report in the same population.[15] We observed higher C_{max} values in more premature neonates compared to the term. This is attributed to the significantly higher fat mass in the premature groups compared to term neonates; the most plausible reason for this being the administration of total parenteral nutrition in the former group. Total parenteral nutrition has been shown to increase the neonatal fat mass (almost 21% higher compared to enteral nutrition at the same age).[17] The currently administered dosage regimen in our critically ill neonates ranges between 4 and 5 mg/kg every 24, or 36, or 48 h depending on the gestational age and post-natal age.[18] We observed that this dosing regimen is inadequate to reach therapeutic goals at least in one third of the neonates. Our previous study using Bayesian pharmacokinetic modeling also revealed that the inadequacy of the current dosing regimen to achieve the optimum pharmacodynamic-pharmacokinetic target and a higher dosing was recommended.[19] A higher dose as estimated in the present study based on fat-free mass is likely to achieve the desired pharmacodynamic target in almost all the neonates. Zao et al.[20] observed through physiologically based pharmacokinetic modeling that a dose of 6 mg/kg resulted in a higher efficacy with less than a tenth resulting in toxicity. Similarly, Bergenwall et al.[21] suggested 8–9 mg/kg every 72 h in neonates ≤ 850 g could likely to result in the target gentamicin concentrations. O'Connor et al.[22] observed that subtherapeutic gentamicin concentrations were achieved with a regimen of 2.5 mg/kg and recommended increasing the dosage to 3.5 mg/kg which is efficacious in 98% with more than four-fifths having a non-toxic concentration. However, we should also keep in mind that an increased dose may also result in increased trough concentrations of gentamicin. Although we did not observe any increased risk of toxicity amongst neonates with trough concentrations above 2.0 μg/ml, future studies are needed to establish the safety of the dosing regimen before adapting it to the clinical practice. In case, the fat-free mass cannot be measured, at least the gentamicin dose can be adjusted based on the median proportion of body fat reported in the same population or estimated from closely related populations. Although we used regression methods for predicting the changes in C_{max} and consequently the dosing requirements based on fat-free mass-based dosing, it is prudent to carry out a population pharmacokinetic approach for evaluating the inter-individual and between-subject variabilities in the key pharmacokinetic parameters with fat-free mass as a covariate. Future studies in this direction are needed. Studies should be attempted in evaluating the influence of fat-free mass-based gentamicin dosing on distribution of the drug as significant changes may happen due to renal development in the early stages of life.

This is the first report evaluating the influence of fat-free mass on the C_{max} and C_{min} of gentamicin in critically ill neonates. However, we could not externally validate the predicted gentamicin doses based on fat-free mass. Additionally, the concentrations were predicted using the Bayesian forecasting method rather than estimating through rich time-points of blood samplings that led to a great variation in the concentration values, and modeling using population pharmacokinetic model indigenous to the population; minimum inhibitory concentration values were not available and so pharmacokinetic-pharmacodynamic target was not considered; predicted/estimated C_{max} from observed C_{min} provide limited information on the volume of distribution and hence on C_{max}, especially without considering the covariates; and severity of illnesses of the study participants could not be ascertained due to absence of any validated tool in this population. Slight differences were observed between the Neofax recommended doses and doses administered to the study participants which is mainly explained due to differences in the rounding of the body weights. The limited samplings also precluded us from exploring the estimation of parameters using multi-compartment models. Due to resource limitations, minimum inhibitory concentrations (MICs) for the isolated micro-organisms were not carried out and so a more appropriate pharmacokinetic-pharmacodynamic measure (C_{max}/MIC) could not be estimated.

In conclusion, we examined the association of fat-free mass with model-predicted gentamicin exposure (C_{max} predicted by BestDose from a single trough measurement) in a neonatal population. Fat-free mass dosing may be considered for obtaining optimal therapeutic effects in neonatal population. However, future population pharmacokinetic approaches and dose optimization studies are needed for the validation of this approach.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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