Administration of Higher Doses of Amikacin in Early Stages of Sepsis in Critically Ill Patients

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Abstract- High-dose extended-interval dosage (HDED) regimen of aminoglycosides is now considered as the standard dosage strategy in sepsis. Although safety and efficacy of this dosing regimen is well studied, but new experiments show increased the risk of resistance development associated with $\%T_{>MIC}$ less than 60% of the dosing interval following extended interval dosing. Moreover, limited information is available about safety of more frequent administration of high dose aminoglycosides. Authors studied nephrotoxicity following seven days' exposure to more frequent administration of higher doses of amikacin comparing with HDED regimen. In addition to Serum Creatinine (SrCr) and estimated glomerular filtration rate (eGFR), nephrotoxicity was studied with Neutrophil gelatinase-associated lipocalin (NGAL), a direct marker of tubular injury. A total of 40 patients with sepsis were quasi-randomized in two groups. Seven days' course of treatment with a moderate dose of amikacin (12.5 mg/Kg) was administered every 12 hours, known as the moderate-dose non-liberal-interval dosage (MDNLD) regimen compared with the high-dose extended-interval dosage (HDED) regimen (25mg/Kg every 24 hours). The pharmacokinetic/pharmacodynamic (PK/PD) goal of the MDNLD regimen was the $C_{max}>40$ and the $\%T_{>MIC}$ more than 60% during the PK/PD goal for the HDED regimen was the $C_{max}>60$. The eGFR change from the baseline was the primary outcome of the study with a minimum clinical significance of 20ml/min (estimated SD of 20, Power>90%, $P<0.05$). No difference was observed between groups for the values of eGFR change and the SrCr percent change from the baseline (P=0.359 and P=0.114, respectively). Frequency of acute kidney injury also did not differ between groups (P=0.342). Serum NGAL level values' change from the baseline was more in the HDED regimen in comparison with the MDNLD regimen at third day and fifth day of the treatment (P=0.001 and P=0.002, respectively). This indicates a safer pattern of moderate doses with more frequent administration of amikacin at the tubular injury level. Higher doses of amikacin could be safely administered to achieve PK/PD goal of $C_{max}>40$ and $\%T_{>MIC}$ more than 60% of the dosing interval. This dosing regimen would be considered as an alternative to minimize the resistance development associated with the extended-interval dosing in septic patients with multi-drug resistant gram-negative organisms.
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Introduction

In recent years, aminoglycosides have become the mainstay of combination antimicrobial chemotherapy against multi-drug resistant gram negatives. Many guidelines consider aminoglycosides and specially amikacin to be one of the best choices of treatment in sepsis and septic shock in critically ill patients (1,2). However, increase in minimum inhibitory concentration (MIC) of some of these pathogens namely Acinetobacter baumannii has raised concerns about the future of sepsis control (3-6). The MIC breakpoints for amikacin against

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sensitive A. baumannii is now considered as high as 8 mg/lit (7).

In conventional dosing regimens, most experts use moderate doses of amikacin (15-20 mg/Kg) with the pharmacokinetic goal of C_{max} 40-60 mg/lit every 24 hours and low doses of amikacin (7.5-10 mg/Kg) with the pharmacokinetic goal of C_{max} 20-30 mg/lit every 12 hours as the two standard regimens (8).

Concerning recent amikacin MIC breakpoints for A. baumannii and growing evidence for the impact of reaching C_{max}: MIC of at least eight to achieve sufficient effects (9,10), many practitioners have settled on the high dose amikacin in sepsis control to reach the C_{max} goal of 60-80 mg/lit (estimated dose of 25mg/Kg) (5). Because of concerns about the nephrotoxicity of higher doses, most of these regimens are designed to provide highest levels of C_{max} while maintaining the C_{min} and AUC values at lower levels by means of the lowest theoretical effective frequency of every 24 hours (11). Considering the post antibiotic effect (PAE) of aminoglycosides, these regimens known as the high-dose extended-interval dosage (HDED) regimens are believed to be more effective than conventional dosing regimens. The PAE of aminoglycosides is reported to be 0.5 to 8 hours after the drug concentration drops under MIC levels (11). Many studies have confirmed the efficacy of HDED amikacin regimens (>25mg/Kg every 24 hours) in settings with a high prevalence of high-resistant pathogens (5). However, it is estimated that up to 50% of the patients may experience concentrations lower than MIC for more than 10 hours within dosing intervals (%$T_{>MIC}$ less than 60% of the intervals) (12).

Although the body of the literature supports the C_{max}: MIC as the major pharmacokinetic/pharmacodynamic (PK/PD) goal to prevent aminoglycoside resistance, one should not ignore the importance of keeping the %$T_{>MIC}$ longer than 60% of the intervals as another PK/PD goal. Aminoglycosides are short half-life agents (2-3 hours) with limited PAE (0.5-8 hours) duration; Therefore, probability of developing drug resistance that is associated with extended-interval dosing might be challenging (13). Despite satisfactory results regarding the HDED amikacin regimen's efficacy against high-resistant pathogens, it should not be interpreted as the capability to prevent antibiotic resistance. Information about drug resistance development associated with the HDED regimens is not sufficient in clinical practice. Zazo *et al.,* have described the association of the extended interval regimens with drug resistance development and discussed the need for more frequent administration of amikacin and other aminoglycosides to

prevent it (12). In the lack of data about the nephrotoxicity potential of more frequent dosing of the high dose aminoglycosides, it would be unsafe to apply these recommendations in clinical practice without further investigation.

The present study investigates nephrotoxicity of a new amikacin dosing regimen, moderate-dose non-liberal-interval dosage (MDNLD), in comparison with standard HDED amikacin regimen (25mg/kg every 24 hours) in ICU patients with sepsis. Neutrophil gelatinase-associated lipocalin (NGAL) as a direct marker of tubular injury is used in this study in addition to other indirect markers including serum creatinine (SrCr) and estimated glomerular filtrations rate (eGFR). Serum NGAL could predict kidney injury events 24-48 hours beyond the seven days' course of follow-up with an acceptable sensitivity (14).

The new MDNLD amikacin regimen provides more frequent (every 12 hours) dosing to preserve the %$T_{>MIC}$ longer than 60% of the dosing intervals while enjoying the lower range of acceptable C_{max} value of 30-50 mg/lit with moderate doses of amikacin (12.5 mg/Kg).

Materials and Methods

Trial design

This trial was a quasi-randomized clinical trial (quasi-RCT) with parallel intervention and historical control groups. These study groups were subgroups of a previous trial, conducted to compare the nephrotoxicity of the high dose once daily, the moderate dose once daily and the moderate dose twice daily of amikacin regimens. Because of several limitations, the authors decided not to investigate all three groups simultaneously. Comparison of a high dose and the moderate dose once daily regimens was considered as the first phase of the investigation (2009-2011). In this phase of the trial, authors compared the nephrotoxicity of the moderate dose twice daily of amikacin with the historical control group of the high dose once daily of amikacin. The reasons for ICU admission of the patients, patient-to-nurse ratio, ICU equipment, pattern of antibiotic resistance and therapeutic protocols have not changed during the six months gap between the two studies.

Participants

Patients admitted to the general ICU ward of Sina Hospital affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran from August 2011 to March 2013 were screened for the study eligibility

during ICU stay. Inclusion in the study required the patient to be younger than 65 years with no renal impairment stage three and less (defined as eGFR < 60 ml/min estimated with Cockcroft-Gault equation) and to have sepsis indicating empiric combination antibiotic therapy including amikacin against gram negative pathogens.

Patients with the following conditions were excluded from the study: Acute renal injury development according to RIFLE criteria in the first 72 hours of inclusion, a moribund condition at the baseline, major cardiac, pulmonary, hepatic or hematologic disorders, neutropenia, history of recent antineoplastic or immunosuppressive chemotherapy, neuromuscular diseases, pregnancy, extreme body weights (BMI>35 or <18.5), ages below 18 years old and amikacin discontinuation or death before the fifth day of the treatment. Informed consent was obtained either from the patients or first-degree relatives. The study was conducted according to the declaration of Helsinki regarding study the human subjects.

Interventions

Sepsis workup is performed for every patient at the baseline and all relative routine critical care laboratory, and clinical monitoring parameters including serum creatinine, hemodynamic parameters and SOFA score (an index of severity of illness) are followed and documented by bedside daily visits.

The amikacin dose contents in this study were categorized by the extent of amikacin dose to achieve a specific C_{max} goal, calculated with population pharmacokinetic estimation. Doses with the C_{max} goal of less than 30 mg/lit are suggested as low dose amikacin (dosing range of 5-10 mg/Kg), doses with the C_{max} goal of 40-60 mg/lit are suggested as moderate dose amikacin (dosing range of 10-15 mg/Kg) and doses with the C_{max} goal of more than 60 mg/lit are considered as high dose amikacin (dosing range of 20-25 mg/Kg).

In this study, nephrotoxicity of a 7 days treatment course with moderate doses of amikacin (dose of 12.5 mg/Kg) every 12 hours, known as the moderate-dose non-liberal-interval dosage (MDNLD) regimen was compared with high doses amikacin (dose of 20 mg/Kg) every 24 hours, known as the high-dose extended-interval *dosage* (HDED) regimen as the standard of care for sepsis antibiotic therapy. All dosing calculations were based on patients adjusted body weight (ABW). The moderate dose amikacin used in this study was estimated to reach a calculated C_{max} goal of >40 mg/lit and $\%T_{>MIC}$ more than 60% of

the dosing interval, while keeping AUC (calculated by Dosing rate/Clearance) comparable with HDED regimen.

Outcomes

Serum creatinine and eGFR calculated by Cockcroft-Gault equation were used as the indirect index of nephrotoxicity and tubular injury. These indices are readily available in the daily practice setting and are feasible for sufficient response to kidney damage.

Serum neutrophil gelatinase-associated lipocalin (sNGAL) was used as a more specific marker of tubular insult with a good sensitivity to predict early acute kidney injury (14,15). Considering inaccessibility to this marker in clinical setting, sNGAL was measured at the end of the study of all cases with serum specimens collected at first, third, fifth and seventh days of the study.

Primary outcome of the study was the value of decline in eGFR from the baseline. The secondary outcomes were number of patients developing AKI and the difference of sNGAL concentrations compared with the baseline value.

To measure the sNGAL concentrations, 5 ml venous blood samples were taken from a central catheter at baseline (sNGAL1) fallowed by third day (sNGAL3), the fifth day (sNGAL5) and the seventh day (sNGAL7) thereafter. Plasma was separated after centrifugation at 4500 rpm for 15 minutes. Samples were stored at −80°C until the time of analysis.

Sample size

With a total sample size of 40 patients, the power of the study was 94% to detect a difference of at least 20 ml/min from the baseline between the treatments when applying a two sided t-test at the level of 5%. The minimum clinically important difference of eGFR decline (20 ml/min) was assumed based on similar studies (16).

Sampling and blinding of patients

All patients with eligibility criteria allocated to the intervention group. Patients were blinded to antibiotic regimen during the experiment. After completion of the study, sex, age and critical illness severity (APACHE II score) were used to describe the baseline differences in patients' characteristics.

Statistical methods

All the analyses were performed using SPSS statistical package, version 20 for windows. Fisher's Exact Test was used to compare the proportions in 2×2 tables. All variables were tested for normality of

distribution with Kolmogorov-Smirnov test. Student's t-test and Mann– Whitney U test were used to examine the differences between groups at the each time point for parametric and nonparametric variables, respectively. To assess the value of change from the baseline between groups, values were reproduced with subtraction or percentage change calculation and then independent sample t-test or Mann-Whitney U test between groups were used (depending on the nature of the variable's distribution). The significance of the difference between sNGAL concentrations within groups was tested with Freidman's 2-way ANOVA by ranks.

To specify the time points which are significantly different from the other levels, Wilcoxon Signed Rank test was used to compare all time points in a pairwise manner and *P*-values were adjusted with Bonferroni correction.

Results

Participant flow and recruitment

A total of 24 patients were assigned to the intervention group where 4 cases excluded based on the exclusion criteria. The excluded participants

included one patient with AKI within first 72 hours, one death and two patients with antibiotic discontinuation before 5th day of the treatment. At the end of the study, a total of 40 patients were analyzed for the primary outcome. Patients recruited to the study from August 2011 to March 2013 with the intention to treatment goal of 7 days.

Baseline data

Table 1 describes baseline characteristics of the study population. The difference between study groups was not significant regarding age, gender, ideal body weight (IBW), APACHE II score, SOFA score, serum creatinine (SrCr) and estimated glomerular filtration rate (eGFR) at the baseline.

The mean administered dose of amikacin (mg/dose) was 755 ± 5 and 1493 ± 31 in MDNLD and HDED regimen, respectively. Considering more frequent dosing in MDNLD regimen, the median dosing rate (total daily dose) based on patient's adjusted body weight (mg/Kg/day) did not differ significantly between the groups with a median of 21.8 ± 0.5 and 22.4 ± 0.4, respectively (*P*.value=0.735).

Table 1. Comparison between baseline characteristics of intervention and control groups

Frequencies	HDED Amikacin Regimen (N=20)	MDNLD Amikacin Regimen (N=20)	Sig. (2-sided)
Male gender	14(70%)	16(80%)	0.716 [a]
Measures	**Mean ± S.E**	**Mean ± S.E**	**Sig. (2-tailed)**
Age (year)	44.0±3.2	40.5±3.0	0.285[b]
APACHE II at the baseline	12.1±1.3	12.8±1.0	0.674[b]
SOFA at the baseline	6.15±0.52	6.00±0.48	0.833[b]
Pretreatment SrCr (mg/dL)	0.77±0.04	0.78±0.04	0.863[b]
Pretreatment GFR (ml/min)	114±6	120±8	0.543[b]
sNGAL1 (ng/ml)	97.22±11.28[¥]	111.96±12.63[¥]	0.344 [c]
IBW (Kg)	65.0±1.6[¥]	68.0±1.6[¥]	0.786 [c]
Dosing Rate Per Kg of ABW (mg/Kg/day)	22.4±0.4[¥]	21.8±0.5[¥]	0.735 [c]

[a] Tested with Fisher's Exact Test
[b] Tested with Independent sample t-test
[c] Tested with Mann-Whitney U test
[¥] Values are mentioned as median ± S.E
Abbreviations: HDED: high-dose extended-interval dosage; MDNLD: moderate-dose non-liberal-interval dosage; sNGAL1: serum NGAL level at 1st day; IBW: ideal body weight; ABW: adjusted body weight; S.E: standard error

Outcomes and estimation

Table 2 describes the primary and secondary outcomes of the present study. The difference values of eGFR before and after the treatment as the primary outcome were not statistically significant between groups (*P*=0.359, mean the difference= -7.5, Power=0.65). Other secondary outcomes tested include difference of AKI occurrence during the study between

groups, change in SOFA score and percentage change of serum creatinine from the baseline after the treatment that were not statistically significant (*P*=0.342, *P*=0.949 and *P*=0.114 respectively).

The values of sNGAL concentrations in four consecutive time-points are illustrated in figure 1 for each group. The changes of sNGAL concentrations within groups were only significant in HDED group

(*P*=0.044). Comparison between the sNGAL levels within HDED group showed statistical significance

between sNGAL3 and sNGAL1 levels (*P*=0.048 after Bonferroni correction n=6) (Figure 1).

Table 2. Measurements of outcomes

frequencies	HDED Amikacin Regimen (N=20)	MDNLD Amikacin Regimen (N=20)	Sig. (2-sided)
Frequency of AKI	2(10%)	1(5%)	0.342[a]
measures	**Mean ± S.E**	**Mean ± S.E**	**Sig. (2-tailed)**
Value of SOFA score difference	1.10 ± 2.84	1.05 ± 1.93	0.949[b]
Percentage change of SrCr	12.7 ± 7.53[¥]	2.5 ± 10.97[¥]	0.114[c]
value of GFR difference	-11.75 ± 24.09	-4.25 ± 26.91	0.359[b]

[a] Tested with Fisher's Exact Test
[b] Tested with Independent sample t-test
[c] Tested with Mann-Whitney U test
[¥] Values are mentioned as median ± S.E
Abbreviations: HDED: high-dose extended-interval dosage; MDNLD: moderate-dose non-liberal-interval dosage; S.E: standard error

The difference value of sNGAL concentration from the baseline in each time point was compared between groups as another outcome. Table 3 compares the value of change in sNGAL levels from the baseline in each

time point in both groups. The difference was statistically significant at third day and fifth day between groups (*P*=0.001 and *P*=0.002, respectively).
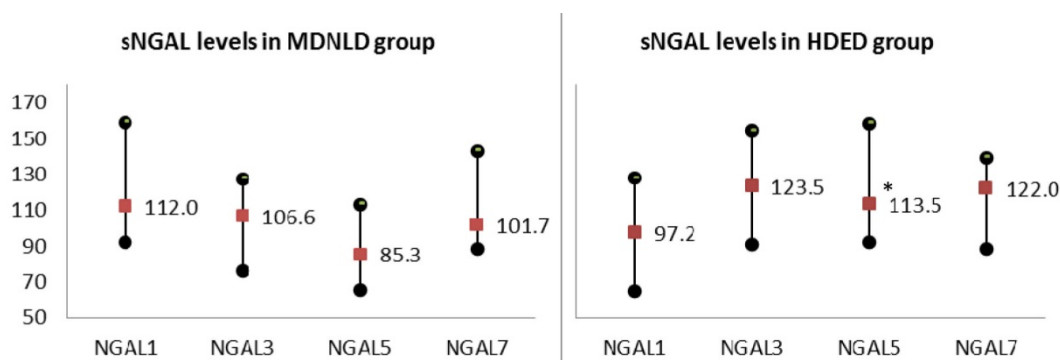

Figure 1. Values of sNGAL levels within 7 days of study (median and quartiles);*: statistical significance with *P*.value<0.05

Table 3. Difference values of sNGAL from the baseline

	HDED Amikacin Regimen (N=20)	MDNLD Amikacin Regimen (N=20)	Between subject U test
	Median (Lower band, Upper band)	Median (Lower band, Upper band)	P value
sNGAL3 diff	27.33 (2.38,63.45)	-11.43(-38.66,8.19)	0.001
sNGAL5 diff	26.55(-8.12,54.75)	-18.45(-75.67,3.83)	0.002
sNGAL7 diff	15.14(-19.95,63.00)	2.25(-53.21,32.96)	0.204

sNGAL3 diff: Change of serum NGAL level at third day from the baseline; sNGAL5 diff: change of serum NGAL level at fifth day from the baseline; sNGAL7 diff: the change of serum NGAL level at seventh day from the baseline

Discussion

Current study results show tubular exposure to the Moderate-dose non-liberal-interval dosage (MDNLD) regimen of amikacin does not seem to be more

nephrotoxic than the high-dose extended-interval dosage (HDLD). This comparison was made by both indirect indices of the kidney injury (serum creatinine and eGFR) and NGAL as a direct marker of tubular insult.

Large amounts of studies are in the literature which have compared the nephrotoxicity of conventional low doses with more frequent amikacin dosing regimen (C_{max} goal of 20-30 mg/lit every 12 hours) with moderate-high doses with extended intervals (C_{max} goal 40-60 mg/lit every 24 hours) in various setting and subpopulations. Controversial results of these studies indicate a small trend toward the more nephrotoxic pattern of more frequent regimens, although it has been challenged with numerous meta-analysis studies (8,17,18).

MDNLD regimen of amikacin may not be considered equivalent to conventional regimens, because its goal is to reach desirable C_{max} values (>40 mg/lit) of each administered dose while keeping the %$T_{>MIC}$ higher than 60% of the dosing intervals. Considering present study as the first one which investigated the nephrotoxicity of higher doses of amikacin during more frequent intervals, authors used moderate doses (with estimated C_{max} >40 mg/lit) instead of high doses (goal C_{max} of 60-80 mg/lit) to prevent AUC and C_{min} to reach inconvenient values.

One of the limitations of this study is an application of moderate doses of amikacin that may not reach the PK/PD goal of C_{max}: MIC >8. However, authors were not concerned about insufficient efficacy for this regimen because of comparable AUC: MIC values with the MDNLD and HDED regimens. Tam *et al.*, reported that in spite of guideline's emphasis on keeping C_{max}: MIC value as high as possible, AUC: MIC in more frequent dosing regimens of aminoglycosides may still be as a reliable PK/PD goal (19).

The seven days treatment course of the study may also be noted as a relatively short tubular exposure to aminoglycosides while treatments beyond 10 days are associated with a higher incidence of nephrotoxicity. Using NGAL in this study would be considered as a modality to provide the prediction of renal failure occurrence (with the cut-off value of 300ng/ml) in next 24-48 hours after the follow-up (total of 8-9 days) (14, 15).

Quasi-randomization of this trial is another limitation. However, the equivalent characteristics of the patients at the baseline would minimize any external source of error to affect the results.

In our current situation with increasing prevalence of extensively drug-resistant (XDR) and pan drug-resistant (PDR) pathogens (5), risk of drug resistance development seems to be serious. The authors recommend that future studies could evaluate potential of moderate-dose non-liberal-interval dosage (MDNLD)

regimen of amikacin to prevent drug resistance development with pharmacokinetic/pharmacodynamic techniques.

In addition, Pharmacokinetic changes of the patients' parameters during the acute phase of sepsis (first 48-72 hours) (20) may indicate even higher doses of amikacin with more frequencies as the early goal therapy (15-25mg/Kg every 8-12 hours). However, individualization of therapy would be necessary after the acute phase with the goal of C_{max}: MIC>8 and %$T_{>MIC}$ more than 60% of the dosing intervals. Regarding these recommendations, investigating the safety of high-dose non-liberal-interval dosage (HDNLD) regimens of amikacin (C_{max} 60-80 every 12 hours) in early stages of sepsis could be an attractive aria of interest.

In addition, it must be considered that antibiotic therapy in sepsis is a single part of the care plan. In spit of using combination antibiotic therapy with optimal dosing regimen design, sepsis would be a hard situation to handle; while the outcome of the treatment depends on other modalities including sufficient hemodynamic and nutrition support beside appropriate antimicrobial chemotherapy.

In the current study, authors have introduced moderate-dose non-liberal-interval dosage (MDNLD) regimen of amikacin to the clinical practice of sepsis management with comparative nephrotoxicity pattern to the standard high-dose extended-interval dosage (HDED) regimen.

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