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Research Article

Tigecycline in CR-Kp Associated VAP with High Dose *vs.* Conventional Dose: Adverse Events are the Key Superiority-determiner

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ABSTRACT

Background: Multi-drug Resistant (MDR) pathogen Carbapenem-Resistance *Klebsiella pneumonia* (CR-*Kp*) associated Ventilator-Associated Pneumonia (VAP) is a serious infectious disease and tigecycline with high or conventional dose, is one of the last resort potential antibiotics for its treatment.

Objective: The major objective of this study was to evaluate the key role of adverse events in preferring the better dosing option of tigecycline.

Methods: Total 45 middle-aged MDR-CR-*Kp* associated VAP patients and treated with high (200 mg/day) and conventional dose (100 mg/day) of tigecycline (intravenous) distributed into two groups. Group-wise microbiological eradication rate, secondary infection rate, 30 days mortality rate and dose-related adverse events were analyzed and compared, accordingly.

Result: After 5 days, highest microbiological eradication was observed in HD-group (79.17%) than CD-group (47.62%) with low rate of secondary infections (8.33% versus 33.33%). The 30 days mortality rate was relatively higher in HD-group (45.83% versus 38.10%). Severity and frequency of high-dose associated adverse events were higher in HD-group at all parameters than CD-group (elevation of ALT: 33.33%/23.81%; AST: 41.67%/28.57%; bilirubin: 37.50%/19.05%; reduction of blood pH: 45.83%/9.52%, respectively).

Conclusion: High dose of tigecycline showed relatively higher therapeutic response in MDR-CR-*Kp* associated VAP treatment than conventional dose but, with increased rate of adverse events, which questioned its practice.

Keywords: Carbapenem-resistance *Klebsiella pneumonia*; Ventilator-associated pneumonia; Tigecycline; Conventional dose; High dose

INTRODUCTION

Emerging Multidrug-Resistant (MDR) gram-negative bacteria, also known as superbugs, are now the burning issue in global healthcare sector. Day-by-day increasing number and severity of growing antibiotic-resistance and the relevant resistance-mechanisms among gram-negative bacteria against most potent last resort antibiotics, are considered as major threat to global human health [1]. In the beginning of 21st century, Carbapenem-Resistance *Enterobacteriaceae* (CRE) with its fastest MDR building mechanisms mostly, against the reserved antibiotics, was spot-lighted in global attention. Worldwide, *Klebsiella pneumoniae* Carbapenemase (KPC) producing Carbapenem-Resistance *Klebsiella pneumonia* (CR-*Kp*) is one of the most serious MDR pathogens in the *enterobacteriaceae* family [1,2]. KPC is capable of hydrolyzing cephalosporins, beta-lactamase inhibitors, monobactams and carbapenems [3]. In China, CHINET showed that CR-*Kp* isolates increased 11% in just 9 years (2005 to 2014) [4]. Currently, widespread use of carbapenem antibiotics worldwide has surprisingly enhanced the emergence of CR-*Kp* associated bacterial infections like, Ventilator-Associated Pneumonia (VAP) and being considered as a vital threat for global human-existence [2,5].

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VAP is the most common incidence of the mechanical ventilation process in critically ill patients of the intensive Care Unit (ICU). The complicated MDR-pattern of *K. pneumoniae* in VAP and the current scarcity of new potential antibiotics to fight against CR-*Kp*, is now the matter of stress for healthcare providers [5]. Tigecycline is one of the most potent last resort antibiotics available in hand to intend in alleviating this emergence [5,6].

Tigecycline (TGC) is the first antibiotic in glycylcycline class and became available in the mid-1900s in the world drug-markets. Though TGC is structurally related to minocycline, through structural modification, it has gained its expanded spectrum antibacterial properties against gram-negative, gram-positive and even anaerobic organisms [7]. TGC was approved in Europe for its Conventional Dose (CD) (100 mg loading dose and then, 50 mg twice daily) in the treatment of complicated skin and skin-structures infections and complicated intra-abdominal infections [8]. A recent black-boxed warning announcement of Food and Drug Administration (FDA) of United States mentioned TGC associated high rate of mortality, and this information discouraged to use TGC in severe nosocomial infections such as, VAP. Some researchers found that High Dose (HD) of TGC shows good *in-vivo* pharmacokinetic characteristics and obtain good therapeutic outcomes especially in VAP [9]. However, due to the massive scarcity of potent antibiotics in CR-*Kp* associated infections, TGC has been incorporated in the treatment-lineup without hesitation [10]. The main objective of this study was to observe the key-role of TGC associated adverse events in discriminating the superior TGC dosing system (CD versus HD) in CR-*Kp* associated VAP.

MATERIALS AND METHODS

This prospective, observational study was conducted in ICU of a tertiary level private hospital in Bangladesh. The study period was 14 months (October 31, 2017 to November 30, 2018). During that time, total 1,081 patients were admitted in the ICU and among them, 206 patients were found with VAP, admitted in the ICU and were supported by mechanical ventilation. The use of TGC with CD and HD in CR-*Kp* Associated VAP treatment in that ICU was practicing before enrolling the study. The prime objective of this study was to observe the prospective outcomes of current practices of TGC in that ICU. The usual trend of patient admission, drugs' use management and use of existing treatment protocols in that ICU were not changes for conducting this study.

Sample inclusion and exclusion criteria

According to the microbiological Culture and Sensitivity (C/S) test reports of Tracheal and Aspirates (T/A), 119 patients were found with CR-*Kp* associated VAP and at that moment, all the patients were on carbapenem antibiotics (meropenem and doripenem). Among those 206 patients, 109 patients were found with MDR CR-*Kp* associated VAP, and only TGC and polymyxins were found sensitive to that organism on the basis of the Minimum Inhibitory Concentration (MIC) of the nominated antibiotics. Finally, for the study purpose, 58 patients were included in the study as considering the age of the patients (considered the middle-aged patients: 45-65 years), similar pattern of the infections, no prominent cardiovascular co-morbidity and no previous history of taking tigecycline (HD or CD) within the last 3 months. The major patient exclusion criteria were simultaneously, gram-positive and gram-negative bacterial infection in the same patient, discharged from the hospital and post-surgical patients.

Study design

After getting the C/S reports, carbapenems in all prescriptions were stopped (due to the presence of CRE). All the 58 patients were distributed into two distinct groups. 27 patients were taken in CD-group and treated with CD-TGC (100 mg as loading dose intravenously then, 50 mg twice daily intravenously). Another 31 patients were taken in HD-group and treated with HD-TGC (200 mg as loading dose intravenously then, 100 mg twice daily intravenously). All the necessary laboratory investigation data of every patient of both groups were recorded just before going to start the targeted group-wise antibiotic therapies. During the study period, 6 patients and 7 patients of CD-group and HD-group, respectively, were excluded from the study due to discharged from that hospital against medical advice, expired with cardiac arrest and shifted to another hospital. Finally, study was completed with 21 patients and 24 patients in CD-group and HD-group, respectively, with a total of 45 (N) patients. After 5 days of the initiation of the TGC therapy, repeated C/S of all biological samples including T/A was done for every patients of both the groups and observed the eradication rate of CR-*Kp* in VAP and occurrence rate of secondary infections. Patient wise 30 days mortality rate (from first TGC-day to 30th day) in ICU was calculated in both the groups. During the study period, all the drug or dose-related Adverse Events (AE) were recorded on regular basis. After initiating the TGC's dose-variable therapies in both the groups (CD and HD), the biochemical abnormalities, such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), bilirubin and blood pH of both the groups' patients, in response to the different group-wise TGC-doses (CD and HD) were recorded as 'dose-related AE'. The severity of the diseases in all the patients of both the groups (CD and HD-group) were measured by using 'Acute Physiology And Chronic Health Evaluation' (Apache) II Scoring system (range: 0-71). The ethical approval for this study was taken from the "Square Hospital Ethical Committee" on July, 2017. Written consents of the patients were taken before including them in the study.

Data analysis tools

All the data of this study were analyzed by using IBM SPSS statistics (version 22) software. Statistically, variables were considered significant below 0.050 (estimated p-value). For microbiological C/S analysis, the testing methodology (broth dilution) and equipments (BD Phoenix™ M50 Automated Microbiology System) of that microbiology lab were validated with the standards of Clinical and Laboratory Standards Institute (CLSI), United States of America. For observing the blood pH, Arterial Blood Gas (ABG) was monitored in regular interval using the auto-blood-analyzer (Rapidpoint 400 by Siemens). The anti-biogram (2017) of that hospital was considered for this study purpose.

RESULTS

All the characteristics of the study-populations of both the groups were divided into two stages; the pre-and post-antibiotic stage, based on before and after initiating the antibiotic therapy, respectively. The pre- and post- antibiotic stages were mentioned in the Table 1.

The mean age of the patients of both the groups (CD-group: 53.67 years; n=21 and HD-groups: 55 years; n=24) were closed but, statistically not significant (p-value: 0.111) (Table 1). Female patients were relatively higher in number in both the groups (Table 1). The laboratory tests results including infection markers, renal

function test, and hepatic function test and blood pH were taken after introducing the antibiotic therapy for CR-*Kp*-VAP treatment. As per the laboratory reports, the mean procalcitonin level of CD-group patients was 55.97 ng/mL where HD-group patients had 50.51 ng/mL with insignificant, less variable highest procalcitonin level in both the groups' patients (CD-groups: 98.60 ng/mL; HD-group: 99.10 ng/mL) (p-value: 0.703) (Table 1). The mean serum creatinine levels of both the groups were closed (CD-group: 2.3 mg/dL; HD-group: 2.27 mg/dL) but statistically not significant enough (p-value: 0.37) (Table 1). Though the Apache II scores among the patients of the two groups (CD and HD) was not statistically significant (calculated p-value: 0.867) but, the mean values are closed to each other (CD-group: 15.81; HD-group: 15.42) (Table 1). Comparing the mean ALT levels in the patients of both the groups, an increased mean value was found in the HD tigecycline group patients (169.85 unit/L) (p-value was 0.02). Patients in the HD-group were found with higher mean AST level (114.12 units/L) and bilirubin level (1.83 mg/dL) than the CD-group's patients mean AST level (85.42 units/L) (p-value: 0.458) and bilirubin level (1.21 mg/dL) (p-value: 0.4) (Table 1).

The comparison of dose-based therapeutic potentialities of TGC therapies in term of 'CR-*Kp* eradiaction rate' was taken after 5 days of the initiation of TGC in both the groups, where HD-group showed relatively higher eradication rate (79.17%; n=24) than CD-group (47.62%; n=21) (Table 2). A total 29 patients (64.44%; N=45) from both the groups (CD and HD) were found with complete CR-*Kp* eradication (Table 2). Low-TGC dosed group (CD) represented relatively higher (33.33%; n=21) new secondary infections (5 cases of bacteremia and 2 cases of urinary tract infections) after 5 days of TGC treatment in comparison to high-TGC dosed group (2 septicemia cases; 8.33%; n=24) (Table 2). All the patients of both the groups had central venous catheters, arterial catheters, nasogastric tubes, and urinary catheters during the study period. During 30 days mortality monitoring period, 19 patients (42.22%; N=45) were expired during this time frame and among those died-patients, 11 (45.83%; n=24) patients were from HD-group showing relatively higher mortality rate comparing with CD-group (38.10%, n=21) (Table 2). The acidic pH of the blood was observed higher in the HD-group's patients with a mean value of 7.34 than the CD-group's patients (mean: 7.39) and statistically, data were not significant (p-value was 0.672) (Table 1).

All the TGC's dose-related AEs (elevation of ALT, AST, bilirubin and reduction of blood pH) were mentioned in comparison-table for dose-related AEs and according to all AE-parameters, HD-group's (n=24) patients were found relatively more experienced with high dose-related AEs in comparison to CD-group's patients (n=21) (Table 3).

DISCUSSION

In this study, we found that high dose of TGC (200 mg as loading dose intravenously then, 100 mg twice daily intravenously) in HD-

Table 1: Baseline characteristics of the patients including laboratory data.

Characteristics	Variables		p-value
	CD-group (n=21)	HD-group (n=24)	
Pre-antibiotic stage			
Age (year)			
Mean	53.67	55	0.111
Range (min[a]-max[b])	47-62	45-63	
Gender			
Male	9	11	
Female	12	13	
Procalcitonin (<0.1 ng/mL)			
Mean	55.97	50.51	0.703
Range (min-max)	10.60-98.60	13.28-99.10	
Serum creatinine (0.8-1.4 mg/dL)			
Mean	2.3	2.27	0.37
Range (min-max)	0.9-3.2	0.8-3.0	
Apache II Score (0-71)			
Mean	15.81	15.42	0.867
Range (min-max)	Aug-28	Aug-26	
Post-antibiotic stage			
ALT (13-69 units/L)			
Mean	89.64	169.85	0.02
Range (min-max)	14.52-336.48	19.53-652.43	
AST (15-46 units/L)			
Mean	85.42	114.12	0.458
Range (min-max)	15.30-399.56	16.59-463.86	
Bilirubin (0.2-1.2 mg/dL)			

Mean	1.21	1.83	0.4
Range (min-max)	0.4-3.2	0.5-4.3	
Blood pH (7.35-7.45)			
Mean	7.39	7.34	0.672
Range (min-max)	7.28-7.45	7.22-7.45	

min[a]: minimum; max[b]: maximum

Table 2: Comparisons of therapeutic responses and 30 days mortality rate.

Group	After 5 days, CR-Kp eradication	After 5 days, total microbiological eradication	After 5 days, new secondary infection developed	30 days mortality rate	Total 30 days mortality rate
	n (%)	(N=45) n (%)	n (%)	n (%)	(N=45) n (%)
CD (n=21)	10 (47.62)	29 (64.44)	7 (33.33)	8 (38.10)	19 (42.22)
HD (n=24)	19 (79.17)		2 (8.33)	11 (45.83)	

Table 3: Comparison of dose-related AEs.

Group	Elevation of ALT n	Elevation of AST	Elevation of Bilirubin	Reduction of blood pH
	%	n (%)	n (%)	N (%)
CD (n=21)	5 (23.81)	6 (28.57)	4 (19.05)	2 (9.52)
HD (n=24)	8 (33.33)	10 (41.67)	9 (37.50)	11 (45.83)

group's patients was found with superior therapeutic outcome in term of CR-*Kp* eradication rate (79.17%; n=24) in VAP in comparison to low dose group (CD-group; 47.62%; n=21) (100 mg as loading dose intravenously then, 50 mg twice daily intravenously). However, degree of dose-related adverse events in all parameters (ALT, AST, and bilirubin and blood pH) was higher and more frequent in HD-group than the CD-group. Some previous studies found that high dose of TGC showed higher therapeutic outcome in severe MDR gram-negative bacterial infections, because the area under the plasma drug concentration (AUC) versus time curve and microorganism's Minimal Inhibitory Concentration (MIC) ratio (AUC/MIC) is the major strength behind this high TGC dosing phenomenon [11,12]. Clinical experience with high dose TGC (>100 mg daily) is not huge but all available evidences show effective clinical outcomes with HD-TGC in severe infections [13,14]. The pathophysiological changes in the ICU-patients alter the Pharmacokinetics (PK) of antibiotics including tigecycline and one study showed that in patients with sepsis, high dose TGC responded more effectively and better PK characteristics when type and susceptibility of pathogens are selective and PK is targeted [15]. In 2005, US Food and Drug Administration (FDA) approved TGC for complicated skin and skin structure infections, complicated intra-abdominal infections and community acquired pneumonia at its conventional dose (100 mg/day), but not approved in hospital acquired pneumonia including VAP [16].

The presence of endotracheal tube, associated risk factors, compromised host-immune functions and easy access of the invading MDR CR-*Kp* bacteria are the complex interplaying facts for developing CR-*Kp*-VAP in ICU patients [17]. TGC was structurally modified to overcome two major reasons of tetracycline resistance (altered efflux mechanism and ribosomal protection) and hence, became extensively sensitive to targeted MDR-bacteria including CR-*Kp* [18-20]. In our study, TGC was considered as the only antibiotic therapy with two different dosing systems (CH and HD) against the superbug pathogen CR-*Kp* and observed a significantly superior response in HD-TGC group (79.17%) than CD-group (47.62%). TGC is highly protein bound (71%-89%) and shows large volume of distribution (7-9 L/kg in healthy volunteers). Following a conventional dose intravenously, TGC is highly accumulated in bile (AUC_{0-24}=537) whereas less in serum (AUC_{0-12}=1.73 μg·h/mL), in lung (AUC_{0-24}=2), in alveolar cells (AUC_{0-12}=134 μg·h/mL) and in Epithelial Lining Fluid (ELF) (AUC_{0-12}=2.28 μg·h/mL) and the overall penetration ability of TGC in extracellular lung compartment of critically ill mechanically ventilated patients with underlying pulmonary pathophysiology is relatively very low; although ELF (intrapulmonary site) is considered as an important reservoir of TGC concentration because it produce the potential defense against the extracellular pathogens including CR-*Kp* [21-23]. To maintain a safe, steady and effective concentration in the respiratory tract, multiple studies showed that high dose TGC is relatively more successful than the conventional dose to maximize the AUC/MIC for treating serious MDR-CR-*Kp* associated infections including VAP [24-26]. Similar superior clinical outcomes with HD of TGC were observed in our study in VAP patients. Moreover, CD of TGC attains a relatively low serum concentration (0.655 mcg/mL in the steady state) that ultimately raises the risks of happening secondary infections mostly, bacteremia [27]. Our study found higher secondary infections rate in CD-group (33.33%) including highest number of bacteremia (5 cases) than the high dosed TGC group (8.33%).

High dose of TGC was found with different AEs in multiple studies especially on critically ill patients. A study found that out of 134 patients, 35 patients suffered from different AEs, such as hepatic injury (elevation of ALT and bilirubin) (51.4%; 18 out of 35) and diarrhea (51.4%; 18 out of 35) when treated with HD-TGC [5]. Multiple studies showed that TGC associated AEs were mostly dose-dependent and frequency of AEs were increased with increasing TGC dosage [3,6,14]. In this study, we found HD-TGC associated hepatic impairments through determining elevated ALT, AST, bilirubin and acutely reduced blood pH (mentioned in Table-3). A review study on CABP studies showed that even in conventional dose of TGC, ALT (2.6%) and AST (2.1%) elevation was recorded, respectively as AE [21]. Recent multiple meta-analyses and retrospective studies show that TGC in serious gram-negative bacterial infections including CR-*Kp*-VAP is associated with low survival rate, high mortality rate and causes serious AEs,

and these are very crucial to identify and manage, accordingly [28-30]. TGC associated mortality rate is higher and for this reason, FDA discourages to use TGC in severe infections [3]. A study found that in VAP patients, HD of TGC was associated with higher microbiological eradication rate than CD (57.1% versus 30.4%) but mortality rate was relatively higher (57%) [12]. In our study, according to 30 days mortality rate, 42.22% (19; N=45) patients were died with highest number in HD-group (11; n=24). Our study assumed that higher and frequent incidences of AEs in HD-group patients treated with HD TGC ultimately resulted in a relatively higher 30 days mortality rate than CD-group. So, HD of TGC shows better MDR-CR-*Kp* eradication rate in VAP-patients with superior clinical outcomes and fewer occurrences of secondary infections than conventional dosing of TGC. Notwithstanding, frequent AEs in HD-TGC therapy are the re-thinkable issue for the infectious disease practitioners in discriminating the actually considerable therapeutic benefits of HD versus CD therapy in CR-*Kp*-VAP treatment, indeed. Small sample size and lack of discussion on the mechanisms of bacteria not responsive to even HD of TGC are the major limitations of this study. In future, some Randomized Controlled Trials (RCT) are required to analyze the exact mechanisms of developing TGC-induced AEs in critically ill patients, especially with HD of TGC. The impotency of HD of TGC to kill the targeted MDR bacteria may be the major objective of further investigations in future; even analysis of the MDR-gene of certain bacterial isolates collected from the dead patients may be an efficient way of investigating the mechanism of HD-TGC in failing to kill MDR gram-negative bacterial isolates.

CONCLUSION

In conclusion, MDR-CR-*Kp* associated VAP is a cumbersome treatable-state of infectious diseases because of the shortage of potential antibiotics in global antibiotic-reserve against this pathogen. Last resort tigecycline is a potential option in MDR-CR-*Kp*-VAP treatment. High or exact double dose of tigecycline as mono-therapy shows better therapeutic outcomes than conventional dose but frequent HD-TGC associated AEs in critically ill VAP-patients are the major considerable facts for prioritizing high dose versus conventional dose of TGC in CR-*Kp* associated VAP.

CONFLICT OF INTEREST

No conflict of interest to declare.

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