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Original Article

Pharmacology Section

A Combination Strategy of Ceftriaxone, Sulbactam and Disodium Edetate for the Treatment of Multi-Drug Resistant (MDR) Septicaemia: A Retrospective, Observational Study in Indian Tertiary Care Hospital

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ABSTRACT

Introduction: Previous studies have suggested the use of rational combination therapy for the treatment of multi-drug resistant (MDR) infections. An antibiotic adjuvant entity (AAE) of ceftriaxone, sulbactam and disodium edetate (Elores) was approved for multi-drug resistant infections in India.

Aim: This study was designed to investigate the efficacy and safety of this AAE in patients with sepsis due to extended spectrum beta lactamse (ESBL) and metallo-beta lactamase (MBL) producing pathogens.

Materials and Methods: A retrospective observational study was conducted in patients admitted in intensive care unit (ICU) at tertiary health care site in India, with enrollment from 24 March, 2012 to 7 Aug, 2012. Patients eligible for enrollment had clear infection of bacterial septicaemia, were aged 12-65 years, and were considered for treatment with Cephalosporins categories of antibiotics.

Results: Total 18 patients were included in the study and all assigned to combination of ceftriaxone, sulbactam and disodium edetate. Complete clinical cure in terms of relief and no-disease symptoms had observed in 15 (83.3%) subjects, however 3 (16.6%) showed treatment failure (TF). Similarly for bacteriological eradication response, 15 (83.3%) patients displayed complete bacteriological eradication response and 03 (16.6%) subjects showed TF. No serious side effect was observed during the study.

Conclusion: This study recommends the use of combination of ceftriaxone, sulbactam and disodium edetate (EDTA) for the treatment of MDR septicaemia associated with ESBL and MBL producing microbes.

Keywords: Antibiotic adjuvant entity, Bacterial septicaemia, Combination therapy

INTRODUCTION

Bacterial septicaemia and sepsis are the oldest and most elusive disorders and can become life threatening if managed inappropriately [1,2]. Sepsis is widely prevalent in patients with skin, lungs, abdomen and urinary tract infections and requires rapid diagnosis, initiation of rational antibiotic and supportive therapy to save the lives of patients. Antimicrobial therapy remains gold standard for the management of sepsis patients. However, rapid development of multi-drug resistance (MDR) in microbes has limited there use in this deadly intrication. Prevalence of drug resistance in sepsis is particularly important because of rising number of cases and high mortality rate associated with this serious malady [3].

In Indian hospitals, extended-spectrum beta lactamase (ESBL) and metallo-beta lactamase (MBL) producing Gram-negative microbes are the most prevalent organisms responsible for rendering many antibiotics worthless [4]. Rising incidences of these difficult to treat infections exposed patients to highly reserve antibiotics like carbapenem and colistin which further complicated resistance scenario. Recent reports of resistance to colistin and carbapenem posed serious therapeutic crisis to health care workers and risk of 'Panresistance' i.e. resistance to all antimicrobials seems a reality [5].

Newer therapeutic strategies are needed to be explored to avoid the problems of developing resistance and to save the future of antibiotics. Previous reports suggested that rational combination therapy of 2 or more antibiotics may be a suitable approach to reduce the frequency of drug resistance in microbes [6,7]. Antimicrobials with different target of actions provides additional mechanism of action and may confer synergistic action. Few reports have recommended the use of ß-lactam/ß-lactamase inhibitor (BL/BLI) combinations like piperacillin-tazobactam and cefoperazone-sulbactam for patients with less severe sepsis, hence restricting usage of carbapenem only to severe cases only [8]. A recent meta-analysis demonstrated that combination of piperacillin and tazobactam can be useful for management of patients with bloodstream infections due to ESBL-E coli if active invitro [9]. Hence use of carbapenem class of drugs can be limited that may ultimately decrease the resistance rate.

An antibiotic adjuvant entity (AAE) of ceftriaxone, sulbactam and disodium edetate is developed for the MDR ESBL and MBL producing pathogens. The rationale behind addition of sulbactam and disodium edetate (EDTA) with ceftriaxone was to provide multiple mechanisms of antibacterial actions. Sulbactam, a BLI can be effective against various beta lactamase producing microbes. EDTA delivers its antibacterial action through antibiofilm and metal chelating property. It also enhances the penetration of drug by increasing the membrane porosity, which in turn decreased minimum inhibitory concentration (MIC) values of drugs [10].

This combination of ceftriaxone, sulbactam and disodium edetate has been approved by the Indian regulatory authority; Drug Controller General of India (DCGI) for the treatment of MDR ESBL/MBL associated infections. The present study was designed to evaluate the efficacy and safety of this novel AAE for the treatment of patients with septicaemia because of ESBL/MBL producing pathogens like *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*.

MATERIALS AND METHODS

Study design and population: A retrospective observational study was conducted among patients who received AAE (a fixed dose combination of ceftriaxone (2000 mg), sulbactum (1000 mg) and edetate (74 mg) given intravenous infusion, once daily with proven Gram-negative infections between from 24 March, 2012 to 7 Aug, 2012 at tertiary care hospital of India. Patients with sepsis admitted in intensive care unit (ICU) were included in the analysis if they: (i) were 12-65 years of age; (ii) blood cultures positive for *A. baumannii*, *E. coli*, *K pneumoniae* and *P. aeruginosa*; (iii) had received combination of ceftriaxone, sulbactam and disodium edetate for >72 hours. Patients were excluded from the study if they had clinically significant cardiovascular, renal, hepatic, gastrointestinal, neurological, psychiatric, respiratory, haematological or malignant disease or other condition which may interfere with the assessment. Patients with history of uncontrolled diabetes mellitus, human immunodefeciency (HIV) and hepatitis-B virus infection were also excluded. Medical records were reviewed by the trained person and parameters like age, sex, duration of ICU stay, severity of infection, microbiological data, duration of treatment and final bacteriological and clinical outcomes were evaluated. Adverse events were recorded on the basis of system organ class (SOC), severity (mid, moderate and severe) and causal relationship (definitely, possibly, probably & unrelated).

Analysis of gene characterization of different identified microbial strains- A total of 18 clinical isolates of *A. baumannii*, *E. coli*, *K pneumoniae* and *P. aeruginosa* were collected. Screening of all clinical isolates was carried out according to Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. Detection of ESBL and MBL genes and characterization was carried out according to the methods described in detail by Chaudhary and Pyasi [10,12-14].

Ethical clearance: Procedures were followed in accordance with Institutional ethical committee and approval was obtained.

STATISTICAL ANALYSIS

Descriptive statistics, including the mean and standard deviation were used for description of continuous variables.

RESULTS

Total 18 patients of septicaemia were included in the study as per the inclusion and exclusion criteria. Out of which 10 were males and 8 were females. The mean age of the patients and average duration of ICU stay was 48.5+12.1 years and 14.5+4.5 days respectively.

Assessment of severity of infection: In addition to positive blood culture, symptoms and signs compatible with bacteraemia and systemic inflammatory response syndrome (fever or hypothermia, systolic blood pressure, <90 mmHg, tachycardia >90 beats/min and white blood cell count >11 000 cells/mL or, < 4000 cells/mL) were used to evaluate the severity of infection. Among all 18 subjects, 2 (11.1%) subjects revealed moderate infection while 16 (88.9%) subjects displayed severe infection. No subject showed mild infection [Table/Fig-1].

Analysis of Duration of treatment: Out of 18 patients treated with Elores 3g, 07 (38.8%) subjects completed the treatment within 4-5 days however 8 (44.4%) subjects completed the treatment within 6-7 days. Three (16.6%) subjects completed the treatment in >7 days [Table/Fig-2].

Analysis of Clinical and Bacteriological Response: Total 18 (100%) subjects were screened for the treatment of bacterial septicaemia. Fifteen (83.3%) subjects had complete clinical cure in terms of total relief and no-disease symptoms however 03 (16.6%) subjects revealed treatment failure (TF). With respect to bacteriological response, 15 (83.3%) subjects showed complete bacteriological eradication while 03 (16.6%) subjects showed TF [Table/Fig-3]. In general, the settlement or stabilization of clinical signs and symptoms along with settlement of deranged lab parameters with negative culture was treated as cured subjects. The persistence of clinical signs and symptoms compatible with bacteraemia and systemic inflammatory response syndrome (fever or hypothermia, systolic blood pressure, <90 mmHg, tachycardia), more than 90 beats/min and white blood cell count >11 000 cells/mL or, < 4000 cells/mL) were considered as treatment failures.

Indication	Severity	Percentage
Bacterial Septicaemia	Mild	0 (0.0%)
	Moderate	2 (11.11 %)
	Severe	16 (88.9%)
	Total	18 (100%)

[Table/Fig-1]: Assessment of severity of Infection in bacterial septicaemia

Indication	Duration of Treatment		
		N	%
Bacterial Septicaemia	3 Days	0	0
	4-5 Days	7	38.80%
	6-7 Days	8	44.44%
	> 7 days	3	16.66%
Total		18	100.00%

[Table/Fig-2]: Analysis of duration of treatment for combination of ceftriaxone, sulbactam and disodium edentate

Clinical response		
	N (No. of patients)	%
Cured	15	83.30%
Failure	3	16.60%
Total	18	
Bacteriological response		
	N (No. of patients)	%
Eradication	15	83.30%
Failure	3	16.60%
Total	18	

[Table/Fig-3]: Evaluation of clinical and bacteriological response of combination of ceftriaxone, sulbactam and disodium edetate in bacterial septicaemia

Bacterial Septicaemia			
Bacterial species	Screening/End of treatment (EOT)	N	%
A. baumannii	Screening	6	100.00%
	EOT	1	16.66%
E. coli	Screening	7	100.00%
	EOT	1	14.20%
K. pneumoniae	Screening	1	100.00%
	EOT	0	0%
P. aeruginosa	Screening	4	100.00%
	EOT	1	25.00%
Grand Total	Screening	18	100.00%
	Culture positive	18	100%
	EOT	3	16.60%

[Table/Fig-4]: Analysis of Microbiological data in bacterial septicaemia infection N= No. of patients

Analysis of Microbiological data: Microbiological data of patients revealed infection of 4 micorbes- *A. baumannii*, *E. coli*, *K. pneumonia* and *P. aeruginosa* distributed in 6, 7, 1 and 4 subjects respectively in all 18 subjects [Table/Fig-4].

Analysis of Gene Characterization of identified strains: The gene characterization data of 4 microbes (*A. baumannii*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*) identified in all patients. Gene characterization data of *A. baumannii* revealed that most of the

Indication	Screening Lab Data	Gene characterization	Interpretation
Bacterial septicaemia	*A. baumannii*	ESBL:TEM-1, SHV-2 MBL:NDM-1	Most of the identified genes were of ESBL type and few were of MBLs. All genes displayed sensitivity towards ceftriaxone+sulbactam and disodium edetate
	A. baumannii	ESBL: AmpC, CTX-M, OXA-1	
	A. baumannii	ESBL: TEM-1, SHV-10 MBL: VIM-1	
	A. baumannii	ESBL: OXA-48 MBL: NDM-1	
	A. baumannii	ESBL: TEM-1, AmpC MBL: IMP-1	
	A. baumannii	ESBL: TEM-1, OXA-48	
	E. coli	MBL: NDM-1, IMP-1	All ESBLs and MBLs genes displayed sensititvty towards ceftriaxone+sulbactam and disodium edetate
	E. coli	ESBL:TEM-1 MBL: NDM-1	
	E. coli	ESBL: OXA-48, CTX M MBL: IMP-1	
	E. coli	ESBL: TEM-1, SHV-1 MBL: IMP-1	
	E. coli	ESBL: CTX-M, TEM-1 MBL: NDM-1	
	E. coli	MBL: VIM-1 ESBL: OXA-1, SHV-1	
	E. coli	ESBL: SHV-1, AMP-C MBL: VIM-1	
	K. pneumoniae	ESBL: KPC-1, TEM-1, CTX-M	All ESBLs producers were sensitive towards ceftriaxone+sulbactam and disodium edetate
	Pseudomonas aeruginosa	ESBL: TEM-2, SHV-1 MBL: IMP-1	Most of the identified genes were of ESBL type and few were of MBL. All genes displayed sensitivity towards ceftriaxone+sulbactam and disodium edetate
	Pseudomonas aeruginosa	ESBL: OXA-48, CTX-M, SHV-1	
	Pseudomonas aeruginosa	ESBL: VIM-1, TEM-1 MBL: NDM-1	
	Pseudomonas aeruginosa	ESBL: SHV-1, AMP-C MBL: NDM-1	

[Table/Fig-5]: Analysis of Gene Characterization of identified strains

System Organ Class (MedDRA)*	Adverse event for combination of Ceftriaxone, sulbactam and disodium edentate (N=18)
Gastrointestinal disorders	6 (33.33%)
General disorders and administration site conditions	1 (5.56%)
Nervous system disorders	2 (11.11%)
Grand Total	9 (50.00%)

[Table/Fig-6]: Display of adverse events as per system organ class
*MedDRA- Medical dictionary for regulatory activities, N= No. of patients

Severity	Adverse event for combination of Ceftriaxone, sulbactam and disodium edentate (N=18)
Mild	5 (27.78%)
Moderate	3 (16.67%)
Severe	1 (5.56%)
Grand Total	9 (50%)

[Table/Fig-7]: Display of adverse events as per severity
N= No. of patients

identified genes were of ESBL producing (TEM-1, SHV-2, AmpC, CTX-M, OXA-1) and few were of MBL (NDM-1, VIM-1, IMP-1) positive strains. All microbial genes displayed sensitivity towards ceftriaxone+sulbactam and disodium edetate. For *E. coli*, *K. pneumoniae* and *P. aeruginosa* also similar resistance pattern was observed and all ESBL and MBL producing strains demonstrated sensitivity towards ceftriaxone+sulbactam and disodium edentate [Table/Fig-5].

Relationship with Drug	Adverse event for combination of Ceftriaxone, sulbactam and disodium edentate (N=18)
Definitely	1 (5.55%)
Possibly	2 (11.11%)
Probably	2 (11.11%)
Unrelated	4 (22.22%)
Grand Total	9 (50%)

[Table/Fig-8]: Display of adverse events as per causality
N= No. of patients

Evaluation of adverse effects during course of treatment

Based on system organ class (SOC): A total of 09 adverse events were reported among 18 subjects. 6 (33.33%) subjects displayed Adverse Events (AEs) related to gastrointestinal disorders (nausea and vomiting), 1 AE (5.56%) was related to general disorders and site of administration (pain at site of infection). Two subjects (11.11%) showed AEs related to nervous system disorders (headache and dizziness) [Table/Fig-6].

Based on severity: A total of 09 adverse events were reported among 18 subjects, 5 (27.78%) AEs were of mild grade, 3 (16.67%) were of moderate and 1 (5.56%) was of severe grade as judged by the investigators. No event developed into serious adverse event (SAE) and all AEs were closely monitored by investigators and recuperated by concomitant therapy [Table/Fig-7].

Based on causal relationship: In bacterial septicaemia, among 18 (100%) subjects, 9 reported AEs (50%) on basis of casual relationship as assessed by investigators. 1 (5.55%) AE was of definite, 2 (11.11%) were of possible, 2 (11.11%) were of probable and 4 (22.22%) AEs were unrelated with the study medication [Table/Fig-8].

DISCUSSION

MDR septicaemia and sepsis are often fatal and requires prompt diagnosis and treatment to prevent associated organ dysfunction or mortality. Irrational and overuse of broad-spectrum antibiotics made this scenario worse. Carbapenem and colistin are the most reserve antibiotics and usage is recommended only in severe cases not responding to other antibiotics [15]. However, increase in use of these reserve antibiotics and development of resistance to them is directly proportional and clearly visible in Indian hospitals [16]. Sepsis due to MDR in microbes is one of the most pressing problems in today's medicine and posed the risk of imminent death associated with this malady. Newer strategies are the need of current time to save the future of antibiotics era.

In this study, we identified 18 subjects suffering from moderate to severe grade MDR bacterial septicaemia due to ESBL/MBL producing pathogens [17]. Indian hospitals are filled with ESBL/MBL producing Gram-negative microbes and many clinicians suggest the use of BL/BLI to prevent the spread of this deadly infection. The likelihood of achieving targeted infection control through BL/BLI combination is not optimized due to lack of clinical data.

Microbiological data indicates that *E. coli* (7) was the most prevalent microbe among septicemic patients followed by *A. baumannii* (6), *P. aeruginosa* (4) *K. pneumonia* (1) in all 18 subjects. Data of microbiological characterization suggests the infection of both ESBL and MBL producing organisms in all patients. This MDR pattern of resistance has complicated the treatment scenario and made many antimicrobials futile. ESBLs mediate resistance to extended spectrum cephalosporins such as cefotaxime, ceftriaxone and ceftazidime. The carbapenems and MBLs can hydrolyze all beta-lactam antibiotics and can display resistant to these antimicrobials. In this study all 4 microbes were ESBL and MBL producers and displayed MDR pattern of resistance. This resistance can also be the result of reduced levels of drug accumulation or

increased expression of pump efflux. Development of BL antibiotics safe, effective and stable against ESBL/MBL producers is time consuming and exhaustive process however combination of BL/BLI seems to be a good alternative to counteract this resistance concern. Results of this study indicate that this combination therapy (BL/BLI+disodiumedetate) is highly effective against ESBL/MBL producing organisms. The enhanced susceptibility of ceftriaxone, sulbactam and disodium edetate against all 4 microbes is likely to be associated with synergistic activity of this combination. Here presence of disodium edetate enhances permeability of ceftriaxone and sulbactam and thereby enhances activity against ESBL microbes synergistically. Disodium edetate can also chelate the divalent ions required for the activity of MBLs thus deactivating the MBLs which in turn increase the susceptibility of ESBL/MBL producing microbes towards this combination. Hence frequent use of carbapenem class of drugs can be avoided to treat infections by MDR bacteria in high risk patients.

Here this AAE was found to be highly effective in septicaemia cases as it resolved 15 patients (83.3%) clinically. Earlier Chaudhary and Pyasi demonstrated its superiority over ceftriaxone per se in the treatment of skin, skin structure infections (SSSIs), bone and joint infections (BJIs) due to ESBL/MBL producing pathogens [17]. A significant bacteriological eradication response was also observed for this combination strategy in septicaemia cases. The reason for this enhanced synergistic efficacy and susceptibility profile can be linked to multiple mechanisms of antibacterial actions present in different constituent of this AAE formulation. Safety analysis revealed that treatment with this AAE was not associated with any SAE. Nausea, vomiting, headache, dizziness and pain at site of infection were the main AEs associated with this therapy.

This study highlights the development of MDR (ESBL/MBL positive) in Gram-negative microbes and suggests the use of carbapenem sparing BL/BLI therapy in these resistant infections. Other antimicrobial combinations like cefoperazone/sulbactam, cefepime/tazobactam and amoxicillin/clavulanate are widely used globally but clinical data regarding use in resistant infections is lacking [16]. In this study combination therapy of ceftriaxone, sulbactam and disodium edetate resolved the septicaemia patients and raised the hope of carbapenem sparing strategy for MDR infections that can rapidly become life threatening.

LIMITATION

The major limitations of our study were its sample size, single center, retrospective and observational designs.

CONCLUSION

AAE of ceftriaxone, sulbactam and disodium edetate was found to be safe and effective in MDR (ESBL/MBL positive) Gram-negative septicaemia patients and can minimize the misuse of available reserve drugs (carbapenem class drugs). Hence we recommend the use of this combination strategy in resistant cases of septicaemia. However, more clinical data from multicenter cohort studies with robust analysis is required to corroborate our findings.

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