“Comparative Study of Clinical Outcomes and Safety between Colistin and Tigecycline for Multi-Drug Resistant Gram Negative Bacteria.”

Protocol study

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Comparative Study of Clinical Outcomes and Safety between Colistin and Tigecycline for Multi-Drug Resistant Gram Negative Bacteria.

I. Introduction:

The Centers for Disease Control and Prevention (CDC) and the European Center for Disease Prevention and Control have defined Multi-drug resistant (MDR) Gram-negative bacteria as acquired non-susceptibility to at least one drug in three or more antimicrobial categories. Extensively drug-resistant (XDR) Gram-negative bacteria was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). Pan drug-resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories (1).

MDR, XDR and PDR of Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Acinetobacterbaumannii, and Pseudomonas aeruginosa have been known by difficult-to-treat (DTT) infections that not respond to treat with as β-lactams, including carbapenems, extended-spectrum cephalosporins such as ceftazidime, ceftriaxone, and cefepime and β-lactam/ β-lactamase inhibitor combinations, and fluoroquinolones(2).
In the past few decades, bacteria developed various mechanisms of resistance to almost available antibiotics as tetracycline, beta-lactams, fluoroquinolones and aminoglycosides. Colistin and tigecycline have become the last treatment for MDR gram negative bacteria(3)(2).

Colisin is polymyxin E antibiotic. Colistin has a unique mechanism of action against MDR and XDR bacteria regardless of the resistance. Colistin has an antimicrobial activity against aerobic Gram-negative bacteria(4). Colistin is the last choice treatment for life-threatening infections, such as carbapenem-resistant P. aeruginosa, E. coli, A. baumannii, K. pneumoniae, and other Enterobacteriaceae(3).
Although, colistin has a good antimicrobial activity against MDR and XDR, some old literatures reported that colistin associated with high side effects as neuorotoxicity, neuromuscular blockade, hematoxicity and nephrotoxicity and mortality risk (5)(6).In 1970, the use of colistin was limited for treatment patients with cystic fibrosis only. Latterly, some new studies reported that colistin's side

effects are less common than old studies and they resolved after discontinuation of colistin in severe cases (7).

Tigecycline belongs to a tetracycline class that used for the treatment of MDR infections (gram negative and gram positive bacteria). In 2005, the Food and Drugs Administration (FDA) approved tigecycline that administrated in a parenteral form. The FDA reported in 2010 that the treatment with tigecycline was associated with high risk for mortality (8). Recently, tigecycline has been used for treatment complicated intra-abdominal infections (CIAI), complicated skin and skin structures infections (CSSTI) with the exclusion of diabetes foot infection, and community-acquired bacterial pneumonia (CAP) as monotherapy in adult(9).

The FARES and the clinical trial studies suggested that tigecycline administration associated with gastrointestinal symptoms (nausea, vomiting and diarrhea), pancreatitis, increased hepatic function, jaundice, cholestatic, bleeding risk, thrombocytopenia and Steven-Johnson syndrome(8)(10).

The objective of this study to prospectively compare between the clinical outcomes and safety of colistin and tigecycline in patients with MDR gram negative bacteria in Intensive Care Unit.

II. Aim and objectives:

Objective from this study to compare the clinical outcomes and safety between colistin and tigecycline for multi-drug resistant gram negative bacteria.

III. Method and material:

Study site:

Study will be in Beni-Suef university hospital.

Study design:

Prospective randomized controlled study. The method of randomization was a sealed envelope technique.

Study duration:

The study will be conducted from December 2024 to May 2025.

Study population:

- **Group I**: 66 patients received intravenous **colistin** 300 mg colistin base activity (CBA) as **loading dose, followed by** 2.5–5mg/kg/day of CBA in 2 divided doses as **a maintenance dose** in intensive care unit to treat their MDR infection.(11)
- **Group II**: 66 patients received intravenous **tigecycline**100 mg single dose as **loading dose**, followed by 25-50 mg every 12 hours **maintenance dose** in intensive care unit to treat their MDR infection(12).

Sample size technique:

Sample size was calculated using G*Power (3.1.9.4) software for windows using Fisher analysis test**.** A total sample size of 132 participants was estimated for 95% power, α- error probability 0.05. Analysis of data was performed using IBM SPSS v. 25 (Statistical Package for Social science) for Windows.

Sample size calculation:

Exact - Proportions: Inequality, two independent groups (Fisher's exact test)
Options: Exact distribution
Analysis: A priori: Compute required sample size

Input:	Tail(s)	= Two
	Proportion p1	= 0.58
	Proportion p2	= 0.261
	α err prob	= 0.05
	Power (1-β err prob)	= 0.95
	Allocation ratio N2/N1	= 1
Output:	Sample size group 1	= 66
	Sample size group 2	= 66
	Total sample size	= 132
	Actual power	= 0.9501125
	Actual α	= 0.0316077

Inclusion criteria:

Study will include adult patient (male, female), (age from 18 to 70 years) admitted to intensive care unit in study period (six months) who received intravenous colistin or tigecycline as antimicrobial drug for treatment their MDR gram negative infection (13).

Exclusion criteria:

- Patient admitted to intensive care unit younger than 18 years or older than 70 years (14).
- Liver transplantation patients.
- Patients are chronic kidney disease (CKD on hemodialysis or baseline creatinine clearance (crcl) < 10 ml/min (estimated by Cockcroft Gault equation).
- Patients received renal replacement therapy before or during admission.
- Patient is on any other nephrotoxic drug (vancomycin, aminoglycosides, NSAIDs, cyclosporine, amphotericin B, etc.) (Aggarwal & Dewan, 2018).
- Pregnant and lactating women (16).
- Patients refused the consent of the study.

Study procedure:

- Demographic and medical history for all patients included in this study will be recorded.
- Complete physical examination for all patients included in this study will be taken.
- Basic routine investigation for all patients included in this study will be measured as Complete blood Count test (CBC), blood pressure and temperature.
- Improvement of signs and symptoms after the end of antibiotic course as temperature.
- **Renal function** tests will be measured **before** patients received colistin or tigecycline and **after 72 hours from first dose**:

  - Serum creatinine level (scr).
- **Hepatic function** tests will be measured **before** patients received colistin or tigecycline and **after 72 hours from first dose:**
  - Alanine transaminase (ALT)
  - Aspartate transaminase (AST)
  - Serum total bilirubin (TBIL)
- **14 days Survival rate after starting colistin or tigecycline will be recorded.**
- The severity of the illness will be assessed by using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system will be calculated.(Wu et al., 2022).

Statistical analysis:

All statistical analysis will be performed by using SPSS version 23. The demographic and clinical characteristics of patients will be expressed as mean ± standard deviation (SD). Student's t-tests or Mann-Whitney tests will be used to compare between groups. Chi-square tests or exact tests (Fisher's exact test or likelihood ratio test) will be used to detect the existence of association between variables.

Ethical consideration:

An ethical approval will be obtained from ethical committee of Faculty of medicine Beni-Suef University.
All patients in study agree to participate of their own free will and that they have been fully informed regarding the procedures of the research project and any potential risks.
If any patient included in study want to withdraw, stop study in this patient immediately.
The study will start after approval of the research ethical committee and according to guideline of the Declaration of Helsinki.

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