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CONTINUOUS VERSUS INTERMITTENT INTRAVENOUS MEROPENEM IN SEVERE SEPSIS

Tamer Abdallah Helmy, Aglan Ahmed abdelghaffar, Elsakkar Mohamed fathy

Critical Care Medicine Department, Faculty of Medicine, Alexandria University, Egypt

***Corresponding Author Email:** dr.sakkar@yahoo.com

ABSTRACT

Background:*Severe infections and increasing antibiotic resistance are major healthcare problems affecting morbidity and mortality in the field of critical care medicine.Meropenem has abroad spectrum activity against Gram-negative (including Pseudomonas), Gram positive and anaerobic bacteria.It remains a suitable choice as amonotherapy for treatment of severe infections in critically ill patients.* ***Aim of work:*** *Was to study outcome of continuous versus intermittent application of meropenem (culture based) in critically ill patients with severe sepsis.* ***Patients:*** *This prospective comparative randomized study included 100 adult patients admitted to the Critical Care Department of Alexandria Main University Hospital with severe sepsis between October 2013 and November 2014. They were randomized into 2 groups, group I (Infusion group):patients received a loading dose of 2g of meropenem I.V over 30 minutes followed by continuous infusion of 4g of meropenem over 24 hours and group II (Bolus group): patients received 2g of meropenem over 30 minutes every 8 hours.* ***Methods:*** *Patients were assessed for SOFA score, WBCs count, CRP levels, microbiological outcome, meropenem related length of ICU stay and mortality (28days).* ***Results:*** *There were no statistically significant differences between the two groups as regard age, sex, site of infection, microbiological outcome and mortality while ICU stay, SOFA score, CRP levels and WBCs count were significantly decreased in group I.* ***Conclusion:*** *Administration of Meropenem infusion on cultured based treatment was associated with significant reduction of WBCs count, CRP levels, SOFA score and ICU stay. While microbiological outcome and mortality were better in infusion group but not reaching the statistically significant levels.*

KEY WORDS

meropenem, severe sepsis, CRP,WBCs

INTRODUCTION

Antibacterial drug discovery and development have slowed considerably in recent years. [1,2]

The effort to maximize antibiotics activity has led in recent years to the interest for optimal dosing based on their pharmacodynamic and pharmacokinetic properties. [3]

Meropenem is an ultra-broad spectrum injectable antibiotic used to treat a wide variety of infections. It is a beta-lactam and belongs to the subgroup of carbapenems similar to imipenem and ertapenem. It penetrates well into many tissues and body fluids including the cerebrospinal fluids, bile, heart valves, lungs, and peritoneal fluid.[4] It is a bactericidal except against listeria monocytogenes where it is a bacteriostatic. It inhibits bacterial wall synthesis like other beta-lactam antibiotics. In contrast to other beta-lactams, it is highly resistant to degradation by beta-lactamases or cephalo sporinases. It is metabolized in the liver to open beta-lactam form (inactive). Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the

urine over 12 hours, after which little further urinary excretion is detectable.[5]

Meropenem have broad spectrum activity against Gram-negative (including Pseudomonas) and Gram -positive organisms and anaerobic bacteria, it remains a suitable choice for treatment of severe sepsis in critically ill patients. It is currently established that meropenem,like other β-lactam antibiotics, displays time-dependent bactericidal activity.[6]

Debate persists about whether traditional intermittent bolus dosing (IB) or continuous infusion (CI) is clinically preferable for administration of beta-lactam antibiotics. This is despite the fact that beta-lactam pharmocodynamic (PD) data suggests more advantages for CI.[7], showing time-dependent activity and demonstrating that the duration of time (T) the free drug concentration remains above the minimum inhibitory concentration (MIC; fT>MIC) best describes its bacterial kill characteristics.[8]Thus, administration via CI may be advantageous, because it inevitably produces higher and sustained antibiotic concentrations above the MIC. It is also noteworthy that IB yields an unnecessary high peak and low trough concentrations below MIC for much of the dosing interval.[9] The constant and sustainable antibiotic concentrations provided by CI are particularly important for pathogens with high MIC values. Such pathogens are relatively common in the ICU. [10,11]

Despite these theoretical advantages, a global practice shifts toward CI of beta-lactam antibiotics has not taken place yet.This is mostly because, although CI has been shown to be superior to IB dosing during in vitro[12] and in vivo [13] experimental studies and comparative clinical trials have so far failed to demonstrate significant differences in patient outcome. Furthermore, meta-analyses of these clinical trials had found similar outcomes between CI and IB, in heterogeneous hospitalized patients. [14] This dissociation between preclinical data and clinical reports raises uncertainty for the treating clinicians. Importantly, most trials had important methodological flaws and used inconsistent methods and therapeutic endpoints.[11] There is still also a lack of general consensus about which patient groups should be investigated and the appropriate methodology that should be employed to identify whether clinical outcome differs between these two dosing approaches.

The use of continuous administration of β-lactams was studied in some trials, [15] but strong evidence of clinical efficacy of this alternative is lacking.

SUBJECTS AND METHODS

This prospective comparative randomized study included 100 adult patients who were admitted to the Critical Care Department of Alexandria Main University Hospital with severe sepsis between October 2013 and November 2014. They were divided into two equal groups 50 patients each, group I (infusion group) and group II (bolus group), the number of studied patients was based on sample size calculation. Patients taking immunosuppressant drugs prior to admission, with cultures resistant to meropenem, with acute or chronic renal failure, pregnant females, those with neutropenia (absolute neutrophil count < 1,000 cells/mm^3) and those younger than eighteen years old were excluded from the study. On admission to the ICU and after an informed consent was taken from every patient or from his next of kin as well as approval from local ethical committee, all patients included in the present study were subjected to detailed history, comprehensive physical examination, Laboratory evaluation, ECG,ABG and assessment of severity of illness by acute physiology and chronic health evaluation (APACHE) II score on admission,C-Reactive

Protein(CRP)mg/l and white blood cells count(WBCs) 10^3/mcL were measured on days (1,3,5,7,9). Also SOFA score (Sepsis-related Organ Failure Assessment) on start and at end of meropenem therapy. Microbiological outcome, meropenem related length of ICU stay and mortality (28days) were assessed in both groups.

RESULTS

There were no statistical significant differences between the two studied groups as regard age, sex, site of infection, type of infecting organism and APACHE II score.

Regarding the microbiological outcome (culture and sensitivity at the end of antibiotics therapy), there was no significant differences between the two studied groups (p= 0.198), where the c/s was –ve with no growth in 37 patients (74%) in group I compared to 31 patients (62%) in group II, the c/s was +ve with growth in 13 patients (26%) in group I compared to 19 patients (38%) in group II.

Regarding mean CRP (Table 4), in day (1) mean CRP level were high in the two groups with a mean of 228.18 ± 14.10 in group I compared to 232.86 ± 10.20 in group II and p value =0.060,with no significant difference. In day (3) there was a decrease in value of mean CRP in the two studied groups with no statistical significant differences (p=0.214) where it was 194.06 ± 20.99 mg/l in group I compared to198.58 ± 14.54 mg/l in group II. In day (5) there was a drop in mean CRP to 154.38 ± 28.14 mg/l in group I compared to 163.64 ± 23.40 mg/l in group II but this drop was not significant (p= 0.077) In day (7) there was steady decrease in mean CRP to be 115.44 ± 26.64 mg/l in group I compared to 127.37 ± 24.22 mg/l in group II and this was statistically significant (p= 0.035).

Table (1): Comparison between the two studied groups according to SOFA score on start and at end of meropenem therapy

There was no statistical difference between the two studied groups regarding SOFA score on start of therapy where it had a mean of 9.94 ± 0.93 in group I compared to a mean of 10.38 ± 1.44 in group II. But the mean value of SOFA score at end of therapy was lower in group I with a mean of 3.66 ± 0.94 compared to a mean of 5.81 ± 1.68 in group II and this difference was significant (p < 0.001).

	Group I (Infusion group) (n= 50)	Group II (Bolus group) (n= 50)	Test of Sig.	P
SOFA score on start of therapy				
Min. – Max.	8.0 – 11.0	8.0 – 12.0	t=1.811	0.074
Mean ± SD.	9.94 ± 0.93	10.38 ± 1.44		
Median	10.0	10.0		
SOFA score at end of therapy				
Min. – Max.	3.0 – 5.0	4.0 – 8.0	t=7.304*	<0.001*
Mean ± SD.	3.66 ± 0.94	5.81 ± 1.68		
Median	3.0	5.0		

t: Student t-test

***: Statistically significant at p ≤ 0.05**

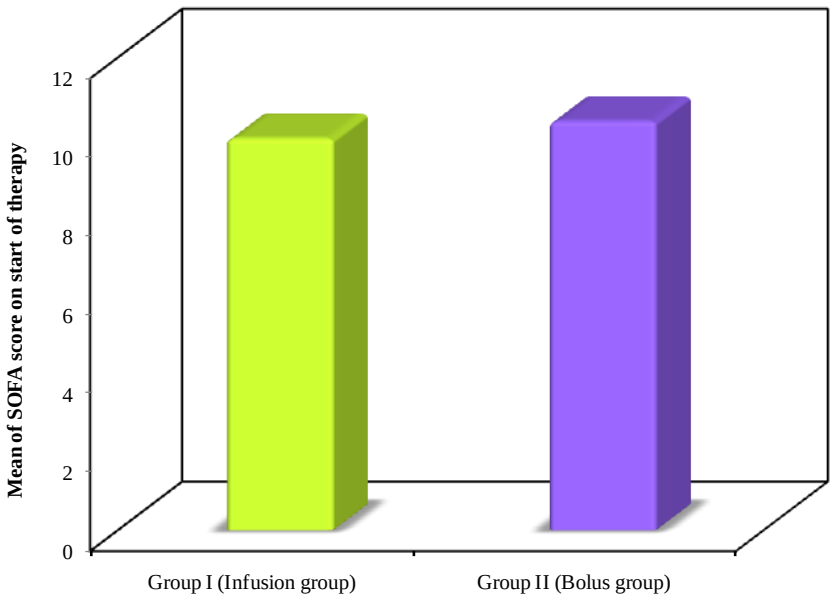

Figure (1): Comparison between the two studied groups according to SOFA score on start of therapy

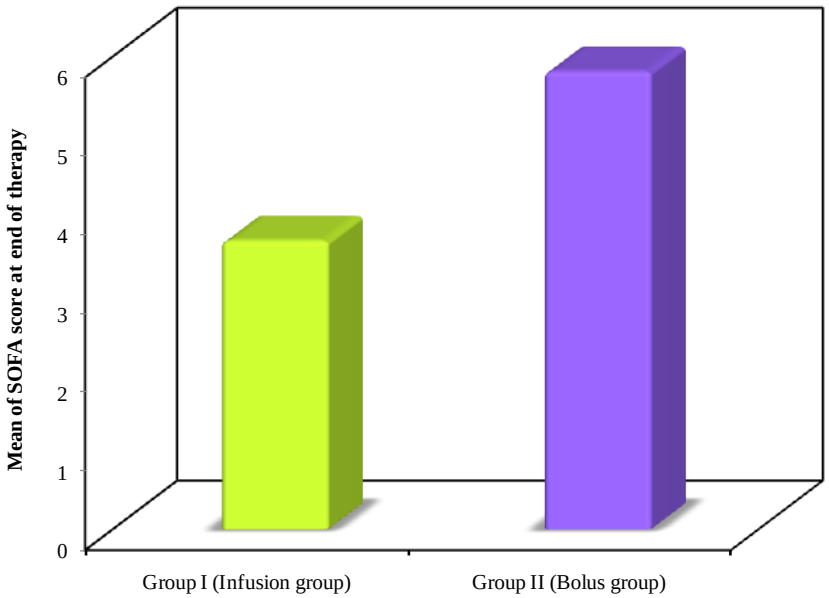

Figure (2): Comparison between the two studied groups according to SOFA score at end of meropenem therapy

Table (2): Regarding the mean WBC in the two studied groups.

In day (1) of treatment, WBCs were high in the two groups with a mean of (25.28 ± 3.07 ×10^3) in group I compared to (26.34 ± 2.75×10^3)in group II and p value =0.072,with no significant differences .

In day(3) WBCs decreased in the two studied groups with a more drop in group I (mean of 21.05 ± 3.45×10^3) compared to (22.13 ± 3.72×10^3) in group II but with no statistical significant differences (p= 0.137).

In day (5) more drop occurred in the two groups but it was significantly more in group I (p =0.037) with a mean of (17.34 ± 3.47×10^3) compared to (18.94 ± 4.05×10^3) in group II.

In day (7) there was steady drop in the two studied groups but it was significantly more in group I (p =0.042) with a mean of (14.66 ± 3.92×10^3) compared to (16.55 ± 4.43 ×10^3) in group II.

Table (2): Comparison between the two studied groups according to mean white blood cell count (WBCs)

WBC×10^3/uL	Group I (Infusion group)	Group II (Bolus group)	T	p
Day 1	n = 50	n = 50		
Min. – Max.	18.46 – 31.33	21.23 – 33.60	1.821	0.072
Mean ± SD.	25.28 ± 3.07	26.34 ± 2.75		
Median	25.05	26.32		
Day 3	n = 50	n = 50		
Min. – Max.	15.93 – 28.11	17.32 – 31.57	1.499	0.137
Mean ± SD.	21.05 ± 3.45	22.13 ± 3.72		
Median	20.54	21.15		
Day 5	n = 50	n = 50		
Min. – Max.	9.42 – 26.16	14.03 – 28.30	2.119*	0.037*

Mean ± SD.	17.34 ± 3.47	18.94 ± 4.05		
Median	16.89	17.41		
Day 7	n = 41	n = 45		
Min. – Max.	8.33 – 24.98	11.22 – 25.33	2.068*	0.042*
Mean ± SD.	14.66 ± 3.92	16.55 ± 4.43		
Median	13.79	14.58		

t: Student t-test

***: Statistically significant at p ≤ 0.05**

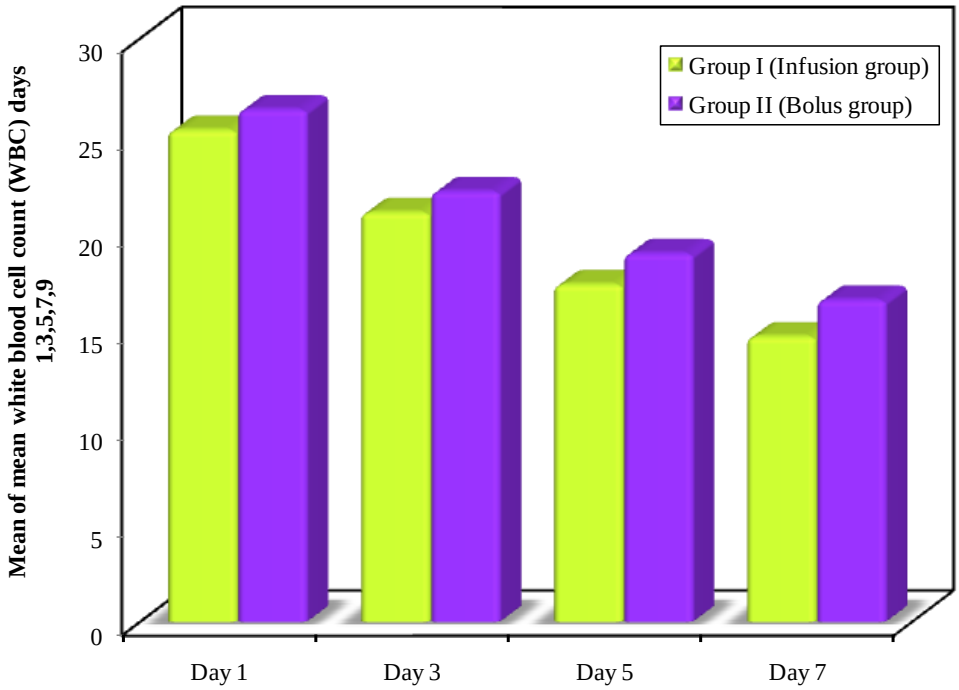

Figure (3): Comparison between the two studied groups according to mean white blood cell count (WBC) days 1, 3,5,7,9.

Regarding mean CRP (Table 3), in day (1) mean CRP level was high in the two groups with a mean of 228.18 ± 14.10 in group I compared to 232.86 ± 10.20in group II and p value =0.060,with no significant differences.

In day (3) there was a decrease in value of mean CRP in the two studied groups to show no statistical significant differences (p=0.214) between them where it was 194.06 ± 20.99 mg/l in group I compared to198.58 ± 14.54 mg/l in group II.

In day(5)there was drop in mean CRP to154.38 ± 28.14 mg/l in group I compared to 163.64 ± 23.40 mg/l in group II but this drop was not significant (p= 0.077).

In day (7) there was steady decrease in mean CRP to be 115.44 ± 26.64 mg/l in group I compared to 127.37 ± 24.22 mg/l in group II and this was statistically significant(p= 0.035).

Table (3): Comparison between the two studied groups according toC-reactive protein(mg/l).

CRP(mg/l)	Group I (Infusion group)	Group II (Bolus group)	T	P
Day 1	n =50	n = 50		
Min. – Max.	192.0 – 247.0	207.0 – 247.0	1.901	0.060
Mean ± SD.	228.18 ± 14.10	232.86 ± 10.20		
Median	233.0	235.0		
Day 3	n =50	n =50		
Min. – Max.	146.0 – 222.0	166.0 – 220.0	1.252	0.214
Mean ± SD.	194.06 ± 20.99	198.58 ± 14.54		
Median	199.0	201.0		
Day 5	n =50	n =50		
Min. – Max.	92.0 – 216.0	112.0 – 199.0	1.789	0.077
Mean ± SD.	154.38 ± 28.14	163.64 ± 23.40		
Median	158.50	170.50		
Day 7	n = 41	n = 43		
Min. – Max.	79.0 – 199.0	92.0 – 179.0	2.145*	0.035*
Mean ± SD.	115.44 ± 26.64	127.37 ± 24.22		
Median	109.0	119.0		

t: Student t-test

***: Statistically significant at p ≤ 0.05**

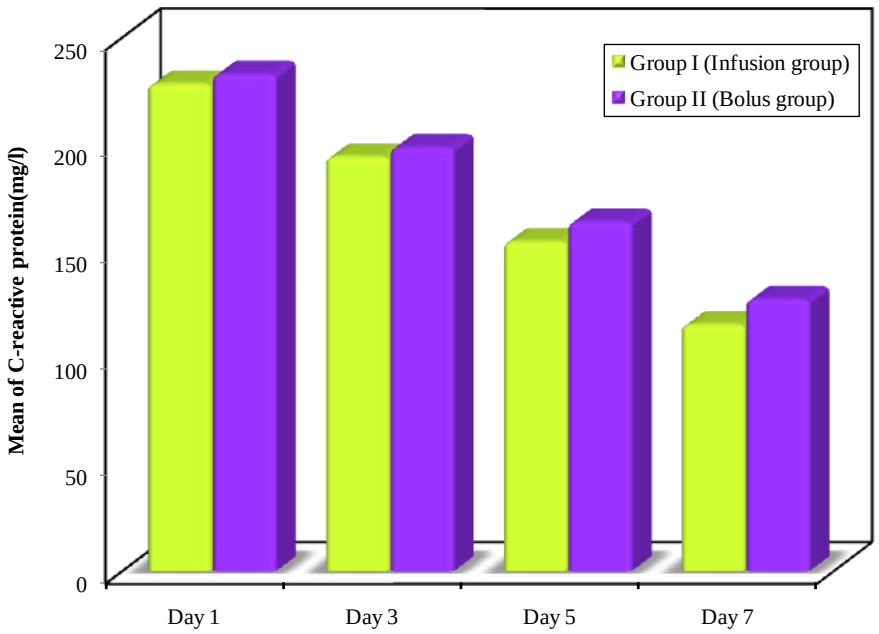

Figure (4): Comparison between the two studied groups according to C-reactive protein(mg/l).

Table (4): Regarding themicrobiological outcome (culture and sensitivity at theend of antibiotics therapy), there Table (4): Comparison between the two studied groups according to Culture and sensitivity (C/S) at end of therapy.

	Group I (Infusion group)		Group II (Bolus group)		χ^2	P
	No.	%	No.	%		
C/Sat end of therapy						
No growth	37	74.0	31	62.0	1.654	0.198
Growth	13	26.0	19	38.0		

χ^2: Chi square test

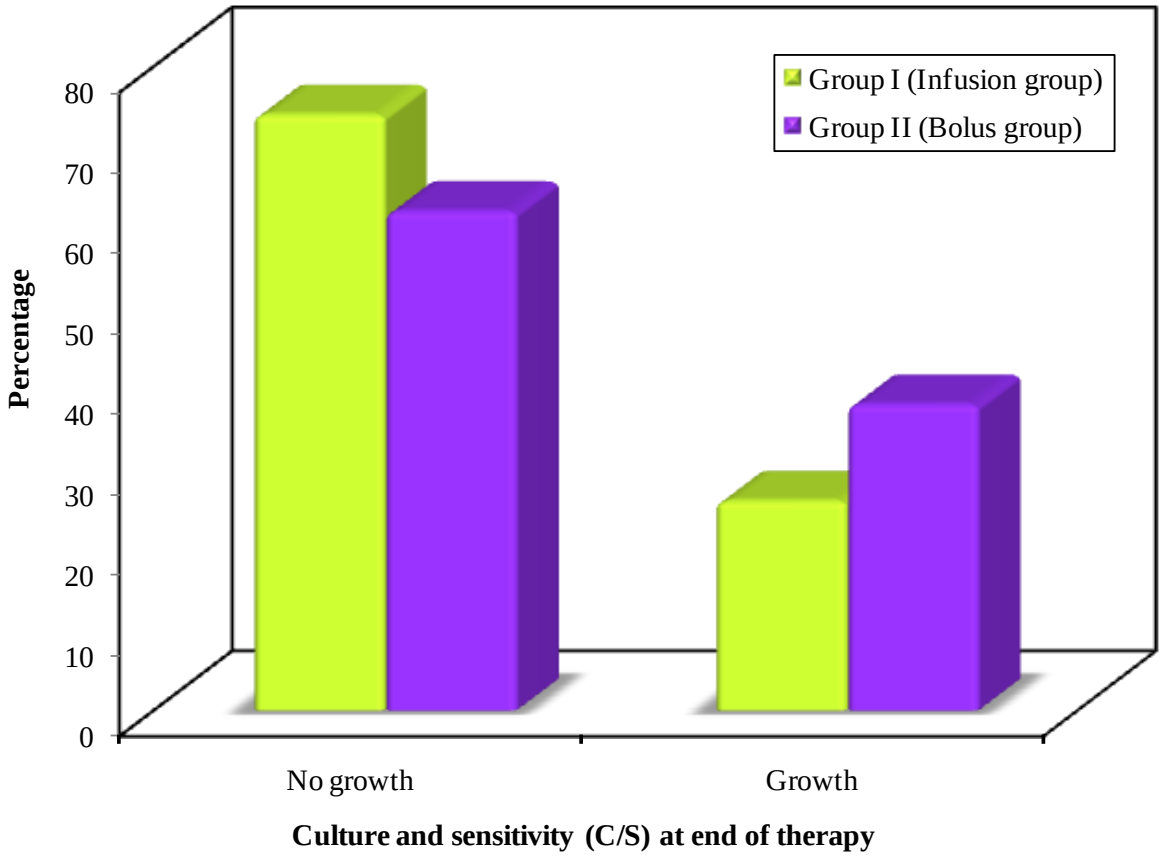

Figure (5): Comparison between the two studied groups according to Culture and sensitivity (C/S) at end of therapy.

Table (5): Regarding ICU stay (the number of days from beginning of meropenem therapy to the discharge from ICU),there was significant difference between the two studied groups .Group I had a significant(p = <0.001) shorter ICU stay with a mean of 9.72 ± 1.50 days compared to group II with a mean of 12.48 ± 1.82 days.

Table (5): Comparison between the two studied groups according to meropenem regimen related length of ICU stay.

	Group I (Infusion group)	Group II (Bolus group)	t	P
Meropenemrelated lengthof ICU stay(days)				
Min. – Max.	7.0 – 14.0	9.0 – 17.0	8.275*	<0.001*
Mean ± SD.	9.72 ± 1.50	12.48 ± 1.82		
Median	10.0	12.0		

t: Student t-test

*: Statistically significant at p ≤ 0.05

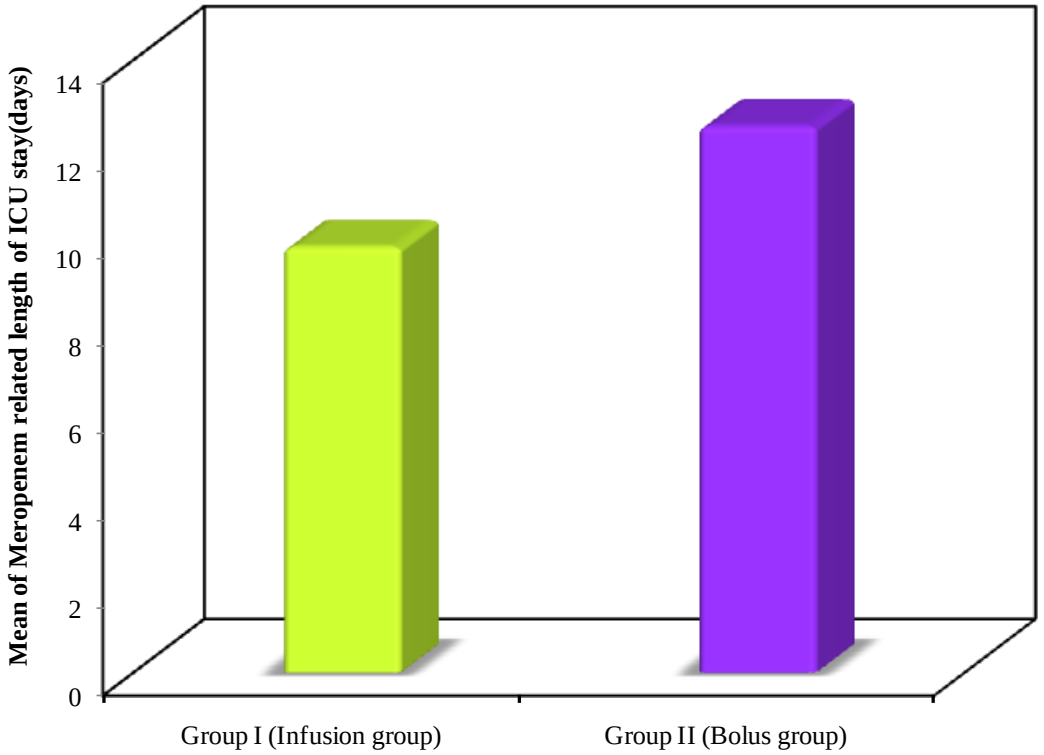

Figure (6): Comparison between the two studied groups according to meropenem regimen related length of ICU stay.

Table (6): Shows comparison between group I and group II regarding mortality (28 days). It illustrated that, in group I 37 patients (74%) survived compared to 31 patients (62%) in group II while in group I 13 patients (26%) died compared to 19 patients (38%) in group II. There was no statistical significant differences between the two studied groups regarding mortality (P=0.198).

Table (6): Comparison between the two studied groups according to mortality (28 days)

	Group I (Infusion group)		Group II (Bolus group)		χ^2	P
	No.	%	No.	%		
Survived	**37**	**74.0**	**31**	**62.0**	**1.654**	**0.198**
Died	**13**	**26.0**	**19**	**38.0**		

χ^2: Chi square test

DISCUSSION

Sepsis is a leading cause of acute hospital admission and often complicates the clinical course of patients hospitalized for other reasons. Despite the advent of innovative therapeutic strategies and a vast body of knowledge related to its pathophysiology, the mortality rate from severe sepsis remains high. [16]

In the current work, WBCs, CRP levels, ICU stay (in days) and SOFA score were significantly reduced in the meropenem infusion group. On the other hand, reduction in bacterial growth, and decreased mortality were better in the infusion group but not reaching the statistically significant level.

A retrospective cohort study was conducted by Lorente L et al [17] in 2006 on 89 patients with VAP caused by gram-negative bacilli who received initial empirical antibiotic therapy with meropenem (not after culture and sensitivity as in the present study). Also the dose regimen was different from the present study, where one group received meropenem by continuous infusion (1 g over 360 min every 6 h) as in the present study. The second group received meropenem by intermittent infusion 1 g over 30 min every 6 h (instead of 2g every 8h he as in the present study). There were no significant differences between the two groups as regard to gender, age, APACHE-II score, diagnosis, microorganism responsible for VAP, or organ dysfunction severity. Lorente L et al [17] concluded that the group who received medication by continuous infusion showed a significant cure rate than the group treated with intermittent infusion (38 of 42, 90.47%, vs 28 of 47, 59.57%, respectively, with OR 6.44 [95% CI 1.97 to 21.05; $p < 0.001$]).

In a randomized prospective controlled study done by Wang et al[20] in 2009 on 30 patients in the ICU with HAP due to *Acinetobacterbaumanii* Meropenem was given as1 g(1-hour infusion) every 8 hours (not as 2g every 8h as in the present study). The second group received Meropenem 500 mg (not 1 gas in the present study) every 6 hours (3-hour infusion). Wang concluded that bacterial eradication at 7 days and rates of relapse were similar between the two groups (both $p>0.05$).

In a study published by Ivan Chytra et al [18] in 2012 on 240 ICU patients treated with meropenem were randomized either in the Infusion group (n = 120) or in the Bolus group (n = 120). Patients in the Infusion group received a loading dose of 2 g of meropenem followed by a continuous infusion of 4 g of meropenem over 24 hours (the same as in the present study). Patients in the Bolus group were given 2 g of meropenem over 30 minutes every 8 hours as in the present study. The two groups had no significant differences in age, gender, severity of illness (APACHE II and SOFA scores), in the type of infection, in the type, or MICs of isolated pathogens. There were no differences in the rate of combined antimicrobial therapy and in

the type of concomitant antibiotics**.** Ivan Chytra concluded that the rate of clinical cure and improvement in clinically evaluable patients was comparable between the treatment groups *P* = 0.180. As for patients with culture-based therapy, he found a trend for better clinical outcome in the Infusion group (86.0%) against the Bolus group (74.3%); (*P* = 0,051; RR = 1.1581; 95% CI = 1.007 to 1.3314). Microbiological cure rate was higher in the Infusion group (87 patients with overall pathogen eradication (90.6%) vs. 80 (78.4%); *P* = 0.020; RR = 1.156; 95% CI = 1.024 to 1.303). The rate of colonization and super infection during meropenem therapy did not differ. The occurrence of resistance in infusion and bolus group was low (2.1% vs. 3.9%) and developed in a typical pathogens with lower susceptibility to meropenem (*Acinetobacter* spp and *Stenotrophomonasmaltophilia*).

In 2013 Dulhuntyetal[19] published a prospective, double-blind, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate conducted in 5 intensive care units across Australia and Hong Kongonon 60 adults with severe sepsis. Meropenem was given 1g (not 2g as in the present study) every 8h as bolus and 1g every 8h (not every six h as in the present study) as infusion. Other study arms were piperacillin-tazobactam and ticarcillin-clavulanate. Meropenem plasma concentrations were higher with infusion vs. bolus (p=0.001) and clinical cure were greater for all 3 infusion groups combined vs. bolus; no difference in other outcomes (eg, time to clinical resolution, length of stay in ICU, survival) was observed.

In 2014 a study was published by Feher et al [22],it was a retrospective observational study. The subjects were neutropenic patients who presented with fever after receiving haematopoietic stem-cell transplantation or induction of chemotherapy for acute myeloid leukaemia. Eighty-eight patients received meropenem 1 g/8 h(not 1gevery 6hours as in the present study) as infusion and 76 received the same dose 1g/8h(not 2 gm every 8hours as in the present study)as bolus. Treatment success on day 5 was superior in the infusion group [52/76 (68.4%) versus bolus group 36/88 (40.9%)(*P*<0.001). Meropenem administered in infusion was independently associated with success (OR 3.13, 95% CI 1.61–6.10). Using Kaplan–Meier survival analysis a more prompt defervescence and a faster decrease in C-reactive protein concentration were observed in the infusion group (*P*=0.021 and *P*=0.037, respectively). There were no significant differences in the length of hospital stay and in the mortality rate.

A meta-analysis reported in a study by Falagas et al[21] in 2013 among 16 studies (1229 patients oncarbapenems or piperacillin/tazobactam, bolus versus infusion) Mortality was lower among patients receiving extended or continuous infusion of carbapenems or piperacillin/tazobactam compared to those receiving short-term (risk ratio [RR], 0.59; 95% confidence interval [CI], .41–.83). Patients with pneumonia who received extended or continuous infusion had lower mortality than those receiving short-term infusion (RR, 0.50; 95% CI, 0.26–0.96). Data for other specific infections were not available.

A meta-analysis of 5 studies of extended/continuous carbapenem infusions compared to standard administration done by Falagas et al[34] in 2013 did not identify a mortality benefit (risk ratio [RR] 0.66, 95% confidence interval [CI] 0.34 to 1.30).There was also no difference in clinical cure between these strategies (RR 1.16, 95% CI 0.82 to 1.65).

The previous studies and the present one did not identify a mortality benefit of continuous

infusions compared to standard administration (bolus therapy) , ICU stay, SOFA score and bacterial eradication were different among all the previous studies but with better outcome. This might be due to several factors included in those studies .The large variability in the number of patients included in the studies as 100 patients in the present study compared to 240 patients in Ivan Chytra study[18] and 30 patients in Wang study[22] ,and 89 in Lorente study[17]with its impact on statistics may be one of the contributing factors .

The differences in the pathology where in the present study patient had severe sepsis, some studies had patients with VAP (Lorente), HAP (Wang), severe sepsis (Ivan Chytra) or patients with febrile neutropenia following hematopoietic stem cell transplant or induction of chemotherapy for acute myeloid leukaemia (Feher) may be another factor .

The regimen and the dose of meropenem used were different among these studies may also a role in the different results.

Also, meropenem was given after culture and sensitivity in the present study and Wang study, but it was an empirical therapy in Fehre and Lorente studies, and mixed empirical and culture based meropenem in Ivan Chytra study.

Study limitations:

1. It was not blinded.
2. It was conducted in one center.
3. The dose of meropenem in the bolus group (6 g/24 hrs) might be potentially confounding, despite that it was used in accordance with the recommendations for the critically ill patients. Using this dose, the concentration of meropenem could reach T > MIC for 100% of dosing interval in the susceptible pathogens with relatively low MIC. This may potentially favor the bolus group patients and mask the pharmacodynamic benefit of a continuous regimen.

CONCLUSION

- In conclusion, administration of meropenem on cultured based treatment as 1g/6h infusion compared to 2g/8h bolus was associated with significant reduction of WBCs count, CRP levels, SOFA score and ICU stay. Reduction in bacterial growth, and decreased mortality were better in the infusion group but not reaching the level of statistical significance.
- The overall question of whether meropenem infusions provide any substantial clinical benefit remains largely unanswered.

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*Corresponding Author:
dr.sakkar@yahoo.com