

## Research Article



## Do Prolonged Infusions of Beta Lactams Improve Clinical Cure? A Meta Analysis

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### ABSTRACT

New dosing strategies of beta lactams by utilizing the pharmacodynamics and pharmacokinetic properties had been used in order to achieve the maximum therapeutic effect of the antibiotics. Prolonging infusion may be able to increase the time above the minimum inhibitory concentration thus leading to a more effective treatment. A meta analysis was done by including results of clinical trials from the year of 2000 till 2012 comparing standard and extended infusion of beta lactams in order to determine whether the strategies will have an effect on clinical cure of the patients. Relevant studies were identified from PubMed, Medline and EMBASE using specific search terms. Two reviewers searched for literature and identify whether it is eligible for the analysis. A study is included if it (1) was a randomized controlled clinical trial, (2) compared prolonged with intermittent intravenous administration of the same antibiotic, and (3) assessed the clinical cure of both treatment. Jadad scale was used for quality assessment of the studies. "Comprehensive Meta Analysis" software was used to run statistical analysis. Heterogeneity of the study was assessed by the  $I^2$  value. Considerable heterogeneity was indicated by  $I^2 > 50\%$ . Pooled odd ratios (OR) and 95% confidence intervals (CI) for clinical cure were calculated. A total of twelve studies had been included in the analysis. A total of 472 patients were included in the intermittent arm and 470 patients in the prolonged infusion arm. Pooled odds ratios and 95% CIs for clinical cure was calculated by using the Mantel-Haenszel fixed effects model. Test of heterogeneity of all studies based on fixed effect model showed  $I^2$  value of 15% and a p value of 0.301 ( $> 0.05$ ) indicating that there was no significant heterogeneity between all of the studies. The estimated pooled odds ratios were 0.756 (95% CI 0.52-1.09) with the random effects model ( $p=0.137$ ). There is no clinical advantage in adapting prolonged infusion of beta lactams compared to standard infusion in improving clinical cure of patient with serious bacterial infection. However, limited data on the sensitivity of the responsible pathogens making it impossible to run an analysis on the effect of the infusion strategies on specific pathogens and also to a specific target group of patient. A bigger multi centered study is required in the future.

**Keywords:** Beta-lactams, antibiotics, continuous, prolonged, intermittent, infusion, sepsis.

### INTRODUCTION

Traditionally, beta lactams have always been given as intermittent doses as per instructions of individual product leaflet of the drugs. This method has been used for years regardless of the patient's condition, severity of illness or the responsible microbial causing the infection. Beta lactams have known to be time-dependent antibiotics. Theoretically, for all time-dependent antibiotics, increasing the drug exposure time at concentration level above the minimum inhibitory concentration of pathogen will lead to better killing efficacy. Clinicians have viewed this as a possible way to improve the outcome of patients with severe bacterial infection. In current clinical setting, the treatment of severe bacterial infection is a challenging issue due to microbial resistance and also the limitation of low numbers of newly developed antibiotics. The alternative way is to optimize the antibiotic delivery by tailoring it with its special pharmacokinetics and pharmacodynamics properties.

Multiple clinical trials have been carried out in several settings to compare intermittent infusion of beta lactams with prolonged or continuous infusion<sup>1-12</sup>. However, the results of those studies have been found to be conflicting.

This is due to the studies has not been able to include bigger sample size, which could warrant a result with better significance and power. Furthermore, the main outcomes studied were different in each study. Therefore, we decided to run a meta-analysis on those studies by focusing on the most important aspect to be achieved, which is improved clinical outcome.

### MATERIALS AND METHODS

#### Definition

Intermittent infusion is defined as standard infusion of beta lactams as per instruction on package inserts of individual drug. It serves as the control group for the purpose of this analysis. Prolonged infusion may consist of either extended infusion or continuous infusion of beta lactams. Extended infusion is defined as infusion that lasts up to 3 hours or more. Continuous infusion is defined as administration of beta lactams over the period of 24 hours at fixed rate.

#### Data Sources

Relevant studies for this analysis were identified from Cochrane Central Register of Controlled Trial (CENTRAL), Medline and EMBASE. Studies were searched without time constraint on the year of publication. The search



terms used include “continuous”, “prolonged”, “extended”, “intermittent”, “bolus”, “dosing”, “infusion”, “administration”, “antibiotics”, and “beta lactams”. Only English articles were searched.

### Study Selection

Two reviewers searched for literatures and identify whether the literatures eligible for the analysis. Any differences between the two reviewers were discussed and resolved in meetings with all the authors, while any discrepancies between reviewers were resolved by consensus of all study members. The initial abstract screening and selection has broader inclusion criteria compared to the final full text selection. A study was included if it (1) was a randomized controlled clinical trial, (2) compared prolonged with intermittent intravenous administration of the same antibiotic, and (3) assessed the clinical cure of both treatment.

### Data Extraction

Data extracted from selected studies were clinical setting, number of patients studied, antimicrobial agents and doses used, and clinical outcome. Jadad scale was used for quality assessment of the studies that includes three important criteria, which are blinding, randomization, and withdrawals and dropouts<sup>13</sup>.

### Outcome

The only outcome sought from the selected studies was clinical cure. Clinical cure was defined by the discretion of respective authors because of the multiple study population, variety of responsible pathogens and infection sites.

### Data Analysis

“Open Meta Analyst” software was used to run the statistical analysis<sup>14</sup>. The heterogeneity between the studies was assessed by the I<sup>2</sup> value. Considerable heterogeneity was indicated by I<sup>2</sup>>50%. Publication bias assessment was done using the funnel plot method utilizing Egger’s test<sup>15</sup>. Pooled odds ratios (OR) and 95% confidence intervals (CI) for clinical cure were calculated.

## RESULTS

### Selected Studies

Our initial search resulted in 2,976 potentially relevant articles. Among the numbers, 134 were found to be duplicates and were excluded. Two of the reviewers then reviewed the titles and abstracts of the articles. 2,795 articles were found to be irrelevant to the subjects. The full text of 47 remaining articles were then assessed and studied carefully. 8 of the papers were found to be non-comparative and were excluded. The remaining studies were then compared with our final inclusion criteria. After careful and detailed evaluation of the remaining studies using Jadad scale, 12 of the randomized controlled trials were found to be satisfactory to be included in our analysis.

### Trial Characteristics

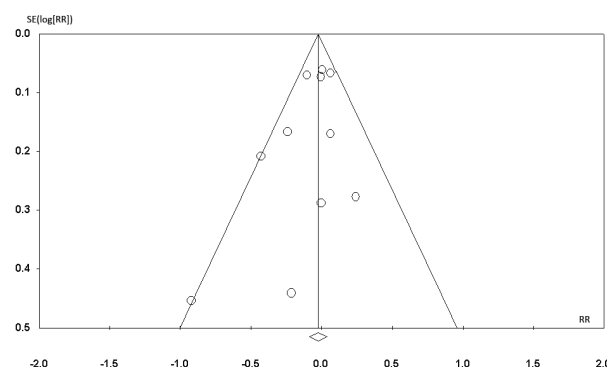
Among the 12 selected studies, 10 of them compared standard intermittent infusion with continuous infusion. Only 2 of the studies compared standard infusion with extended infusion. The infusion time in these studies ranges from 3 hours to 7 hours.

8 studies of run trials were focusing on critically ill patients in intensive care units. One of them was carried out on non-critical patients<sup>1</sup>. 3 of the studies did not specify their patient population. The sample size differs from each study, ranging from 10 to 258 samples. Studies were carried out in 4 different continents, with the majority came from North America. The year of publications ranges from year 2000 to 2013.

Most of the studies did not show evidence of any concomitant antibiotics was used with the drug of study. Two of the studies combined amikacin or tobramycin infusion in their trial protocol to all selected patients. Another study did not combine other antibiotics with the studied drug but allow concomitant antibiotics to be used if deemed necessary. The characteristics of each study are summarized in Table 1.

### Assessment of Risk of Bias

All of the selected studies were randomized controlled trials. Few of the studies have adequate sample sizes in order to determine their clinical outcome. Methods of randomization were only detailed in 4 studies, while masking was done in 3 studies. All the studies clearly defined their inclusion and exclusion criteria satisfactorily. 6 studies received funding from pharmaceutical companies. A funnel plot was performed to screen for evidence of publication bias by comparing clinical cure outcome of intermittent and prolonged infusion of beta lactams (Figure 1). The plot was found to be relatively symmetrical, thus suggesting minimal publication bias. Based on the qualitative and quantitative analysis, the studies have not found to be influenced by publication bias ( $p=0.119$ ).



**Figure 1:** Funnel plots demonstrating low probability of publication bias among the studies comparing intermittent and prolonged infusion of beta lactams

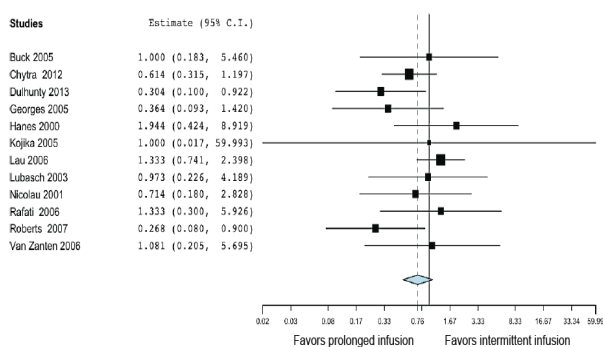
### Clinical Cure

All of the selected studies reported results on comparison of clinical effectiveness of intermittent versus prolonged

intravenous infusion of beta lactams. The studies compared the same type of antibiotic in both arms. A study included 3 types of antibiotics for comparison, but both arms must have the same type of antibiotic.

Definitions of clinical cure vary between studies. Those definitions were listed out in Table 1. There were 942 episodes of infection, with 472 cases in the intermittent group and 470 cases in the prolonged infusion group. Amongst the studies, 4 showed significant results favoring the use of prolonged infusion compared to intermittent bolus. All of the studies were done on critically ill patients and used continuous infusion instead of extended infusion.

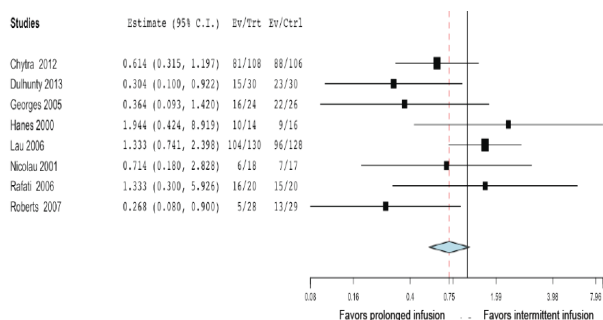
The analysis showed no statistically significant heterogeneity between the selected studies ( $p=0.301$ ,  $I^2=15\%$ , 95% CI 0-0.65). Figure 2 presents the ORs with 95% CI for all the studies included in the meta-analysis of clinical cure. The estimated pooled OR for clinical cure was 0.756 (95% CI 0.52-1.09) with the random effects model ( $p=0.137$ ) for intermittent compared to prolonged infusion of beta lactams, and 0.774 (95% CI 0.57-1.06) for fixed effects model ( $p=0.108$ ).



**Figure 2:** Clinical cure comparing intermittent infusion and prolonged infusion of beta lactams in hospitalized patients

**Clinical Outcome of the Critically Ill**

We further analyzed the studies by only focusing on a specific group of patient population, the critically ill. We selected 8 studies that were carried out in the intensive care units. The analysis showed no significant heterogeneity among the studies ( $p=0.085$ ,  $I^2=44\%$ , 95% CI 0-0.62). The estimated pooled OR was 0.747 ( $p=0.086$ , 95% CI 0.54-1.04). The finding is shown in Figure 3.



**Figure 3:** Clinical cure comparing intermittent infusion and prolonged infusion of beta lactams in critically ill patients.

**DISCUSSION**

This meta-analysis included few new clinical trials with significant results since previous analysis were done and published<sup>16,17</sup>. Our study showed that clinical cure was higher in prolonged infusion group but with no statistical significance after the results of 12 clinical trials were analyzed with both random effects model and fixed effect model. In addition, our finding was found to be comparable to the previous published results.

Among the most important aspects to be considered when choosing a drug treatment to treat a disease is the pharmacodynamics, the biological and physiological effects of drugs, the pharmacokinetics, the mechanism of absorption and the distribution of the drug itself. The time-dependent bactericidal activity of beta lactams is an important pharmacodynamics factor to be considered when selecting the best mode of administration of the drug<sup>18</sup>. In order for the antibiotics to exhibit bactericidal activity, the free drug concentrations of MIC (%T>MIC) of beta lactams has to be around 40%T> MIC of the treatment exposure<sup>19</sup>. Studies have shown that the new dosing strategies have significantly improved the time above MIC for beta lactams concentrations<sup>20-22</sup>. This is shown in clinical setting by improved clinical outcome, as reflected by the result of our analysis although it is not statistically significant.

The pharmacodynamics and pharmacokinetics aspects have often been neglected and not taken into consideration in clinical practice. Drugs such as beta lactams may have different pharmacokinetics in critically ill patients compared to normal ward patients. Critically ill patients might develop changes in their volume of distributions or in drug clearance. Several reviews have found that pharmacokinetic parameters of beta lactam antibiotics in seriously ill patients are significantly different compared to healthy volunteers<sup>23,24</sup>. Our analysis also showed that critically ill patients benefit from prolonged infusion although the result was not statistically significant.

Prolonged infusion of beta lactams may have better impact towards several patients' population in long term. Several studies suggested that the use of prolonged infusion of beta lactams might lead to a reduction in antibiotic resistance<sup>25,26</sup>. Further clinical trials should be carried out by focusing on several strains of specific responsible pathogens instead of diagnosis. However, routine uses of this type of administration are bound with several issues. The drugs selected must have sufficient safety and stability data to be used as prolonged infusion. The stability studies should be tailored with a wide variant of climate throughout the world. Secondly, care should be taken if prolonged infusion is to be used as it could lead to increase in intravenous line related infections.

Our meta-analysis has several important limitations. Firstly, we did not have substantial amount of data on responsible pathogens to do a sub-group analysis



focusing on specific groups of pathogens. The microbiology data were generally scarce and were not available in every study. Secondly, the sample sizes of the studies were generally small. However, there were

several studies with good sample size but the number of studies were only few. Finally, the selected trials have low quality scores when assessed by Jadad scale.

**Table 1:** Characteristics of selected controlled trials

| Author         | Country                  | Drug   | Dosage   |  | Definition of Clinical Cure   | Clinical Cure |           | Infusion Types | Setting       | Diagnosis                             |
|----------------|--------------------------|--|--|--|---|---------------|-----------|----------------|---------------|---------------------------------------|
|                |                          |  | Intermittent   | Prolonged  |   | Intermittent  | Prolonged |                |               |                                       |
| Buck 2005      | Germany                  | Piperacillin/Tazobactam                        | 4g/0.5g every 8 hours  | 2g loading dose over one hour then 8g per day over 24 hours                      | Fever resolution, reduced CRP, leukocytes normalization, chest x ray improvement and improvement of clinical and laboratory signs of infections                   | (8/12)        | (8/12)    | Continuous     | Non ICU       | Various                               |
| Chytra 2012    | Czech Republic           | Meropenem                                      | 2g every 8 hours   | 2g loading dose over 30 minutes then 4g per day over 24 hours                    | Complete or partial resolution of leukocytosis, temperature, and clinical signs and symptoms of infection (defined as cure or improvement)                        | (81/108)      | (88/106)  | Continuous     | ICU           | Various                               |
| Dulhunty 2013  | Australia & Hong Kong    | Meropenem, Augmentin & Piperacillin/Tazobactam | Placebo 24 hours infusion and active boluses of augmentin, tazocin and meropenem | Active 24 hours infusion and placebo boluses of augmentin, tazocin and meropenem | Disappearance of all signs and symptoms related to the infection or marked or moderate reduction in the severity and/or number of signs and symptoms of infection | (15/30)       | (23/30)   | Continuous     | ICU           | Various                               |
| Georges 2005   | France                   | Cefepime                                       | 2g every 12 hours  | 2g every 12 hours over 12 hours infusion   | Complete resolution of signs of infection without further need of antibiotics   | (16/24)       | (22/26)   | Continuous     | ICU           | Pneumonia<br>Bacterimia               |
| Hanes 2000     | United States of America | Ceftazidime                                    | 2g every 8 hours   | 2g loading dose over 30 minutes then 60 mg/kg per day over 24 hours              | Resolution of all signs and symptoms of disease or improvement in sign and symptoms of disease  | (10/14)       | (9/16)    | Continuous     | ICU           | Pneumonia                             |
| Kojika 2005    | Japan                    | Meropenem                                      | 0.5g every 8 hours   | 0.5g every 8 hours over 3 hours infusion   | Resolution of fever and reduction of white blood cell count into normal range   | (5/5)         | (5/5)     | Extended       | Not specified | Abdominal infection                   |
| Lau 2006       | United States of America | Piperacillin/Tazobactam                        | 3g/0.375g every 6 hours  | 2g loading dose over 30 minutes then 12g/1.5g per day over 24 hours              | Complete disappearance of clinical signs and symptoms or improvement  | (104/130)     | (96/128)  | Continuous     | ICU           | Abdominal infection                   |
| Lubasch 2013   | Germany                  | Ceftazidime                                    | 2g every 8 hours   | 2g loading dose over 30 minutes then 2g every 12 hours over 7 hours infusion     | Resolution of exacerbation  | (36/40)       | (37/41)   | Extended       | Not Specified | Chronic obstructive pulmonary disease |
| Nicolau 2001   | United States of America | Ceftazidime                                    | 2g every 8 hours   | 1g loading dose over 30 minutes then 3g per day over 24 hours                    | Complete resolution of pneumonia or lack of progression of abnormalities on chest radiograph  | (6/18)        | (7/17)    | Continuous     | ICU           | Pneumonia                             |
| Rafati 2006    | Iran                     | Piperacillin/Tazobactam                        | 3g every 6 hours   | 2g loading dose over 30 minutes then 8g per day over 24 hours                    | Reduction of APACHE II score, fever resolution and normalization of white blood cell count  | (16/20)       | (15/20)   | Continuous     | ICU           | Various                               |
| Roberts 2007   | Australia                | Ceftriaxone                                    | 2g every 24 hours  | 0.5g loading dose as bolus then 2g per day over 24 hours                         | Disappearance of all signs and symptoms of related infection  | (5/28)        | (13/29)   | Continuous     | ICU           | Septicemia                            |
| VenZenten 2006 | Netherland               | Cefotaxime                                     | 1g every 8 hours   | 1g loading dose over 30 minutes then 2g per day over 24 hours                    | Improvement of chest x ray result, clinical improvement, and requiring no antibiotic treatment in duration of 48 hours after cefotaxime discontinuation           | (40/43)       | (37/40)   | Continuous     | Not specified | Chronic obstructive pulmonary disease |

**CONCLUSION**

Prolonged infusion of beta lactams might have a wider role in clinical application in the future. It appears to have an advantage in bringing out better clinical outcome when compared to traditional intermittent infusion. It might have better benefits on specific subsets of patients such as the critically ill or patients with highly resistant infections. Better-designed controlled trials are needed in the coming years in order to truly evaluate the advantages of prolonged infusion of beta lactams.

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