COMPARISON OF CONTINUOUS VS INTERMITTENT ADMINISTRATION OF PIPERACILLIN-TAZOBACTAM IN HIGH RISK INFECTIONS: A META ANALYSIS

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Introduction:

As early as 1940, researchers discovered that the best way to treat infections with penicillin was to keep inhibitory concentrations of the antibiotic in the body's tissue throughout the entire treatment. [1] The authors noted that Penicillin is most rapidly effective if its concentrations at the focus of the infection remain continuously above those necessary to kill the bacterial at the maximum rate. Such levels could be provided by continuous drip or repeated small doses at intervals of approximately 2-4 hours. [2]

Beta-lactam antibiotics like Piperacillin/Tazobactam display concentration-independent pharmacodynamics, whereby the duration of time that concentrations remain above the MIC correlate best with bacterial kill. [4] This is commonly referred to as the free drug time above the MIC. [5] The protein bindings of Piperacillin and Tazobactam in human plasma are 20-30% and 20-23% respectively. [3] Whereas free drug concentrations above the MIC for 50% of the dosing interval are required for bactericidal effects, administering this agent as a 24 h continuous infusion can achieve 100% time above the MIC. [4] As a result of this knowledge, numerous approaches have been made to maximize the free drug time above the MIC by altering antibiotic dosage regimens in an effort to improve patient outcomes and lower antibiotic-related costs. [6] We carried out a meta-analysis comparing the effects of continuous infusion of Pipperacillin/Tazobactam as compared to intermittent administration.

Objectives:

To compare the efficacy of continuous administration of Piperacillin-Tazobactam vs intermittent infusion.

a. To compare the clinical outcome of intermittent infusion from continuous infusion of Piperacillin/Tazobactam.

Research Question:

In patients who have high risk infection, does continuous infusion of Piperacillin/Tazobactam more effective as compared with intermittent infusion?

Materials and Methods:

A. Literature Search:

Electronic literature searches were performed on the Pubmed, Medline, Medscape, Evidence Based Medicine, New England Journal of Medicine, Journal of Antimicrobial Therapy and Journal of the American Society for Microbiology for clinical trials to locate published research in the area of continuous infusion versus intermittent infusion of Piperacillin/Tazobactam. Search terms used were 'piperacillin-tazobactam', intermittent infusion' and 'continuous infusion'. We also conducted a manual search of article abstracts from Medical journals. We examined not only the reference of all retrieved articles but also researched national and pharmaceutical industry sources to ensure a complete and comprehensive search of the published literature. Abstracts of the articles selected in this search were reviewed and those meeting the inclusion criteria were recorded.

B. Study Selection and Data Extraction

The following selection criteria were applied to determine which studies would be included in the review: (i) the study design was a prospective, randomized, open-label controlled trials; (ii) study population include those patient who were prescribed piperacillin-tazobactam during their hospital stay; (iii) patients of age 18 or above who received a minimum of 3 full days of piperacillin-tazobactam therapy (iv) whose clinical signs and symptoms were consistent with types of infection for which Piperacillinn-tazobactam would be deemed appropriate (v) outcome measures such as length of time of recovery were assessed at after completion of therapy. Reporting of duplicated studies was excluded by examining the author list, sample size, and results of each report. The selection criteria were appraised independently by at least two reviewers, for which when disagreements in interpretation occurred, they were resolved by discussion.

C. Quality Assessment

The quality of each complete published trial was assessed by the following Jadad criteria: (i) randomization; (ii) allocation concealment; (iii) investigator blindness; (iv) description of withdrawals and dropout; (v) efficacy of randomization. Two investigators independently assesses each trial for quality score (maximum score is 5, >3 have been reported to indicate high quality). Any differences were resolved by consensus.

D. Statistical Analysis

The mean percentage of patients with successful outcome was calculated and expressed as the weighted mean (and corresponding confidence interval). For the metaanalysis, the homogeneity test was based in the Chi2 test and I2, the I2 statistic was to assess the heterogeneity on the results, this statistic described the percentage of the variability in effect estimates that it was due to heterogeneity rather than sampling error (chance). Due to low power of this test, a minimum cut off p value of 0.1 and I2 value >50% was established as threshold for homogeneity; $p<0.1$ and I2 >50% indicated heterogeneity and prevented us from relying on the combination of results. Meta-analysis was performed by combining the risk ratios (RR) of the individual studies, using a fixed effect model. All calculations were performed with Review Manager 5.0.

Results:

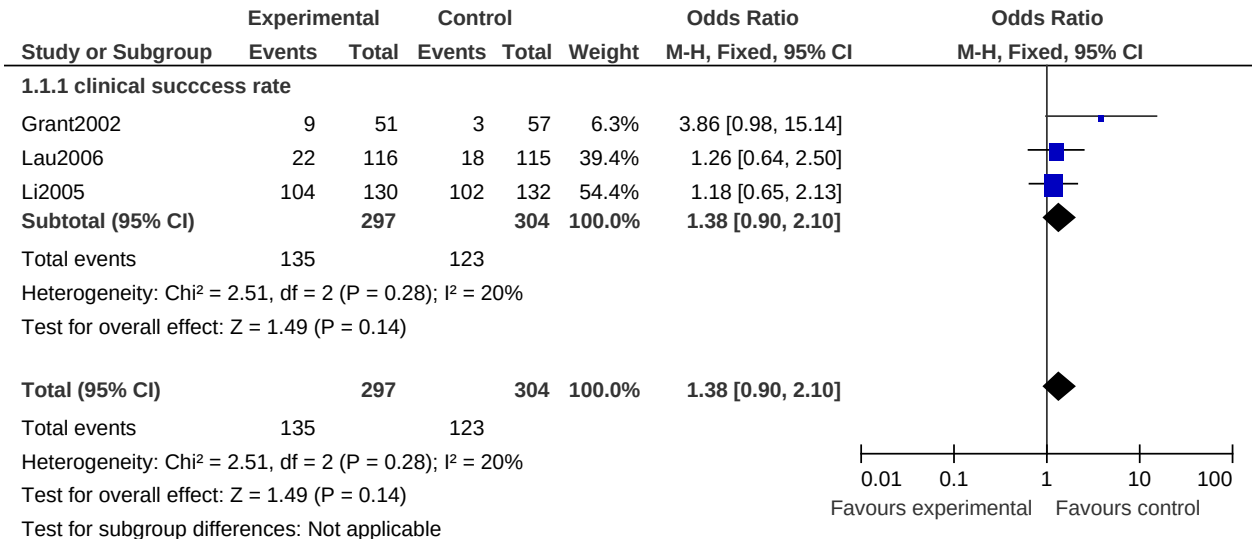
Study Selection and Analysis:

All randomized controlled trials comparing the clinical outcomes of continuous versus intermittent infusion of Piperacillin-Tazobactam were identified through search process were eligible for this review. Three studies were identified by the defined search strategy and fulfilled the inclusion criteria, containing the necessary data for the planned comparison. These studies included 591 subjects (298 subjects in the continuous infusion group and 294 subjects in the intermittent infusion group), compared the effects of continuous versus intermittent infusion of Piperacillin-Tazobactam. The main characteristics of the three studies are summarized in Table 1.

Table 1: Main characteristics of RCTs included in the metaanalysis

Study (first author)	**Cases**	**Jadad scores**	**Continuous infusion**	**Intermittent Infusion**
Grant2002	98	3	4g/0.5g over 24 hours	3g/0.375g over 30 minutes every 6 hours
Li2005	262	3	12g/1.5g over 24 hours	3g/0.375g over 30 minutes every 6 hours
Lau2006	231	3	12.5g/1.5g over 24 hours	3g/0.375g over 30 minutes every 6 hours

Table 2: Measure of Successful Outcome of continuous infusion versus intermittent infusion of Piperacillin-Tazobactam in patients with high Risk infections



Sensitivity Analysis:

The meta-analyses were limited to studies with a quality score of ≥3 (which has been reported to indicate high quality. The individual assessment of quality is shown in Table 1.

Discussion:

Evidence based medicine is a new paradigm that helps in making treatment decisions for individual patients. Applying the knowledge gained from large clinical trials to patient care promotes consistency of treatment and optimal outcomes, helps establish national standards of patient care, and sets criteria to measure and reward performance-based medical practice. In processing data, systemic review and meta-analyses are important in the process. Systematic reviews identify and summarize medical literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies and that uses appropriate statistical technique to combine valid studies while meta-analyses summarize and quantify the results of systematic reviews.

Our metaanalysis shows that the odds ratio is 1.38. Thus, the results of the study show that continuous infusion and intermittent infusion of Piperacillin-Tazobactam has no significant difference on the clinical outcome. This is incongruent with previous recommendations on the use of continuous infusion of Piperacillin-Tazobactam due to its beneficial effect on the clinical outcome of patient. However, due to the limited number of studies available, further investigations need to be conducted before a conclusion can be made on which manner of infusion should be done or if there is really no difference between the two in terms of clinical outcome.

Due to their comparable effects on the clinical outcome, the clinician's choice of which manner of infusion should be guided by other factors such as comfort of the patient, length of hospital stay and cost effectiveness. These factors should also be included in future studies concerning pharmacologic treatment of high risk infections.

Conclusion:

The conclusion of this metaanalysis is that continuous infusion of Piperazillin-Tazobactam has no significant difference with intermittent infusion of Piperacillin-Tazobactam among patients with high risk infections.

Limitations/Recommendations:

What are the limitations of this metaanalysis? As with all metaanalysis, the quality of the included studies is the primary priority (Jadad score>3). Another limitation is the small number of RCTs that were included in this metaanalysis (n=3). Trials included were carried out with varying factors like population with different risks and presence of other co-morbidities.

What are the clinical implications of this metaanalysis? Piperacillin-Tazobactam has no difference whether to infuse continuously or intermittently. However, it is recommended that a more specific analysis be done on RCTs comparing the cost effectiveness or economic impact of each type of infusion. In that way, this metaanalysis will be a more conclusive analysis.

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