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RESEARCH ARTICLE

ERTAPENEM VERSUS PIPERACILLIN/TAZOBACTAM FOR THE TREATMENT OF DIABETIC FOOT INFECTIONS-A RETROSPECTIVE STUDY

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ABSTRACT

The aim of this study is to compare ertapenem and piperacillin/tazobactum for the treatment of diabetic foot infection (DFI), in terms of measurable end points as efficacy, safety, compliance of treatment and decreased microbial resistance. We are also looking for cost effectiveness while choosing these two antibiotics.

Methods: This is a retrospective study involving patients who were admitted under General surgery through A and E of Rashid hospital with diabetic foot infection. Patient selection was done by reviewing the history, complete physical examination, limb and ulcer examination. Culture and sensitivity of blood, wound swabs and deep tissue swab were checked, along with the imaging. Patients were then divided in two groups, one received intravenous ertapenem (1gm daily), the other group received intravenous Piperacillin-Tazobactam (4.5 gm every 8 hours).

Results: Results were analysed statistically and conclusions were drawn.

Conclusion: Overall results show that in terms of wound healing, length of stay, and debridement ertapenem is superior to tazocin. Ertapenem is also more cost effective as compared to Tazocin. However as more patients had to be switched over from ertapenem to tazocin as they were notresponding, therefore further big scale studies are required to compare the effectiveness of these two antibiotics in DFI patients.

INTRODUCTION

The lifetime risk of a foot ulcer for patient with diabetes (type 1and2) may be as high as 25%. Diabetic foot infection is associated with substantial morbidity and mortality.Infection can be caused by Gram-positive aerobic, Gram negative aerobic and anaerobic bacteria, singly or in combination. The principle of management is to diagnose infection, culture the bacteria responsible and treat aggressively with antibiotic therapy.The aim of this study is to compare ertapenem and piperacillin/tazobactum for the treatment of diabetic foot infection, in terms of measurable end points as efficacy, safety, compliance of Rx and decreased microbial resistance. We are also looking for cost effectiveness while choosing these two antibiotics without compromising the standard of care in the treatment of moderate to severe diabetic foot ulcer.

MATERIALS AND METHODS

Study population

142 patients with diabetes mellitus (type 1 or type 2) who were treated for diabetic foot infection from 2010-2013

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Inclusion criterias

- Adult patient with DM1and2 with foot infection not extended above knee.
- Features of local infection with purulent discharge, tenderness, warmth, erythema >2cm, or involving structures deeper than skin and subcutaneous tissues (e.g abscess, osteomyelitis, septic arthritis, fasciitis).

Signs of SIRS

- Temperature- >38 C or < 36 C
- Heart rate- >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 <32mmhg
- WBC- >12000 or <4000 cells/ microlitre or >10% immature(band) forms.

Exclusion criterias

- Mild infection that need oral antibiotics
- Caused by thermal burns
- Resistant to antibiotics that we are using in the study
- Pregnant and lactating women.
- Known case of allergy to these antibiotics.

- Arterial insufficiency of the affected limb needing revascularization.
- Pt with terminal illness.
- Using immunosuppressant /corticosteroid therapy (40 mg prednisone daily or its equivalent)

Study design

- Retrospective study involving patients who were admitted under General surgery through AandE of Rashid hospital with diabetic foot infection.
- Patient selection was done by reviewing the history, complete physical examination, limb and ulcer examination, time of wound healing, length of stay and debridement.
- Laboratory parameters were also checked including the microbiologic investigations of the culture and sensitivity of blood, wound swabs or deep tissue.
- Imaging was also reviewed including the plain radiographs +/- MRI.
- The study was conducted by dividing patients in two groups using category group A andgroup B.
- **Group A**: patients who received intravenous ertapenem (1 gm once daily)
- **Group B**: patients who received intravenous Piperacillin-Tazobactam (4.5 gm every 8 hours).

RESULTS

We studied a total number of 142 DFI patients. All the patients in our study were above 40years of age, out of this 76% were male patients. According to our study, 37.9% of patients (11 out of 29) were switched from Ertapenemtotazocin and 10.6% of patients (12 out of 113) were switched from Tazocin to Ertapenem. Out of these 4.4% of patients who were receiving tazocin were switched over to Ertapenem as they were not responding to tazocin, and 24.1% of patients who were receiving ertapenem were switched over to Tazocin as they were not responding Table 1**.**

Table 1.

Switchover of antibiotics	Frequency	Percent
No	117	82.4
Ertapenem to Tazobactum	11	7.7
Tazobactum to Ertapenem	12	8.5
No data	2	1.4
Total	142	100.0

In terms of wound healing, 28% of patients of both groups improved by 3 days. 24% of patients who were given Ertapenem and 17% who were given Tazobactum, improved by 7 days, 28% of patients of both groups improved by 14 days, whereas 14% of patients who were given Ertapenem and 20% who were given Tazobactum, did not improve by 14 days Table 2.

In terms of length of stay, 28% of the patients who were given Ertapenem and 17% of the patients who were given Tazobactum, stayed in the hospital for less than 10 days. 31% of the patients who were given Ertapenem and 36% of the patients who were given Tazobactum, stayed in the hospital for 10 to 29 days.

Table 2.

Wound healing	Antibiotic		Total
	Ertapenem	Tazobactum	
Not applicable	2	1	3
	6.9%	0.9%	2.1%
Not improved	4	23	27
	13.8%	20.4%	19.0%
Improved by 3 days	8	32	40
	27.6%	28.3%	28.2%
Improved by 7 days	7	19	26
	24.1%	16.8%	18.3%
Improved by 14 days	8	32	40
	27.6%	28.3%	28.2%
No data	0	6	6
	0.0%	5.3%	4.2%
Total	29	113	142
	100.0%	100.0%	100.0%

10% of the patients who were given Ertapenem and 20% of the patients who were given Tazobactum, stayed in the hospital for 30 to 49 daysTable 3.76% of patients in the Ertapenem group and 81% of patients in the Tazobactum group had debridement.

Table 3.

Length of stay grouped	Antibiotic		Total
	Ertapenem	Tazobactum	
Less than 10	8	19	27
	27.6%	16.8%	19.0%
10 to 29	9	41	50
	31.0%	36.3%	35.2%
30 to 49	3	22	25
	10.3%	19.5%	17.6%
50 to 69	4	16	20
	13.8%	14.2%	14.1%
70 to 89	0	3	3
	0.0%	2.7%	2.1%
90 days or more	4	11	15
	13.8%	9.7%	10.6%
Died	1	1	2
	3.4%	0.9%	1.4%
Total	29	113	142
	100.0%	100.0%	100.0%

DISCUSSION

At some time in their life, 25% of diabetic patients develop foot ulcers. 85 % of amputations are preceded by an ulcer (Pecoraro *et al*., 1990) and there is an amputation every 30 seconds throughout the world (Bakker *et al*., 2005). The main reason for this is that foot ulcers are highly susceptible to infection (Reiber, 2001) this may spread rapidly leading to overwhelming tissue destruction and need for amputation. Important factors that increase the risk of diabetic foot infection (DFI) include a wound for which probe to bone test is positive, ulcer present for more than 30 days, history of recurrent foot ulcers, a traumatic foot wound, the presence of peripheral vascular disease in the affected limb, a previous lower extremity amputation, neuropathy and renal insufficiency. New development son the diagnosis and treatment have been reviewed by Lipsky (Lipsky *et al*., 2004; Lipsky, 2004; Lipsky, 2008 and Lipsky *et al*., 2004).

Osteomyelitis

Evaluation for osteomyelitis is an important consideration in the management of diabetic foot infections. The following factors increase the likelihood of osteomyelitis in patients with diabetic foot infections (Berendt *et al*., 2008; Berendt *et al*., 2008; Edmonds *et al*., 2008; Grayson *et al*., 1995 and Dinh *et al*., 2008):

- Grossly visible bone or ability to probe to bone
- Ulcer size larger than *2 x 2* cm
- Ulcer duration longer than 1 to 2 weeks
- ESR >70 mm/h

Patients with diabetic foot infections should have initial evaluation with conventional radiographs. Those with one or more of the above factors and whose radiographs are indeterminate for osteomyelitis should undergo magnetic resonance imaging (MRI); such imaging is especially useful to guide decision-making regarding bone biopsy for histopathology and culture and choice and duration of antimicrobial therapy.

Microbiology of the diabetic foot

Most diabetic foot infections are polymicrobial, with up to five or seven different specific organisms involved. The microbiology of diabetic foot wounds is variable depending on the extent of involvement (Karchmer *et al*., 1994 and Wheat *et al*., 1986):

- Superficial diabetic foot infections are likely to be due to aerobic gram-positive cocci (including Staphylococcus aureus, *S. agalactiae, S. pyogenes*, and coagulase-negative staphylococci). Patients who are severely ill at the time of presentation should be empirically treated with antibiotics covering Methicillin Resistant Staphylococcus Aureus.
- Ulcers that are deep, chronically infected, and/or previously treated with antibiotics are more likely to be polymicrobial. Such wounds may involve the above organisms in addition to enterococci, Enterobacteriaceae, Pseudomonas aeruginosa, and anaerobes.

Wounds with extensive local inflammation, necrosis, or gangrene with signs of systemic toxicity should be presumed to have anaerobic organisms in addition to the above pathogens. Potential pathogens include anaerobic streptococci, Bacteroides species, and Clostridium species (Sapico *et al*., 1984; Sims *et al*., 1984). It is also important to note that diabetic patients with chronic foot wounds who receive repeated and prolonged courses of antibiotics represent an important risk group for development of vancomycin-resistant Staphylococcus aureus infections.

Organisms cultured from superficial swabs are not reliable for predicting the pathogens responsible for deeper infection (Sapico *et al*., 1984; Sims *et al*., 1984 and Senneville *et al*., 2006). Deep tissue cultures should be done, and for evaluation of osteomyelitis, bone biopsy is needed. In almost all reported Diabetic foot osteomyelitis series, S. aureus is the most common pathogen cultured from bone samples, followed by Staphylococcus epidermidis (Wheat *et al*., 1986; Senneville *et al*., 2006; Lavery *et al*., 1996 and Lesens *et al*., 2011). Among the gram-negative bacilli, Escherichia coli, Klebsiellapneumoniae, and Proteus species are the most common pathogens, followed by P. aeruginosa. The frequency of isolation of obligate anaerobes (mostly Peptostreptococcus, Peptococcus and Finegoldia magna) is low.

Treatment

The development of infection constitutes a foot care emergency, which requires referral to specialized foot-care team within 24 hours. The underlying principles are to diagnose infection, culture the bacteria responsible, treat aggressively with antibiotic therapy and consider the need for debridement and surgery.

According to the IDSA recommendations

- For mild to moderate infections in patients who have not recently received antibiotic treatment, suggested therapy is to target aerobic gram-positive cocci (GPC).
- For most severe infections, it is recommended to start broad-spectrum empiric antibiotic therapy, pending culture results and antibiotic susceptibility data.
- Empiric therapy directed at P. aeruginosa is usually unnecessary except for patients with risk factors for true infection with this organism.
- Consider providing empiric therapy directed against MRSA in a patient with a prior history of MRSA infection; when the local prevalence of MRSA colonization or infection is high; or if the infection is clinically severe.

It is recommended that definitive therapy for DFI be based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen. The suggested initial antibiotic course for a soft tissue infection is of about 1–2weeks for mild infections and 2–3 weeks for moderate to severe infections. Antibiotics vary in how well they achieve therapeutic concentrations in infected diabetic foot lesions (Nicolauand Stein, 2010). This is related to the pharmacodynamics properties of the specific agent and the arterialsupply to the foot, rather than to diabetes per se. A randomized controlled double-blind trial study carried out on 586 patients by Lipsky, 2005 compared Ertapenem vs piperacillin/tazobactam (IV) in patients with moderate to severe DFI which concluded that clinical and microbiological outcomes for patients treated with ertapenem were equivalent to those for patients treated with piperacillin/tazobactam, suggesting that this once-daily antibiotic should be considered for parenteral therapy of diabetic foot infections, when deemed appropriate.

A Cost minimization analysis of treatment of diabetic foot infections conducted by lipsky in May 2007 on patients enrolled in a double-blind randomized trial who were treated as inpatients showed that, compared with piperacillin–tazobactam given four times daily, i.v., ertapenem given once daily was associated with lower drug acquisition and supply costs and less time and labour devoted to preparation and administration

of intravenous therapy (Lipsky *et al*., 2005).In patients with osteomyelitis no data supports the superiority of any specific antibiotic agent or treatment strategy, route, or duration of therapy. Thus the antibiotic therapy based on the culture of bone (compared withempiric therapy) is associated with a significantly higher rate of resolution of the bone infection without surgery after a mean of 12 months' follow-up (Senneville *et al*., 2006). The most appropriate duration of therapy for any type of DFO depends on the presence and amount of any residual dead or infected bone and the state of the soft tissues.

It is also important to assess the arterial supply to the foot and consider revascularization either by angioplasty or bypass if the foot is ischemic. Also to optimize the metabolic control to improve outcome. Thus infection in the diabetic foot needs full multidisciplinary treatment. The team managing these infections should preferably include, or have ready access to, an infectious diseases specialist as well as microbiologist.

Conclusion

Overall results show that in terms of wound healing, length of stay, and debridement ertapenem is superior to tazocin. Ertapenem is also more cost effective as compared to Tazocin. However as more patients had to be switched over from ertapenem to tazocin as they were not responding, therefore further big scale studies are required to compare the effectiveness of these two antibiotics in DFI patients.

No Conflict of Interest

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