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Cost-Effectiveness Study Comparing Cefoperazone-Sulbactam to a Three-Drug Combination for Treating Intraabdominal Infections in an Indian Health-Care Setting

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ABSTRACT

Objective: This article presents the methodology and results of the pharmacoeconomic analysis of the Magnex Against Standard COmbination Therapy study comparing cefoperazone-sulbactam (Magnex) versus ceftazidime+ amikacin+metronidazole, in the treatment of intra-abdominal infections.

Methods: This prospective, open label, phase IV study was conducted at 17 study sites in India and randomized subjects to receive either cefoperazone-sulbactam or the combination. Pharmacoeconomic analysis was included as a secondary objective and conducted in the clinical efficacy-evaluable (CEE) and the successfully treated patients. All comparisons between treatment groups were conducted using analysis of variance (ANOVA) or Wilcoxon Two-Sample tests. All costs were reported as Indian Rupee (INR) and actual unit costs collected in 2006 were used for the analyses [1 USD ~ 40 INR; 1 Euro ~ 56 INR].

Results: In the CEE and the successfully treated subset of patients, the average cost of treatment was numerically lower in the cefoperazone-sulbactam arm (not statistically significant). The analyses found that the cost-effectiveness ratio (CER) for cefoperazone-sulbactam was INR 17,640.53 and that for the comparator group was INR 22,075.16. Additionally, the incremental CER results showed that the cost of treatment was INR 21,505.59 lower per additional successfully treated patient in the cefoperazone-sulbactam group.

Conclusions: The present study was the first of its kind to be conducted in the "price sensitive" Indian health-care setting. Though study was not powered for the difference in average cost of treatments, there was a trend favoring cefoperazone sulbactam. The findings from this study should encourage further conduct of similar analyses and increase the knowledge regarding pharmacoeconomics in India.

Keywords: cefoperazone-sulbactam, cost-effectiveness, intra-abdominal infections, pharmacoeconomics.

Introduction

Indian Health-Care Scenario

The state of India's health care is growing at a rapid pace. Health-care cost as a percentage of the gross domestic product (GDP) is 5.1% and is designated as a priority for the government. Health-care spending is expected to increase from $21 billion in 2005 to $45 billion in 2012. Public spending is anticipated to grow from the present amount of 0.9% of the GDP to 2% of the GDP by 2009. India carries a mixed disease burden—age-old infectious diseases; reemergence of diseases like tuberculosis and malaria; dreaded diseases like cancer and AIDS; lifestyle diseases like cardiovascular (CV), diabetes, and depression. Disease burdens are projected to rise rapidly with 60% of the global CV burden by 2020 and 73 million diabetic patients by 2025. The changing disease profile therefore calls for more advanced and innovative therapies [1].

A substantial share of the Indian population (i.e., about 200 million middle class with disposable incomes) are increasingly able to afford to pay for medicines. "Self-pay" or out-of-pocket payment currently accounts for 75% of all health-care spending (the central or state governments pay for 19%, other public spending accounts for 3%, and other private spending accounts for the remaining 3%) and will remain the key payment mode. Approximately 15% of the population has some form of prepayment coverage but the growth in health insurance coverage is hampered by regulatory provisions. Medications comprise approximately 20% of total health-care spending and the per capita expenditure on medicines, currently at $5.60, is likely to increase substantially with improved literacy rates, increased access to medical information, and the rise in income levels [2]. The evolving status of India's health care makes it important to perform

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research studies/cost-efficacy analysis (CEA) to justify the "value proposition" from the patients "perspective" as well from the perspective of various other stakeholders, e.g., regulators, pricing authority, insurers and doctors, which can bring about the improvement of the health-care system in the country.

Magnex Against Standard COmbination Therapy (MASCOT) Rationale and Design

Intraabdominal infections are often polymicrobial and include aerobic as well as anaerobic bacteria. Antibiotics used to treat intraabdominal infections should target organisms such as Enterobacteriaceae and Bacteroides fragilis, which are commonly known to cause these infections [3]. Combinations of a third-generation cephalosporin, an aminoglycoside, and metronidazole are often used to treat intraabdominal infections in surgical settings. An alternative treatment for these infections is a beta lactam-beta lactamase inhibitor combination such as cefoperazone-sulbactam.

The safety and efficacy of cefoperazone-sulbactam was compared to ceftazidime plus amikacin and metronidazole (comparator treatment) in a randomized, open-label, multicenter (17 sites across India), phase IV study for the treatment of intraabdominal infections. At the end of treatment visit, a clinical outcome evaluation was performed and categorized as success, defined by complete resolution of baseline signs and symptoms; improvement, defined as resolution of some, but not all baseline symptoms and no further systemic antimicrobials administered; or failure, which was defined by the need for additional systemic antimicrobial therapy, the need for more than one surgical procedure or death 48 h after initiating therapy. Those participants who achieved clinical success or improvement at the end of the treatment visit were evaluated after 30 days and categorized as having either continued resolution, defined by the continued absence of, or minimal, signs and symptoms not requiring further therapy, or relapse, defined as a return or worsening of signs and symptoms requiring therapy. Subjects who could not be categorized into any of the outcomes were regarded as indeterminate. The primary efficacy variable was the proportion of efficacy-evaluable subjects having a clinical outcome of continued resolution at the Test of Cure (TOC)/30-day follow-up visit.

In total, 92% of cefoperazone-sulbactam-treated subjects had continued resolution at the follow-up visit compared with 82% in the comparator group ($P = 0.015$). The difference between treatments was 10.1% (95% CI 2.1–18.1%). The lower limit of the 95% CI was higher than the predefined noninferiority limit of >−12.5%; thus noninferiority was demonstrated. Superiority of cefoperazone sulbactam was demonstrated for both the clinical efficacy-evaluable (CEE) population and the modified intent to treat (MITT) population (lower limit of 95% CI for the difference between treatments >0%). In the MITT analysis, 89.3% of subjects treated with cefoperazone sulbactam had continued resolution of their clinical signs and symptoms at the 30-day follow-up visit compared with 79.2% in the comparator group.

In addition, cefoperazone-sulbactam was found to have a better safety profile compared with the comparator with a lower number of treatment-related adverse events (AEs) and discontinuations due to treatment-related AEs. The details of the efficacy and safety of cefoperazone-sulbactam are presented separately [4].

Objectives

The primary objective of the MASCOT study conducted in India was to evaluate the efficacy of cefoperazone-sulbactam in comparison with ceftazidime plus amikacin and metronidazole for intraabdominal infections. The secondary objectives of the MASCOT study included the assessment of the safety profile of cefoperazone-sulbactam and the analysis of relevant pharmacoeconomic data for cefoperazone-sulbactam. During the past 15 years, a substantial international interest has developed in the economic evaluation of health-care and medical technologies [5]. The present study evaluating the pharmacoeconomic data of cefoperazone-sulbactam versus a comparator was the first of its kind to be conducted in India. It was also the first study that compared a mono-therapy with a three-drug combination in the Indian health-care setting. The objectives of this article are to present the methodology and results of the economic evaluations conducted as part of the MASCOT study.

Methods

MASCOT was planned as a noninferiority study. Noninferiority trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin. Subjects with intraabdominal infections were stratified based on age and baseline Acute Physiology, Age, and Chronic Health Evaluation II scores and randomized to receive either cefoperazone-sulbactam or the combination of ceftazidime, amikacin, and metronidazole. Subjects were treated with the study medication intravenously (IV) for a minimum of five days and not more than 14 days. Subjects were assessed daily during the treatment period and the end of treatment visit occurred within 12 h of the last dose of study medication. Details of the trial design and methodology will be presented in detail as a separate article.

Comparison of pharmacoeconomic data for cefoperazone-sulbactam versus the comparator was one of the secondary objectives of the MASCOT study. The following costs were analyzed: the cost of medications; hospitalization charges; cost of interventions

done for source control (e.g., surgical interventions, laparoscopy, laparotomy, etc.); and cost of consultations, referrals, and investigations. The case report form (CRF) used in the study captured the units for each cost item (the different cost items are presented in Appendix A). Both costs for the primary source intervention or surgery and complications which resulted in secondary interventions or surgeries were considered in the cost analysis. But, the costs of concomitant medications or switches have not been included in this cost analysis because many generics are available with varying costs. Hence, if a patient failed the study drug and was started on another therapy, that cost (of new medication) was not included in this study. Nevertheless, if the patient was transferred to an intensive care unit or required reintervention, then that cost was included.

A standardized unit cost (Indian Rupee or INR value) was assigned to the data collected in the CRF. Actual unit costs for each cost item from across sites participating in the study were collected for both government/municipal and private hospitals in 2006 and were used to compute the total cost of treatment of patients at their hospitals. This cost was then used to calculate the average total cost in the two therapeutic arms. All costs are reported as INR [1 USD ~ 40 INR; 1 Euro ~ 56 INR].

A CEA was conducted as part of this study. The average cost-effectiveness ratio (CER) was calculated for each treatment alternative, and the incremental CER (ICER) was calculated The ICER is defined as a ratio of the difference in costs between two alternatives to the difference in the effectiveness between the alternatives and is calculated as follows:

$$\begin{aligned}\text{ICER} &= (\Delta\text{Cost})/(\Delta\text{Effect}) \\ &= (\text{Cost}_{\text{New Alternative}} - \text{Cost}_{\text{Comparator}})/ \\ &\quad (\text{Effect}_{\text{New Alternative}} - \text{Effect}_{\text{Comparator}})\end{aligned}$$

where "cost" and "effect" are defined consistently with those used to compute the average CER.

In this study specifically, the ICER was calculated as follows:

$$\begin{aligned}\text{ICER} = &(\text{Total cost of treatment A} - \\ &\text{Total cost of treatment B})/ \\ &(\text{Success rate of treatment A} - \\ &\text{Success rate of treatment B})\end{aligned}$$

The overall objective of the pharmacoeconomic analyses was to determine whether there was any difference in the average cost of treatment per patient between the two treatment arms (i.e., cefoperazone-sulbactam vs. comparator). To meet this objective, analyses were conducted in the CEE patients. All comparisons between treatment groups were conducted using analysis of variance (ANOVA) or Wilcoxon Two-Sample tests.

Table 1 Baseline demographics

Characteristic	Cefoperazone-sulbactam (n = 154)	Comparator (n = 152)
Male, n (%)	119 (77.3)	113 (74.3)
Mean age, years (SD)	36.4 (15.4)	35.7 (16.3)
<18 (n)	15	18
18–44 (n)	87	93
45–64 (n)	42	28
≥65 (n)	10	13
Mean weight, kg (SD)	55.4 (11.7)	54.1 (11.3)
Mean height, cm (SD)	159.6 (10.7)	159.6 (10.8)

Results

Demographics

At baseline, 306 patients were randomized to treatment in the MASCOT study with 154 patients in the cefoperazone-sulbactam arm and 152 patients in the comparator arm. In both treatment arms, a majority of patients were male (cefoperazone-sulbactam: 119, 77.3%; comparator: 113, 74.3%). The mean age of patients in the cefoperazone-sulbactam group was 36.4 years (SD = 15.4) and that in the comparator group was 35.7 years (SD = 16.3). Most of the patients in both treatment arms were between the ages of 18–44 years (cefoperazone-sulbactam: 87, 56.5%; comparator: 93, 61.2%). The mean weights and heights in both treatment arms were similar. Details of the study demographics at baseline are presented in Table 1.

Cost Comparisons

Of the cost items, the biggest drivers of cost were surgeries, hospitalization cost, disposable syringe sets, IV fluid packs, IV sets, and arterial blood gas analysis. Although the average costs for these cost items were lower in the cefoperazone-sulbactam arm than in the comparator arm, there were no significant differences between the two arms (Table 2).

MITT population. There were 152 subjects in each arm. Although the average cost of treatment per patient in the cefoperazone-sulbactam arm was lower than that of the comparator arm, there was no significant difference between the treatment arms (cefoperazone-sulbactam: INR 17,111.05 (SD = 11,661.27); comparator: INR 18,446.57 (SD = 14,732.5); $P = 0.3816$). The difference in the average cost of treatment per patient between the two arms was approximately INR 1336. Similarly, the average cost of treatment per patient in the cefoperazone-sulbactam group was lower in both the government/municipal hospitals and private hospitals but there were no significant differences between the groups in either the government/municipal or private hospital settings (for government/municipal hospitals: cefoperazone-sulbactam: INR 11,682.35 (SD = 7231.67); comparator: INR 13,221.91 (SD = 8998.31); $P = 0.5698$) (for private hospitals:

Table 2 Biggest cost drivers in the two treatment arms

Cost item	Average costs for cefoperazone-sulbactam (INR)	Average costs for comparator (INR)	Cost difference (cefoperazone-sulbactam-comparator)	*P*-value
Surgeries	3454.80	4037.10	−582.30	0.45
Hospitalization cost (general ward and special care unit)	1114.60	1393.60	−279.00	0.33
Disposable syringe sets	811.87	1146.50	−334.60	0.34
Intravenous fluid packs	754.82	944.33	−189.50	0.29
Intravenous sets	441.46	631.13	−189.70	0.15
Arterial blood gas analysis	381.04	487.38	−106.30	0.12

INR, Indian Rupee.

cefoperazone-sulbactam: INR 29,669.18 [SD = 6792.84]; comparator: INR 35,457.40 [SD = 17,854.97]; $P = 0.1648$). The differences in average cost of treatment per patient between the two treatment arms in the government/municipal hospitals and private hospitals were INR 811.4 and INR 5788, respectively (Table 3). Additionally, it was found that the average cost of treatment per patient in the government/municipal hospitals was significantly lower than in the private hospitals ($P < 0.0001$).

There was no significant difference in the average drug cost of treatment per patient between the two treatment arms (cefoperazone-sulbactam: INR 5412.98 [SD = 3170.26]; comparator: INR 5869.91 [SD = 3035.35]; $P = 0.2003$). The difference in average drug cost per patient between the two treatment arms was approximately INR 457 (Table 4). Additionally, the average length of hospitalizations was very similar between the cefoperazone-sulbactam and the comparator groups (cefoperazone-sulbactam: 10.52 days [SD = 5.29]; comparator: 10.49 days [SD = 6.19]). Nevertheless, duration of hospitalization in the "special care unit/ICU" was significantly longer in the comparator arm ($P = 0.03$) (Table 5).

CEE subset. At the end of the study, there were 134 clinically evaluable patients in the cefoperazone-sulbactam arm and 132 patients in the comparator arm. CEE population is a subset of ITT, which was evaluated for efficacy. Subjects excluded from the CEE analysis population were all excluded due to protocol deviations like prohibited concomitant antimicrobial medication use, insufficient therapy, evidence of malignant disease, intestinal tuberculosis or amoebic pathology; lack of post baseline clinical assessments, death within 48 h of study therapy, patients did not meet eligibility criteria, suspected source of intra-abdominal infection was not confirmed.

Cost-Effectiveness Analyses

Of the 134 patients treated with cefoperazone-sulbactam, 125 patients were treated successfully (i.e., CEE subjects who presented themselves with continued resolution at the 30-day follow-up visit/TOC visit) and of the 132 patients treated with comparator, 108 patients were successfully treated. Therefore, the cefoperazone-sulbactam treatment arm had a higher success rate (91.79%) compared to the comparator treatment arm (81.82%). The CER or the average cost per successfully treated patient for cefoperazone-sulbactam was INR 17,640.53 and that for the comparator group was INR 22,075.16 [CEE population]. The CER calculated for MITT population was 19,704.11 for cefoperazone-sulbactam and 26,333.43 for the comparator. Therefore, the average cost per successfully treated patient was INR 6629.32 lower in the cefoperazone-sulbactam group than in the comparator group (Table 6).

Table 3 Average treatment cost per patient—modified intent to treat population

	Cefoperazone-sulbactam	Comparator	*P*-value	95% CI
Overall			0.3816	(−4,335, 1,663.5)
N	154	152		
Average cost/patient	INR 17,111.05	INR 18,446.57		
SD	11,661.27	14,732.5		
Government/municipal hospital			0.5698	(−3,621, 1,998.4)
N	128	130		
Average cost/patient	INR 11,682.35	INR 13,221.91		
SD	7,231.67	8,998.31		
Private hospital			0.1648	(−1,3686, 2,109.7)
N	24	22		
Average cost/patient	INR 29,669.18	INR 35,457.40		
SD	6,792.84	17,854.97		

INR, Indian Rupee.

Table 4 Average drug cost per patient—modified intent to treat population

	Cefoperazone-sulbactam (n = 154)	Comparator (n = 152)	*P*-value	95% CI
Average cost/patient	INR 5412.98	INR 5869.91	0.2003	(−1,157, 243.62)
SD	3170.26	3035.35		

INR, Indian Rupee.

Discussion

MASCOT was the first prospective study with pharmacoeconomic endpoints in India. Results demonstrated that cefoperazone-sulbactam was superior to the comparator used in the study (i.e., combination of ceftazidime, amikacin, and metronidazole) and that it also had a better safety profile. In addition to its clinical advantage in treating intraabdominal infections, the MASCOT study found that in the CEE population of patients, the average cost of treatment per patient overall, as well as in both the government/municipal and private hospital settings was lower in the cefoperazone-sulbactam group than the comparator group (but no significant difference was found in any of these cases). As expected, the average cost of treatment per patient in both the arms was significantly lower in the government/municipal hospitals than in the private hospitals. Additionally, the study also found that there was no significant difference in the average drug cost of treatment per patient between the two treatment arms and that the average length of hospitalizations was very similar between the two arms. The average drug cost per patient for the successfully treated population was lower in the cefoperazone-sulbactam group, although there was no significant difference between the two treatment arms. Additionally, the ICER results showed that the cost of treating a patient with cefoperazone-sulbactam was over INR 21,000 less per additional successfully treated patient.

Clinical trials are often considered artificial treatment environments, and may not provide all the economic information needed by decision-makers. Trial populations may not commonly reflect patient groups treated in clinical practice, and the time horizon for trials often may not reflect the duration of impact of the intervention [2] One of the limitations of the pharmacoeconomic evaluation in the present study was the lack of inclusion of costs of alternative therapy in event of failure of study medication. Nevertheless, we did capture the cost of complications that might have occurred in these patients. The primary efficacy variable was the proportion of efficacy-evaluable subjects having a clinical outcome of continued resolution at the 30-day follow-up or TOC visit. Another limitation was that we did not capture any costs that might have incurred during the 30-day interval. Nevertheless, in retrospect, this can be justified on the account that the there were no additional failures during this period and the success rates for both the arms remained consistent (additional costs unlikely). Another limitation is that the study uses a surrogate end point. Future studies in this premise should also include collection of utility weights from amongst the patient population to build a CER using QALY methods.

The MASCOT study was not only the first study comparing a monotherapy versus a three-drug combination in the Indian setting, it was also the first study to conduct a pharmacoeconomic analysis to show the overall cost advantages of the treatment options within this health-care environment. In India, where the current health-care system requires patients to "self-pay" for their treatments, and therefore prescribers are sensitive to prices, it is important for a treatment to show a pharmacoeconomic advantage. Cefoperazone-sulbactam had a lower drug cost per patient and a lower overall average cost of treatment per patient when compared to the comparator. Though this differ-

Table 5 Length of hospitalizations—modified intent to treat population

	Cefoperazone-sulbactam Mean (SD)	Comparator Mean (SD)
Hospitalizations	10.52 days (5.29) n = 151	10.49 days (6.19) n = 148
Special care unit	0.47 days (1.23) n = 130	1.04 days (2.74)* n = 131
Special nursing care	0.37 days (1.18) n = 128	0.52 day (1.91) n = 124

*$P = 0.03$.

Table 6 Results of cost-effectiveness analyses

	Cefoperazone-sulbactam	Comparator
Number of MITT patients	154	152
Number of clinically evaluable (CEE) patients	134	132
Number of patients successfully treated	125	108
Success rate for CEE population	91.79%*	81.82%
Success rate for MITT population	81.2%†	71.2%†
Average CER (calculated for MITT population)	INR 19,704.11	INR 26,333.43

*Odds ratio 2.52; 95% CI 1.18–5.38; $P = 0.015$.
†95% CI 2.0% to 18.3%; $P = 0.015$.
CEE, clinical efficacy-evaluable; CER, cost-effectiveness ratio; INR, Indian Rupee; MITT, modified intent to treat.

ence was not significant (the study was not powered for this end point), it reflects a trend in costs.

With emerging privatized health care in India, the results will have considerable impact on how hospital groups may decide to purchase medications for patients. It will be important to consider not only the drug acquisition costs when making a treatment decision, but to consider the lower overall treatment cost when treating patients with intraabdominal infections. The results from this study demonstrated the importance of pharmacoeconomics and will likely influence the methodology of future treatment comparison trials conducted in India.

Conclusions

This is the first prospective study with pharmacoeconomic endpoints in India. As the science is still in its nascent stage, more pharmacoeconomic work will be necessary to establish sound methodologies in the Indian health-care context.

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Appendix A Costs Items

1. Medication Cost
   a. Drug costs including details of the drug and number of days of treatment
      i. Study medication
      ii. Concomitant medications (drugs started postrandomization)
      iii. Posttreatment medications (drugs started at the end of treatment (EOT) for ongoing symptoms. This will include additional/ alternative antimicrobials for treatment failures)
   b. Cost of consumables
      i. IV fluids
      ii. IV sets
      iii. Disposable syringes and needles
2. Hospitalization charges including the number of days of hospitalization (including special care units)
   a. Bed charges
   b. Nursing charges
3. Cost of intervention for source control including the type and number of interventions
   a. Primary procedure for source control
   b. Additional procedure, if performed
4. Cost of investigations including the type and number of investigations (investigations performed at the screening visit was not included as part of the pharmacoeconomic analysis)
   a. Clinical laboratory tests
   b. Radiological investigations
   c. Microbiological tests
5. Consultation charges (except treating surgeon) including the number of referrals made by the treating surgeon
   a. Physicians
   b. Physiotherapists
   c. Occupational therapists
   d. Intensive care specialists