EFFECTIVENESS AND ECONOMIC OUTCOMES OF GENERIC AND BRAND-NAME IMIPENEM/CILASTATIN IN THAI PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

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ABSTRACT: Generic imipenem/cilastatin (Yungjin®) has been available at Rajavithi Hospital since 2008. No study has investigated effectiveness and economic consequences of generic and branded imipenem/cilastatin (Tienam®) in hospital-acquired pneumonia (HAP). The objective of this study was to compare clinical effectiveness and economic consequences between both of drugs. Medical records of adult patients were diagnosed HAP and received imipenem/cilastatin at least 48 hours between January 2008 and April 2012 including imipenem/cilastatin treatment costs (direct medical costs) were reviewed. The economic perspective was hospital perspective. The effectiveness and economic consequences of 154 patients who received each drug was compared using less than 10% of favorable outcome difference. The study revealed that among 308 patients, the overall favorable outcomes in the generic and branded imipenem/cilastatin were 24% and 37.6%, respectively (OR 0.5, 95% CI 0.3 to 0.9, estimated absolute difference -13.6%, 95% CI -23.8% to -3.4%, estimated number needed to treat (NNT) = 7, p = 0.010). The adverse drug reactions in both groups were not significantly different. Length of stay (LOS) in the generic and branded drug were 50.1 and 81.0 days respectively (p = 0.020). The total treatment costs and cost per case using generic drug treatment were roughly 7.52 million baht and 0.20 million baht, respectively. For branded drug total treatment costs and cost per case were roughly 13.60 million baht and 0.23 million baht, respectively. An incremental cost-effectiveness ratio (ICER) was roughly 0.29 million baht per patient. Univariate sensitivity analysis indicated that ICER was sensitive to changes in drug costs and consumer price index. In conclusion, these results suggest that generic imipenem/cilastatin (Yungjin®) could not prove for equivalent effectiveness to branded imipenem/cilastatin (Tienam®) in HAP, but associated with lower treatment costs.

Keywords: Effectiveness, Economic consequences, Generic drug, Imipenem/cilastatin, Hospital-acquired pneumonia

INTRODUCTION

Hospital-acquired pneumonia (HAP) is a crucial nosocomial infection around the world and associated with high morbidity and mortality. HAP is defined as "Pneumonia that occurs 48 hours or more after admission". The manifestation of HAP has increased hospitalization by an average of 7 – 9 days per patient and has been reported to produce an excess cost of more than $40,000 per patient [1]. HAP is associated with crude mortality rates up to 70% and attributable mortality rates as high as 33% to 50% [2]. In 2010, HAP was the highest mortality (1.95 per 100,000 populations) in disease under surveillance in Thailand [3]. Imipenem/cilastatin is one of the first-line empirical treatments in patients with late-onset (five days or more) HAP or with multidrug-resistant pathogens and all disease

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severity [1-5]. In addition, imipenem/cilastatin is one of the high cost antibacterial agents in Thailand and the drug expenditures have increased every year. The average 5-year total expenditure from 2006 to 2010 was 505 million baht per year, with was 32% of carbapenems expenditures [6]. Similary, in Rajavithi Hospital imipenem/cilastatin was among top 10 high-cost drugs between 2006 and 2010 and the average 5-year total expenditure was 18.9 million baht.

The generic substitution policy has been implemented in Thailand over the past five years. Patients, therefore need to receive a generic drug for all type of insurance schemes, such as the Universal Coverage, the Universal Coverage Scheme (UCS), Social Security Scheme (SSS) and the Civil Servants Medical Benefit Scheme (CSMBS). Few Generic imipenem/cilastatin have been available for HAP patients, for example, Yungjin® at Rajavithi Hospital, with is tertiary care setting since 2008. Nevertheless there are growing concerns over the clinically equivalence of the generic drug from many healthcare professionals and patients. However, there is no study to prove this equivalence to HAP patients. Only investigated generic imipenem/cilastatin (Yungjin®) in general infections [7]. They found that generic drug was not clinically equivalence to branded imipenem/ cilastatin, in term of, decrease cure rate and improvement.

From an extensive literature search, no study has been carried out to compare the effectiveness and economic consequences of the generic imipenem/cilastatin in HAP patients. Thus, this study was aimed to compare clinical effectiveness and economic consequences of generic and branded imipenem/cilastatin in HAP at Rajavithi Hospital

MATERIALS AND METHODS

This observational study with a retrospective approach was approved by the ethics committee of Rajavithi Hospital in 2012. It was carried out by obtaining the data of hospitalized patients using either the generic (Yungjin®) or branded imipenem/cilastatin (Tienam®) from January 2008 to April 2012. Details of the research methods are elaborated below.

Patients and samples

Patients included in this study were inpatients aged 18 or over, diagnosed as hospital-acquired pneumonia (HAP) based on International Statistical Classification of Diseases and Related Health Problems 10th Revision version for 2010 (ICD-10) and received imipenem/cilastatin either generic (Yungjin®) or branded drug (Tienam®) at least 48 hours during their stay on different wards, i.e., Medicine, Surgery or others, between January 2008 and April 2012. Patients were excluded if their medical records were not available, the lab results were incomplete or unable to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [8], or those received imipenem/cilastatin less than 48 hours or other generic imipenem/cilastatin apart from Yungjin®. Additionally, patients who received both generic and branded imipenem/cilastin continuously within the same admission, suffered from duplicated infections in many organs, declined to complete the course of treatment for various reasons, or had incomplete cost data were also removed from the study. The sample size was calculated according to the overall favorable response rate of 70% [7] in the control group using the branded drug and the effect size at least 10% [9, 10]. Given the significance level (α) determined at 0.05 (two-tailed) and 80% power, 330 patients in each group, or totally 660 patients, were required. In order to make control and case groups more comparable, propensity score matching (PSM) [11, 12] was utilized to take account of two covariates, i.e. the number of comorbidities and APACHE II scores (with patients' age included). With the "nearest neighbor matching" plan of 1:1, the case group was matched with the control without replacement based on the closet estimated propensity scores of 1.0. A matching "caliper" of 0.175 standard deviations of the logit of the estimated propensity scores provided the best match. The PSM was performed using PASW Statistics 19 (SPSS-IBM Co., Chicago, IL).

Study instrument

A data collection form was developed to collect all relevant data. It was divided into three parts. Part 1 included patients' characteristics and medical conditions, e.g., gender, age, departments, the number of comorbidity, computed APACHE II scores, the use of other antibiotics within 30 days, the type of bacteria. Part 2 was involved in an effectiveness evaluation, such as clinical and microbiological outcomes, whereas an economic evaluation from a hospital perspective was recorded in Part 3. With respect to the medicines, the generic imipenem/cilastatin (Yungjin®) injection is widely used in Thai hospitals and worldwide. It has been manufactured by Yungjin Pharmaceutical Co. Ltd. in South Korea and imported by So Jarunphaesat Co., which is a local distributor. The branded imipenem/cilastatin

(Tienam®) is produced by Merck & Co., Inc. in the US and marketed by the company.

APACHE II scores

The patients' overall conditions were assessed within 24 – 48 hours after their admission using the Acute Physiology and Chronic Health Evaluation (APACHE) II [8]. It is a clinical scoring system used to classify the severity of illness by means of the last values in the last 24 hours and to predict the death rate [8], which can be roughly presented as an equation below

$$\text{APACHE II score} = \text{Acute physiologic score} + \text{Age points} + \text{Chronic health points}$$

Effectiveness evaluation

In this study, the drug effectiveness was assessed at the end of treatment with numerous indicators as follows:

Clinical outcomes: The clinical response that was a primary outcome was evaluated from medical records, i.e., admission notes, progress notes, pharmacist notes, nurse notes, and consultation forms. The outcomes embraced 'cure' (a complete resolution of symptoms and signs, or the lack of progression of abnormalities on the chest X-ray film without the addition of other antibiotics), 'improvement' (the same as for cure, but with partial resolution of symptoms and signs), 'worsening or persistence' of the infection, or 'death' [10]. Moreover, the overall favorable response including both 'cure' and 'improvement' was employed for statistical purposes. As part of clinical outcomes, all adverse drug reactions (ADRs) were also recorded based on the progress or nurse notes. No causality assessment using the Naranjo's algorithm or WHO's ADR assessment was formally carried out due to the patients' conditions. Nevertheless, the temporal sequence and documented evidence were primarily utilized to determine any ADRs caused by imipenem/cilastatin.

Microbiological outcomes: The microbiological response was also a primary outcome obtained from the two drugs. The outcomes were presented as 'eradication' (the elimination of causative organisms during or at the completion of treatment), 'persistence' (failure to eradicate the original causative organisms), 'super-infection' (a new lower respiratory tract infection during treatment due to new organisms), or 'undetermined' in case the blood samples were not available for the evaluation of the microbiological response [10]. Other outcomes, i.e., the duration of treatment, discharge status, and length of stay, that were gathered from the discharge summary report in patients' medical records were also noted.

Economic evaluation

The economic aspect of the medication use in this study was considered from the hospital perspective. It was the imipenem/cilastatin treatment in HAP. The former was concerned with the laboratory, room, administration and imipenem/cilastatin costs (based on dosing regimen for moderate to severe infection: 1 gram intravenous every 6 hr) for the total treatment costs (or direct medical costs). The total treatment costs based on the diagnosis-related group (DRG) charges from the patients' admission to their discharge or death. All costs were converted to Thai baht in the year 2013. Therefore, the consumer price index (CPI) for medical care service in the year 2011 was used.

Data collection

Patients' data were initially retrieved from the Department of Medical Records and the Department of Computer Center of Rajavithi Hospital. As shown in Figure 1, a case group consisting of 368 HAP patients with the generic imipenem/cilastatin (Yungjin®) and a control group of 280 HAP patients with the branded drugs (Tienam®) were identified. After considering the eligibility criteria, 184 and 160 HAP patients were included in the case and control group, respectively. With the one-to-one propensity score matching, only 154 patients in each group were assessed for the effectiveness and economic outcomes. The researcher (KK) made use of the data collection form to gather data from the digital database and hard copies of medical records. All data were then entered into Excel to facilitate a data analysis.

Statistical analysis

The patients' data were analyzed using both descriptive and inferential statistics in PASW Statistics 19 (SPSS-IBM Co., Chicago, IL). For patients' characteristics, continuous variables, such as age, the number of comorbidity, or APACHE II scores, were compared between two matched groups by a paired t-test (two-tailed) and categorical variables by a McNemar test. Regarding the effectiveness analysis, odds ratios (OR), estimated absolute differences, and estimated number needed to treat (NNT) were computed for clinical and microbiological responses to better compare the impacts of two imipenem/cilastatin preparations as to whether they were different (or two-tailed test). A paired t-test was also performed

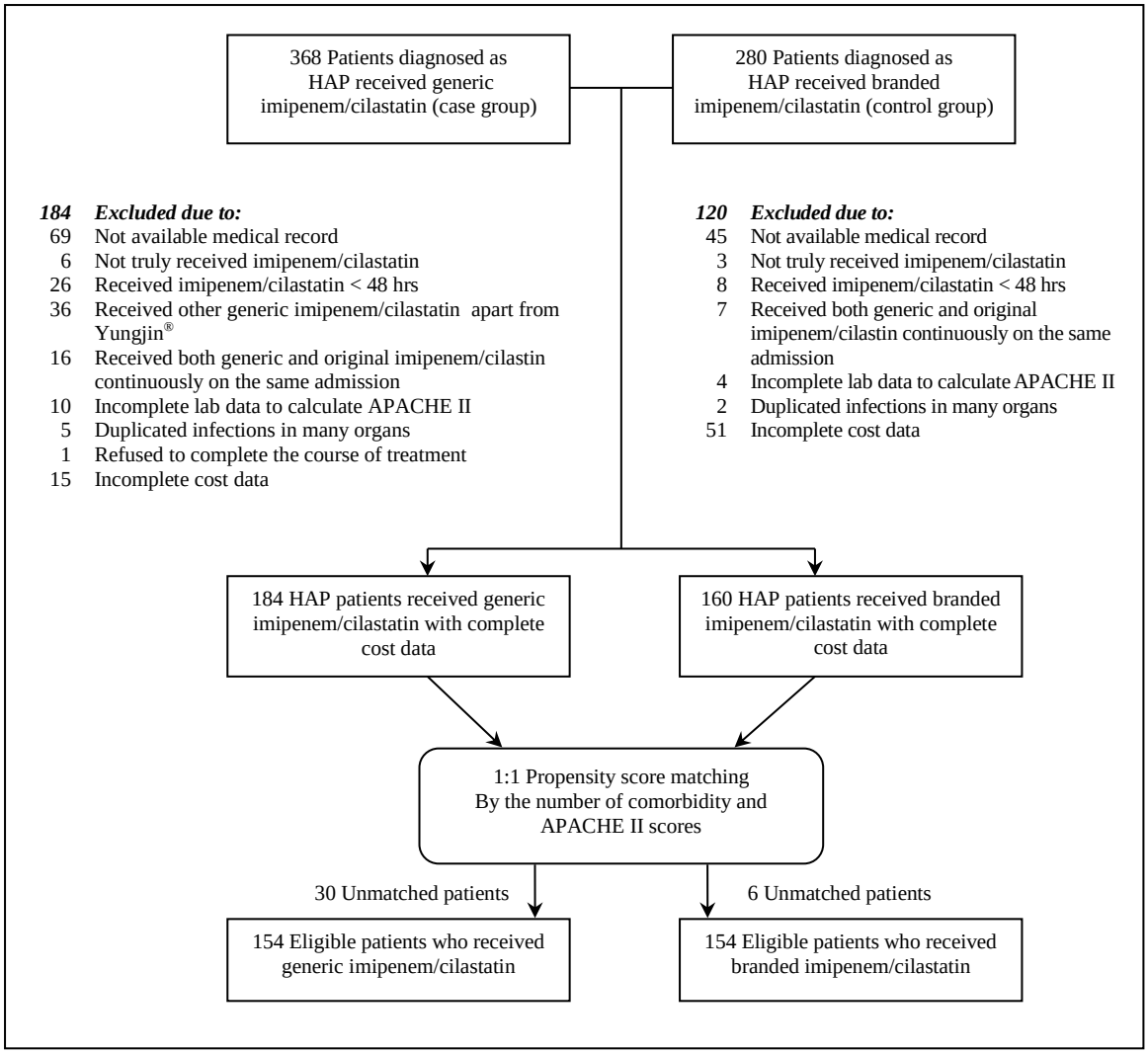

Figure 1 Study flow diagram

for the rest of effectiveness assessments and Wilcoxon Signed Ranks test was substituted when the data is not normally distributed. The significance level (α) was set at 0.05. With respect to the economic outcomes, costs relating to the imipenem/cilastatin treatment in HAP were summed up based on the duration of treatment. An incremental cost-effectiveness ratio (ICER) was then calculated according to the effectiveness – overall favorable response (i.e., cure plus HAP improvement). ICER is the ratio of the change in costs to incremental effectiveness of a generic drug compared with the control (or branded drug). As many parameters might be fluctuated over a period of time, a univariate or one-way sensitivity analysis was conducted to assess robustness of the results – the effects of varying individual parameters on the outcomes.

RESULTS

Table 1 shows the patients were male slightly more than half in both groups (generic imipenem/cilastatin 55.9% vs branded imipenem/cilastatin 52.6%) whereas the mean age of patients were statistically significant differences between both groups (generic imipenem/cilastatin 60.9 ± 17.5 vs branded imipenem/cilastatin 72.6 ± 15.3, $p < 0.001$). About fifty percent of patients were 60 - 79 years and the most of the patients were hospitalized at the department of medicine.

Top five pathogens were *Acinetobacter.baumanii* MDR, *Escherichia coli* ESBLs, *Pseudomonas aeruginosa* MDR, MRSA *and Klebsiella pneumonia* ESBLs. The number of comorbidity and APACHE II scores were nearly 9 and 18. Many patients had hypertension, diabetes

Table 1 Patients' characteristics and medical conditions

Characteristic	Generic mipenem/cliastatin (n=154)	Branded imipenem/cliastatin (n=154)	*P-value*
Gender			
Male	86 (55.9%)	81 (52.6%)	0.661
Female	68 (44.1%)	73 (47.4%)	
Age (years): Mean ± SD	60.9 ± 17.5	72.6 ± 15.3	< 0.001
18 – 39	20 (13.0%)	5 (3.2%)	
40 – 59	44 (28.6%)	22 (14.3%)	
60 – 79	70 (45.4%)	71 (46.1%)	
> 80	20 (13.0%)	56 (36.4%)	
Department			
Medicine	113 (73.4%)	116 (75.3%)	0.795
Surgery	37 (24.0%)	33 (21.4%)	
Other	4 (2.6%)	5 (3.3%)	
Type of bacteria			
Acinetobacter baumannii MDR	38 (24.7%)	39 (25.3%)	1.000
Escherichia coli ESBLs	24 (15.6%)	16 (10.4%)	0.215
Pseudomonas aeruginosa MDR	19 (12.3%)	14 (9.1%)	0.458
MRSA	8 (5.2%)	6 (3.9%)	0.791
*Klebsiella pneumonia*e ESBLs	5 (3.2%)	5 (3.2%)	1.000
Enterococcus spp.	6 (3.9%)	1 (0.6%)	0.125
Number of comorbidity			
Mean ± SD	9.4 ± 3.0	9.6 ± 3.5	0.678
Underlying diseases			
Hypertension	53 (34.4%)	79 (51.3%)	0.003
Diabetes Mellitus	37 (24.0%)	59 (38.3%)	0.014
Cancer (All types)	28 (18.2%)	25 (16.2%)	0.771
Chronic kidney diseases	11 (7.1%)	12 (7.8%)	1.000
Congestive heart failure	11 (7.1%)	6 (3.9%)	0.332
APACHE II score			
Mean ± SD	18.2 ± 6.5	18.7 ± 6.1	0.407
Use of other antibiotics within 30 days	141 (91.6%)	141 (91.6%)	1.000

SD = Standard deviation; MDR = Multidrug-resistant; ESBLs = Extended-spectrum β-lactamases; MRSA = Methicillin-resistant *Staphylococcus aureus*

mellitus, cancer, chronic kidney diseases and congestive heart failure. Ninety-one percent of the patients received previous antibiotics within 30 days. Finding in detail of the study are shown below.

Outcomes and effectiveness

Table 2 presents the effectiveness of imipenem/cilastatin in HAP.

Clinical outcomes: This study found that overall favorable response in the generic and branded imipenem/cilastatin were 24% and 37.6%, respectively (OR 0.5, 95% CI 0.3 o 0.9, estimated absolute difference -13.6%, 95% CI -23.8% to -3.4%, estimated NNT = 7, p = 0.010), worsening or persistence were 41.6% and 29.2% (OR 1.7, 95% CI 1.1 to 2.6, estimated absolute difference 12.2%, 95% CI 1.6% to 22.8%, estimated NNT = 9, p = 0.040).

Microbiological outcomes: Super-infections in the generic and branded imipenem/cilastatin were 35.7% and 17.5% (OR 2.9, 95% CI 1.6 to 5.2, estimated absolute difference 18.2%, 95% CI 8.4% to 27.8%, estimated NNT = 6, p < 0.001), undetermined were 48.1% and 63.7% (OR 0.5, 95% CI 0.3 to 0.8, estimated absolute difference -15.6%, 95% CI -26.5% to -4.6%, estimated NNT = 6, p = 0.005). These clinical and microbiological outcomes were statistically significant differences between generic and branded imipenem/cilastatin.

Adverse drug reactions: The adverse drug reactions in both groups were not significantly different. Length of stay in the generic and branded imipenem/cilastatin (50.1 ± 51.7 vs 81.0 ± 125.5, median 34.0 vs 42.0) were statistically significant differences between both groups (p = 0.020).

Economic outcomes

As shown in Table 3 from hospital perspective, the total treatment costs and the cost per case for imipenem/cilastatin treatment receiving generic were lower than patients receiving branded imipenem/cilastatin. ICER for imipenem/cilastatin treatment was roughly 0.29 million baht.

Figure 2 to 3 present univariate sensitivity analyses. The effect of changing CPI was the most

Table 2 Effectiveness of generic and branded imipenem/cilastatin in hospital-acquired pneumonia

Outcomes	Generic imipenem/cliastatin (n=154)	Branded imipenem/cliastatin (n=154)	Odds Ratio[a] (95% CI)	Estimated absolute difference (95% CI)	Estimated number needed to treat	*P-value*
Clinical outcomes						
Overall favorable response	37 (24.0%)	58 (37.6%)	0.5 (0.3 to 0.9)	-13.6% (-23.8% to -3.4%)	7	0.010
- Cure	8 (5.2%)	11 (7.1%)	0.7 (0.3 to 1.8)	-1.9% (-3.7% to 7.8%)	52	0.490
- Improvement	29 (18.8%)	47 (30.5%)	0.5 (0.3 to 0.9)	-11.7% (-2.1% to -21.2%)	9	0.022
Worsening or persistence	64 (41.6%)	45 (29.2%)	1.7 (1.1 to 2.6)	12.2% (1.6% to 22.8%)	9	0.040
Death	53 (34.4%)	51 (33.2%)	1.1 (0.7 to 1.7)	1.2% (-9.3% to 11.8%)	77	0.904
Microbiological outcomes						
Eradication	12 (7.8%)	18 (11.7%)	0.6 (0.3 to 1.4)	-3.9% (-10.9% to 2.9%)	26	0.327
Persistence	13 (8.4%)	11 (7.1%)	1.2 (0.5 to 2.6)	1.3% (-4.9% to 7.7%)	77	0.839
Super-infections	55 (35.7%)	27 (17.5%)	2.9 (1.6 to 5.2)	18.2% (8.4% to 27.8%)	6	<0.001
Undetermined	74 (48.1%)	98 (63.7%)	0.5 (0.3 to 0.8)	-15.6% (-26.5% to -4.6%)	6	0.005
Adverse drug reactions						
Central nervous system	5 (3.0%)	1 (0.6%)	5.0 (0.6 to 42.8)	2.6% (-0.7% to 7.8%)	39	0.219
- Generalized tonic-clonic (GTC) seizure	1 (0.6%)	1 (0.6%)	-	-	-	
- Myoclonus seizure	1 (0.6%)	-	-	-	-	
- Nonspecific seizure	3 (1.8%)	-	-	-	-	
Dermatological reaction						
- Skin rash	2 (1.2%)	1 (0.6%)	2.0 (0.2 to 22.1)	0.6% (-2.4% to 4.0%)	154	1.000
Duration of treatment (days)						
Mean ± SD	14.7 ± 10.1	14.4 ± 12.3	-	-	-	0.786
Length of stay (days)[b]						
Mean ± SD	50.1 ± 51.7	81.0 ± 125.5	-	-	-	0.020
Median (Q1-Q3)	34.0 (20.0-60.0)	42.0 (22.8-87.3)	-	-	-	
Discharge status						
Complete recovery	9 (5.8%)	4 (2.6%)	2.3 (0.7 to 7.3)	3.2% (-1.4% to 8.5%)	31	0.267
Improved	30 (19.5%)	45 (29.2%)	0.6 (0.3 to 1.0)	-9.7% (-19.3% to -0.1%)	11	0.063
Not improved	6 (3.9%)	8 (5.2%)	0.7 (0.2 to 2.3)	-1.3% (-6.5% to 3.7%)	77	0.774
Death	109 (70.8%)	97 (63.0%)	1.4 (0.9 to 2.4)	7.8% (-2.7% to 18.2%)	13	0.175

CI = confidence interval; SD = standard deviation; Q = Quartile.

[a] For pair-matched odds ratio calculation the reference is branded imipenem/cilastatin

[b] Wilcoxon Signed Ranks test were calculated due to the data were not normal distribution

Table 3 Economic outcomes of generic and branded imipenem/cilastatin in hospital-acquired pneumonia from the hospital perspectives

Drug	Total treatment costs (baht)[a]	Incremental cost (ΔC)[b]	No. of cured or improved patients	Incremental effect (ΔE)[c]	Cost per case (baht)[d]	Incremental cost-effectiveness ratio (ICER=ΔC/ΔE)
Generic drug	7,519,735.20	6,080,117.88	37	21	203,236.09	289,529.42
Branded drug	13,599,853.08	-	58	-	234,480.23	-

[a] Total treatment costs included the laboratory, room, administration and imipenem/cilastatin costs

[b] Incremental cost (ΔC) = The difference between total treatment costs of branded drug (13,599,853.08 baht) and generic drug (7,519,735.20 baht)

[c] Incremental effect (ΔE) = The difference between number of cured or improved patients (overall favorable response from Table 2) in branded drug (58 patients) and generic drug (37 patients)

[d] Cost per case were calculated by dividing the total treatment costs in each drugs by the number of cured or improved patients (overall favorable response)

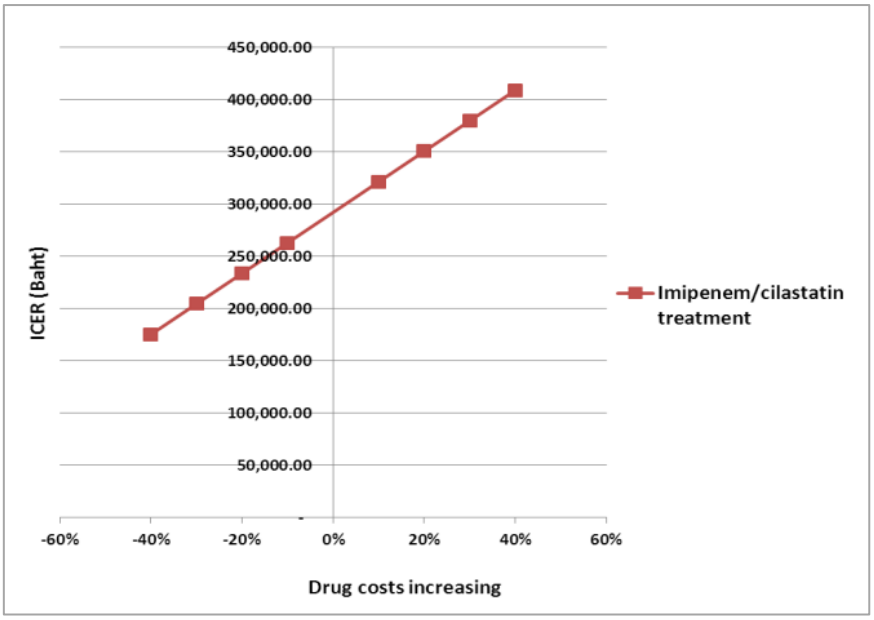

Figure 2 Effect of changing drug costs on ICER

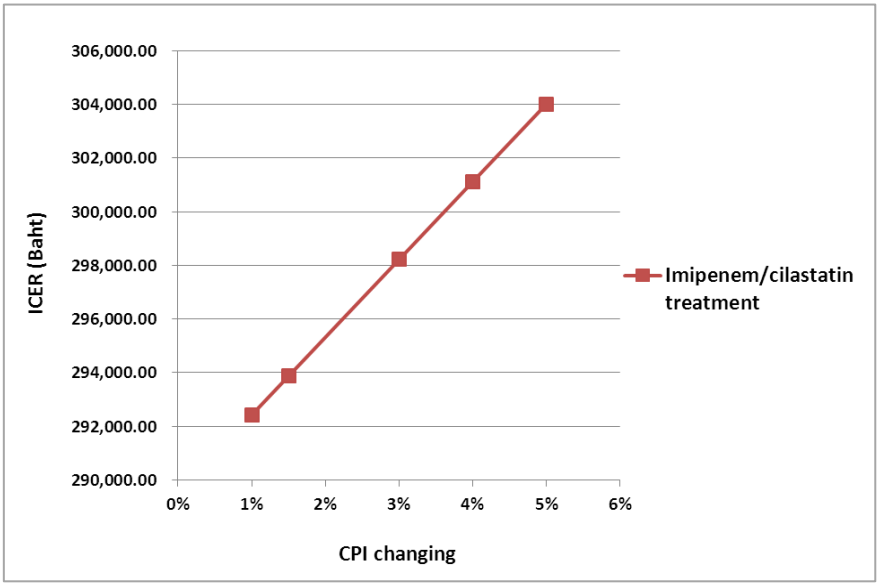

Figure 3 Effect of changing consumer price index (CPI) on ICER

influence parameter on ICER. Other influential parameters included the effect of changing drug costs (including generic and branded imipenem/cilastatin) on ICER.

DISCUSSION

This is the first study that has been performed to evaluate effectiveness and economic consequences of generic and branded imipenem/cilastatin in HAP in Thailand. As shown in Table 1, Half of the patients were elderly male (60-79 years) in medicine department with many comorbidities and high severity of illness, the mean APACHE II scores in both groups were nearly 18. Probable cause explanation of that the risk factors predisposing a patient to development of HAP in Asian countries were male gender, elderly age, APACHE II scores > 15, previous use of antibiotics for more than 2 weeks, diabetes, immunosupression, dialysis, pre-existing pulmonary disease, multiple organ system failure, the presense of intubation or enteral feeding, mechanical ventilation and supine position [2]. The most common pathogens in HAP were gram negative bacteria such as *A. baumanii* MDR were roughly 25% in both groups, followed in order of frequency by *E. coli* ESBLs, *P. aeruginosa* MDR, MRSA *and K. pneumoniae* ESBLs. These data were comparable to previous study at Siriraj Hospital and Thailand [2, 7, 13]. The patient characteristics in both groups were no significant differences except mean of age because age was not a covariate in PSM but age was included in age points to calculate APACHE II score that was one of covariates in PSM.

These effectiveness results are consistent with a previous study [7] that overall favorable outcomes were different between both groups moreover were statistically significant differences in several outcomes. The estimated absolute difference in overall favorable outcomes, improvement, worsening or persistence and super-infections between both groups were more than 10% and estimated NNT were less than 10. In contrast, branded imipenem/cilastatin has shown length of stay significantly higher than generic imipenem/cilastatin due to the Civil Servants Medical Benefit Scheme (CSMBS) that mostly received original drugs and prolonged hospitalization.

ICER for imipenem/cilastatin treatment were roughly 0.29 million baht from hospital perspective. This meant incremental of imipenem/cilastatin treatment for HAP 0.29 million baht per one patient who was cured or improved (favorable outcome) between generic and branded imipenem/cilastatin. The total treatment costs were 7.52 million baht and 13.60 million baht for 154 patients from each generic and braned drug, respectively. The cost per case meant one favorable outcome of HAP patients using imipenem/cilastatin treatment were roughly 0.20 million baht and 0.23 million bath for generic and braned drug, respectively. These total treatment costs and cost per case of generic imipenem/cilastatin were less expensive than branded imipenem/cilastatin because drug costs were lower than branded drug. From univariate sensitivity analysis indicated that ICER was sensitive to CPI and drug costs changing.

LIMITATIONS OF STUDY

First, this study was a retrospective study and many clinical and cost data were not complete. Thus, the results of this study are the patients to a number limitation and the number of eligible patients in this study were smaller than calculated from sample size (308 instead of the 660 required in this study) which results in a wider CI therefore the 95% CI should be interpreted with caution. Second, generic imipenem/cilastatin from this study was Yungjin® in HAP and in super-tertiary care setting (Rajavithi Hospital) so could not be generalized to other generic imipenem/cilastatin products and other different settings. Further studies should investigate in societal perspective that include direct non-medical costs (out of pocket expense e.g. food, transportation etc.) and indirect costs (loss of productivity costs or opportunity costs), other type of infections, other settings or other study design (e.g. randomized controlled trial).

CONCLUSION

These results suggest that generic imipenem/cilastatin (Yungjin®) could not prove for equivalent effectiveness to branded imipenem/cilastatin in HAP, but associated with lower treatment costs.

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