ORIGINAL ARTICLE

COST-EFFECTIVENESS ANALYSIS OF CONTINUOUS VENOVENOUS HEMOFILTRATION THERAPY IN THE TREATMENT OF SEPSIS IN HOSPITAL UNIVERSITI KEBANGSAAN MALAYSIA: A COMPARISON BETWEEN HIGH VOLUME AND STANDARD DOSE HEMOFILTRATION

A M Rizal [1], M H Enna [1], S M Aljunid [1], A G Rohana [2], Z Soehardy [2], C T K Norella [2]

[1] Department of Community Health, [2] Department of Medicine, Faculty of Medicine, UKM

ABSTRACT

Background: *A randomised clinical trial was carried out to study the cost-effectiveness of continuous venovenous hemofiltration using high volume and standard volume.*

Methods: *Study was done through interviews involving patients or their relatives and document review on patients' treatment and progress note during the hemofiltration therapy in the Intensive Care Unit, Hospital University Kebangsaan Malaysia. Study also involved secondary data analysis and a structured questionnaire survey to assess the treatment and medical cost incurred by the hospital during the continuous venovenous hemofiltration therapy.*

Results: *The result of this study showed that the continuous venovenous hemofiltration given at high volume 4-6 litres/hour is more cost effective than standard volume of 2 litres/hour. The Sequential Organ Failure Assessment (SOFA) score reduction in the high volume hemofiltration is 3.0 units over 24 hours. This reduction is higher than the standard volume hemofiltration which is only 0.5 unit over 24 hours.*

Conclusions: *High volume hemofiltration is more cost effective than standard volume therapy, where only RM 5,552 compared to RM 23,512 is needed for every one unit of SOFA score reduction respectively.*

Key words: *cost-effectiveness analysis, continuous venovenous hemofiltration, sepsis.*

INTRODUCTION

Severe sepsis occurs in 25 percent of patients admitted to intensive care units. It is associated with a high mortality rate, ranging from 30 percent to 50 percent.[1] Severe sepsis remains both an important clinical challenge and an economic burden in intensive care. Sepsis patients are generally treated in intensive care units where close supervision and intensive care treatment with adequate equipment can be provided. Sepsis is a major cause of death in intensive care units worldwide, with mortality rates that range from 20% for sepsis to 40% for severe sepsis to more than 60% for septic shock. In the United States, sepsis is the leading cause of death in non-coronary ICU patients, and the tenth most common cause of death overall according to 2000 data from the Centers for Disease Control and Prevention.[2]

Correspondence to: A M Rizal, Department of Community Health, Faculty of Medicine, Hospital UKM, Cheras Kuala Lumpur
Tel: 03-91702531, Fax: 03-91737825
(e-mail: mrizal@mail.hukm.ukm.my)

The direct cost of caring for patients with sepsis has been shown by Lee et al. in 2004 to be six times higher than caring for patients without sepsis.[3] The manifestations of sepsis include those related to the systemic response to infection (tachycardia, tachypnea, alterations in temperature, and leukocytosis) and those related to organ-system dysfunction (cardiovascular, respiratory, renal, hepatic, and hematologic abnormalities).[4] Cytokines have been implicated as being important endogenous mediators in the pathogenesis of sepsis and shock. Studies by Taniguchi et al. demonstrated that serum tumour necrosis (TNF), interleukin-6 (IL6), and interleukin-8 (IL8), are the three of the most prominent cytokines, increase during sepsis and are associated with an increased occurrence of shock and death.[5]

Continuous Venovenous Hemofiltration Therapy

Continuous Renal Replacement Therapy (CRRT) was first described by Peter Kramer in 1977. CRRT offers extraordinary advantages over intermittent hemodialysis dan peritoneal dialysis.[6] With CRRT,

volume control is continuous and immediately adaptable to the changing clinical circumstances that are common in the care of critically ill patients. CRRT is easily tolerated and becomes a useful tool for control of intravascular and extravascular volume. Patients with acute renal failure and septic shock are particularly suited to CRRT. In these patients hemodynamic instability is very common, and oliguric and anuric are typical. If appropriate fluid resuscitation, nutrition, blood and blood products administration is to take place under optimal physiologic circumstances, CRRT must be used.

Hemofiltration improves cardiopulmonary function and survival by removal of inflammatory mediators from the circulation through filtration or adsorption. In continuous venovenous hemofiltration, vascular access is achieved by the insertion of a double-lumen catheter into a great vein. The blood pump is typically set to deliver approximately two litres/hour (standard dose). A servomechanism drives the replacement fluid pump at a rate computed either to balance the inflow and loss of fluid of to maintain a predetermined rate of fluid. High volume hemofiltration (four litres/hour) for short periods (four to six hours) appeared to improve hemodynamic and metabolic acidosis status promptly.[7,8]

Cost of sepsis and hemofiltration

The direct cost of treating patients with sepsis has been shown to be six times higher than treating patients without sepsis. Cost analysis study by Angus et al. in 2001 done in seven selected hospitals revealed the average length of hospital stay were 19.6 days and cost per case were USD 22,000.00 (RM 83,600.00).[1] European studies, Burchardi and Schneider, have given estimates direct costs per sepsis were ranging from 23,000 Euro to 29,000 Euro (RM 110,400.00 to RM 139,200.00).[9] The total cost of treating sepsis in intensive care unit (ICU) is mainly dependent in the length of ICU stay, staffing cost, pharmaceuticals and consumables costs. Staffing costs represent from 40 percent to 60 percent of the total ICU budget. According to Weber et. al, ICU drug costs accounted for 38.4 percent of the total budget.[10] To date the cost effectiveness of hemofiltration therapy in the treatment of sepsis has not been established in Malaysia. There is limited information on the hospital costs and resource use associated with the care of septic patients. An essential element of this research is therefore to ascertain the efficiency of hemofiltration therapy.

Cost-effectiveness analysis

Cost-effectiveness analysis is one of the technique of economic evaluation designed to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing. In cost-effectiveness analysis, the benefits are expressed in non-monetary terms related to health effects. The aim of cost-effectiveness is to maximize the level of benefits, health effects relative to the resources available.[11] Budget constraints increasingly determine the provision of health care services.

Primary objective

The primary objective of this study is to compare the cost-effectiveness of two methods of continuous venovenous hemofiltration for septiceamic patients in the intensive care unit, Hospital Universiti Kebangsaan Malaysia. The two method of treatment are the high volume (four to six litres/hour) hemofiltration and the standard volume (two litres/hour) hemofiltration.

Specific objectives

The specific objectives of this study are:

a) to carry out cost analysis and to compare between the two methods of treatments
b) to measure the interleukin-6 level before and after intervention
c) to measure the Sequential Organ Failure Assessment (SOFA) before and after intervention
d) to perform cost-effectiveness analysis and compare between the two methods of treatments

Hypothesis

It is hypothesized that continuous venovenous hemofiltration therapy at high volume for treatment of sepsis is more cost effective compared to standard dose.

METHODOLOGY

Patient enrollment

This is a clinical trial that evaluated the therapeutic effect of continuous venovenous hemofiltration therapy for treating sepsis at the intensive care unit, Hospital Universiti Kebangsaan Malaysia. This study was conducted in 33 adults aged 21 years to 79 years who presented to the hospital with infection, systemic inflammatory response syndrome, dysfunctional organs or systems and septic shock.

Any patient with end-stage renal disease, underlying malignancy, acquired immuno-deficiency syndrome and a life expectancy less than six months were excluded from the trial.

Intervention

The treatment was randomized at an individual level using block randomization comprising of three groups of ten patients of equal allocation of patients towards High-Volume Hemofiltration (HVHF) and Continuous Veno-Venous Hemofiltration (CVVH, standard dose). The patients were blinded to the subject's treatment status. Patients were randomly assigned to six hours of high volume hemofiltration in addition to the usual care (n=15), or to standard dose of continuous venovenous hemofiltration in addition to the usual care (n=18). The treatment started within four hours of fulfillment of randomization criteria. Patients were subjected to the standard intensive care unit treatment protocol and the usual resuscitative measures were optimized.

Measurements of clinical outcomes

The patients were assessed every 24 hours till discharge using the Sequential Organ Failure Assessment (SOFA) score. The SOFA score is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure. The aggregate score (total maximum SOFA score) is calculated summing the worst scores for each of the organ systems during the ICU stay. The SOFA scores were calculated at the time of recruitment and daily thereafter until death or discharge from the intensive care unit, or at 28 days whichever is earlier. Any complications such as bleeding, hematoma, arterial puncture and vascular thrombosis were recorded. Patients were closely monitored for any deteriorating conditions. The concentration levels of inflammatory mediator, the interleukin-6 were measured before intervention, at three hour, six hour and 24 hour of patient's hospital stay.

Identifying and Measuring Costs

The cost data was collected to identify the cost incurred for the management of sepsis with hemofiltration therapy from the provider's perspective. The resources utilized for the management of sepsis with hemofiltration therapy and their unit costs were measured in order to determine the cost of treatment. We enumerated every input consumed by the patient and then its unit cost. This is known as micro-costing. The measurement of the resources utilized was from the time of recruitment and during the study period. The medical cost to the hospital was the expenditure incurred by the hospital administration after randomization. The medical costs were divided into two categories, the capital and recurrent costs.

The capital costs included the building and equipment costs. The recurrent costs included operational costs, the services provided by the medical personnel, the medications, the laboratory investigations, the imaging investigations, and the consumables. We estimated the building costs based on 20 years lifespan at five percent discount rate times the proportion of the intensive care unit surface area. We estimated the equipment costs based in five years lifespan at five percent discount rate. The operational cost includes the utility costs, engineering and maintenance costs, cleaning, gardening, clinical waste disposable management, laundry and costs of food. We estimated the operational cost based on average length of stay and unit surface area of the intensive care unit. The costs of service provided by the medical personnel, was calculated based on their salary times the proportion of their time spent rendering to the treatment. The costs of drugs and consumables were the manufacture's wholesale price. We estimated the laboratory and the imaging investigation costs using the hospital's inpatient charges. The cost of treatment for a patient, at the intensive care unit, Hospital Universiti Kebangsaan Malaysia, was calculated by summing the average costs calculated per day multiply by the total length of stay.

Statistical and Economic Analysis

The costs of the treatment for each patient was calculated by dividing the total costs with the number of respondents. The median of the total medical costs which included the capital and the recurrent costs were estimated. We also calculated the median of the capital and the recurrent costs in both HVHF and CVVH groups.

For the purpose of calculating the cost-effectiveness ratio for each group, we used total medical costs as the numerator and the difference in the SOFA score as the denominator (difference of SOFA score between the time of recruitment and at 24 hours after intervention).

The Statistical Package for the Social Science (SPSS) version 11.0 was used for the statistical analyses. The difference of socio-demographic and economic status, capital costs, recurrent costs, SOFA score and plasma concentration level of interleukin-6 between the high

volume and the standard dose were analyzed using the non-parametric test, Mann-Whitney U test. A $p<0.05$ was considered significant. Results are reported as median.

RESULTS

Clinical Outcomes

A total of 33 patients were selected in the study and were randomized to hemofiltration at high volume (n=15) and hemofiltration at standard dose (n=18) groups. The socio-demographic and economic status of the patients in the two groups were similar as shown in Table 1. The health outcomes in the high volume hemofiltration group were favorable but failed to reach significant level. The high volume hemofiltration group showed clinically more reductions in concentration level of interleukin-6. The SOFA scores found to be decreased after 24 hours intervention in both groups. However, the reduction was more in the high volume hemofiltration compared to the standard dose hemofiltration (Table 2).

Table 1: The socio-demographic and economic status of respondents

		Number of patient (%)		p value
		High volume hemofiltration n=15	**Standard dose hemofiltration n=18**	
Gender	Male	8 (42.1)	11 (57.9)	0.653
	Female	7 (50.0)	7 (50.0)	
Age	0-30 years	1 (33.3)	2 (66.7)	0.867
	31-60 years	8 (44.4)	10 (55.6)	
	61-90 years	6 (50.0)	6 (50.0)	
Ethnic	Malay	10 (50.0)	10 (50.0)	0.793
	Chinese	4 (40.0)	6 (60.0)	
	Indian	1 (33.3)	2 (66.7)	
Monthly income	0-RM 500	10 (47.6)	11 (52.4)	0.491
	RM 501-RM 1000	3 (37.5)	5 (62.5)	
	RM 1001-RM 1500	2 (50.0)	2 (50.0)	

Table 2: Clinical outcomes

Health Outcomes	**High volume hemofiltration**	**Standard dose hemofiltration**	**p value**
Interleukin-6			
Before intervention	119.5 (24.7-317.8)	159.9 (21.4-303.2)	0.745
At 3 hour	119.2 (14.1-312.4)	131.1 (19.3-313.2)	0.613
At 6 hour	61.3 (11.0-304.2)	162.3 (0-301.8)	0.406
At 24 hour	63.8 (10.3-319.0)	190.2 (27.7-311.5)	0.423
SOFA score			
Before intervention	13.0 (5-20)	9.5 (6-22)	0.336
At 24 hour	10.0 (3-21)	9.0 (4-21)	0.691

Cost and Effectiveness Outcomes

The average total cost of treating a sepsis patient with high volume hemofiltration was RM 16,657. The average total cost of treating a sepsis patient with standard dose hemofiltration was RM 11,756 (Table 3). The hospital spent a total of RM 249,849.00 for 15 septic patients selected for the hemofiltration at high volume. The hospital had to spend a total of RM 211,612.00 for 18 septic patients selected for the hemofiltration at standard dose (Table 3). However, the median cost of treating septic patients incurred by the hospital in the high volume and the standard dose hemofiltration, were not significantly different. The median capital costs and recurrent costs were similar in both groups (Table 4).

The cost-effectiveness of the treatment is shown in Table 5. Results showed that RM 5,552 is required for every one unit reduction of SOFA score for high volume hemofiltratration. On the other hand, about RM 23,512 had to spend for every one unit reduction of SOFA score in the standard dose hemofiltration. The high volume is more cost-effective compared to the standard dose hemofiltration.

Table 3: Cost analysis on treatment of septic patient with high volume and standard dose hemofiltration in the intensive care unit based on year 2004 expenditure (in Ringgit Malaysia).

		High Volume Hemofiltration	Standard Dose Hemofiltration
Capital cost	Building	264	198
	Equipment	27,484	20,613
Recurrent cost	Operational	538	403
	Staff	93,304	69,978
	Pharmaceutical	74,781	61,728
	Laboratory	23,293	22,554
	Imaging	2755	4515
	Consumables	27,430	31,623
Total cost		249,849	211,612
Total number of patient		15	18
Average length of stay		16	11.3
Cost incurred for each patient		**RM 16,657**	**RM 11,756**

Table 4: Cost analysis of hemofiltration treatments

Category	High volume hemofiltration		Standard dose hemofiltration		p value
	Median	Range	Median	Range	
Capital cost					
Building	11.85	3.09-39.14	9.27	3.90-33.99	0.125
Equipment	1234.64	322.08-4079.68	966.24	322.08-3542.88	0.125
Recurrent cost					
Operational	24.15	6.30-79.80	18.90	6.30-69.30	0.125
Staff	4191.40	1093.41-13849.86	3280.23	1093.41-12027.51	0.125
Pharmaceutical	3281.86	1221.32-13816.43	3291.47	419.71-12310.13	0.368
Consumables	3019.21	1920.30-6472.79	2963.89	2079.24-5974.16	0.387
Imaging	95.00	45.00-430.00	170.00	40.00-830.00	0.651
Laboratory	1387.50	710.00-4007.00	1319.00	500.00-3603.00	0.387

Table 5: Cost-effectiveness of hemofiltration treatment (based on cost of every one unit reduction in SOFA score)

	High volume hemofiltration	Standard dose hemofiltration
Before intervention	13.0	9.5
After 24 hours intervention	10.0	9.0
Difference in SOFA score	3.0	0.5
Total cost	RM 16,657	RM 11,756
Cost-effectiveness		
RM per one unit SOFA score reduction	**RM 5,552**	**RM 23,512**

DISCUSSION

Continuous venovenous hemofiltration is well established and a cost-effective strategy for reducing sepsis mortality. It is also widely accepted. Continuous venovenous hemofiltation is increasingly used to treat acute renal failure in critically ill patients, but a clear definition of an adequate treatment dose has not been established. Delivering hemofiltration at higher volume in the treatment of septicemia could be of benefit in reducing septicemia mortality and morbidity. Any changes recommended in the rate of hemofiltration from its standard dose (two litres/hour), needs reasonable justification in terms of efficacy and costs. Our study showed that high volume hemofiltration four to six litres/hour had beneficial effects on the reduction of SOFA score. This gives an important costs implication.

In Malaysia, there is little information on the costs associated with the treatment of septicemia and renal replacement therapy. In this study, the average cost of treating septicemia with standard dose hemofiltration was RM 11,756 per episode of in patient admitted to the intensive care unit, Hospital Universiti Kebangsaan Malaysia. The average cost of treating septicemia with high volume hemofiltration was RM 16,657 per episode. The total cost of the high volume hemofiltration were 40 percent more than the total cost of the standard dose. The differences are noted on the aspects of staff and equipment. However these differences are not statistically significant. The cost-effectiveness ratio was calculated as the total costs divided by the difference in health outcomes. The unit of health interest and the effectiveness measure for this study was the reduction of SOFA score before and after 24 hours intervention. We believe that it is a pragmatic and good proxy measure for septicemia morbidity and mortality for assessing cost-effectiveness.

This study showed that, high volume hemofiltration (4-6 litres/hour) was more cost-effective compared to the standard dose hemofiltration. A total of RM 5,552 had to be spent for every one unit of SOFA score reduction in high volume hemofiltration. Comparatively, estimated about RM 23,512 had to be spent for every one unit of SOFA score reduction for the standard dose hemofiltration.

A sensitivity analysis were performed, where the discount rates on capital costs was changed to one percent and ten percents, and the hospital stay was changed to minimum and maximum duration. Sensitivity analysis of the results helps to determine its robustness and its performance in a dynamic environment, where variations in costs and benefits occur due to variation in measurements and implementation of the intervention. The sensitivity analysis results remained the same where the high volume hemofiltration is more cost-effective compared to the standard dose hemofiltration.

The average costs of septicemia treatment in the intensive care unit, Hospital Universiti Kebangsaan Malaysia, was 5.9 times cheaper, and 1.5 times less in average length of stay compared to the cost of septicemia treatment in United States of America. The cost of treatment in developing countries is considerably less because of diverse health care systems, different hospital capacity, their scope and their sources of funding, price differences in the pharmaceuticals and consumables. The main contribution of total costs for treating septicemia with continuous venovenous hemofiltration in our study were staffing (40 percent), pharmaceutical (33 percent), consumables (14 percent) and laboratory (11 percent) respectively. The severity of illness and the length of hospital stay were the most important contributors of total cost. As expected, the use of intravenous fluids and antibiotics inflated the costs of treatment. The costs of original drugs were more

expensive compared to the generic drugs. According to Carnahan, cost of generic drugs in United States of America is 74 percent more cheaper than the original brand.[12] The cost of generic drugs in Canada is 38 percent cheaper than the original drugs.

Septicemia is a clinically defined entity of altered and malfunction of multiple organs function resulting from a systemic response to infection. The management of patient with severe sepsis includes combination of various drugs such as antibiotics, inotropic agents, parenteral nutrition, and others. Cost analysis study by PrincewaterhouseCoopers, found that hospital incurred 38.8 percent for staffing costs, and 24 percent for pharmaceuticals costs from the overall inpatient expenditure.[13]

The cost of consumables (hemofilter, blood and fluid lines, double lumen catheter, replacement fluid, empty bag, manifold three way spike, and normal saline), for each episode of high volume hemofiltration therapy in our unit was RM 1,461 and for each episode of standard dose hemofiltration therapy was RM 1,640. This findings was definitely cheaper that the costs of hemofiltration done by Forni and Hilton.[14] They found that for treatment lasting an average of 9.3 days, with replacement of extracorporeal circuit every 2.5 days, the cost of consumables for each episode of acute renal failure was USD 1,614 (RM 6,133).

CONCLUSION

An emphasis on the costs and economic benefits of an alternative therapy is an important aspect of health services research. This study showed that cost-effectiveness analysis is a good and accurate form of economic evaluation in which the costs of alternatives treatments are compared. We found that severe sepsis consumes considerable health care resources, and is associated with a high mortality rate. This study found that despite the total cost per episode is higher in the high volume hemofiltration, it is more cost-effective compared to standard dose. The cost savings and the attractive cost-effectiveness indicates the need to further assess the role of high volume hemofiltration therapy in the treatment of acute renal failure in a larger and more varied population.

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