Early Versus Late Blood Transfusion in Puerperal Septic Shock Patients with Anemia - a Quasi-Experimental Controlled Trial

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ABSTRACT

Objective: To compare the outcome of early blood transfusion i.e. within 6hrs. (hours) of admission VS late blood transfusion (after 6 hrs.) in puerperal septic shock patients with anemia. Study design: A prospective quasi-experimental controlled trial in ICU(intensive care unit) of lady Willingdon hospital, a tertiary care hospital of Obstetrics and gynecology from Aug2013 to July 2016. Population: Patients admitted with septic shock and anemia during puerperium in ICU. Methods: 74 patients were included in the study by purposive sampling technique. Exclusion criteria were an irreversible shock, chronic lung, and heart disease or those requiring surgical intervention. Surviving sepsis campaign guidelines were followed for the management of these patients. Effect of blood transfusion on the recovery of these subjects was studied. The study group consisted of 43 patients in which blood was transfused within 6hrs. of admission. Control group had 31 patients in whom blood could not be transfused within this period. The demographic features and outcome of both groups were recorded and entered on spss20 statistical package. Results: The time of recovery from hypotension, tachycardia, pulmonary edema, ventilator and cardiac support was significantly shorter in the study group compared to the control. A lesser number of blood transfusions was required to treat anemia in the study group. Maternal mortality was less in the study group (23.25%) as compared to control group (48.39%) with an odds ratio of decrease in maternal mortality of 0.323 (.119-.877). Conclusion: Early blood transfusion shortens the time of recovery and decreases maternal mortality and morbidity in puerperal septic shock patients with anemia.

Keywords: puerperium, septic shock, anemia, mortality, morbidity

1. INTRODUCTION

Septic shock is a major cause of maternal mortality in the developing world¹,². According to an estimate, the incidence of death in septic shock is 50-75%³. Risk factors for the development of maternal sepsis include home birth in unhygienic conditions, poor nutrition, anemia, prolonged rupture of membranes, prolonged labor, and multiple vaginal examinations in labor (more than five), caesarean section and obstetrical maneuvers². Shock in sepsis is characterized by intense vasodilatation and increased vascular permeability resulting in hypotension and third space fluid losses due to endothelial damage caused by exotoxins and endotoxins released by infecting microorganisms. The resulting hypoperfusion and poor uptake of oxygen into the tissues lead to more endothelial damage, end organ failure and worsening of shock⁴,⁵,⁶.


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Resuscitation of septic shock is done with aggressive IV (intravenous) fluid therapy according to Surviving Sepsis Campaign guidelines which may prove unhelpful or harmful in anemic patients when hypotension is no longer fluid-responsive due to increased permeability of vessels. In this situation, a blood transfusion may also be required to restore and maintain circulating volume along with crystalloid solutions\(^7\). Delay in restoring blood volume and pressure results in tissue hypoxia, irreversible shock, renal failure and ultimately death. Blood transfusion increases intravascular osmotic pressure due to large molecular weight proteins, and it can improve oxygen carrying capacity to the tissues by increasing hemoglobin level in anemia secondary to sepsis and blood loss during puerperium\(^8\). It can also treat thrombocytopenia, leukopenia and functional deficiencies of coagulation factors in severe sepsis and septic shock\(^9\). The risk of blood reaction can be overcome with careful screening, cross matching and transfusion of fresh blood. The purpose of this study was to compare the outcome of early vs. late blood transfusion along with intravenous(IV) fluids in puerperal septic shock patients with anemia and to find out the role of early blood transfusion in the management of these patients.

2. METHODS

This study was conducted in ICU of lady Willingdon hospital over a period of 3 years as a prospective quasi-experimental controlled trial. Ethical approval was taken for the study from the institutional review board of King Edward Medical University. Septic shock was assigned after confirming the source of sepsis i.e. vaginal discharge, foul-smelling lochia, lower abdominal tenderness, APACHE II score of >20 and fulfilling two of the four SIRS criteria (systemic immune response syndrome) i.e. high-grade fever, hypotension, tachycardia and tachypnea. 162 patients with septic shock were admitted in ICU from emergency and labor room during this period. Inclusion criteria were obstetric patients in puerperium with septic shock and anemia. Comorbidities like eclampsia, preeclampsia, diabetes mellitus and hepatitis were included in the study. Exclusion criteria were an irreversible shock at the time of admission, chronic lung, and heart disease, septic conditions requiring surgical intervention and shock due to conditions other than sepsis. 74 patients were selected for the study. Consent was taken from husband or surrogate for blood transfusion and for all the treatment required. Participants were assigned either study group or control group. Patients in which blood was transfused within 6hrs and consent was taken for transfusion were put in the study group. In control group, patients could not be transfused blood within 6 hrs. due to nonavailability during this period and blood transfusion was carried out later on. In both groups, initial resuscitation was done with repeated boluses of 30cc/kg IV fluid till recovery of pulse and blood pressure followed by slow maintenance infusions. A pulse oximeter was attached and broad spectrum antibiotic cover was given(inj ampicillin 2gms IV 8hrly, Inf Flagyl 500mgIV 8hrly and inj ceftriaxone 1gIV 12hrly) which was later changed to antibiotic according to blood culture and sensitivity report. Blood pressure was restored by administration of vasoactive agents (noradrenaline, Vasopressin) and Ionotropic support i.e. (inj dobutamine) in infusions if IV fluids alone were not effective. Positive pressure oxygen inhalation was given with mechanical ventilator. Investigations i.e. blood group, complete blood and urine examination, blood sugar levels, liver function tests, renal function tests, serum electrolytes and test for arterial blood gasses were sent at the 8hrly interval. Patients were continuously monitored for the pulse, temperature, blood pressure, oxygen saturation and intake output. Study and control groups were assigned by anesthesia consultant and were concealed from a medical officer in ICU who recorded demographic features and outcome measures on a proforma.

Data analysis

Minimal sample size was calculated to be 73 at p-value of 5 % (Estimated percent of obstetric patients out of all ICU septic shock admissions in previous studies ), confidence interval = 95% and margin of error(e) =0.05

\[
\text{Sample size (n) = } Z^2(pq)/e^2 = 1.96^2\times0.05\times0.95/0.05^2 = 72.9904
\]

74 patients(31 of the control group and 43 of the study group) were selected during the study period by purposive sampling technique including all subjects fulfilling inclusion and exclusion criteria. This sample size was assessed on pass 15 .NCSS software with COX proportional hazard regression model of survival studies .It gave a statistical power of 90% at \(a\) value of .15 and hazard ratio of .355. The number of events(deaths)required to achieve this power was 28. It was anticipated that proportion of subjects having


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events during the study was 0.5 in control group and 0.3 in the study group with constant hazard ratio.

Data was entered on SPSS package 20. Demographic variables were not normally distributed according to Shapiro-Wilks test (P > 0.05 for a normal distribution). So the data was reported in terms of the median (range) and distribution of demographic features of both groups was compared by nonparametric test (Mann-Whitney U test). Outcome parameters with normal distribution were compared by T-test of mean±SD and those not normally distributed by Mann-Whitney U test. Chi-square test was applied to compare the outcome of study and control groups (P < 0.05). Correlation between end organ failure and mortality was noted during the study and was confirmed by calculation of Kendall’s tau correlation coefficient (r). The odds ratio of mortality for both groups was calculated to find out the role of blood transfusion in the study population (P ≤ 0.05).

3. RESULTS

Fig1: Distribution of population in study and control group

74 patients with puerperal septic shock and anemia were enrolled in the study. 43 (58%) patients were included in the study group and 31 (42%) patients in control group according to blood transfusion being carried out in first 6 hours or not respectively. The demographic features recorded were age, parity, BMI (basal metabolic index), Hb%, and comorbidities i.e. hepatitis, hypertension, diabetes and hyperglycemia. The difference in parameters of demographic features of both groups was not significant by Mann-Whitney U test (P ≤ 0.05).

<table>
<thead>
<tr>
<th></th>
<th>Study group, n=43</th>
<th>Control group, n=31</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32(20-40)</td>
<td>33(24-40)</td>
<td>0.651</td>
</tr>
<tr>
<td>Parity</td>
<td>5(1-8)</td>
<td>5(1-9)</td>
<td>0.969</td>
</tr>
<tr>
<td>BMI</td>
<td>28(22-35)</td>
<td>27(20-38)</td>
<td>0.672</td>
</tr>
<tr>
<td>Hb%</td>
<td>8(1.5)</td>
<td>8.2(1.10)</td>
<td>0.227</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>10(2.25%)</td>
<td>6(19.35%)</td>
<td>0.690</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11(25.58%)</td>
<td>10(32.25%)</td>
<td>0.532</td>
</tr>
<tr>
<td>H/o diabetes</td>
<td>6(13.95%)</td>
<td>4(12.90%)</td>
<td>0.897</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>33(76.74%)</td>
<td>21(67.74%)</td>
<td>0.393</td>
</tr>
</tbody>
</table>

The survivors of septic shock were kept in ICU till their recovery. Most of the survivors of both groups showed recovery within first 24 hours of critical care. Mean duration of pulmonary edema was remarkably shortened by blood transfusion.

It was observed that duration of stay in ICU, cardiac and ventilatory support was decreased if patients were given blood transfusion during resuscitation within 6 hours. More blood was transfused in control group as compared to study group and results proved significant by Mann-Whitney U test.

Maternal mortality could not be prevented in 25 patients of the study population due to the development of irreversible shock and pulmonary edema, but it was decreased in the study group as compared to control group. The odds ratio of decrease in maternal mortality in the study group was 0.323 (95% CI: 0.119 - 0.877) with early blood transfusion. Chi-square test (chi-square value = 5.086, sig = 0.024) also showed a significant association between early blood transfusion and decreased maternal mortality.

According to the results, early blood transfusion was likely to reduce maternal mortality from 48% to 23% in the study group as compared to control (Cramer’s v = 0.262, the small effect size in this study).

Fig2: Outcome of survivors of septic shock in anemic population

Table 2: Comparison of outcome of survivors of study group and control group

<table>
<thead>
<tr>
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<th>Study group, n=33</th>
<th>control group, n=16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pulmonary edema</td>
<td>8.3939±2.46145</td>
<td>40.3125±7.54293</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>duration of cardiac support</td>
<td>15.9394±6.42232</td>
<td>20.1250±4.30310</td>
<td>0.023</td>
</tr>
<tr>
<td>ventilator support</td>
<td>12.4545±4.92501</td>
<td>15.8750±3.22232</td>
<td>0.015</td>
</tr>
<tr>
<td>stay in ICU</td>
<td>21.00±5.788</td>
<td>26.69±3.842</td>
<td>0.001</td>
</tr>
<tr>
<td># of blood transfusions</td>
<td>2(1-3)</td>
<td>3(2-4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>End organ failure</td>
<td>1(3.03%)</td>
<td>4(25%)</td>
<td>.003</td>
</tr>
</tbody>
</table>

mean± standard deviation, median(range), number(proportion), P≤.05

Table3: Comparison of Mortality in study and control group

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>control group</th>
<th>Pearson chi-square value</th>
<th>P Value</th>
<th>Carmer’s V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study group</td>
<td>10/43(23%)</td>
<td></td>
<td>5.086</td>
<td>0.024</td>
<td>0.262</td>
</tr>
<tr>
<td>Control group</td>
<td>15/31(48%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio for study group (1)</td>
<td>0.481(CI; 0.25-0.924)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio for study group (2)</td>
<td>1.487(CI; 1.018-2.171)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio for mortality (1/2)</td>
<td>0.323(CI; 0.119-0.877)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

An interesting observation in this study was a high incidence of end organ failure among the population who did not survive in both groups. There was only one case of end organ failure in survivors (n=33) and 7 cases in non-survivors (n=10) of blood transfusion group. Similarly, there were 4/16 cases of end organ failure among survivors and 12/15 cases among non-survivors in control group. This association of end organ failure with mortality was proven by Pearson chi-square value of 22.729(P≤0.0001) in blood transfusion group and 9.378(P=0.002) in control group. Kendall’s tau b test showed a statistically significant moderate to large positive correlation between end organ failure and mortality in blood transfusion group(r=0.5, P=0.003), control group(0.727, P≤0.0001) and entire study population(r=0.665, P≤0.0001).

**Fig3: End-organ failure in study population**

- 70% in blood transfusion group
- 25% in control group
- 80.00% in survivors
- 3.03% in nonsurvivors

4. DISCUSSION

Sepsis is defined as an exaggerated immune response to an infective stimulus\(^{(12)}\). In this study, Apache II score>20, 2 of the 4 SIRS criteria and source of sepsis have been applied as inclusion criteria of septic shock. The same criteria have been used to define septic shock patients in a local descriptive study by Ali Asghar et al. at the time of admission\(^1\).

The incidence of sepsis in last decade is 9.37% of all ICU admissions in the developed world\(^{(1)}\). Globally, it is considered to be much higher in developing countries. The incidence of severe sepsis and septic shock has been reported to be 43.23% of all ICU admissions in a local tertiary care hospital with 6.1% mortality associated with 6.1% anemia in blood transfusion group\(^{(10)}\). In Pakistan, as most of the women are being delivered in low-resource settings in unhygienic conditions and anemia is very common during pregnancy, the mortality associated with sepsis and septic shock is very high. In this study, demographic features showed that participants mostly belonged to low socioeconomic class and illiteracy and anemia was common. Sepsis in these patients was associated with intervention by untrained paramedics.

The results of this study showed that timely and aggressive management with IV fluids and blood administration had significantly less mortality as compared to patients in which blood could not be transfused within first 6 hours. The survivors in control group received more blood transfusions and vasoconstrictor and ionotropic support later on and had a delayed recovery in ICU. The early blood transfusion not only decreased morbidity and mortality but also shortened the time of recovery from pulmonary edema, ionotropic support, cardiac support, and ventilator support and total requirement of blood transfusion.

In this study, patients with septic shock with pulmonary edema had a better recovery in study group and chest became clear in shorter time. The improved myocardial function in these patients was reflected by early normalization of pulse and blood pressure. The early goal directed therapy protocol by Dellinger et al. favors blood transfusion at a hematocrit of less than 30% if oxygen saturation is less than 70%.9. In the septic shock study of Rivers et al., the effect on pulmonary edema have not been observed individually but overall results of early goal-directed therapy are much better as compared to standard therapy and the main difference between the two protocols is that of blood transfusion\(^{(10)}\). The Royal colleges of Obs & gynae in England and Ireland both recommend early goal-directed therapy in septic shock patients\(^{(11,12,13)}\). The role of early blood transfusion has not been proven by ProCESS and ARISE trials\(^{(14,15)}\). In the trial of low VS high Hemoglobin threshold, the mortality was not decreased by keeping a high threshold for hemoglobin\(^{(16)}\). This difference may be attributed to the difference in criteria of the population studied. In this study population was of young reproductive age group and study was carried out in a hospital which deals absolutely with gynae and Obst patients. This is in contrast to other studies which were carried out in general or surgical ICU with an average age of population above 60 years. The number of serious admissions is much lower in these settings compared to high-income settings.

comorbidities included in international studies was also high which could be by themselves be the cause of death irrespective of sepsis and were adversely affected by excessive fluid which is required to restore normal blood pressure. Another difference was a follow-up of 90 days in those studies which are a confounding factor for death in aged patients\textsuperscript{1,2,3,4}. In this study, Obstetric patients did not give a long time during shock, and they either showed signs of recovery within 24 to 72 hrs. or developed irreversible shock resulting in mortality.

In this study, Comorbidities like the history of hypertensive disorders, diabetes mellitus, hyperglycemia, and hepatitis were included. The commonest problem was hyperglycemia in both groups. Afzal et al. have also found hyperglycemia to be a common problem in sepsis patients and if remain uncontrolled, can be a cause of increased mortality\textsuperscript{4}. There were more cases of organ dysfunction in control group as compared to study group and mortality were higher in patients who developed organ dysfunction. This fact is in accordance with soap study (65% mortality with 4 or more organ dysfunction). Mortality is much high in a local descriptive study of Ali Asghar (51.1%), as compared to this study (33.78%). Although management protocol about blood transfusion has not been mentioned in that study, the mortality is comparable to control group (48.38%) of our study and much higher than blood transfusion group (23.25%)\textsuperscript{4,5}.

The major limitation of this study is that results are of a public sector hospital and it is a quasiexperimental trial as randomization was not justified. So the results cannot be applied to our general population. The protocol of early goal-directed therapy was followed except monitoring of central venous oxygen saturation to transfuse blood and monitoring of serum lactate levels as this facility was not available in the hospital. The benefit is that it is a first controlled trial which precisely includes obstetric population. There is still a lot of uncertainties in the field of septic shock although intensive studies have been carried out to find the pathophysiology and treatment of sepsis. The time period in which endotoxins and inflammatory mediators will cause endothelial injury is short and unpredictable. The time in which the response to antibiotics is achieved and endotoxins and inflammatory mediators are removed from circulation is also uncertain, and the real therapeutic measure which quickly reverses endothelial injury is not available yet. Till the time such treatment modality can be discovered, it is the osmotic pressure inside the vascular tree which can keep the fluid in blood vessels. The role of blood transfusion in septic shock of obstetric patients needs further clinical trials at national and international levels to improve septic shock outcome.

5. CONCLUSION

Early blood transfusion therapy has a role in the treatment of obstetric patients with sepsis and septic shock. The mortality and morbidity are significantly decreased if blood transfusion can be arranged as soon as possible. The delay results in prolonged hospital stay, ionotropic and ventilator support and increased risk of end-organ failure esp. hepatic and renal dysfunction.

CONFLICTS OF INTERESTS

There are no conflicts of interest associated with this study.

DISCLAIMER

The authors have expressed her own views and observations in this article and not on the position of the institution.

CONTRIBUTION TO AUTHORSHP

All authors designed and carried out the study with equal contribution. The study was blinded by DR Imran Azem, and statistical calculations were carried out by Dr. Shazia Saaqib. The results of the safety profile of blood transfusion in septic shock were informed to Prof Arshad Chohan, Head of the department gyn and obstetrics Lady Willingdon Hospital, Lahore, Pakistan and his permission was taken as supervisor to carry out the study.

FUNDING

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ABBREVIATIONS

c/s cesarean section, OBG: Gynae and Obstetrics

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