the signs and symptoms of these diseases and availability of treatment, but also about the permanent and distressing consequences on their reproductive functions, if these diseases are not treated in time.

In India, there has been a move in this direction, and an important step was the launching of the Reproductive and Child Health Programme in 1997. This programme includes the management of reproductive tract infections (RTIs) and sexually transmitted infections (STIs) as an integral part of the Child Survival and Safe Motherhood Programme. Another important step was taken in 1999 by launching a ‘Family Health Awareness Campaign’ (FHAC) to create awareness about HIV/AIDS along with providing facilities for detection and screening of patients with RTIs and STIs covering 100 districts in all the states. Subsequently, the entire country (except Jammu and Kashmir, Bihar, Gujarat and West Bengal) was covered under this programme during 2000. India CLEN coverage evaluation—2000 showed that FHAC was a useful programme. Its relevance and implementation strategy was widely accepted by providers, support groups (spouses, elders, local non-governmental organizations) and clients. However, the programme services could cover only 19% of rural and 13% of eligible individuals residing in urban slums and high-risk areas (personal communication, K. Anand). Therefore, there is a need to increase the outreach of the programme in subsequent rounds.

Early haemodynamic manipulation in severe sepsis and septic shock improves outcome


**SUMMARY**

An insight into the pathophysiology of severe sepsis and septic shock has shifted therapeutic goals from mere infection control to intensive haemodynamic monitoring and measures to arrest the cytokine cascade. Earlier studies in critically ill patients have shown that haemodynamic goal-directed therapy in the intensive care unit (ICU) improves outcome.

The present study was a prospective, randomized, controlled trial conducted in the Emergency Department (ED) of a tertiary care hospital over a period of 3 years. A total of 236 adult patients with severe sepsis, septic shock or the sepsis syndrome were randomized to receive a 6-hour trial of either standard therapy (control group) or early goal-directed therapy (study group) in the ED before they were shifted to the ICU.

Patients in the standard therapy group were treated at the clinicians’ discretion, the end-points of therapy being a central venous pressure (CVP) of 8–12 mmHg, mean arterial pressure (MAP) >65 mmHg and a urine output >0.5 ml/kg/hour. These patients were given inpatient care as soon as possible. Those patients enrolled in the early goal-directed therapy group were treated in the ED for 6 hours and then transferred to inpatient beds. All these patients received a central venous catheter and the central venous oxygen saturation (ScvO₂) was continuously monitored. The treatment in this group consisted of normalization of the CVP (8–12 mmHg), MAP (≥65 mmHg and ≤90 mmHg) and ScvO₂ (≥70%). This was achieved by the administration of crystalloids, vasoactive drugs (vasopressors/vasodilators) and infusion of red cells. Patients in whom these goals could not be met were sedated and ventilated to reduce oxygen consumption.

The outcome measures included severity of illness scores, haemodynamic end-points at 0, 6 and 7–72 hours, mortality and consumption of hospital resources. Patients were followed up for 60 days or until death. It was seen that patients who received standard therapy stayed for a significantly shorter time in the ED. The combined haemodynamic goals were achieved (CVP, MAP, urine output) in 86% of patients in the standard therapy group as compared to 99.2% of patients in the early goal-directed therapy group (p<0.001) in the first 6 hours of treatment. Between 7 and 72 hours of treatment, patients in the standard therapy group had a significantly higher heart rate, lower MAP, lower ScvO₂, higher lactate level and lower pH. This group of patients had higher APACHE II, SAPS II and MODS scores.

In-hospital mortality was also significantly higher in the standard therapy group (46.5%) compared to the early goal-directed therapy group (30.5%; p=0.009). On follow up, patients in the standard therapy group had a significantly higher 28- and 60-day mortality. Sudden cardiovascular collapse as a cause of death was significantly higher in the control group (21%) than in the study group (10.3%; p=0.02).

Local leaders, *panchayat* members and non-governmental organizations should also be involved in the planning, coordination and implementation of this programme. Involvement of private practitioners should be given importance, as most women prefer private health services to public health ones. A strong political will is needed to ensure sustainability of the programme which is still in its infancy.

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Patients in the study group received significantly more fluid, red cell transfusions and inotropes in the first 6 hours. Therefore (7–72 hours), those in the standard therapy group received more haemodynamic support and ventilation. Consumption of healthcare resources (duration of vasopressor therapy, mechanical ventilation and hospital stay) was similar in both the groups. The investigators concluded that early institution of goal-directed haemodynamic therapy improved the survival of patients with severe sepsis and septic shock. This benefit was achieved on account of early interventions aimed at identifying patients at risk of cardiovascular collapse and restoring the balance between oxygen consumption and demand.

COMMENT

Despite the best management protocols, septic shock is associated with a high mortality, ranging between 20% and 63% in various studies. The presence of shock is an independent predictor of mortality over and above that expected from sepsis alone. The continuum from systemic inflammatory response syndrome (SIRS) to severe sepsis to septic shock is associated with increasing cytokine levels and toxic free radical-mediated cellular injury, which translates clinically into multisystem organ failure and increasing crude mortality. Hence, the cornerstones of management are three-fold: arresting infection with appropriate antimicrobial therapy and/or surgical drainage, early institution of haemodynamic monitoring and measures to stem the cytokine cascade.

Septic shock is the prototype of distributive shock, which is characterized by increased cardiac output and decreased systemic vascular resistance. This results in global tissue hypoperfusion. Besides, loss of autoregulation in the cerebral, renal and splanchic microcirculation leads to maldistribution of cardiac output causing regional ischaemia and organ failure. Most of the routine haemodynamic variables monitored in the ICU are indicators of global tissue perfusion; indices of oxygen consumption–delivery mismatch and regional hypoperfusion are altered only after the onset of frank organ failure.

Early studies on goal-directed haemodynamic therapy, wherein an attempt was made to achieve supraphysiological levels of cardiac index and mixed venous oxygen saturation (SvO₂) had shown conflicting results. Studies on surgical patients have shown decreased mortality with such therapy, whereas studies in patients with sepsis or mixed groups of critically ill patients failed to show any significant reduction in mortality.

About half the patients who succumb to septic shock do so as a result of multiorgan failure. Refractory hypotension is the other major cause of death in these patients. Sudden cardiovascular collapse is a common occurrence in sepsis and hence there is a need for intensive haemodynamic monitoring and early detection and intervention is logical to improve the outcome.

A combination of ScvO₂ and some indices of splanchnic hypoperfusion (urine output, liver function tests, gastric intramucosal PCO₂) would be a reasonable alternative.

Transfusion of red blood cells to increase oxygen delivery in patients with a decreased ScvO₂ seems a logical step; however, studies suggest that increasing oxygen content by transfusion is not as effective in restoring splanchnic perfusion as it is in increasing cardiac output. Accordingly, though the optimal haemoglobin level for patients with sepsis has not been defined, most patients will not require transfusion if their haemoglobin is in the 8–10 g/dl range.

This study showed a definitive survival benefit with early intervention to detect and restore the oxygen demand–supply imbalance in patients with severe sepsis and septic shock, but had no impact on reducing the length of hospital stay or requirement of other treatment in the hospital among the survivors. However, it required intensive monitoring in the ED that may be logistically difficult to provide in resource-poor countries. Moreover, the efficacy of early goal-directed therapy in a mixed group of critically ill patients remains ill-defined and it is perhaps best suited to patients with severe sepsis who are at special risk for circulatory collapse.

Interrupting the cytokine and coagulation cascade is an important goal in the treatment of sepsis. Recent studies have shown promising results with the replacement of protein C in patients with sepsis.

Treatment of severe sepsis and septic shock remains a challenge to intensivists and despite some achievements, we have a long way to go.

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