Protocol-based care for early septic shock

ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terrnudrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. (University of Pittsburgh, Pittsburgh; Ohio State University, Columbus; University of Alabama at Birmingham, Birmingham; Brigham and Women’s Hospital, Boston; Maricopa Medical Center, Phoenix; Massachusetts General Hospital, and Beth Israel Deaconess Medical Center—both in Boston; University of Pittsburgh, Pittsburgh, USA.) A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683–93.

SUMMARY

In this multicentre, randomized controlled trial in patients with early septic shock, the investigators sought to determine whether a protocol-based management of early septic shock (ProCESS) is better than standard care, protocol-based or otherwise. A total of 1341 patients with early septic shock, from 31 academic emergency departments in the USA, were randomly assigned to one of three groups for the first 6 hours of their management: (i) protocol-based early goal-directed therapy (EGDT); (ii) protocol-based standard therapy (ST) in which central venous catheter (CVC) placement, inotrope infusion or blood transfusions were not mandatory; and (iii) usual care. The ST group included adequate peripheral venous access, administration of fluids and vasopressors to achieve time-sensitive goals for blood pressure and shock index (heart rate divided by systolic blood pressure), and clinical assessment of fluid status and hyperperfusion. Patients in the usual care group were treated at the discretion of the bedside attending physician. The primary outcome was 60-day in-hospital mortality. Secondary outcomes included mortality at 90 days and 1 year, and the organ support required.

Adherence to protocols in the first two groups (EGDT and ST) was high (88.1% and 95.6%, respectively). The volume of intravenous fluids administered in the first 6 hours after randomization was 2.8 L, 3.3 L and 2.3 L in the EGDT, ST and usual care groups, respectively (p<0.0001), while vasopressors were used in 54.9%, 52.2% and 44.1% of patients in the three groups, respectively (higher in the two protocol-based groups as compared to the usual care group; p=0.003). CVCs were placed in 93.6% of the EGDT group as against 56.5% of the ST group and 57.9% of the usual care group for inability to attain adequate peripheral access in the latter two groups. Dobutamine use and packed red-cell transfusions were more in the EGDT group as compared to the ST group. Antibiotics were administered early in almost all the patients; in around 75% of them, antibiotics were given before randomization and in around 97% within the first 6 hours in all three groups (p=0.9 between groups for both time periods).

Mortality at 60 days, the primary outcome, was 21%, 18.2% and 18.9%, respectively in the three groups (p=0.83 for comparison between the two protocol-based groups with the usual care group; p=0.55 for individual comparisons between the three groups). Significant differences between the groups were not present in the 90-day mortality or in the cumulative mortality at 90 days or 1 year. The incidence of acute renal failure was higher in the protocol-based ST group as compared to the other two groups, though the duration of renal replacement therapy was not longer. All other secondary outcomes were similar in the three groups.

COMMENT

Septic shock has a high mortality and over the past two decades several efforts have been made to reduce mortality by optimizing therapy for this condition. Earliest among these, the landmark study by Rivers et al. stressed on the importance of EGDT for haemodynamic optimization in patients with septic shock.1 While previous studies attempted to optimize haemodynamic end-points in patients after ICU admission, the recognition that ‘golden hours’ are lost before ICU admission prompted Rivers et al. to start goal-directed therapy in the emergency room, before ICU admission. The stress was on the early recognition of shock and the rapid management of the same, with some haemodynamic end-points as ‘goals’ in the first 6 hours after diagnosis of severe sepsis or septic shock. Placement of arterial catheters and CVCs soon after recognition of shock, targeting a central venous pressure (CVP) between 8 and 12 mmHg, a central venous oxygen saturation (ScvO2) over 70% and a haematocrit over 30% were the important haemodynamic targets to optimize tissue oxygen delivery. Volume management, titration of vasopressors to achieve a target mean blood pressure (MAP) over 65 mmHg, packed red blood cell transfusion and inotropic support with dobutamine were important interventions. A substantial reduction in 60-day mortality from 46.5% to 30.5% was found, with other measures of secondary outcome also better in the EGDT group as compared to the ST group.

The ‘surviving sepsis guidelines’ quickly incorporated these principles in the management protocols of sepsis, and early goal-directed management of severe sepsis and septic shock has since been the norm.2,3 However, implementing this protocol is not possible in all settings as this requires placement of a CVC, access to monitoring ScvO2, and the requisite expertise and resources for the same.4 Hence, these guidelines are not without criticism and controversy.5,6

Further, a retrospective study on patients with septic shock, done in a similar time period as the one by Rivers et al. showed that patients presenting to the emergency room were less sick and probably presented earlier.7 These patients did not have CVPs which were as low or ScvO2 as low as that found by Rivers et al. The mortality was also lower (28.8%). These and subsequent studies questioned the generalizability of the findings of Rivers et al.

Subsequent reviews on the management of sepsis acclaimed the surviving sepsis guidelines for a reduction in mortality from septic shock. However, this reduction could be attributed to the entire sepsis ‘bundle’ of management and not the haemodynamic optimization alone. Important among the components of the ‘bundle’ are early antibiotic administration and optimal fluid resuscitation.

The utility of lactate clearance as a substitute to ScvO2 monitoring was tested by Jones et al. in a multicentre study of 300 patients admitted to the emergency room with severe sepsis or septic shock.8 Patients were assigned to one of two resuscitation protocols. Apart from normalization of CVP and mean arterial pressure, resuscitation was further fine-tuned to achieve a ScvO2 >70% in one group of patients, and lactate clearance >10% in the other group. They showed that lactate clearance was not inferior to ScvO2 monitoring.6

The ProCESS study is the largest trial that compares three
different methods of haemodynamic optimization in patients with septic shock. The vastly different results, however, need explanation. First, since the publication of the study by Rivers et al., several other interventions including lower tidal volume ventilation, moderate glycemic control and more conservative transfusion thresholds have contributed to an overall reduction in mortality from critical illnesses such as septic shock. Small differences in mortality, which may have been due to better haemodynamic optimization, could have been nullified due to the overall reduced mortality. Second, several authors have pointed out that patients in the study by Rivers et al. were sicker and had probably presented later to the hospital (as evidenced by lower values of CVP and higher values of ScvO2). Also, these patients were older and had many more comorbid conditions. Hence, the results obtained by Rivers et al. could not be generalized. Perhaps, differences in end-of-life care practices also influenced the difference in mortality. The strength of the current study is that all patients were identified and managed early and received antibiotics and fluid resuscitation early. This early identification and management of septic shock in itself may have contributed to a reduced mortality in all the patients.

The important message for us from the developing world is that ‘sophisticated’ management strategies are perhaps not always required. Early recognition of septic shock, early administration of antibiotics, and early resuscitation with fluids and vasoactive agents with clinical end-points of haemodynamic resuscitation can save many lives. We must also remember that patients often do not present ‘early’ in India. The last word on the haemodynamic end-points of resuscitation of patients with septic shock has not yet been said. Results from two large, ongoing, similar trials in patients with septic shock are awaited.8

REFERENCES


BANANI PODDAR
Department of Critical Care Medicine
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow
bananip@hotmail.com

Pasireotide for prevention of pancreatic leak: Is there light at the end of the tunnel?


SUMMARY

This study is a single-centre (Memorial Sloan Kettering Cancer Center, New York, USA), randomized, double-blind trial to assess the efficacy of pasireotide in preventing postoperative pancreatic fistula. Two groups of patients were included: those who underwent pancreaticoduodenectomy (PD) and those who underwent distal pancreatectomy (DP)—in the former, a pancreaticoenteric anastomosis was present, and in the latter, the stump was closed. Seven surgeons performed the procedures, and while PD was followed by a duct-to-mucosa pancreaticojejunostomy, the stump of the DP was either suture closed or stapled, with reinforcement. Thus there was some variation in technique among the cases. The surgeons also recorded the texture of the gland as soft or firm. Drainage of the peritoneal cavity was done selectively and not routinely (in about a quarter of the cases). A total of 300 patients were randomly assigned to receive either 900 µg of subcutaneous pasireotide twice daily for 7 days or placebo. Stratification was performed on the basis of the type of resection (PD or DP) and whether the pancreatic duct was dilated or not. The primary end-points studied were the development of pancreatic fistula, leak or abscess (The MSKCC Surgical Events Scoring System was used and Grade 3 or more was required for the primary end-point to be reached). Patients with prolonged QT interval on ECG or those with raised levels of blood sugar were excluded. The results were astonishing—of an overall primary end-point rate of 15%, the pasireotide group had 9% whereas the placebo had 22%. This applied to both PD and DP groups and also whether or not the pancreatic duct was dilated. Further, of an overall 13.2% rate of postoperative pancreatic fistula (these patients had drains inserted for intra-abdominal collection), the pasireotide group had 7.9% type B fistula rate and placebo 16.9% (B or C fistulas; with 5 of these patients having a type C pancreatic fistula). Overall, pancreatic complications were also significantly higher in the control group. Post-hoc analysis showed that 25% of those who had a drain placed at the time of surgery reached the end-point of grade 3 complication, compared to 11% of those who did not, suggesting that drains were placed for cases where the surgeons regarded the anastomosis to be at higher risk; even in this high-risk group, patients in the pasireotide arm had fewer complications.