

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.*,¹ several other interventions including lower tidal volume ventilation, moderate glycaemic 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

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

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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.

COMMENT

Pancreatic leak and fistula continue to be the Achilles' heel of pancreatic resection despite many advances in the technique. These result in the formation of intra-abdominal abscesses, and may even cause haemorrhage. Prevention of pancreatic leak has been the Holy Grail for surgeons the world over. Numerous techniques have been devised in a futile bid to decrease or eliminate pancreatic leakage, with variable results.¹ The somatostatin analogue, octreotide was used a decade ago in an attempt to inhibit pancreatic secretion and thereby decrease leak and fistula. Whereas results from Europe showed some benefit, the results from the USA did not, and the use of octreotide is not widely recommended.^{2,3} It is possible that the mixed results with octreotide were due to a lack of standardization of what constituted pancreatic leakage, which is now available with the International Study Group for Pancreatic Fistula (ISGPF) system.⁴

Pasireotide is a new analogue of somatostatin and is an orphan drug developed for the treatment of pituitary lesions. It has a considerably longer duration of action (half-life of 11 hours *v.* 2 hours of octreotide), and its affinity to the somatostatin receptor is higher (it binds to somatostatin receptor types 1, 2, 3 and 5 with affinity of 5 to 40 times as octreotide; the latter binds only to receptors 2 and 5).⁵

This unique study may well be a landmark publication in the search for preventive solutions to postoperative pancreatic leakage. However, there are concerns, which may be grouped into issues of applicability and efficacy. Dose-limiting nausea was observed in 17% of patients in the pasireotide group, and the drug was not used if blood sugar levels were >250 mg/dl or if the QT interval was abnormal. Over 50 patients in each arm were deemed ineligible. Many patients who undergo pancreatic resection either have diabetes or may have associated cardiac problems, and this raises the issue of how applicable this drug is in all patients eligible for pancreatic resection. The completion of pasireotide therapy occurred in only 75.7% and thus a quarter of patients did not receive the full quota of the drug. It could be argued, however, that the results in the pasireotide were better despite this shortcoming.

Outcomes following DP and PD are substantially different. In PD there is a pancreaticoenteric anastomosis with issues of postoperative feeding, whereas the pure pancreatic leak following DP is easier to manage. Further, first, routine peritoneal drains are placed after resection in most if not all centres that perform pancreatic surgery around the world. However, the authors of the

paper have not performed routine drainage, and this has prevented application of the ISGPF grading system for pancreatic fistula in assessing the results; second, a variety of techniques have been used in closure of the pancreatic stump or in pancreaticoenteric drainage and they may impact on the outcomes of the study; third, ductal dilatation is only one factor which affects outcome after surgery. The soft nature of the gland, friability and fat content have all been implicated, and since the prevalence of these characteristics has not been studied, there is a possibility that the final outcome may not be applicable to the high-risk pancreatic anastomosis.⁶

Regardless of these limitations, the observations represent an important step forward. It remains for future trials to substantiate and reproduce the results of this trial. Two questions arise: (i) will pasireotide fulfil this early promise, and (ii) in view of the high cost of pasireotide, is it a good time to resurrect octreotide and study its efficacy one more time?

Octreotide was evaluated in the pre-ISGPF era and heterogeneity in trial design and lack of definite end-point definition may have resulted in studies failing to show efficacy.

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Is double-fortified salt a panacea for iron-deficiency anaemia in India?

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Science, Pennsylvania State University, University Park, Pennsylvania, USA; Micronutrient Initiative and International Development Research Centre, Ottawa, Ontario, Canada; Mathile Institute for the Advancement of Human Nutrition, Dayton, Ohio, USA.) Double-fortified salt is efficacious in improving indicators of iron deficiency in female Indian tea pickers. *J Nutr* 2014;**144**:957–64.

SUMMARY

This study reports the findings of a double-blind randomized controlled trial conducted to assess the efficacy of double-fortified salt (DFS) (iron and iodine) in improving the iron status of women. It was done