Commentary

Recently published papers: Sugar, soap and statins – an unlikely recipe for the critically ill

David Bacon and Lui G Forni

Department of Critical Care, Worthing General Hospital, Worthing, UK

Corresponding author: Lui G Forni, Lui.Forni@wash.nhs.uk

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Abstract

The eagerly awaited SOAP (Sepsis Occurrence in Acutely ill Patients) study is published and its observational data provide much of interest, not least in generating further hypotheses on improving treatment in this challenging group. Glycaemic control in the critically ill is once more the focus of attention, and we discuss three studies in this area. Not least among these reports is that from the van den Bergh group, who provide further data on their intensive insulin protocol in a more heterogeneous group, namely medical intensive care unit patients. Finally, we discuss another good reason to take statins.

"Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing"

Francois-Marie Arouet Voltaire

Some nonphysicians may argue that little has changed since the 18th century. However, the advent of the clinical trial and multicentre studies may have helped to shed some light on practice. To this end the results of the SOAP (Sepsis Occurrence in Acutely ill Patients) study [1], published recently in *Critical Care Medicine*, will cause a stir. That prospective study of 3147 patients took place in early May 2002 and joins the ranks of other such epidemiological work on the subject. The study was endorsed by the European Society of Intensive Care Medicine, and 24 European countries were involved, encompassing almost 200 intensive care units (ICUs). Patients were followed for up to 60 days, or until discharge or death if this occurred before 60 days. The volume of data collected is impressive, and further insight into outcomes from sepsis, as defined by the classical consensus conference criteria, can be gleaned.

The incidence of sepsis approached 40% (37.4%), with the lung being the commonest site of infection [1]. Unsurprisingly, *Staphylococcus aureus* was the most frequent organism, but rather worryingly 14% of isolates were methicillin resistant. There was a marked difference in the frequency of sepsis between countries, and higher frequencies of sepsis were mirrored by higher ICU mortality rates. It is difficult to correlate this finding with any one factor but it may well reflect regional differences in ICU resources as well as variations in case-mix and thresholds for ICU admission. The multivariate analysis applied to the data provides few surprises. Patients with sepsis had a longer length of stay both in the ICU and in hospital, and they had more severe organ dysfunction and higher mortality rates. The prognostic variables for ICU mortality included the usual suspects. Age, cancer, medical admission and septic shock were all associated with a worse outcome. Also, an observed increase in patient mortality was associated with the degree of organ dysfunction, but interestingly there was little difference between the sepsis and nonsepsis groups in this regard, cementing the view that organ dysfunction is a bad thing whether sepsis is present or not.

The SOAP study [1] is interesting and a triumph in organizational terms, but its findings also contain one extremely important point that may provide a focus for several more studies. Cumulative fluid balance within the first 72 hours of onset of sepsis was an independent predictor of outcome in the sepsis group. Although multivariate analysis has attracted many criticisms, including its inability to account for unmeasured differences, this is still an intriguing finding, especially when it is viewed in tandem with findings reported by Rivers and coworkers [2]. Perhaps this indicates that early, appropriate recognition of critical illness, and treatment of it, should be our aim and with this may come improved outcomes.

One aim in treatment that has been embraced with great vigour is that of intensive insulin therapy and tight glycaemic control in the critically ill. This followed the landmark study by

ICU = intensive care unit.

van den Berghe and colleagues in 2001 [3], who demonstrated an impressive mortality benefit in surgical intensive care patients, such that previously ignored elevations in blood glucose have now become high priority therapeutic targets. That study and the wholesale implementation of intensive insulin therapy based on its findings have not been without their critics, given that the original work represented data from a single centre that was biased toward cardiac surgery with a relatively low severity of illness. Few data are currently available regarding treatment of the more severely ill. However, the impact on clinical practice is unquestionable. Recently published guidelines of the Surviving Sepsis Campaign [4] recommend intensive insulin therapy despite a lack of overwhelming evidence. It was hoped that the latest study from Belgium [5] would yield answers to some of these questions.

Van den Berghe and colleagues [5] enrolled 1200 patients over a 3-year period from 2002 on an intention-to-treat basis. All were patients on a medical ICU who had a predicted length of stay of at least 3 days on the unit. Patients not for active treatment were excluded. Patients were randomly assigned either to intensive insulin therapy (insulin infusions to keep blood glucose between 4.4 and 6.1 mmol/l [80–110 mg/dl]) or to standard therapy (insulin to be administered if blood glucose exceeded 12 mmol/l [215 mg/dl] and eased when levels fell below 10 mmol/l [180 mg/dl]). The results were somewhat surprising. Overall, there was no significant difference in survival at 28 and 90 days for each patient group. More strikingly, there appeared to be a worse outcome in the intensive therapy group who were discharged to the general wards fewer than 3 days from admission to ICU. However, in keeping with their previous work, the investigators found that patients who were on the ICU for longer than 3 days exhibited an apparent morbidity and survival benefit, which was significant following intensive insulin therapy. This included reductions in days to wean from intermittent positive pressure ventilation, incidence of renal impairment (but not incidence of dialysis) and incidence of hyperbilirubinaemia.

The investigators suggested that, for the protective effect of strict normoglycaemia to be realized, the therapy must be established for longer than the first few days of the illness, although they proposed no reason for the observed increase in mortality in the group treated for fewer than 3 days [5]. What is clear is that hypoglycaemia was far more frequently observed in the intensive treatment than in the conservative group, and this was demonstrated to be an independent predictor of death.

Leading on from this, Egi and colleagues [6] reported on a study designed to assess the risks and benefits of intensive insulin therapy in postoperative ICU patients. They selected a cohort of patients with clinical features similar to those of the cohort described by van den Berghe and coworkers [3]. For the 783 patients studied, all information on glucose control was retrieved, although none of the units employed specific protocols for insulin therapy. There overall findings suggested that 102 patients would have to be treated with intensive insulin treatment to prevent one death. They also calculated that treatment of 13 patients would lead to one episode of harm, in this instance severe hypoglycaemia (defined as <2.2 mmol/l). However, these results did vary widely depending on the clinical setting and case-mix. This is a difficult study to draw major conclusions from. Clearly, comparing the ultimate end-point with transient hypoglycaemia is far from ideal, but the study does alert us to the fact that application of intensive insulin therapy may not, as suggested previously, be universally applicable and is not without risk.

This latter point was addressed by Vriesendorp and coworkers [7]. Since employing more intensive insulin treatment regimens, those investigators have noticed an increase in hypoglycaemic events, similar to those reported by van den Berghe and colleagues. They therefore set out to identify the factors that may make this such a common scenario within their patient population. Over a 2-year period they examined all patients who had at least one episode of hypoglycaemia during the ICU stay. A total of 156 patients were identified from 2272 in all. Vriesendorp and coworkers examined several parameters and found that diabetes, sepsis, need for inotropic support, use of bicarbonate-buffered replacement fluid during haemofiltration and decreased nutrition without insulin adjustment were independently associated with hypoglycaemia.

So where do these studies leave us? Certainly, the days of ignoring high blood sugars on the basis of an 'adaptive response' are gone. However, the dictatorial constraints of the van den Bergh protocol may not be applicable to those of us who work in a predominantly medical ICU. Perhaps the way forward may well be a slightly more relaxed approach, certainly during the first 72 hours of admission, similar to the proposal by Finney and colleagues in 2003 [8] who speculated that a blood glucose level below 8.0 mmol/l should be the preferred treatment aim. This could be followed by a more intensive regimen to maximize any potential benefit.

Assuming that we have identified our patient with sepsis and of course treated the blood glucose appropriately, what then? When we are dispensing our polypharmacy, we should perhaps consider continuing the patient's statin therapy. Some studies have implied that statins may have diverse effects other than just lowering lipids. Hackam and colleagues [9], in the *Lancet*, reported that statin therapy in patients with cardiovascular disease may have additional benefits in preventing sepsis. In their observational study conducted in 141,487 patients in Canada, they found reduced rates of sepsis, severe sepsis and fatal sepsis. This protective association was observed in all groups including those deemed to be at higher risk, such as patients with diabetes and renal failure. Although not ICU based, this is an interesting study and well worth a look.

Competing interests

The authors declare that they have no competing interests.

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