Editorial

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Quick response code

Fluid resuscitation in severe sepsis and septic shock: Shifting goalposts

Annual incidence of sepsis is reported to be 20–300/100,000 population with a mortality rate ranging between 30% and 80%.[1,2] No definitive data on the incidence of sepsis in India is available, but it could be well above this.[2] Sepsis, when associated with abnormalities such as intravascular volume depletion, peripheral vasodilatation, increased metabolism and decreased cardiac output (CO) leads to tissue hypoxia and shock. This transition occurs during the critical 'golden hours', when definitive recognition and intervention provide maximal benefit in terms of outcome.[3]

In 2001, Rivers *et al*.[4] conducted a randomized controlled trial (RCT) in patients presenting to the emergency department (ED) with severe sepsis and septic shock to know whether specific protocol guided intervention termed as early goal-directed therapy (EGDT) improves outcome when compared to usual therapy. The protocol for EGDT called for placement of central venous catheter (CVC) for monitoring of central venous oxygen saturation ($ScvO_2$) and central venous pressure (CVP) to guide use of intravenous (IV) fluids, vasopressors, inotropes and packed red blood cell (PRBC) transfusion. Trigger points recommended were infusion of crystalloids or colloids if CVP was <8 mmHg; vasopressors when CVP was >8 mmHg but mean arterial pressure (MAP) was <65 mmHg; use of inotropes when $ScvO_2$ was <70%, but haematocrit was >30%; and transfusion of PRBC if haematocrit was <30%. Patients were followed up for 60 days or until death. The authors found that in-hospital mortality rates were significantly higher in the standard-therapy group than in the early-therapy group (46.5% vs. 30.5% mortality, P = 0.009), as was the mortality at 28 days (P=0.01) and 60 days (P=0.03).

Since then, EGDT has been incorporated into the 6-h resuscitation bundle of the surviving sepsis campaign (SSC) guidelines as a key strategy to decrease mortality. However, Rivers' study was single centric, and its external validity was uncertain.[5,6] In the year 2008, SSC recommended international guidelines, which included administration of broad-spectrum antibiotics within 1-h of diagnosis of septic shock; administration of either crystalloid or colloid for fluid resuscitation; vasopressors (norepinephrine or dopamine) to maintain MAP >65 mmHg; inotropes when CO remains low despite fluid resuscitation; stress-dose steroids only when fluids and vasopressors fail to improve CO; recombinant activated protein-C in severe sepsis; targeting haemoglobin of 7–9 g/dL; measurement of serum lactate levels within 6-h of presentation; and tight glycaemic control.[7] Subsequently in the year 2012, the guidelines were updated to include reassessment of antimicrobial therapy daily for de-escalation; infection source control within 12-h of diagnosis; addition of albumin in patients who continue to require substantial amounts of crystalloid to maintain MAP; avoidance of hetastarch formulations; fluid challenge to be continued as long as haemodynamics improve, based on either dynamic or static variables; norepinephrine as the first-choice vasopressor followed by epinephrine and vasopressin; dopamine not to be used except in highly selected circumstances.[8]

Recently, the effectiveness of few individual elements of EGDT have been questioned in ProCESS (Protocolized Care for Early Septic Shock) and ARISE (Australasian Resuscitation In Sepsis Evaluation) trials.[9,10] In the ProCESS trial[9] published in 2014, total of 1341 patients with septic shock were randomized to

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one of three groups for 6-h of resuscitation: EGDT based protocol group with mandatory placement of CVC to continuously monitor $ScvO_2$ and CVP (n = 439), or to less aggressive protocol based standard therapy, in which fluids and vasoactive agents were administered targeting systolic blood pressure and shock index (the ratio of heart rate to systolic blood pressure) instead of CVP and $ScvO_2$ monitoring (n = 446), or to usual care group without any prompted protocol (n = 456). Patients in the usual care group received the least amount of IV fluids during the first 6-h after randomisation (2.3 L in usual care vs. 2.8 L in EGDT vs. 3.3 L in the protocol based standard therapy group). EGDT and Protocol based standard therapy resulted in increased use of CVC, IV fluids, vasoactive agents, and PRBC transfusions as compared to usual therapy. The authors found no differences in 60 days mortality between the groups (21% vs. 18.2% vs. 18.9% respectively) and concluded that protocol based resuscitation offers no additional benefit.

Similarly, in the multicentric ARISE trial,[10] the investigators randomly assigned 1600 patients presenting to the ED with early septic shock to receive either EGDT or usual care. Usual care did not include resuscitation guided by measurement of $ScvO_2$ during the 6-h intervention period. Patients in the EGDT group received statistically larger volume of IV fluids in the first 6-h after randomisation (1964 ± 1415 ml vs. 1713 ± 1401 ml) (mean ± standard deviation [SD]), more vasopressor infusions (66.6% vs. 57.8%) and PRBC transfusions (13.6% vs. 7.0%), and dobutamine (15.4% vs. 2.6%) than did those in the usual care group. The authors found no mortality benefit of EGDT at 90 days. Monitoring of CVP and $ScvO_2$ did not result in better outcomes and led to unnecessary inotrope infusion, blood transfusion and more CVC insertion. In the 3rd multicentric RCT, "Protocolised Management in Sepsis" published in March 2015, Mouncey *et al*.[11] showed that on average, EGDT increased the treatment cost as reflected by more days of receiving advanced cardiovascular support and longer stays in the intensive care unit.

Does this mean that protocols don't work? Or do we need to include different and reliable goals of resuscitation in the protocol? If we critically analyse these trials,[9,10] the median time from admission to the ED until randomisation was almost 3-h (half of the critical 'golden hours'). Patients in all the groups received on an average more than 2-L of IV fluids prior to randomisation and more than 75% of patients received antibiotics, both of which are critical parts of SSC bundle. In ARISE trial,[10] 2515 ± 1244 ml (mean ± SD) of IV fluid in the EGDT group versus 2591 ± 1331 ml of IV fluid in the usual care group had been administered at baseline. Hence, all the patients irrespective of the group are given similar treatment in the initial 3 h, possibly due to the influence of EGDT protocols on treating physicians. $ScvO_2$ guided the administration of dobutamine had found to be of no benefit in both the trials.[9,10] However, dobutamine being an inotrope will be of help only when the cardiac index (CI) is <2.5 L/min/m^2 and should not be used to increase the CI to supernormal levels. Monitoring of CI in these trials would have addressed this issue. Transfusion of PRBC in patients with haemoglobin level >7 g/dL should anyway be discouraged.[12-14]

The optimal physiologic targets of fluid resuscitation remain unknown. Lactate measurement[15] and static haemodynamic monitors like CVP, $ScvO_2$ and pulmonary artery occlusion pressure are unreliable.[9,10,16] Till the time we get new therapeutic goals, early intervention with the administration of antibiotics and adequate volume resuscitation with 2–3 litres of crystalloids should be continued.[17,18] Dynamic indices like respiratory changes in the vena caval diameter, radial artery pulse pressure, aortic blood flow peak velocity, brachial artery blood flow velocity and increase in CO in response to passive leg raising manoeuvre are recently found to be more accurate predictors of fluid responsiveness than static measures.[19,20] However, large-scale RCTs are required to prove their superiority before they can be routinely used in the management of sepsis.

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Announcement

Conference Calender - 2015

Name of the conference: 63rd Annual National Conference of the Indian Society of Anaesthesiologists, ISACON 2015
Date: 25th to 29th December 2015
Venue: B. M. Birla Auditorium & Convention Centre, Jaipur, India
Organising Secretary: Dr. Suresh Bhargava
Contact: +91 98290 63830
E-mail: suresh3559@yahoo.com
Website: www.isacon2015jaipur.com

Name of the conference: TRISZAC 2015, 31st Annual Conference of Indian Society of Anaesthesiologists, South Zone and 39th Annual Conference of Kerala State Chapter
Date: 6th to 9th August 2015
Venue: Hotel KTDC Samudra & Uday Samudra Beach Hotel, Kovalam, Trivandrum
Organising Secretary: Dr. Gopakumar D
Contact: +91 98476 39616
E-mail: triszac2015@yahoo.in
Website: www.triszac2015.com

Name of the conference: KISACON2015, 31st Annual Conference of Indian Society of Anaesthesiologists, Karnataka State Chapter
Date: 9th to 11th October 2015
Venue: S N Medical College, Bagalkot
Organising Secretary: Dr. Ramesh Koppal
Contact: +91 98455 04515
E-mail: rameshkoppaldr@gmail.com
Website: www.kisacon2015.com

Name of the conference: 6th National Airway Conference 2015 (NAC 2015)
Date: 18th to 20th September 2015
Venue: Workshop: Srinagar, Conference: Gulmarg (J&K)
Organising Secretary: Dr. Zulfiqar Ali
Contact: +91 94190 86761
E-mail: nacsrinagar2015@gmail.com
Website: http://aidiaa.org/NAC2015/NAC_home.html

Name of the conference: 48th Gujarat State Conference of Indian Society of Anaesthesiologists 6th National Airway Conference 2015 (GISACON 2015)
Date: 9th to 11th October 2015
Venue: Shanku's Water World Resort (Ahmedabad-Mehsana Highway)
Organising Chairman: Dr. R G Agrawal
Organising Secretary: Dr. H G Bhavsar
Contact: +91 98242 33694
E-mail: info@gisacon2015.com
Website: www.gisacon2015.com

Name of the conference: 7th Annual Conference of ICA
Date: 13th to 15th November 2015
Venue: Hotel Savera, Chennai
Organising Chairman: Dr. K Balakrishnan
Contact: +91 98410 29259

Name of the conference: 16th North Zone ISACON 2015
Date: 16th to 18th October 2015
Venue: Dr. Rajendra Prasad Govt. Medical College, Kangra, TANDA (HP)
Organising Chairman: Dr. Sudarshan Kumar