Liberal or restrictive dilemma—that's a CLASSIC!

Ximena Watson[1], Maurizio Cecconi[2]

[1]Department of Anesthesia, Kingston Hospital, Kingston, UK; [2]Intensive Care Unit, St Georges Hospital, London, UK

Correspondence to: Ximena Watson. Anaesthetic Department, St Helier Hospital, Wrythe Lane, Sutton, Carshalton, sm5 1AA, UK. Email: ugm2xw@doctors.org.uk.

Hjortrup *et al*. recently published the results of the CLASSIC study (1). In this randomised parallel group multicentre feasibility study, the effects of a protocol restricting resuscitation fluid *vs.* a standard care protocol were assessed after initial resuscitation in patients with septic shock. Patients in nine ICU's who fulfilled the criteria for sepsis, circulatory impairment and ongoing shock as defined by the requirement for continuous infusion of noradrenaline, and who had received at least 30 mL/kg of crystalloid fluid were randomised to the restrictive or standard protocol. In both intervention groups, the administration of resuscitation fluid was per protocol and a mean arterial pressure (MAP) of at least 65 mmHg was targeted and maintained with noradrenaline infusion. In the fluid restrictive group, patients received fluid boluses of isotonic crystalloid only if there was evidence of severe hypoperfusion defined as either: plasma concentration of lactate of at least 4 mmol/L, MAP below 50 mmHg in spite of noradrenaline infusion, mottling beyond the edge of the kneecap or oliguria. This is in contrast to the standard care group where fluid boluses were administered on the basis of an improvement in both static and dynamic haemodynamic variables. In total, 153 patients were randomised. The co-primary outcome measures were the amount of resuscitation fluid received in the first 5 days post randomisation and during the entire ICU stay. The results of the study demonstrated that cumulated resuscitation fluid volumes were lower in the restricted group at both five days (mean difference −1.2 L, P<0.001) and at the end of the ICU stay (mean difference

−1.4 L, P<0.001). With regards to secondary outcomes, there was no statistical significant difference between total fluid inputs and balances in the ICU at 5 days post randomisation and at end of the ICU stay. There was no significant difference in any of the exploratory outcomes (death at day 90, ischaemic events, days alive without mechanical ventilation or RRT) except from worsening acute kidney injury where the number of patients was lower in the fluid restricted group.

We would like to comment on different aspects of the paper. The background to the study will be reviewed and the methodology and results of the study will be analysed. We will conclude by discussing the future for fluid administration in the ICU and what further research is required.

Background

We feel that the CLASSIC study addressed an important and relevant clinical question. Over recent years there has been an increasing awareness of the deleterious effects of fluids and the effects of a positive fluid balance and fluid overload has been investigated with considerable interest. Fluid overload is defined as the total input minus total output divided by initial body weight and is known to be associated with adverse outcomes when reaching more than 10% (2). In 2009, Murphy *et al*. published a landmark study which demonstrated that patients with sepsis complicated by acute lung injury (ALI) who received early fluid management followed by late conservative fluid

therapy (defined as two consecutive negative fluid balances within the first seven days of shock) had the lowest mortality (3). In 2014, Malbrain *et al.* published a systematic review which examined the association between a positive fluid balances and outcomes in critically ill patients. This review concluded that a restrictive fluid management was associated with a reduced mortality compared to patients treated with a more liberal fluid strategy (24.7% *vs.* 33.2%) (4). A similar finding was published in Critical Care in 2015 by Achaempong *et al.* which demonstrated that in patients with sepsis, persistence of a positive daily balance was associated with an increased mortality in septic patients (5). The SOAP study published in 2008 also found that fluid overload in septic patients with AKI was associated with a higher mortality at 60 days (6). At present, it is recommended that patients with septic shock receive at least 30 mL/kg of intravenous fluid during the initial resuscitation period and to continue to receive fluids if haemodynamics or markers of perfusion improve (7). However, high quality data supporting these recommendations is limited and we currently still lack knowledge on the volume and duration of fluid therapy that these patients should receive. It is well known that fluid management in the ICU is complex and patients with septic shock represent not only a severely unwell cohort but also a vastly heterogeneous population. As with many other studies, the authors developed two standardized protocols detailing when to administer intravenous fluid boluses. As clinicians, many of us know the triggers of when to start fluid therapy but may not be as aware of the triggers to stop fluid resuscitation hence leading to fluid overload and its well-known adverse effects (4). This was explored in the FENICE study which interestingly found that the response to the initial fluid challenge actually made no difference to the decision on whether to administer more fluids. As noted by the authors, this behaviour appears harmful and highlights the need for further education (8).

The CLASSIC study was an innovative study designed with the primary aim of assessing the effects of a restrictive fluid protocol on fluid volumes and fluid balances in patients with septic shock. The authors have stated that they chose to focus on volumes of resuscitation fluid instead of total input of fluid balances as they felt that 'resuscitation fluid was likely to have a different balance between benefit and harm compared to fluids given for maintenance or nutrition'. This is in contrast to other studies which have assessed the effects of total fluid input or fluid balance on patient outcomes. The results of the study will be analysed in detail but whether this was the most appropriate end point to measure could be questioned.

The authors of the study concluded that a protocol aimed at restricting fluid resuscitation was feasible and resulted in reduced volumes of resuscitation fluid compared to the standard care group both during the first five days of randomization and throughout the entire ICU stay. As mentioned previously, the restrictive group were only to receive fluid boluses if there was evidence of severe hypoperfusion defined as either: plasma concentration of lactate of at least 4 mmol/L, MAP below 50 mmHg in spite of noradrenaline infusion, mottling beyond the edge of the kneecap or oliguria, whereas the standard group used both dynamic and static markers of fluid responsiveness. Therefore, both groups were in fact using a form of goal-directed therapy (GDT) to guide fluid administration although it could be argued that the goal in the restricted protocol was tissue perfusion, which could be seen as more 'physiological' than the static or dynamic markers used in the standard group. It is also worth questioning why there were a significant number of protocol violations in both groups but particularly in the restricted group (45% *vs.* 30%? This is surprising when we consider that fluids are administered to improve tissue perfusion which is what the restricted group were targeting yet 36% of patients received fluid boluses outside the indications specified in the protocol and 21% received colloids which were absolute violations. These interventions would undoubtedly have had an impact in the restricted group and most likely would have contributed to the total fluid inputs and cumulative fluid balance. Interestingly, the FENICE study demonstrated that only 8% of clinicians use markers of inadequate perfusion such as lactate or mottling as an indication for a fluid challenge (8). Other simpler clinical signs such as hypotension and oliguria were found to be the most common indicators for a fluid challenge. It may therefore be necessary to design a protocol whereby the restrictive protocol incorporates some of these commoner clinical signs in order to reduce the amount of protocol violations and increase the chances of achieving a restricted fluid balance.

The lack of difference in the secondary outcomes also warrants discussion. Patients in the restricted group received a mean volume of 1,687 *vs.* 2,928 mL in the standard group with a mean difference of –1.2 L over the first 5 days and a mean volume of 1,992 *vs.* 3,399 mL with a mean difference of –1.4 L over the entire ICU stay. Both these outcomes

were statistically significant (P<0.001) but whether these differences were clinically significant is a different matter. In both groups there was no statistically significant difference between total fluid inputs or cumulative fluid balances, both at five days and during the entire ICU stay. Although the authors have commented on this finding and have explained that this was expected, it does raise the question of whether the patients in the restricted group were really that restricted after all. It also highlights that the implementation of a truly restrictive fluid strategy in patients with septic shock in the ICU is challenging and may not actually be that feasible. This again raises the question of whether the endpoint in the study should not have been the amount of resuscitation fluid administered but actually total fluid input or cumulative fluid balance and its effect on the secondary and exploratory outcomes.

The CLASSIC study was associated with many strengths. As stated, it addressed a clinically relevant topic. There was a lower risk of bias as group allocation was concealed and the statistician remained blinded to the intervention. In addition, the majority of patients screened were included with only two patients excluded. However, there are some limitations associated with the study albeit the most significant one being the lack of blinding which although reflects real-world practice, does have an impact on the external validity of the study. There was also a significant number of protocol violations as previously discussed. In addition, the size of the study was relatively small and although the study found a reduced number of patients with worsening AKI in the restricted group, the trial was unfortunately not powered to show a difference in any of these outcomes.

Where do we go from here?

Although the results of the CLASSIC study have demonstrated the feasibility of implementing a protocol which results in reduced volumes of resuscitation fluid being administered, this did not lead to any significant reductions in total fluid input or cumulative fluid balances which is what has been previously associated with a reduction in both morbidity and mortality. As we have discussed, implementing a truly restrictive strategy is challenging in the ICU and this need to be explored in future research trials. Further RCT's which are powered to detect significant differences in exploratory outcomes (mortality at day 90, ischaemic events and AKI) are also warranted. As clinicians, we also need to re-assess our approach to

fluid administration and increase awareness that fluids are not a benign therapy. There is much research ongoing on when to administer fluids in sepsis, how much to give and over what duration but there is reduced emphasis on the importance of withholding or withdrawing resuscitation fluids or 'de-escalation'.

To conclude, the CLASSIC study demonstrated that a restrictive protocol is feasible in the ICU but further larger studies are warranted to determine whether we should be focusing on volume of fluid administered or cumulative balances and their associated effects on morbidity and mortality.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42:1695-705.
2. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76:422-7.
3. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136:102-9.
4. Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014;46:361-80.
5. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19:251.
6. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12:R74.
7. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of

severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.

8.   Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. Intensive Care Med 2015;41:1529-37.