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Guidelines

Guidelines for the choice of intravenous fluids for vascular filling in critically ill patients, 2021☆,☆☆

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ABSTRACT

Purpose: To provide recommendations for the appropriate choice of fluid therapy for resuscitation of critically ill patients.
Design: A consensus committee of 24 experts from the French Society of Anaesthesia and Intensive Care Medicine (Société française d'anesthésie et de réanimation, SFAR) and the French Society of Emergency Medicine (Société française de médecine d'urgence, SFMU) was convened. A formal conflict-of-interest policy was developed at the onset of the process and enforced throughout. The entire guideline elaboration process was conducted independently of any industry funding. The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide their assessment of quality of evidence. The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasised. Some recommendations were left ungraded.
Methods: Four fields were defined: patients with sepsis or septic shock, patients with haemorrhagic shock, patients with acute brain failure, and patients during the peripartum period. For each field, the panel focused on two questions: (1) Does the use of colloids, as compared to crystalloids, reduce morbidity and mortality, and (2) Does the use of some specific crystalloids effectively reduce morbidity and mortality. Population, intervention, comparison, and outcomes (PICO) questions were reviewed and updated as needed, and evidence profiles were generated. The analysis of the literature and the recommendations were then conducted according to the GRADE methodology.
Results: The SFAR/SFMU guideline panel provided nine statements on the appropriate choice of fluid therapy for resuscitation of critically ill patients. After two rounds of rating and various amendments, strong agreement was reached for 100% of the recommendations. Out of these recommendations, two have a high level of evidence (Grade 1 +/−), six have a moderate level of evidence (Grade 2 +/−), and one is based on expert opinion. Finally, no recommendation was formulated for two questions.
Conclusions: Substantial agreement among experts has been obtained to provide a sizable number of recommendations aimed at optimising the choice of fluid therapy for resuscitation of critically ill patients.

1. Introduction

Intravenous fluids used for volume resuscitation are drugs, which are referenced as such in hospital pharmacies, and are the most widely used medicinal products in perioperative and critical care settings. Aside from synthetic colloids, they were until recently poorly studied, and practitioners were largely unaware of their specificities. Due to the arrival of new fluids and the publication of large-scale clinical trials, it is now possible to have a somewhat more precise vision of their prescription specificities, but numerous questions remain unanswered. That is the reason for these guidelines which were drawn up after analysis of the literature of the last fifteen years and should facilitate informed choices of fluids for vascular filling according to the clinical situations encountered.

It was decided to focus solely on choices of the type of intravenous fluids, and not on haemodynamic optimisation or the indications to initiate fluid therapy, subjects that have previously been to some extent the object of guidelines [1–4].

Currently known as fluid therapy (FT), injection of intravenous fluids is one of the most important methods in managing hypotensive patients in critical care and in perioperative and emergency settings.

In the first place, FT is aimed at restoring blood volume or at reducing hypovolaemia. However, FT needs to be determined with regard not only to the quality and quantity of the fluids to be administered, but also the way it is administered. Physiologically, FT increases "constrained" volume and, consequently, mean systemic pressure, whilst reducing resistance to venous return. The combined effect of these two actions is to increase venous return and cardiac output, provided that the cardiovascular system, and in particular the ventricle ejection volume are "preload dependent" (ascending limb of the Starling curve).

In these conditions, the objective of FT is to improve cardiac output (or systolic ejection volume), in situations where the latter does not satisfactorily fit with the metabolic demands of peripheral tissue: hypotension, decreased cardiac output, low venous oxygen saturation. In fact, in most clinical situations characterised by acute circulatory failure, deceased cardiac output is primarily due to (true or relative) hypovolaemia, and only rarely to heart failure (15%–20% of cases) [5,6]. Cardiac output monitoring measuring is mandatory to differentiate these two situations, especially insofar as clinical examination is a mediocre predictor of response to plasma volume expansion [3,7].

The different types of intravenous fluid have also to be defined according to their characteristics. There exist two families of fluids, namely colloids and crystalloids. Among the colloids, synthetic colloids (hydroxyethyl starch, gelatin) are to be distinguished from natural colloids (albumin). Crystalloids are initially classified according to their tonicity. For example, isotonic fluid osmolarity (or osmotic concentration) ranges from 280 to 310 mOsm/L (0.9% NaCl, Plasma-Lyte®, Isofundine®). Fluids with osmolarity lower than 280 mOsm/L are considered as hypotonic (Ringer lactate), while those with osmolarity exceeding 310 mOsm/L are hypertonic (3% NaCl, 7.5% NaCl). Crystalloids are also to be classified in terms of their chlorine concentration and their ionic composition, the objective being to differentiate 0.9% NaCl from the so-called balanced crystalloids, which are due to their ionic composition, which is more similar than 0.9% NaCl to normal plasma concentrations. The different fluids available are summarised in Table 1.

A possible limit to the use of balanced fluids could be the presence of potassium in their composition (4 or 5 mmol/l) (Table 1), especially in patients with hyperkalaemia. It would nonetheless seem that their use, even in those patients, does not entail excess potassium or increased risk, as has been shown in

Table 1
Characteristics of the different fluids utilised in vascular filling.

Composition	Plasma	NaCl 0.9%	Ringer's lactate	Plasmalyte	Isofundine
Na^+ (mmol/l)	142	154	130	140	145
K^+ (mmol/l)	4		4	5	4
Cl^- (mmol/l)	103	154	108	98	127
Ca^{2+} (mmol/l)	2.4		0.9	0	2.5
Mg^{2+} (mmol/l)	1			3	1
HCO_3^- (mmol/l)	27				
Others (mmol/l)	Lactate 2		Lactate 27.6	Acetate 27 Gluconate 23	Acetate 27 Malate 5
Osmolarity (mOsmol/l)	285	308	277	295	309
pH	7.4	5–6.5	6–7.5	6.5–7.5	5–6.5

randomised studies of renal transplant recipients, among whom kalaemia increases to a greater extent in patients receiving 0.9% NaCl than in those receiving Ringer lactate [8,9]. Moreover, the two most recent randomised studies, which cumulatively involved 30,000 patients and compared 0.9% NaCl to balanced fluids, found comparable plasma concentration in the two groups [10,11]. Lastly, from a physiological standpoint it appears coherent to assume that it would not be possible to create potassium excess using a fluid with potassium concentration inferior to the patient's one.

To establish our recommendations, we have limited ourselves to frequently encountered clinical situations that have not been dealt with in previously published specific guidelines. That is why we have excluded from these guidelines: patients with cirrhosis, acute pancreatitis, acute respiratory distress syndrome (ARDS), kidney failure, and children (treated in accordance with a specific recommendation). It also bears mentioning that the field covered by these guidelines will be limited to the type of fluid to be used and will indicate neither the quantity of fluids to administer, nor the way to have them administered.

2. Methods

2.1. General organisation

These recommendations are the result of work by a group of experts brought together by the French Society of Anaesthesia and Intensive Care Medicine (SFAR) and the French Society of Emergency Medicine (SFMU). Prior to participation in the analysis, each expert filled out a competing interest statement. The group's agenda was established in advance. During the initial stage, the organising committee decided in collaboration with the coordinators on the questions to be addressed. The committee then designated the experts who would oversee each one of the questions, which were formulated in accordance with the PICO (Patient Intervention Comparison Outcome) format following the first meeting of the expert group. Analysis of the literature and formulation of the recommendations was then carried out according to the GRADE (Grade of Recommendation Assessment, Development and Evaluation) methodology. A level of evidence was defined for each of the cited bibliographic references according to type of study and could be re-evaluated by considering the methodological quality of the study. An overall level of evidence was determined for each evaluation criterion, considering the level of evidence of each bibliographic reference, the coherence of the results from one study to another, the direct or indirect nature of the evidence, and analysis of the relative magnitude of costs and benefits. A high level of evidence led to formulation of "strong" recommendation (it is recommended to proceed; it is not recommended to proceed: GRADE 1+ or 1−). A moderate or low level of evidence led to the drafting of an "optional" recommendation (it is probably recommended to proceed, or it is probably not recommended to proceed: GRADE 2+ or 2−). When the relevant literature was non-existent, the question could lead to a recommendation in the form of an expert opinion (the experts suggest…). The proposed recommendations were presented and discussed one by one. The goal was not necessarily to provide single and convergent advice on the different propositions, but rather to facilitate the emergence of points of agreement, disagreement, or indecision. Each recommendation was then evaluated by each of the experts and given individual ratings on a scale ranging from 1 (complete disagreement) to 9 (complete agreement). Collective grading was established according to GRADE grid methodology. To validate a recommendation based on a single criterion, at least 50% of the experts had to express a generally concordant opinion, while fewer than 20% expressed a discordant opinion. For a recommendation to be strong, at least 70% of the participants had to express a generally concordant opinion. In the absence of strong agreement, the recommendations were reformulated and once again graded, the objective being to achieve a consensus.

2.2. Fields of recommendations

The formulated recommendations are divided into four fields according to the type of patient: patients with sepsis or septic shock; patients with haemorrhagic shock; patients with acute brain failure; patients during the peripartum period. For each field, the recommendations addressed two main interrogations: (1) What are the potential benefits of using a colloid solution as compared to a crystalloid solution? (2) What are the potential benefits of using one type of crystalloid solution in comparison to others?

At the outset, it was decided to avoid writing recommendations that could not be fully justified by the data in the literature and consequently to limit the number of expert opinions. For example, the paediatric population was excluded from the scope of these guidelines. An extensive bibliographic search covering the last 15 years was carried out from the PubMed™ and Cochrane™ databases and www.clinicaltrials.gov. To be considered for analysis, the publications had to be written in English or French. Analysis was focused on recent data according to order of interest ranging from meta-analyses and randomised trials to observational studies. Size of population and relevance of research were taken into consideration for each study.

2.3. Synthesis of the results

Synthesis elaboration by the experts and application of the GRADE methodology led to the formulation of nine recommendations and three treatment protocols. Out of the nine formalised recommendations concerning adults, two presented a high level of

evidence (GRADE 1+/−), while six showed a moderate level of evidence (GRADE 2+/−). As regards the ninth recommendation, the GRADE method could not be applied, leading to formulation of an expert opinion. After two rating rounds and an amendment, strong agreement was reached regarding the recommendations taken as a whole. For two questions, no recommendation could be formulated.

The SFAR and the SFMU are encouraging all anaesthesiologists, intensivists, and emergency physicians to comply with these guidelines in view of ensuring high-quality patient care. When applying these recommendations, however, a practitioner is called upon to exercise his own judgment, taking into full account the expertise and specificities of his establishment, the objective being to decide on the means of intervention best adapted to the state of the patient of whom he is in charge.

FIELD 1: Patients with sepsis or septic shock

Coordinator: L. Muller (SFAR)

Question 1: In patients with sepsis or septic shock, compared to a crystalloid solution does utilisation of a colloid solution help to reduce morbi-mortality?

Experts: B. Chousterman (SFAR), L. Muller (SFAR), M. Oberlin (SFMU), A. Tran-Dinh (SFAR)

R1.1 – In comparison with non-hypertonic crystalloids, it is not recommended in case of sepsis or septic shock to use hydroxyethyl starch as fluid therapy to reduce mortality and/or renal replacement therapy requirement.

GRADE 1- (STRONG AGREEMENT)

R1.2 – In comparison with non-hypertonic crystalloids, the experts suggest that in cases of sepsis or septic shock, gelatins should not be used as fluid therapy to reduce mortality and/or renal replacement therapy requirement.

EXPERT OPINION (STRONG AGREEMENT)

Rationale

The theoretical interest of synthetic colloids would consist in their guaranteeing, through a theoretical power of expansion greater than that of isotonic crystalloids, more rapid and prolonged haemodynamic stabilisation, which would lead to improved prognosis. This postulate was invalidated by the results of several large-scale randomised controlled trials (RCT) published between 2008 and 2014, in which hydroxyethyl starches (HES) were compared to isotonic crystalloids in resuscitation. The VISEP [12] and 6S [13] studies specifically compared these two types of solutions in sepsis patient populations and showed increased mortality and incidence of acute renal failure following utilisation of HES with high as well as low molecular weight. Two other large-scale RCT (CHEST [14] and CRISTAL [15]) compared the two types of fluids in critical care septic and non-septic patients. In terms of mortality, the two trials did not confirm either higher death rates associated with HES use or its superiority when compared to isotonic crystalloids. The CHEST study reported increased incidence of renal replacement therapy in the HES group [14]. The meta-analyses conducted over the last ten years in patients with sepsis highlighted either the non-superiority of synthetic colloids or higher death rates associated with HES use [16–19]. They also reported increased incidence of renal replacement therapy in the colloid group [16,17,20–22]. If no data on dextran has been rendered available over the last ten years (except for some cases in the CRISTAL study [15]), it is because this therapeutic class has been dropped due to its anaphylactic and renal adverse effects. In 2013, the European Medicines Agency (EMA) recommended that HES no longer be used for volume resuscitation, particularly in sepsis patients, with or without renal failure [23].

As regards gelatins, a prospective observational before-after study (two two-year periods) showed no difference in terms of mortality, length of stay, or mechanical ventilation duration [24]. The study also reported increased risk of renal failure with gelatins as compared to isotonic crystalloids [24]. In the CRISTAL study, a pragmatic RCT comparing colloids *versus* crystalloids and leaving to practitioner discretion the choice of type of colloid or crystalloid, 304/774 patients in the colloid group received gelatins [15]. In this study, no difference in mortality rate was observed between the colloid and the crystalloid groups [15]. Three meta-analyses are available and suggest the non-superiority of gelatins in terms of mortality [25–27]. However, the meta-analyses are quite heterogeneous: comparison of gelatins and other fluid therapies (crystalloids, HES, albumin); surgical studies; studies with mixed populations of critically ill patients (no sepsis sub-group). One of the three meta-analyses showed a higher incidence of anaphylactic reactions with gelatins [27].

R1.3 – In comparison with crystalloids, it is probably not recommended in cases of sepsis or septic shock to use albumin as first-line treatment to reduce mortality or renal replacement therapy requirement.

GRADE 2- (STRONG AGREEMENT)

Rationale

The utilisation of albumin in sepsis cases is based on several pathophysiological hypotheses: 1. Quasi-constant hypoalbuminaemia in sepsis patients is associated with a poor prognosis; 2. The interest of albumin as a possible plasma volume expander; 3. The anti-inflammatory and antioxidant properties of albumin. Several experimental studies, *in vivo* and *in vitro*, have highlighted the benefits of this treatment. However, notwithstanding some encouraging pre-clinical results, up until now, no benefit for patient survival has been shown in a high-quality study. That said, the diversified concentrations of albumin used [4–5% (iso-oncotic) or 20% (hyper-oncotic)] and the differing means of administration (doses, volumes, objectives) render it impossible to make a definitive judgment. Five randomised controlled trials (RCT) have assessed the impact of albumin by using mortality as primary endpoint [15,28–31]. Published in 2004, the SAFE study [28] is up until now the largest randomised trial on the subject (close to 7000 patients). During this trial, 4% albumin was compared to 0.9% NaCl in patients undergoing resuscitation. After adjustment, post-hoc analysis underscored the favourable effect of albumin on mortality, with an OR of 0.71 95% CI (0,52–0.97) [32]. Two trials (ALBIOS [29] and EARSS [30]) appraised treatment by 20% albumin in sepsis patients, the objective in the ALBIOS trial being to maintain an elevated level of serum albumin. The two trials showed no effect on mortality in septic patients ascribable to albumin treatment [ALBIOS: OR 1.00 (0.87–1.14] and EARSS: 0.92 (0.72–1,17)), even though some effect was observed in the sub-group of patients with septic shock in the ALBIOS study (1121 patients, OR 0.87 (0.77−0.99). Concerning these studies, two factors should be taken into consideration: 1) the EARSS study was not published in a peer-reviewed journal (only the abstracts were presented in a congress), 2) the mortality rate reported in the ALBIOS study is pronouncedly inferior to prior estimates (30% observed *vs.* 45% predicted), and more generally, the study is lacking in power. As for the CRISTAL study [15] comparing colloids to crystalloids among patients with (mainly septic) shock, it did not show any benefit in terms of mortality. Regarding this question, six meta-analyses have been carried out [16,18,19,33–35], five of which found no beneficial

effect on mortality of either 4%–5% or 20% albumin. Only the meta-analysis by Xu et al. [35] found a benefit on mortality at day 90 in patients with septic shock [OR 0.81 (0.67−0.97)]. Lastly, it bears mentioning that a potentially deleterious effect of albumin on renal function was suggested in a multicentre observational study [CRYCO study [36]], showing a highest risk of renal failure in patients with shock undergoing treatment with 20% albumin. That said, none of the RCT or meta-analyses carried out to date appear to justify fear of this risk, whether with respect to 4%–5% or to 20% albumin [15,19,22,28–30,32].

ABSENCE OF RECOMMENDATION – After analysis of the literature, the experts were not able to issue a recommendation on the use of albumin as second-line treatment in patients with major hypoalbuminaemia and/or requiring large volumes of fluid therapy.

Rationale

Even though albumin treatment does not show benefits regarding primary endpoints such as mortality or extra-renal purification, several studies have confirmed its benefits in terms of improved circulatory function and lower volume of vascular load, which has also been reported in several small-scale studies. In the SAFE study [28], volume of infused fluids was lower in the albumin group than in the isotonic saline solution group (3011 (+/− 1924) *vs.* 3522 (+/− 2507) mL, $p < 0.001$). In the ALBIOS study [29], the cardiovascular SOFA score was significantly lower in the albumin group than in the crystalloid group (1.20 (0.46–2.31) *vs.* 1.42 (0.60–2.50), $p = 0.03$) as was duration of vasopressor treatment (3 (1–6) *vs.* 4 (2–7) days for the albumin and crystalloid groups respectively, $p = 0.007$). The fluid balance was also lower (at D2, D3 and D4) in the albumin group. The above results from methodologically qualitative trials complement the findings of less ambitious studies [37]. To conclude, even though the 2021 Surviving Sepsis Campaign [38] suggested to use albumin in addition to crystalloids as fluid therapy in sepsis and septic shock patients requiring large volumes of saline, the present-day level of evidence is, according to the experts, not sufficient to justify a recommendation.

Question 2: In patients with sepsis or septic shock, does use of a particular crystalloid solution help to reduce morbi-mortality?

Experts: B. Chousterman (SFAR), L Muller (SFAR), M. Oberlin (SFMU), A. Tran-Dinh (SFAR)

R1.4 – In patients with sepsis or septic shock, it is probably recommended to use balanced crystalloids for fluid resuscitation (rather than 0.9% NaCl), the objective being to reduce mortality and/or occurrence of adverse renal events.
GRADE 2+ (STRONG AGREEMENT)

Rationale

There exists no randomised study specifically comparing the administration of isotonic saline solutions (ISS) and balanced crystalloid solutions (BCS) during sepsis or septic shock. Most of the available data originated from the two-year SMART study, which included 15,802 patients admitted to five critical care units (medical, traumatology, neurology, cardiovascular, surgical) of a large university hospital in the United States [10]. The study was open-labelled, and cluster randomised according to a multiple-crossover study design. Random allocation of ISS or BCS was carried out on the scale of the critical care unit rather than the patient, and each unit was repeatedly crossed over during the study. Study feasibility had been preliminarily assessed in the SALT trial conducted by the same authors [39], with results favouring BCS in patients with sepsis. As regards the SMART study in the subgroup of 2336 sepsis or septic shock patients, as compared to ISS the administration of BCS was associated with fewer major renal events during a 30-day period, a composite criterium consisting in all-cause death, initiation of renal replacement therapy or persistent doubling of baseline serum creatinine [OR 0.80 95% CI (0.67−0.94)] and a trend toward lower in-hospital mortality [OR 0.80 (0.67−0.97)]. It bears mentioning that the study presented several biases: absence of blinding, concomitant administration in some patients of two types of solutions, and low fluid volume administered. Based on this study, two secondary post-hoc analyses were carried out [40,41]. Brown et al. studied 1641 sepsis or septic shock patients who had been admitted to a medical ICU in the original study and received higher amount of fluids. Thirty-day in-hospital mortality and occurrence of composite-criteria of major renal events during the 20 days were lower in the patients having received BCS (OR 0.74 (0.59–0.93)). By contrast, incidence of acute renal failure and renal replacement therapy–free days did not differ [40]. Jackson et al. showed that the beneficial effects of BCS as compared to ISS on intra-hospital mortality at 30 days were more pronounced when BCS was preferred to ISS on admission to an emergency unit rather than on hospitalisation in an intensive care unit [OR 0.68 (0.52–0.89)] [41]. Raghunathan et al. conducted a retrospective study including 53,448 sepsis or septic shock patients treated in 360 American hospitals from 2005 to 2010, and showed in a propensity score analysis of 6730 patients that BCS administration was associated with lower intra-hospital mortality [RR 0.86 (0.78−0.94)] [42]. In this study, however, there was no difference between the two solutions in terms of prevalence of acute renal failure with or without dialysis. The only study not associating BCS utilisation with reduced mortality in sepsis patients was the SPLIT study [43], which compared the respective effects of BCS and ISS among intensive care patients; that said, only 77 out of more than 2000 patients presented with sepsis, a factor rendering interpretation problematically generalisable. A meta-analysis by Tseng et al. published in 2020 covered the available studies and incorporated non-published data from the CRISTAL study [15,19]. The authors confirmed an association of lessened mortality in patients with sepsis having received BCS *versus* ISS [OR 0.84 (0.74−0.95)]. However, a beneficial effect of BCS was not found regarding occurrence of acute renal failure.

FIELD 2: Patients with haemorrhagic shock

Coordinator: A. Harrois (SFAR)

Question 1: In patients with haemorrhagic shock, compared to a crystalloid solution, does use of a colloid solution help to reduce morbi-mortality?

Experts: D. Chaiba (SFMU), E. Futier (SFAR), A. Harrois (SFAR), E. Meaudre (SFAR), G. Rousseau (SFMU), D. Savary (SFMU)

R2.1 – In patients with haemorrhagic shock, whatever the context, it is probably not recommended, in comparison with non-hypertonic crystalloid, to use a colloid solution as fluid therapy to reduce mortality and/or renal replacement therapy requirement.
GRADE 2- (STRONG AGREEMENT)

Rationale

While numerous randomised controlled trials have compared colloid and crystalloid solutions to correct hypovolaemia in intensive care or during surgery, few studies have specifically targeted patients with haemorrhagic shock. Since 2014, the French health authorities (HAS) have restricted the utilisation of hydro-

xyethyl starches, which are indicated only in second-line treatment in the event of blood loss, and when crystalloids are deemed insufficient. The two most recent meta-analyses, which aggregated the trauma patients included in randomised trials, did not report benefits in terms of mortality arising from the utilisation of hydroxyethyl starches or gelatins as compared to crystalloid solutions [19,44]. Nor did Tseng et al. find a difference in renal function when comparing the administration of colloid solutions (hydroxyethyl starches, gelatins) to administration of crystalloid solutions in trauma patients or during surgical procedures entailing haemorrhagic risk [19]. In their meta-analysis, Qureshi et al. found a divergent result, with a difference favourable to colloid solutions, which exposed trauma patients to less risk of renal failure as compared to crystalloid solutions [44]. That said, their meta-analysis included patients having received hypertonic saline solution (HSS)/dextran in the colloid group as well as patients having received HSS in the crystalloid group, which meant that direct conclusions could not be drawn, concerning the effects of colloids as compared to crystalloids. More recently, two studies randomised 1057 patients [45] and 826 patients [46] during abdominal surgery placing them at high haemorrhagic risk to receive either hydroxyethyl starch or 0.9% NaCl. No difference was reported in the two studies regarding the primary composite endpoint, which associated several postoperative complications (renal failure, postoperative infection, etc.). In the FLASH study, renal failure (secondary endpoint) was significantly more frequent in the hydroxyethyl starch group [1.34 (1.0–1.8), p = 0.05] [46]. In a sub-group analysis of surgical patients from the CRISTAL study in which intensive care patients in hypovolaemic shock were randomised to receive colloids *versus* crystalloids (n = 741 out of the 2857 patients in the main study), no difference was found in terms of mortality or renal replacement therapy requirement. [47]. Administration of hydroxyethyl starch during major non-cardiovascular surgery was also associated with haemostasis disorders and a haemorrhagic risk significantly higher than when crystalloid solutions were administered [48]. In ICU, this resulted in higher transfusion requirements [49]. As a result, even though the volume expansion capacity of colloids exceeds that of crystalloids (mean ratio of 1.5) [50], this was not translated by an improved prognosis (mortality or composite criteria of postoperative complications) in patients with haemorrhagic shock. Given the reported risks of renal failure and haemostasis disorder, crystalloid solutions should be preferred as an alternative.

There has been no published study specifically focusing on the interest during haemorrhage of albumin, which is more expensive than the crystalloid solutions. The few studies carried out, which are primarily based on a sub-group analysis of the SAFE study (sub-group of trauma patients without traumatic brain injury), showed no benefit [19,51]. In most cases it is not recommended to administer albumin to patients with haemorrhagic shock.

Question 2: In patients with haemorrhagic shock, does use of a particular crystalloid solution help to reduce morbi-mortality?

Experts: D. Chaiba (SFMU), E. Futier (SFAR), A. Harrois (SFAR), E. Meaudre (SFAR), G. Rousseau (SFMU), D. Savary (SFMU)

R2.2 – In patients with haemorrhagic shock, it is probably recommended to use balanced crystalloids rather than 0.9% NaCl as first-line fluid therapy to reduce mortality and/or adverse renal events.

GRADE 2+ (STRONG AGREEMENT)

Rationale

Up until now, no randomised study has specifically appraised the interest of balanced crystalloids as opposed to non-balanced crystalloids (0.9% NaCl) in patients with haemorrhagic shock. Haemorrhagic shock resuscitation presents a specificity insofar as it requires high volumes of vascular filling, particularly in trauma, where the volume regularly exceeds 5000 mL, and even 10.000 mL, during the first 24 h [52,53]. The high volumes are necessitated both by the vascular volume required to replace blood loss and by the occurrence of systemic inflammation within hours of the trauma [54].

A meta-analysis included ten studies and 3794 trauma patients randomised to receive either 0.9% NaCl or a balanced solution, reported no difference in terms of either mortality [OR 0.95 (0.75–1.20)] or acute renal failure [19]. The same meta-analysis reported no difference in mortality when comparing perioperatively administered 0.9% NaCl and balanced solutions in major surgery on 2348 patients in four studies. More recently, Maheshwari et al. randomised 8616 patients receiving either 0.9% NaCl or Ringer Lactate during (orthopaedic or colorectal) surgery involving moderate haemorrhagic risk [55]. While no difference was reported concerning the incidence of acute renal failure [6.2% *vs.* 6.6% respectively, RR 1.18 (0.99–1.41)], the patients had received only a median volume of 1900 mL of crystalloid solutions. In the SMART study, which included 15,802 ICU patients receiving either a balanced solution (Ringer Lactate® or Plasmalyte®) or 0.9% NaCl, reduced incidence of a major adverse kidney event (MAKE 30: death, two-fold increase in serum creatinine or renal replacement therapy within 30 days) was observed in the balanced solution group. Among these patients, 3328 had been admitted to hospital due to trauma, and no difference in occurrence of major adverse kidney event (MAKE 30 criteria [OR 0.95 (0.74–1.21)]) was found [10]. That said, the median volume received by these patients during their ICU stay was low (1000 mL), and markedly inferior to the volumes usually administered during haemorrhagic shock resuscitation. In addition to these randomised studies, several large-scale observational studies have reported increased mortality in patients presenting with postoperative hyperchloraemia following surgery at high haemorrhagic risk [56] or having received high volumes (> 5000 mL) of chloride-rich solutions in ICU [57]. As regards solution volumes comparable to those utilised in haemorrhagic shock resuscitation, a favourable effect of balanced solutions was found in these studies. Moreover, several authors have reported lower perioperative blood transfusion requirements in patients at high haemorrhagic risk receiving balanced solutions rather than 0.9% NaCl [55,58]. However, this result was not found in all the relevant studies [59]. Lastly, administration of balanced solutions as opposed to 0.9% NaCl is constantly associated with better acid-basic balance [58,60,61].

To conclude, present-day data do not suffice to justify GRADE 1 recommendation of a given type of crystalloid solution in cases of haemorrhagic shock. That said, the potentially deleterious effects on renal function and survival of high-volume chloride-rich solutions should in most cases orient first-line treatment choices toward balanced solutions, while awaiting more robust studies in the context of haemorrhagic shock.

R2.3 – In patients with haemorrhagic shock, it is not recommended in first-line treatment to administer as fluid therapy a 3% or 7.5% hypertonic solution to reduce mortality.

GRADE 1- (STRONG AGREEMENT)

Rationale

Numerous pre-clinical studies have suggested that vascular loading with a small volume of hypertonic saline solution (HSS) could restore haemodynamic balance and reduce mortality. However, all the analyses based on clinical data, three of which were published in 2017, have concluded that HSS has no beneficial effect on mortality.

In these different studies, HSS was administered during initial resuscitation as a single bolus. A meta-analysis by Wu et al. [62] involved 2932 patients randomised in 12 studies including patients with haemorrhagic shock, in prehospital settings (8 studies), in emergency department (3 studies) or in ICU (1 study) and having received HSS [RR 0.96 (0.82–1.12)] or HSS/dextran [RR 0.92 (0.80–1.06)] *vs.* an isotonic solution; no difference was found in terms of mortality, nor was there any difference in fluid volume, transfusion, organ failure or length of stay [63]. More recently, in a randomised controlled study comparing 3% HSS or 7.5% HSS *vs.* Ringer Lactate during prehospital resuscitation of patients with haemorrhagic shock, Han et al. [64] reported more frequent complications in the Ringer Lactate group. However, this study contained numerous biases such as the absence of a clear definition of the complications or the type of solution received following the first bolus, which was the only factor to be randomised (3% HSS or 7.5% HSS *vs.* Ringer Lactate). As regards the utilisation of HSS in scheduled surgery entailing haemorrhagic risk, a meta-analysis of 18 relatively old (1983–2013) randomised controlled studies including 1087 patients analysed the benefit/risk balance of perioperative HSS or of 0.9% NaCl for fluid therapy. Due to a lack of power and pronounced heterogeneity between studies, it was not possible to conclude that perioperative HSS had either a positive or a negative impact on morbi-mortality [65]. Over the ensuing years, several studies conducted in a perioperative context during major surgery, exterior to the specificities of haemorrhage, have yielded disparate results, which do not allow conclusions to be drawn as to the possible benefits of HSS fluid therapy as compared to 0.9% NaCl or Ringer Lactate [66,67].

HSS is consequently not recommended as a solution for volume resuscitation of patients with haemorrhagic shock. However, the experts wish to mention that in situations combining haemorrhagic shock with severe head trauma and focal neurological signs, due to its osmotic effect, administration of an HSS bolus is recommended.

FIELD 3: Patients with acute brain failure

Coordinator: H. Quintard (SFAR)

Question 1: In patients with acute brain injury, compared to a crystalloid solution, does utilisation of a colloid solution help to reduce morbi-mortality?

Experts: C. Ichai (SFAR), H. Quintard (SFAR), N. Peschanski (SFMU), B. Villoing (SFMU)

R3.1 – In acute brain injury patients, it is probably not recommended to use colloids, particularly albumin, as fluid therapy to reduce mortality and/or to improve the neurological prognosis.

GRADE 2- (STRONG AGREEMENT)

Rationale

Very few data on synthetic colloids are presently available. A retrospective study on patients with subarachnoid haemorrhage showed that while utilisation of synthetic colloids had no effect on the incidence of secondary ischaemia, it was associated with worse neurological prognosis at 6 weeks [68]. Another retrospective study found no relation between the occurrence of acute renal failure and the utilisation of synthetic colloids in patients with subarachnoid haemorrhage [69]. A single prospective study comparing synthetic colloids and crystalloids reported a deleterious effect on the neurological prognosis at 6 months in SAH patients in the colloid group [70]. A meta-analysis comparing utilisation of a hypertonic colloid solution (dextran) to utilisation of an isotonic saline solution in patients with brain injury found no difference regarding mortality at 28 days [71].

The SAFE study, which dealt with albumin fluid loading in trauma patients, reported increased mortality in the sub-group of traumatic brain injury patients treated with 4% albumin (n = 460; RR 1.63 (1.17–2.26); p = 0.003) [72]. Concerning cerebrovascular pathologies, the data are less numerous and more controversial. Among patients having presented with a cerebrovascular accident, while the ALIAS study found no clinical benefit in albumin administration (25%), it also described a risk of pulmonary oedema or intracranial haemorrhage [73]. In the group of patients with subarachnoid haemorrhage, conversely albumin seemed associated with an improved neurological prognosis in a retrospective study [74], and reduced mortality when administered during the period at high risk of secondary ischaemia (D5-D14) [75].

Question 2: In patients with acute brain injury, does utilisation of a particular type of crystalloid help to reduce morbi-mortality?

Experts: C. Ichai (SFAR), H. Quintard (SFAR), N. Peschanski (SFMU), B. Villoing (SFMU)

R3.2 – It is probably recommended, to use isotonic crystalloids as first-line fluid therapy in patients with acute brain injury to reduce mortality and/or to improve the neurological prognosis.

GRADE 2+ (STRONG AGREEMENT)

Rationale

Vascular filling is of paramount importance in treatment of patients with acute brain injury [76,77]. The type of solution utilised, particularly as regards its ionic composition and its tonicity, can have a direct impact on cerebral oedema and risk of intracranial hypertension, and consequently on patients' neurological prognosis. A solution is considered as isotonic when its osmolarity ranges from 280 to 310 mOsm/L (0.9% NaCl, Plasmalyte®, Isofundine®). Due to the risk of induced cerebral oedema, hypotonic solutions (< 280 mOsm/L) are to be avoided in patients with acute brain failure. A multicentre study comparing prehospital utilisation of hypotonic solutions such as Ringer Lactate (RL) to isotonic solutions (0.9% NaCl) in patients with traumatic brain injury reported higher mortality in the RL group [300 patients (HR 1.78 (1.04–3.04)]; p = 0.035) [78].

Given the low level of evidence of the existing studies, the experts cannot positively affirm the superiority of isotonic balanced crystalloids as compared to 0.9% NaCl in treatment of patients with acute brain failure. Two randomised controlled studies found no effect on the prognosis except for a significant reduction of the risk of hyperchloraemia [79,80] (respectively on 42 patients: OR 0.28 (0.11−0.7) – p = 0.006; and on 36 patients 89% *vs.* 44%; p = 0.006). The experts emphasise a need for further research.

FIELD 4: Patients during the peripartum period

Coordinator: MP. Bonnet (SFAR)

Question 1: During the peripartum period, does utilisation of a particular type of solution help to reduce maternal and/or neonatal mortality?

Experts: M-P. Bonnet (SFAR), E. Cesareo (SFMU), B. Douay (SFMU), O. Mimoz (SFMU)

ABSENCE OF RECOMMENDATION – Due to the absence of available data in the literature, no specific recommendation can be issued concerning the choice of fluid therapy to be utilised in volume resuscitation of women during the peripartum period.

Rationale

No study comparing the therapeutic efficacy of the different types of fluid therapy is currently available in the specific context of resuscitation of women in a state of peripartum shock. By default, the solution chosen will be the one that is recommended according to the context in the general population.

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