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Hydroxyethyl Starch- Friend or Foe?

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Authors' contributions

This work was carried out in collaboration between all authors. Author KTB designed the review, managed the literature search and wrote the first draft of the manuscript. Authors IA and NVF managed the literature searches and wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Resuscitation with intravenous fluid therapy is considered a corner stone in the management of critically ill patients in most acute conditions. In daily practice, the assessment of individual thresholds in order to optimize cardiac preload and avoid hypovolemia or deleterious fluid overload remains a challenge.

The choice of fluids for intravascular volume replacement has been debated for decades. More recently, this debate has focused not only on colloids versus crystalloids, but more specifically on the choice of colloid solutions.

Hydroxyethyl starch (HES) solutions, developed as less-expensive alternatives to albumin, are commonly employed for volume resuscitation in the perioperative period as well as in ICU patients. However, lately, the resuscitation with HES has become controversial due to its adverse effect regarding impaired coagulation, renal insufficiency and mortality.

Therefore, a narrative review of recent literature was undertaken to establish the current utility and efficacy of HES in clinical practice. Prospective randomized controlled trials published between January 2008 and March 2015 with measures of outcome/mortality and adverse effects of HES administration were included. This review aims at increasing awareness amongst anesthetists and critical care specialist about correct and careful fluid administration.

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Keywords: Fluid resuscitation; hydroxyethyl starch; sepsis; renal replacement therapy.

ABBREVIATIONS

AKI= Acute Kidney Injury; EGDT= Early Goal-directed Therapy; EMA= European Medicines Agency; FDA= US Food and Drug Administration; HES= Hydroxyethyl Starch; ICU= Intensive Care Unit; MS= Molar Substitution; MW= Molecular Weight; RRT= Renal Replacement Therapy; SSC= Surviving Sepsis Campaign.

1. INTRODUCTION

Resuscitation with intravenous fluid therapy is considered a corner stone in the management of critically ill patients in most acute conditions. It has been over a decade since Rivers et al. introduced the concept of early goal-directed therapy (EGDT) [1]. They approached sepsis and septic shock in aggressive manner as to acute myocardial infarction, trauma or stroke. Authors found out that EGDT modulates systemic inflammation and results in significant reductions in morbidity, mortality, and healthcare resource consumption. On the other hand, fluid over hydration is associated with increased mortality in sepsis, partly because of prolonged pulmonary edema and dependency on ventilators [2,3]. In daily practice, the assessment of individual thresholds in order to optimize cardiac preload and avoid hypovolemia or deleterious fluid overload remains a challenge.

The choice of fluids for intravascular volume replacement has been debated for decades. More recently, this debate has focused not only on colloids versus crystalloids, but more specifically on the choice of colloid solutions. Recent studies from Boyd et al. and Raghunathan et al. [4,5] showed that type, timing and amount of fluid may affect the clinical outcome.

Hydroxyethyl starch (HES) products are commonly employed for volume resuscitation in the perioperative period as well as in ICU patients being treated for sepsis and other conditions. Due to higher molecular weight, HES has longer intravascular half-life and thus prolonged effect on volume expansion with significantly lower volumes when compared to crystalloids. HES solutions were developed as less-expensive alternatives to albumin [6,7].

However, lately, the resuscitation with HES has become controversial due to its adverse effect regarding impaired coagulation, renal insufficiency and mortality [8]. Regarding this safety concerns, HES has been withdrawn from use in critically ill patients. In 2013, both the European Medicines Agency (EMA) [9] and the US Food and Drug Administration (FDA) [10] decided that hydroxyethyl starch (HES) solutions should no longer be used in critically ill patients, including those with sepsis. In most developed countries, HES is now only available for limited indications such as perioperative infusion, and that use is also being questioned [11].

The question is now: Has the clinical story of HES come to an end?

To create an adequate conclusion, we need to know the history of HES development, its pharmacology and effects on organ systems. Also, we need to be familiar with the recent literature and the limitations of randomized clinical trials that have led to limited HES use.

2. PHYSIOLOGY OF THE FLUIDS

The first HES product was made available in the United States in the 1970s. Since then, further generations of HES have been developed, differing in their mean molecular weight (MW), molar substitution (MS), and C2/C6 ratio. HES solutions are identified by three numbers (i.e., 10% HES 200/0.5 or 6% HES 130/0.4) [12]:

1. *Concentration* of the solution, which mainly influences the initial volume effect (6% HES solutions are iso-oncotic *In vivo*, with 1 L replacing about 1 L of blood loss, whereas 10% solutions are hyperoncotic, with a volume effect considerably exceeding the infused volume).
2. Mean *molecular weight* (MW) expressed in kilo Dalton (kDa). Small molecules below the renal threshold (45 to 60 kDa) are rapidly excreted, whereas the larger molecules are retained for varying periods of time depending on their size and ease of breakdown.
3. *Molar substitution* (MS). This substitution increases the solubility of the starch in water and, to a varying degree, inhibits the rate of destruction of the starch polymer by

amylase. Hence, older generation HES products with high MS accumulate in the plasma, unlike the latest generation of tetrastarches.

These parameters are highly relevant to the pharmacokinetics of HES (Fig. 1.).

Another thing affects the HES degradation. It is called *C2/C6 ratio*. Hydroxyethyl groups at the position of the C2 atom inhibit the access of α-amylase to the substrate more effectively than do hydroxyethyl groups at the C6 position. Hence, HES products with high C2/C6 ratios are expected to be more slowly degraded [13].

Clearance of earlier generation of HES products (hexastarch and pentastarch) is much slower, resulting that first and second generation HES products are not completely eliminated from the circulation within 24 h [14]. Repeated infusions lead to steadily accumulating residual HES in the plasma. The third generation of HES, the tetrastarches, was developed with lower MS (0.4) to enhance degradation and to minimize retention in the circulation and tissues.

Clearance and residual concentrations of HES are closely related to MS and the C2/C6 ratio. Colloid oncotic pressure depends on the number of available oncotically active particles and not directly on HES concentration [15]. Thus, the degree of plasma and tissue accumulation is highly dependent on structure, the specific HES type, and its physicochemical properties.

We must bear in mind all of these facts in our clinical practice as well as in assessing data from scientific journals. Significant amount of papers was published on the topic of HES, but caution has to be taken on the generation and MW of HES in conducted research, due to the fact that it affects pharmacology.

Also, the HES carrier solution- balanced or unbalanced- is important, due to the recent trials affecting clinical outcome of the patients [5]. There are two types of solution in current use- 0.9% saline and “balanced” solutions that mimic the biochemical composition of human plasma. Although the exact composition of so-called balanced solutions varies, they generally have fewer sodium and chloride ions than saline, but contain potassium and bivalent cations, and metabolizable anions, such as acetate, malate, or lactate [12].

Infusion of high volumes of normal saline may lead to the development of hyperchloremic metabolic acidosis, due to the high chloride load rather than to dilution of bicarbonate [16]. However, it seems that it typically occurs only after the infusion of more than 3 L of normal saline. This may be extremely important for patients undergoing cardiac, orthopedic, and abdominal surgery due to inevitable volume overload, and in elderly patients.

Reductions in MW and MS have led to products with shorter half-lives, improved pharmacokinetic and pharmacodynamic properties, and fewer side effects [17]. Two third-generation starches, one based on waxy maize and other one based on potato, are currently available in various formulations. According to one study, potato and waxy maize-derived HES solutions are not bioequivalent [18]. Waxy maize starch (HES 130/0.4) is largely composed (approximately 98%) of highly branched amylopectin, and potato starch (HES 130/0.42) is a heterogeneous mixture of around 75% of amylopectin. All characteristics are shown in Table 1. Therefore, findings obtained from studies using one type may not be valid for the other.

HES is a bioactive macromolecule which has an effect on many organ systems. It interacts with platelets and the coagulation cascade, causing a decrease in factors such as factor VIII and von Willebrand factor, but the exact mechanisms have still not been fully elucidated. Treib et al. [19] carried out systematic studies on the effects of a range of HES preparations and found that the products with higher MS had a profound effect on coagulation and platelet function but suggested that newer HES preparations should only have minimal effects. The most useful evidence concerning the safety of waxy maize-derived 6% HES 130/0.4 is derived from extensive clinical studies in many types of major surgery, where they have been compared to HES 200/0.5 [20,21]. The authors concluded that HES 130/0.4 was associated with a significant reduction in perioperative blood loss, both estimated and calculated, and that there was a significant reduction in transfusion needs.

HES molecules with a higher *In vivo* MW resulting from increased MS tend to be stored in tissue before being metabolized by serum amylases [22]. Due to the more rapid clearance of the latest generation of tetrastarches, it is expected that tissue accumulation and its clinical manifestations will not be observed with the same frequency as compared to older starches [23].

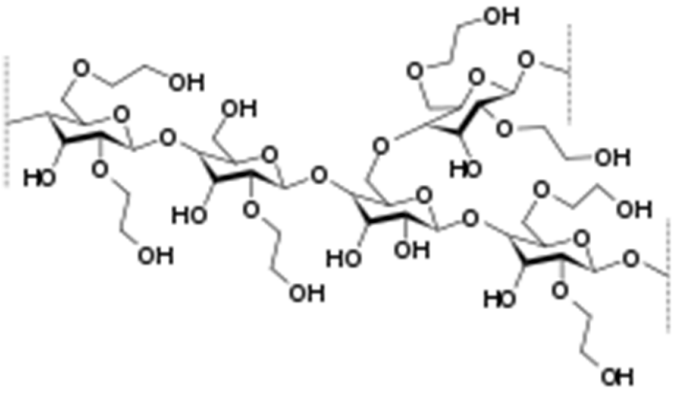

Fig. 1. Hydoxyetil starch molecule

Table 1. Physicochemical differences between waxy maize–derived Hydroxyethyl Starch (HES) 130/0.4 and Potato-derived HES 130/0.42

	Waxy maize- based HES 130/0.4	Potato- based HES 130/0.42
Molar substitution	0.41	0.45-0.46
C2-C6 ratio	9.05:1	6.9-7.7
Degree of branching	6.6 mol%	4.8- 5.1 mol%
Free phosphate	-	34-84 ppm
Total phosphate	15 ppm	205- 290 ppm
Viscosity	K= 2.29 x 10^{-3}	K= 2.73- 3.52 x 10^{-3}

Data source: Sommermeyer et al. [17]
ppm= parts per million

The main clinical manifestation of tissue storage is HES-related pruritus. In randomized study undertaken by Barron et al. [20] high doses of 6% HES 130/0.4 and 6% HES 200/0.5 did not contribute to pruritus. However, two recent meta-analyses did not support the hypothesis that lower MW and substitution decrease tissue uptake of HES [24].

One study with potato-derived HES (130/0.42) reported mild to moderate hyperbilirubinemia as a significant adverse event causing it to be the only tetrastarch absolutely contraindicated in patients with severe hepatic impairment [25]. However, similar findings have not been observed in any studies with waxy maize–derived HES.

Extra caution is always needed when treating high-risk groups, such as the elderly, children, and those with renal impairment. The waxy maize–derived tetrastarch HES 130/0.4 has been thoroughly studied in elderly patients undergoing abdominal surgery and has a well-documented safety profile. Standl et al. [26] reported that waxy maize–derived 6% HES 130/0.4 was as safe and well tolerated as albumin when used in pediatric surgery.

One of the major concerns is the impact of HES on renal function. Almost all large randomized trials are trying to define whether HES impairs renal function and to what extent, thereby giving an answer about its safety.

Lower tendency of third-generation HES products to accumulate may improve their profile with regard to renal function. An important large-scale observational retrospective study on the effects of HES administration on renal function was carried out by Sakr et al. [27]. The study analyzed data of 3,147 critically ill patients and was included in the SOAP study (Sepsis Occurrence in Acutely Ill Patients), resulted that HES *per se* was not an independent risk factor for adverse effects on renal function. Neither the use of HES nor the dose administered was associated with an increased risk for renal replacement therapy, even in the subgroup of patients with severe sepsis and septic shock. These patients had higher risk for renal dysfunction development due to a high incidence of cardiovascular dysfunction and pre-existing renal impairment. Unfortunately, the authors did not distinguish the difference between the types of HES preparations used.

Recent study by Martin et al. [28] found no evidence for renal dysfunction caused by modern waxy maize-derived HES 130/0.40 in surgical patients. Kancir et al. [29] found no evidence of nephrotoxicity after infusion of 6% HES 130/0.4 in patients undergoing prostatectomy with normal preoperative renal function. Also, fluid resuscitation with more than 2000 ml HES (130 kD/0.4) during the first twenty four hours after trauma was not associated with an increased incidence of acute kidney injury (AKI) or need for renal replacement therapy (RRT) in trauma patients compared to patients who were administered less than 2000 ml HES (130 kD/0.4). Authors also did not find any difference in the incidence of AKI or the need for RRT in patients older than 59 years of age [30].

However, the situation is much different in fluid resuscitation in patients with sepsis and septic shock. Recent meta-analysis associate HES with increased acute kidney failure incidence, need for renal replacement therapy and 90-day mortality compared with those receiving crystalloids [31,32].

3. PHYSIOLOGIC EFFECT COMPARED TO CRYSTALLOIDS

Over the last decade, there is an on-going debate colloid vs. crystalloid impact on resuscitation in sepsis and in trauma patients with severe bleeding. Emphasis is mostly put on renal function impact.

Although the volume resuscitation one of the first line of treatment in the majority of cases, it is preferable to distinguish resuscitation in sepsis and in hemorrhagic shock. Due to different etiology and different cascade mechanisms activated, it is desirable to approach them in different manner.

Early fluid therapy is considered essential to optimize hemodynamics and obtain suitable tissue perfusion in the treatment of sepsis. According to latest SSC guidelines initial fluid resuscitation should start with crystalloids. It is advised to avoid HES formulations due to their absence of any clear benefit (SSC) [33]. This recommendation is based on the results of the VISEP [34], CRYSTMAS [35], 6S [36], and CHEST [37] trials. The results of the recently completed CRYSTAL [38] trial were not considered.

Dulu et al. [39] demonstrated that fluid therapy reverses myocardial depression and hypoxia in sepsis. This, once again, validates the practice of aggressive fluid resuscitation in the early stages of sepsis.

Recent studies suggest that HES may have superior resuscitation effect in hemorrhagic shock. A study by Lee et al. [40] was designed to determine the effects of different resuscitation fluids on the production of pro-inflammatory and anti-inflammatory cytokines in an animal model of hemorrhagic shock. Mean blood pressure and serum levels of lactate after resuscitation were not different among Ringer's lactate, HES, and gelatine, but were associated with different post-resuscitation immune responses. The worst outcome had gelatine which was associated with cytokine production favoring a pro-inflammatory response.

Another animal study demonstrated that HES solution was an appropriate resuscitation fluid in hemorrhagic shock. It is considered to be protective, in a manner that HES prevents oxidative stress after acute hemorrhagic episode [41].

It is well documented that limited oxygen delivery to tissues (hypoxia) is common in acute inflammation. Both, hypoxia and inflammation are associated with increased vascular leakage and neutrophil infiltration of tissues. Dietrich et al. [42] suggest that hypoxia-induced increases in vascular leakage and acute inflammation can be attenuated by HES treatment.

4. OUTCOMES

One of the first studies dealing with this debate is certainly VISEP study (Efficacy of Volume substitution and Insulin therapy in Severe SEPsis). This prospective, open label, randomized study investigated the influence of a colloid (pentastarch, 10% 200/0.5) versus crystalloid-based volume resuscitation and an intensified versus a conventional insulin therapy on organ function and survival [34]. The authors reported that the use of pentastarch as administered in this study was associated with a higher rate of acute renal failure and renal replacement therapy as compared to a modified Ringer's lactate solution. Although the study protocol specified a maximum HES dose to 20 ml/kg/day, over 38% of the patients received significantly more than the maximum dose and were treated over a long period (up to 21 days). All this may altered the patients' outcome and final results. It is also not known to what extent

the intensified insulin therapy contributed to the acute renal failure development in the pentastarch receiving group.

Zarychanski et al. [43] pooled data from trials comparing any kind of HES solution vs. crystalloids, albumin, or gelatin in critically ill patients. They found a relative risk of death to be 1.07 (95% CI, 1.00 - 1.14) with HES vs. control. HES was found to be associated with increased mortality (RR 1.09; 95% CI, 1.02 - 1.17) and increased use of renal replacement therapy (RR 1.32; 95% CI, 1.15 - 1.50). Similar results were found in meta-analysis by Gattas et al. [44] where they compared tetrastarch vs. any type of control fluid for resuscitation in acutely ill patients. They report relative death risk of 1.08 (95% CI, 1.00 - 1.17) and statistically significant increased risk of renal replacement therapy (RR 1.25, 95% CI, 1.08 - 1.44) in tetrastarch group.

In the latest CRISTAL study conducted among ICU patients with hypovolemia, the use of colloids vs. crystalloids did not result in a significant difference in 28-day mortality (RR 0.96, 95% CI, 0.88 - 1.04, P = 0.26) [38]. There were no evidence for a colloid-related increased risk for renal replacement therapy (RR 0.93, 95% CI, 0.83 - 1.03, P =0 .19).

Recent meta-analysis state that here is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. Furthermore, the use of HES might increase mortality. As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified [45-47].

So what has precipitated the ‘hero to zero’ downfall of HES solutions?

Latest recommendations were based mainly on three randomized trials in critically ill patients comparing HES with crystalloids, concluding greater risk of kidney injury requiring renal replacement therapy in the HES group- VISEP, 6S and CHEST study [34,36,37]. Recent meta-analyses have also concluded that the use of HES solutions is associated with increased mortality, increased use of renal replacement therapy (RRT) in critically ill patients, or both [43,44,48]. This has ultimately led to a change in international Surviving Sepsis Campaign guidelines regarding initial volume resuscitation in sepsis and in septic shock favoring crystalloids.

These three randomized trials, mentioned above, were high-quality studies and involved modern tetrastarches (HES 130/0.42 and 130/0.4). However, their limitation is that the patients were not recruited into the study until after admission to an ICU, which in most cases will be after the initial, and arguably the most important, period of fluid resuscitation. It suggests that these studies were not optimally designed to assess fluid resuscitation. It would be more challenging to recruit patients earlier (i.e. in the emergency department) since it would provide a better impact insight on colloid vs. crystalloid outcome in the resuscitation phase.

One of the main criticisms of HES is its effect on renal function. Both VISEP and 6S trials showed a higher proportion of patients requiring RRT (31 vs. 19%, P<0.001 and 22 vs. 16%, P=0.04, respectively) in patients treated with HES when compared to other fluids [34,36]. In CRYSTMAS trial the duration of RRT was significantly longer in patients treated with HES (9.1 vs. 4.3 days) [35]. However, HES therapy was associated with an increased risk of RRT. On the other hand patients treated with crystalloids had a higher occurrence of renal failure without RRT, thus suggesting a potential bias in the decision to start RRT among centers.

Conclusion arises that it is more important to initially restore adequate hemodynamics in ICU patients in order to avoid AKI and RRT, and that the type of fluid itself is not as important.

These findings are in contrast to data from CRISTAL trial, which compared fluid resuscitation fluids in hypovolemic patients without sepsis or trauma [38]. Authors found no difference in 28- day mortality and lower 90-day mortality in colloid group. Colloid resuscitation was associated with more rapid weaning from the ventilator and vasopressor therapy discontinuation with no adverse effects on renal function.

The amount of infused HES should also be mentioned. In CRISTAL study patients received a maximum of 30 ml/kg, whereas in previous studies (CRYSMTMAS and 6S) received 50-70 ml / kg. This could that be the reason for frequent incidence of AKI and RRT which ultimately resulted in HES abolition.

There are a number of small trials pointing that postoperative outcomes may be improved by the use of cardiac output monitoring to provide hemodynamic therapy algorithm guide.

The most recent published paper by Pearse et al. (OPTIMISE study) [49] is primarily designed to evaluate clinical effectiveness of a perioperative, cardiac output-guided hemodynamic therapy algorithm. Nevertheless, it also involves types of fluids (HES 130/0.4 vs. Hartmann's solution) used to achieve hemodynamic optimization. It also updated systematic review and meta-analysis from randomized trials published from 1966 to February 2014. Authors report that the use of a cardiac output-guided hemodynamic therapy algorithm compared with usual care did not reduce a composite outcome of complications and 30-day mortality. However, inclusion of these data in an updated meta-analysis indicates that the intervention was associated with a reduction in complication rates.

It is not easy to make conclusions and give guidelines for clinical practice after reviewing the most important trials (Table 2.) [50-52].

Table 2. Recently published systematic review and meta-analysis from randomized trials

Author/Study (year)	Type of patients	HES type	Crystalloid/ albumin	Conclusion
Brunkhorst et al./ VISEP study [34]	Severe sepsis	10% HES 200/0.5	Ringer's lactate	No difference in 28 day mortality and MOF. HES associated with increased rates of ARF and RRT
Zarychanski et al. [43]	Trauma/ sepsis/ hypovolemia/ burns	10% HES 200/0.5; 6% HES 450/0.7; 6% HES 130/0.4	Ringer's lactate; 0.9% NaCl; Albumin (5% and 20%); Gelatin	HES increased mortality and incidence of RRT
Gattas et al. [44]	Acute illness	6% HES 130/0.4; 6% HES 130/0.42	Ringer's lactate; 0.9% NaCl	HES increased mortality and incidence of RRT
Myburgh et al./ CHEST study [37]	ICU patients	6% HES 130/0.4	0.9% NaCl	No difference in 90-day mortality. HES group more treated with RRT.
Annane et al./ CRISTAL [38]	sepsis, trauma, or hypovolemic shock without sepsis or trauma	gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin	isotonic or hypertonic NaCl; Ringer's lactate	No difference in 28- day mortality. Lower 90-day mortality in colloid group. Colloid resuscitation associated with more rapid weaning and vasopressor therapy discontinuation. Not increased risk for RRT.
Perner et al./ 6S [36]	Severe sepsis/ septic shock	6% HES 130/0.4	Ringer's acetate	HES group had an increased 90-day mortality and RRT
Guidet et al./ CRYSTMAS [35]	Severe sepsis	6% HES 130/0.4	0.9% NaCl	Significantly less volume was required to achieve hemodynamic stability in HES group in the initial phase of fluid resuscitation.

Author/Study (year)	Type of patients	HES type	Crystalloid/ albumin	Conclusion
				HES had no negative effect on mortality, kidney function, coagulation or pruritus.
James et al./ FIRST [53]	Trauma	6% HES 130/0.4	0.9% NaCl	In penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.
Bechir et al. [54]	Severe burn injury	6% HES 130/0.4	Ringer's lactate	No evidence that early fluid resuscitation with balanced HES would lead to a volume-sparing effect in severe burn injury
Haase et al. [55]	Severe sepsis	6% HES 130/0.38-0.45	Ringer's lactate; 0.9% NaCl; 20% albumin	HES increased the use of RRT and transfusion with RBC
Feldheiser et al. [56]	Intraoperative goal-directed hemodynamic algorithm	6% HES 130/0.4	Ringer's acetate	Balanced HES solution is associated with better hemodynamic stability and reduced need for FFP
Nevickis et al. [57]	Cardiac surgery-postoperative	10% HES 200/0.5; 6% HES 450/0.7; 6% HES 130/0.4	Albumin	HES increased blood loss and blood product transfusion

The hemodynamic end-point of resuscitation varies between studies. This is mostly due to the fact that the variety of monitored surrogate markers (arterial and central venous pressures, to pulmonary artery occlusion pressures and cardiac output and variables obtained by transpulmonary thermodilution) were used for guidance of the initiation and cessation of fluid therapy [58]. Direct markers of organ perfusion to guide fluid therapy should be better defined to reduce this discrepancy. Early detection and rapid treatment of tissue hypoxia are important goals. There are several newer applications of existing technologies including arterial waveform analysis, intraoperative and bedside critical care echocardiography, esophageal Doppler, and tissue oximetry among others. Several monitoring devices demonstrate positive effect on outcomes, especially when used in conjunction with specific goal-directed therapy protocols to achieve a desired clinical effect [59].

We recommend that high MW HES should not be used in the patients with severe sepsis and in patients with high risk for AKI. However, contemporary HES (6%, 130/0.4) could be a valuable option as an initial fluid resuscitation (limited for initial volume replacement therapy) but should be considered in an algorithm for hemodynamic optimization. Prolonged administration (up to 14 to 21 days) and the high doses should be clearly considered as important risk factors for AKI and coagulation disorders. Moreover, patients with pre-existing renal disease or RRT should not be treated with HES [31].

It is also important to underline that even crystalloid solutions could be associated with adverse events in ICU patients. The use of chloride-rich solution may increase the risk of AKI and may also worsen acidosis and potentially induce gastro paresis [28,30].

Many questions remain in the field of fluid therapy: timing, volume, fluid and sodium balance and the role of balanced fluids. Large randomized trials are urgently required to improve the safety of fluid therapy in both anesthesiology and intensive care. Debates about the HES story will undoubtedly follow.

5. CONCLUSION

Fluids should be considered as drugs and, as is the case with any drug, timing and dose are important. Correct and careful use of fluids is essential regardless of the fluid type. Patients receiving i.v. fluids should be monitored and assessed regularly, complications should be documented and audited.

This review of the available clinical data demonstrates that HES should not be regarded as one homogenous group, and data for one product should not be extrapolated to another. This “gray area” in synthetic colloids solution should be better defined in future randomized trials involving their safety, especially in vulnerable critical care patients.

Until future insight we, as healthcare professionals, should follow international and local practice guidelines.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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