

Clinical Consequences

Should intravenous gelatins have a role in contemporary peri-operative and critical care?

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Last year, Farooque et al. published a case series describing the clinical features and severity of anaphylaxis to intravenous (i.v.) gelatin-based colloid solutions in the peri-operative setting [1]. They reported retrospective data on 12 patients with confirmed hypersensitivity to i.v. gelatin following referral to a drug allergy clinic in the UK between 2013 and 2018. They found that, apart from the treatment of hypotension in one patient, the indication for the use of colloid was unclear. The time between exposure and onset of symptoms was variable, with two patients reacting more than 1 h after exposure. There were three cardiac arrests and six patients were admitted to critical care postoperatively, but there were no deaths. Their work raises several concerns including; most notably, that a delayed onset of reaction may result in misdiagnosis, and, to make matters worse, additional i.v. gelatin might then be used to treat the resultant hypotension. Given the unclear benefits associated with gelatin-based colloids in the peri-operative period, it might be hoped that such concerns have led to a reduction in their use. This instalment of 'Clinical Consequences' examines the possible reasons why this might not yet be the case.

Gelatins in healthcare

Gelatin is a gel-like protein produced by hydrolysis of the collagen found in connective tissues of animals including cattle, chickens, pigs and fish. It has numerous uses in healthcare, including acting as a stabiliser for injectable drugs and vaccines, and in the manufacture of digestible or

absorbable medications and devices such as pharmaceutical capsules and haemostatic sponges [2]. When prepared as an i.v. colloid, gelatin must be modified to prevent it from gelling. This involves chemically degrading gelatin molecules (molecular weight ~100 kDa) into smaller polypeptides and stabilising them through succinylation (e.g. Gelofusine; B. Braun, Melsungen AG, Melsungen, Germany) or urea cross-linking (e.g. Haemaccel; Piramal Healthcare UK, Morpeth, Northumberland, UK). These gelatin-based colloids have molecular weights of approximately 30 kDa; this represents a compromise between viscosity and half-life within the circulation [3]. At present, only succinylated gelatins are available in the UK, and according to the British National Formulary they are indicated for "low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass" [4].

Evidence

Critics may argue that, because the study by Farooque et al. was a retrospective observational case series, we should not change clinical practice as evidence such as this should only be used to generate new hypotheses. Instead, we suggest that the methods used by Farooque et al. are innovative and ideally suited to their subject of interest, and there are good reasons why other study designs might fail to better elucidate the clinical features and severity of anaphylaxis to gelatin-based fluids. For example, randomised controlled trials are unlikely to be a practical method of investigation as the incidence of anaphylaxis is extremely low. Furthermore,

such trials would not be feasible due to issues around: the ethics, practicalities and clinical relevance of interventions and outcomes; statistical power; recruitment; and treatment allocation. Prospective observation might be used to determine the incidence of i.v. gelatin-related anaphylaxis, which has been variably reported. Our current best working estimate, from the 6th National Audit Project (NAP6) [5], is 6.2 cases per 100,000 administrations. However, this excludes grade-1 and -2 (i.e. non-severe) anaphylactic reactions, and the delay in onset described by Farooque et al. brings the accuracy of this figure into question. Although it is likely that anaphylaxis to i.v. gelatin is under-reported, a future prospective observational study of i.v. gelatin anaphylaxis would nevertheless need to be extremely large, and would have to carefully monitor all patients administered i.v. gelatin for several hours. As a result, any such study might fail to add to current understanding to an extent that would justify the resources required. Establishing a national anaphylaxis database would potentially be of most value, as this would help to identify new trends as well as enabling clinicians to describe more accurately the risk of anaphylaxis in their daily practice.

Risks vs. benefits

We believe that the study by Farooque et al. might be seen in the future, if not already, as an important paper in the field of peri-operative allergy, due to the methodology, conclusions drawn and highlighting of the importance of the interface between anaesthetists, surgeons, intensivists and allergy physicians. Case series of this type may have a key role to play in our future understanding of peri-operative complications in general, and a key consequence will be more opportunities for collaboration, funding and closer working ties with clinical and academic colleagues. For example, another group recently employed similar methods to show that a connection between allergy to egg, peanut, soybean or other legumes and the risk of serious allergic reaction to propofol is unlikely [6].

Arguably the most important aspect of the paper by Farooque et al. is that it describes clearly a real and significant risk of i.v. gelatin use. Therefore, as with other drugs that present a relatively high risk of anaphylaxis, such as antibiotics and neuromuscular blocking agents, there should be a clear benefit associated with their use in order to justify this risk. There are now several meta-analyses comparing crystalloid and colloid i.v. fluids in different populations and settings (Table 1). The theoretical benefit of colloids, including gelatins, starches, fresh frozen plasma, albumin and others, is their more efficient action as plasma expanders when treating or preventing hypotension, with a

lower-risk of pulmonary or peripheral oedema. Colloids may also prevent against postoperative nausea and vomiting in the peri-operative period [7]. The risks associated with colloid use, which have been variably demonstrated in meta-analyses, include: increased mortality; acute kidney injury; bleeding; and coagulopathy [8–10].

Weighing these benefits and risks is a complex judgment. Using hydroxyethyl starch solutions as an example, these colloids fell out of favour in 2012 following the publication trials by Myburgh et al and Perner et al., which found no evidence of benefit and an increased incidence of serious adverse effects [11, 12]. Notwithstanding the limitations of this evidence [13], it took until 2018 for the European Medicines Agency to suspend the marketing for these solutions across the European Union. Although some have called for hydroxyethyl starch solutions to be banned [14], their use continues to be reported in clinical trials and recommended in guidelines, and they may continue to be the colloids of choice in developing countries, where alternatives are less easily available. Just as one group of experts might advise against their use, another group might see the evidence differently and come to a different conclusion. Perhaps the most telling evidence is a recent Cochrane review which concludes that the choice of i.v. fluid for the resuscitation of critically unwell adults probably makes no difference to mortality [10]. Overall, although the use of i.v. gelatin might confer some theoretical advantages as compared with crystalloid solutions, and allows for the avoidance of hydroxyethyl starch, there is very little evidence of any associated clinically meaningful benefit.

Succeeding literature

One might expect recent literature regarding gelatin-based colloids to reflect the risk of anaphylaxis as described by Farooque et al. Indeed, a recent review reflects on the lack of evidence for the benefit of i.v. gelatins in the peri-operative period, and makes use of Farooque et al.'s findings in a discussion of the emerging evidence of the risk of life-threatening anaphylaxis [15]. However, a recent randomised controlled trial demonstrated that a pre-operative i.v. gelatin fluid bolus decreased the incidence of hypotension associated with induction of anaesthesia when compared with no pre-operative fluid bolus in the elective surgical setting [16]. Citing Farooque et al., the authors of this study contend that, as the risk of allergic reactions to succinylated gelatine-based colloid fluids is very low, while hypotension associated with induction of anaesthesia is commonplace, the benefits offered by gelatin pre-loading

Table 1 Selected recent meta-analyses comparing crystalloid and colloid i.v. fluids in a range of populations and settings.

Author [reference]	Main question	Included evidence	Main findings/conclusions
Martin and Bassett [19]	Are crystalloids sufficient for volume replacement in critically unwell adults as compared with colloids?	55 randomised controlled trials.	Crystalloids are less efficient than colloids, and there should be better guidance on when to switch between agents. Hydroxyethyl starch solutions were associated with increased mortality when compared with crystalloids.
Kim et al. [7]	Does the choice of peri-operative crystalloid vs. colloid fluid therapy influence the rate of postoperative nausea and vomiting?	Eight randomised controlled trials.	For operations lasting > 3 h, colloid use was associated with less postoperative nausea and vomiting.
Qureshi et al. [20]	Is the evidence comparing crystalloid vs. colloid solutions in critically ill, trauma and surgical patients influenced by the trial design or clinical setting?	59 randomised controlled trials.	Colloid administration did not lead to increased mortality, but did increase the risk of acute kidney injury requiring renal replacement therapy. Sub-group analyses showed increased mortality and renal injury with starch-based solutions in critically ill patients with sepsis.
Raiman et al. [21]	Are hydroxyethyl starch solutions safe for use in the peri-operative period?	13 randomised controlled trials.	There was no difference in mortality, acute kidney injury incidence, and postoperative infection between patients administered i.v. crystalloids as compared with i.v. colloids.
Melchor et al. [8]	To determine the effects of i.v. colloids vs. crystalloids in the incidence of hypotension induced by spinal anaesthesia in elective caesarean section.	11 randomised controlled trials.	The incidence of hypotension was reduced when i.v. colloid pre-loading was used. There was no difference in postoperative nausea and vomiting rates.
Rasmussen et al. [9]	What is the effect of peri-operative crystalloid or colloid fluid therapy on haemorrhage, coagulation competence and outcome?	31 randomised controlled trials.	There was increased blood loss in patients undergoing non-cardiac surgery who received i.v. hydroxyethyl starch-based solutions compared with crystalloids, and a marked reduction in maximum amplitude measured by thromboelastography.
Ghijssels et al. [22]	Are gelatin and hydroxyethyl starches safe when used for cardiopulmonary bypass-priming in cardiac surgery?	10 randomised controlled trials.	There is low-grade evidence that gelatins have a safety profile which is non-inferior to modern-generation tetrastarches or crystalloids.
Lewis et al. [10]	Cochrane review comparing colloids and crystalloids for fluid replacement in critically unwell adults.	65 randomised controlled trials and four quasi-randomised controlled trials.	The choice of fluid probably makes little or no difference to mortality. Starch-based colloids might increase the requirement for blood transfusion and renal replacement therapy.

outweighs the risks. Although it could be argued that the authors of this trial are overly optimistic about the rarity of anaphylactic reactions to i.v. gelatin, and that hypotension might be avoided with other methods (such as the use of crystalloids, cautious dosing of anaesthetic agents and/or the use of vaso-active drugs), their conclusion represents the counterargument most likely held by many, that the real-world risk of anaphylaxis is negligible. This view is also supported by recommendations for the peri-operative use of i.v. gelatin in paediatric fluid guidelines [17] and a recent consensus statement recommending colloid pre-loading to prevent hypotension during caesarean section under spinal anaesthesia [18].

Conclusions

The paper by Farooque et al. concludes with the statement that the use of gelatin-based solutions in the peri-operative setting should be re-assessed. We would go one step further, and suggest there is mounting evidence that the risks outweigh any (potential) benefits. Although the proposed advantages of i.v. gelatins such as the avoidance of hypotension can be achieved by other means, anaphylaxis resulting from its use is severe, delayed, probably more common than epidemiological studies suggest and, in our opinion, unnecessary. We, therefore, call on readers to: continue discussions on the use of i.v. gelatin in their own departments with colleagues; remain

vigilant for delayed reactions to i.v. gelatin; and renew the interest in developing consensus on the choice and use of fluids in the peri-operative period.

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¹Ehrenfeld et al. *J Blood Disorders Transf.* 2014; 5:9. ²Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4. Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer. ³Kamal A, et al. *Open J of Anesth.* 2016 Mar; 6, 13-19. ⁴Imaizumi et al. *Proceedings from the 16th World Congress of Anaesthesiologists* Hong Kong, Abstract #PR607. ⁵Cros et al. *J Clin Monit Comput.* Aug 2019; 1-9. Study utilised a goal-directed fluid therapy protocol with PVI in conjunction with a blood transfusion protocol based on SpHb. ⁶Ribed-Sánchez B, et al. *Sensors (Basel).* 2018 Apr 27;18(5). pii: E1367. Estimated national savings derived from hospital savings extrapolated nationwide. *Data on file.