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Supension of Hydroxyethyl-Starch Solutions to be Re-Examined

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the benefits of infusion solutions containing hydroxyethyl-starch (HES) no longer outweigh their risks, and recommends that the marketing authorisations for these medicines be suspended.

The review was triggered following three recent studies that compared HES with crystalloids in critically ill patients, which showed that patients with severe sepsis treated with HES were at a greater risk of kidney injury requiring dialysis. Two of the studies also showed that in patients treated with HES there was a greater risk of mortality. The PRAC was requested by the German medicines agency, the Federal Institute for Drugs and Medical Devices (BfArM), to assess the evidence and how it impacts on the risk-benefit balance of HES infusion solutions in the management of hypovolaemia and hypovolaemic shock.

The PRAC assessed data from the scientific literature and data submitted by the companies, and took advice from a group of external experts. The PRAC considered that, when compared with crystalloids, patients treated with HES were at a greater risk of kidney injury requiring dialysis, and had a greater risk of mortality. The PRAC also considered that the available data only showed a limited benefit of HES in hypovolaemia, which did not justify its use considering the known risks. The PRAC therefore concluded that the marketing authorisations for these medicines be suspended.

As these medicines are all authorised nationally, the PRAC recommendation will be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a medicines regulatory body representing the EU Member States. If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

Following the recommendation, some of the marketing authorisation holders have requested a re-examination. On receipt and validation of the grounds, the PRAC will re-examine its recommendation and issue a final recommendation. The recommendation will remain in place unless the marketing authorisation holder can provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks. The outcome is expected in the autumn, and will be made public on the EMA website (www.ema.europa.eu).

In the UK the Faculty of Intensive Care Medicine, the Royal College of Anaesthetists, the Intensive Care Society and the College of Emergency Medicine have issued a position statement outlining approaches to fluid therapy pending a definitive decision by the regulatory authorities (www.collemergencymed.ac.uk)

Prone Positioning in Severe ARDS: PROSEVA Results

The Proning Severe ARDS Patients (PROSEVA) Study Group recently published impressive results in the New England Journal of Medicine. This multi-centre, prospective randomised controlled trial looked at the role of prone positioning in patients with early, severe ARDS during mechanical ventilatory support.

Patients were recruited from 26 ICUs in France and one in Spain, all of which have used prone positioning for more than five years. 466 patients were randomly assigned to the supine position or to undergo prone positioning sessions of at least 16 hours. 229 patients were assigned to the prone group, and 237 patients to the prone positioning group. All were treated in standard ICU beds.

At 28 days mortality was 16% in the prone group and 32.8% in the supine group. Secondary end points were mortality at day 90, the rate of successful extubation, time to successful extubation, length of stay in the ICU, complications, use of noninvasive ventilation, tracheotomy rate, number of days free from organ dysfunction, and ventilator settings, measurements of arterial blood gases, and respiratory-system mechanics during the first week after randomisation. The rate of successful extubation was significantly higher in the prone group. The significant difference in mortality persisted at day 90, while the duration of invasive mechanical ventilation, length of stay in the ICU, incidence of pneumothorax, rate of use of noninvasive ventilation after extubation, and tracheotomy rate did not differ significantly between the two groups.

The authors suggest that several factors may explain their results. Patients with severe ARDS were selected on the basis of oxygenation together with PEEP and Fio2 levels. Secondly, patients were included after a 12-to-24-hour period during which the ARDS criteria were confirmed. This period may have contributed to the selection of patients with more severe ARDS who could benefit from the advantages of prone positioning, such as relief of severe hypoxemia and prevention of ventilator induced lung injury. In addition the trial used long prone positioning sessions, the prone position was in place for 73% of the time ascribed for the intervention, and was concentrated over a period of a few days. The tidal volume was lower than in previous trials, and the PplatRS was kept below 30 cm of water. The authors acknowledge that because all patients were returned to the supine position at least once a day, the effect of the prone position itself cannot be distinguished from the effects of being moved from the supine to the prone position over the course of a day.

The technical aspects of prone positioning are covered by two videos provided by the authors on the NEJM website (www.nejm.org).

In an accompanying editorial, Guy W. Soo Hoo comments, “There can no longer be any doubt. Prone ventilation in selected patients with severe ARDS has arrived and is ready for its turn in the management of the disease.”

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