HAUTE AUTORITÉ DE SANTÉ

ANAESTHESIA-INTENSIVE CARE
Review
October 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ISOVOL, RESTORVOL, VOLUVEN (hydroxyethyl starch), colloidal volume replacement solutions

Limited role in 2nd-line treatment of hypovolaemia due to acute blood loss because of the observed excess death rate and cases of sepsis in intensive care.

Main points

- Volume replacement solutions based on hydroxyethyl starch (HES) now only have Marketing Authorization in the treatment of hypovolemia due to acute blood loss when the use of crystalloids alone is not considered sufficient.
- Their use is associated with an excess death rate at 90 days within the framework of sepsis in patients requiring intensive care. To date, it is not possible to extrapolate this risk to cases of acute blood loss.
- Crystalloids are very often sufficient for the rapid re-establishment of the blood volume. Solutions based on HES have a moderate benefit, in the postoperative context only, in the management of acute haemorrhage.

Therapeutic use

- In hypovolaemia due to acute blood loss, crystalloids (sodium chloride solutions, Ringer's solution) are used as first-line treatment while awaiting a possible transfusion, if this is necessary. The doses required to re-establish a satisfactory volume are slightly different from those of colloids (about 1.4 times higher).

- In the rare cases when crystalloids do not permit the rapid re-establishment of the blood volume, it is possible to use solutions based on HES and sometimes albumin solution. Solutions based on HES are reserved for the management of acute haemorrhages and for hypovolaemia secondary to a surgical intervention with a particularly large loss of blood, and in the absence of contraindications.

Clinical data

- The initial efficacy data are of poor methodological quality: low numbers of patients, open studies in some cases, and results relating to surrogate clinical endpoints. For some years now, a number of studies relating to renal safety and medium-term mortality (1 to 3 months) had been published. The studies demonstrated that HES has harmful renal effects in patients with sepsis and for those requiring intensive care treatment in hospital. An excess death rate was found at 90 days in patients presenting with sepsis. Although not providing conclusive evidence, these studies raised doubts relating to an excess death rate linked to HES, whatever the cause of hypovolaemia. After that, three meta-analyses confirmed the effects of HES on an increased recourse to dialysis compared to a crystalloid:
  - two of them demonstrated an excess death rate (RR = 1.09; 95% CI [1.02-1.17] and RR = 1.10; 95% CI [1.02-1.19]),
  - a 3rd meta-analysis produced results that were not significant (RR = 1.08; 95% CI [0.97-1.21]), but which were close to the significance threshold and slightly different from those obtained in the other two meta-analyses (relative risk of the order of 1.1).

- In October 2013, a new randomised, open clinical study (CRISTAL) included 2857 patients with hypovolaemic shock of various causes. The results did not reveal any difference in mortality at 28 days, but at 90 days the mortality was higher after the use of crystalloids: 30.7% of deaths in the colloid group and 34.2% in the crystalloid group (RR = 0.92 ; 95% CI [0.86-0.99]).

- There are no medium-term mortality or renal safety data on the use of crystalloids in the current indication for HES.

- The results as a whole suggest that the use of HES within the framework of sepsis and in patients in intensive care is associated with an increased risk of mortality at 90 days of the order of 1.1. Considering the absence of a mortality and safety study in the current indication and the results of the CRYSTAL study, the ability to extrapolate of the excess death rate to all situations of hypovolaemia, particularly those caused by haemorrhage, remains to be clarified.

Benefit of the medicinal product

- The actual benefit* of ISOVOL 6%, RESTORVOL and VOLUVEN after the failure of crystalloids is moderate in the new indication of the Marketing Authorisation only in the postoperative context or for the management of an acute haemorrhage.

- The Transparency Committee recommends inclusion on the list of reimbursable products for hospital use.

HAUTE AUTORITÉ DE SANTÉ
This document was created on the basis of the Transparency Committee Opinion of 29 October 2014 (CT-13550-13279-12815) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.