Table S1 Outcomes of interest in order of importance.

|  |  |  |
| --- | --- | --- |
|  |  |  |
| **Variable** | **Median\*** | **Value\*\*** |
| Mortality at  28-30 days | 8.5 | CRITICAL |
| Kidney failure | 8 | CRITICAL |
| Adverse effects: coagulopathy | 8 | CRITICAL |
| Adverse effects: clinical haemorrhage | 8 | CRITICAL |
| Adverse effects: anaphylactic reaction | 8 | CRITICAL |
| Pulmonary oedema | 7 | CRITICAL |
| Adverse effects: hypervolaemia | 7 | CRITICAL |
| Time on mechanical ventilation (ICU patients) | 6.5 | CRITICAL |
| Heart failure | 6.5 | IMPORTANT |
| Length of stay in ICU | 6.5 | IMPORTANT |
| Respiratory failure ARDS | 6 | IMPORTANT |
| Surgical site infection | 6 | IMPORTANT |
| Length of hospital stay | 6 | IMPORTANT |
| Time to start of oral intake | 6 | IMPORTANT |
| Sepsis | 6 | IMPORTANT |
| Nausea vomiting | 6 | IMPORTANT |
| Adverse effects: pruritus | 6 | IMPORTANT |
| Myocardial infarction: | 5.5 | IMPORTANT |
| Venous thrombosis | 5.5 | IMPORTANT |
| Pneumonia | 5 | IMPORTANT |
| Quality of life | 5 | IMPORTANT |
| Arrhythmia | 4.5 | IMPORTANT |
| Urinary tract infection | 4.5 | IMPORTANT |
| Gastrointestinal infection | 4.5 | IMPORTANT |

\*Median outcome importance score as assessed by anaesthesiologists (n=4). \*\*According to the GRADE system

Table S2 Search strategy

|  |  |  |
| --- | --- | --- |
| **Clinical question:** General search | | |
| MEDLINE  PubMed | 26.11.2013 | #31 surg\*[ti] 472064  #32 surgery[tiab] 744531  #33 surgical[tiab] 650456  #34 intra-operative[tiab] 7592  #35 intraoperative[tiab] 72583  #36 peri-operative[tiab] 3844  #37 perioperative[tiab] 51257  #38 post-operative[tiab] 36066  #39 postoperative[tiab] 300861  #40 operati\*[tiab] 593840  #41 “Perioperative Care”[MeSH] 119733  #42 “Intraoperative Care”[MeSH] 13350  #43 “Postoperative Care”[MeSH] 50712  **#44** **#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43** **1749605** **[surgery]**  #45 “Fluid Therapy”[MeSH] 13910  #46 fluid replacement[tiab] 1364  #47 fluid treatment[tiab] 150  #48 fluid administration[tiab] 1325  #49 fluid management[tiab] 1167  #50 fluid therapy[tiab] 2132  #54 fluid balance[tiab] 3343  #55 fluid responsiveness[tiab] 432  #56 fluid resuscitation[tiab] 3033  #57 resuscitation fluid\*[tiab] 478  **#58** **#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57** **22575** **[fluid therapy]**  #59 “Hypertonic Solutions “[MeSH] 10632  #60 crystalloid\*[tiab] 4886  #61 “Isotonic Solutions”[MeSH] 7047  #62 saline[tiab] 130917  #63 ringer\*[tiab] 12044  #64 Hartmann\*[tiab] 3068  #65 sodium chloride[tiab] 12515  #67 dextrose[tiab] 7903  #68 SSH[tiab] 1428  **#69** **#59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #67 OR #68** **178108** **[crystalloids]**  #70 “Colloids”[MeSH] 87317  #71 “Hetastarch”[MeSH] 2381  #72 colloid\*[tiab] 38025  #73 dextran\*[tiab] 29125  #74 gelatin[tiab] 17338  #75 hetastarch[tiab] 423  #76 hydroxyethyl starch[tiab] 2251  #77 starch\*[ti] 8512  #78 HES[tiab] 3548  #79 HAES[tiab] 146  #80 tetrastarch[tiab] 22  #81 pentastarch[tiab] 139  #82 albumin[tiab] 110209  **#83** **#70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82** **276926** **[colloids]**  #84 systematic[sb] 216277  #85 review[pt] 1805319  #86 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]) 2802224  #87 "Meta-analysis"[pt] 41882  #88 #84 OR #87 216738  #92 #44 AND #58 4796 [fluid therapy in surgery]  **#97** **#92 AND #88** **207** **[SR in fluid therapy in surgery]**  #100 #69 OR #83 443344  #101 #100 AND #44 36936 [fluids therapy in surgery]  #102 #101 AND #88 460  **#103** **#102 NOT #97** **380** **[SR in fluids in surgery]**  #105 #97 OR #103 587  #106 #83 AND #88 1282  **#107** **#106 NOT #105** **1020** **[SR in colloids]**  #108 #97 OR #103 OR #107 1607  #109 #92 AND #86 1417  **#110** **#109 NOT #108** **1323** **[RCT in fluid therapy in surgery]**  #111 #97 OR #103 OR #107 OR #110 2930  #118 #44 AND #83 17194  #119 #118 AND #86 4431  **#120** **#119 NOT #111** **3997** **[RCT colloids in surgery]** |

Table S3 Evidence and recommendations for the choice of volume replacement fluids (colloids vs. crystalloids) in non-cardiac surgery

|  |  |  |
| --- | --- | --- |
| **Question 1. Which type of fluid (colloids or crystalloids) has the best safety profile for perioperative volume replacement in non-cardiac surgery?** | | |
| **Recommendation** | | |
| In patients undergoing non-cardiac surgery, fluid management with crystalloids is recommended over colloids. | ***Weak recommendation in favour*** | |
| **Justification** | | |
| Available studies have not shown any difference between the use of colloids and crystalloids in terms of critical outcomes such as mortality, impairment of kidney function and coagulopathy, among others (low quality of evidence). Furthermore, colloids are more expensive than crystalloids. For these reasons, a weak recommendation is given in favour of crystalloids. | | |
| **Research recommendations** | | |
| Clinical trials of a higher methodological quality with more appropriate sample sizes are needed to investigate critical outcomes. Studies evaluating the cost-effectiveness of treatment strategies are also needed. | | |
|  | | |
| **From evidence to recommendation** | | |
| ***Quality of the evidence*** | | |
| Three different comparisons were made for each type of colloid: 1) Albumin vs. crystalloids; 2) Hydroxyethyl starch (HES) vs. crystalloids; 3) Gelatins vs. crystalloids. The overall quality of the evidence is low due to the risk of bias and the imprecision of the findings. | | |
| ***Risk-benefit ratio*** | | |
| Generally speaking, no significant differences were observed between the 3 types of colloids and crystalloids for any of the critical or important outcomes analysed.  1. Albumin vs. crystalloids:  Fluid management with albumin showed no significant difference compared with crystalloids in terms of mortality, risk of kidney failure, coagulopathy, clinical haemorrhage, venous thrombosis, length of stay in ICU or length of hospital stay.  2. Hydroxyethyl starch (HES) vs. crystalloids:  Fluid management with HES showed no significant difference compared with crystalloids in terms of mortality, risk of kidney failure, acute pulmonary oedema, coagulopathy, myocardial infarction, length of stay in ICU or length of hospital stay.  3. Gelatins vs.crystalloids:  Fluid management with gelatins showed no significant difference compared with crystalloids in terms of mortality, intraoperative or 24-hour blood loss, heart failure, myocardial infarction, or venous thrombosis. | | |
| ***Importance of the outcomes of interest*** | | |
| No studies on patient values and preferences were found. Nevertheless, due to the unlikelihood of undesirable effects, we do not consider this to be a determining factor in the recommendation. | | |
| ***Use of resources and costs*** | | |
| Colloids are more expensive than crystalloids. | | |
|  | | |
| **Summary of the evidence for effectiveness** | | |
| Eleven systematic reviews (SR) evaluating the effect of colloids and crystalloids on mortality, kidney function and some safety aspects in non-cardiac surgical patients were found. Generally speaking, the SRs included clinical trials conducted in a variety of contexts (perioperative, sepsis, burns, intensive care), except for 1 study that only included patients undergoing abdominal aorta surgery (Toomtong 2010).  *NB: Studies published by Joachim Boldt were excluded because they have been rejected by the scientific community following revelations of research misconduct.*  We performed an aggregate analysis of the individual studies included in the foregoing SRs. All the studies analysed had been published since 2000, and focussed on the perioperative period of non-cardiac surgery, specifically analysing colloids vs. crystalloids in terms of the critical outcomes of interest. Studies on polygelines and dextrans were excluded because these preparations are no longer used in Spain.  We did not analyse colloids vs. crystalloids in terms of groups because according to the literature it is inappropriate to combine effect estimates from studies of different colloids (Perel 2013).  In a Cochrane SR from 2012 (Perel 2013), the effect of colloids vs. crystalloids on mortality in critically ill patients was compared (70 studies, 20407 patients). Eighteen of the studies included analysed fluid management in non-cardiac surgery patients. Of these, 16 compared different types of colloids with crystalloids, but only 2 of these were published in or after 2000.  - Albumin: 1 study (Evans 2003).  - Modified gelatin: 2 studies (Evans 2003, Fries 2004).  Another Cochrane SR published in May 2013 (Mutter 2013), evaluated the effects of HES on kidney function (42 studies, 11399 patients). Eight studies were performed in non-cardiac surgery patients, and only 1 of these compared HES with crystalloids (Yang 2011).  Another SR (Hartog 2011) evaluated third generation starches (molecular weight 130/0.4) in resuscitation (56 RCTs, 3608 patients). Twenty-six studies were performed in perioperative non-cardiac surgery patients. Of these, 10 compared HES with crystalloids (Bulanov 2004, Chen 2006, Jin 2009, Jover 2009, Haentjens 2009, Ko 2007, Langeron 2001, Liang 2006, Mittermayr 2007, Volta 2006).  Another SR (Groeneveld 2011) also reported the evidence available on the safety of HES (42 RCTs, 10382 patients). Of the studies included in this SR, 16 were performed in non-cardiac patients, and of these 2 compared HESs with crystalloids (Innerhofer 2002, Mittermayr 2007).  The Cochrane SR evaluating the effectiveness of different non-blood fluids in abdominal aortic surgery (Toomtong 2010) included 38 studies with a total of 589 patients, 7 of which compared colloids with crystalloids, but only 1 of these was performed after 2000. (Soskic 2005).  Another 6 reviews (Gattas 2013, Guillies 2013, Martin 2013, Van Der Linden 2013 and Saw 2012) were excluded because the studies included had already been incorporated into the aforementioned reviews, with the exception of 2 clinical trials (Parker 2004 and Hung 2012). These latter were also included in the analysis of this question.  Five additional studies were found that had been published after the initial literature search (Hamaji 2012, Topcu 2012, Feldheiser 2013, Rasmussen 2013, Yates 2013). These, with the exception of Topcu 2012 which did not analyse this outcome of interest, were subsequently considered in the analysis of this question.  The following is a summary of the outcomes of interest for each of the colloids analysed. | | |
| **1. Albumin vs. crystalloids** | | |
| **Mortality at 28-30 days** | | |
| Two RCTs (82 patients) evaluated albumin vs. crystalloids without finding any significant reduction in mortality with either treatment. (2 RCTs, 0 events, Risk difference 0 95% CI from -0.07 to 0.07). (Evans 2003, Yang 2011). | | **Quality**  **VERY LOW** |
| **Impairment of kidney function** | | |
| One clinical trial (Yang 2010) found no difference in risk for kidney failure between albumin and colloids (1 RCT, 55 patients, 0 events, Risk difference 0 95% CI from -0.07 to 0.07). The authors did not specify the definition of this outcome. One presented normal BUN and creatinine levels in both groups, and acute kidney injury was not defined according to the RIFLE (Risk, Injury, Failure, Loss, End stage kidney disease) classification. | | **Quality**  **VERY LOW** |
| **Adverse effect: coagulopathy (intraoperative blood loss)** | |  |
| The study published by Yang (2011) describing intraoperative blood loss (55 patients), showed no significant reduction in blood loss with either albumin or crystalloids (1 RCT, 55 patients, 14 ml difference between means in favour of crystalloids 95% CI from -119.24 to 147.24). | | **Quality**  **VERY LOW** |
| **Clinical haemorrhage** | |  |
| The study published by Yang (2011) reported no cases of clinical haemorrhage (1 RCT, 55 patients, risk difference 0 95% CI from -0.07 to 0.07). | | **Quality**  **VERY LOW** |
| **2. Hydroxyethyl starch (HES) 130/04 or 130/042 vs. crystalloids** | | |
| **Mortality at 28-30 days** | | |
| Five RCTs (433 patients) evaluated resuscitation with HES 130/0.4 or 130/0.42 vs. crystalloids, None of the therapies analysed was significantly superior in reducing risk for mortality (5 RCTs, 433 patients, 9 events, RR: 2.57 95% CI from 0.7 to 9.49) (Feldheiser 2013, Hamaji 2012, Hung 2012, Yang 2011, Yates 2013). | | **Quality**  **LOW** |
| **Impairment of kidney function** | |  |
| Only 1 study comparing HES with crystalloids evaluated impairment of kidney function using the standard RIFLE classification (Yang 2011). This RCT included 51 patients and only reported 1 event in the crystalloid group, which was classified in the risk category. Neither therapy was significantly superior in reducing the risk of impairment of kidney function (1 event, RR: 0.32 95% CI from 0.01 to 7.53). | | **Quality**  **LOW** |
| Four RCTs reported findings related to the impairment of kidney function outcome, with no significant differences between the therapies evaluated (4 studies, 353 patients, 5 events RR: 5.79 95% CI from 0.70 to 4.67). (Feldheiser 2013, Hamaji 2012, Yang 2011, Yates 2013).  The studies used different impairment of kidney function definitions: Feldheiser 2013 reported the definition of impairment of kidney function, Hamaji 2012 mentioned that 1 of the patients in the HES group presented an unspecified kidney complication. Yang 2011 used the RIFLE classification, and Yates 2013 described the number of cases with kidney failure, but did not define this outcome. | | **Quality**  **VERY LOW** |
| **Acute pulmonary oedema** | |  |
| One study analysed the incidence of pulmonary oedema (Yates 2013), without finding any significant differences in risk of presenting pulmonary oedema between HES and crystalloids. (1 RCT, 206 patients, 7 events, RR: 2.36 95% CI from 0.47 to 11.88). | | **Quality**  **MODERATE** |
| **Adverse effect: coagulopathy** | |  |
| In 3 studies analysing intraoperative blood loss, no differences between HES and crystalloids were observed (3 studies, 155 patients, difference between means -33.73 ml 95% CI from -180.18 to 112.73). (Hung 2012, Jin 2010, Yang 2011). In 3 studies that analysed 24-hour blood loss, none reported any differences between HES and crystalloids (3 studies, 287 patients, difference between means 329.60 ml IC95% from -69.48 to 728.67). (Hamaji 2012, Rasmussen 2013, Yates 2013) | | **Quality**  **VERY LOW** |
| **Myocardial infarction** | |  |
| In the study reported by Yates (2013) in patients undergoing colectomy, 11 patients in the HES group and 4 in the crystalloids group presented myocardial infarction. However, the authors found no significant differences in risk tor infarction between therapies (1 RCT, 206 patients, 15 events, RR: 2.59 95% CI from 0.85 to 7.88) | | **Quality**  **LOW** |
| **Sepsis** | |  |
| The RCT performed by Yates (2013) found no significant differences in risk for sepsis between HES and crystalloids. (1 RCT, 206 patients, 21 events, RR: 1.53 95% CI from 0.66 to 3.54). | | **Quality LOW** |
| **Length of stay in ICU** | |  |
| Yang (2011) calculated the mean length of stay in ICU in patients undergoing hepatectomy without finding significant differences between HES and crystalloids (1 RCT, 51 patients, difference between means -0.10 days 95% CI from -0.51 to 0.31). | | **Quality**  **LOW** |
| **3. Modified gelatins vs.crystalloids** | | |
| **Mortality at 28-30 days** | | |
| Three RCTs (464 patients) evaluated resuscitation with modified gelatin vs. crystalloids, and reported a total of 28 deaths. No significant differences in reduction of risk for mortality between the therapies were found (4 RCT, 28 events, RR: 2.11 95% CI from 0.98 to 4.55) (Evans 2003, Fries 2004, Parker 2004). | | **Quality**  **LOW** |
| **Adverse effect: coagulopathy** | |  |
| Two studies in patients undergoing cancer surgery and knee arthroplasty evaluated intraoperative blood loss (64 patients). Taken together, the studies found no significant differences in risk for blood loss between modified gelatins and crystalloids (2 RCTs, 64 patients, difference between means 0.33 95% CI from -50.14 to 50.80).  (Innerhofer 2002, Jin 2010).  The study reported by Fries (2004) in patients undergoing knee arthroplasty evaluated 24-hour blood loss without finding significant differences between modified gelatins and crystalloids in preventing blood loss (1 RCT, 40 patients, difference between means 34.00 95% CI from -120.88 to 188.88) | | **Quality**  **VERY LOW** |
| **Heart failure** | |  |
| The study performed by Parker (2004) in 396 patients undergoing hip replacement found no significant differences between modified gelatin and crystalloids in the risk for heart failure. (1 RCT, 396 patients, 21 events, RR: 1.63 95% CI from 0.69 to 3.83). | | **Quality**  **LOW** |
| **Myocardial infarction** | |  |
| The study conducted by Parker (2004) found no significant differences between modified gelatin and crystalloids (1 RCT, 396 patients, 1 event, RR: 3.00 95% CI from 0.12 to 73.20). | | **Quality**  **LOW** |
| **Venous thrombosis** | |  |
| The study conducted by Parker (2004) found no significant differences in the risk for venous thrombosis between modified gelatin and crystalloids (1 RCT, 396 patients, 10 events, RR: 1.00 95% CI from 0.12 to 3.40). | | **Quality**  **MODERATE** |
| **Summary of evidence on the use of resources and costs** | | |
| No cost-effectiveness studies relevant to this question were found. However, in Spain, the cost of colloids far exceeds that of crystalloids (see Tables 2 and 3). | | |

**Table S4 Quality of studies evaluated to determine the outcome of interest: colloids vs. crystalloids (question 1).**

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome evaluated | **Albumin** | **Hydroxyethyl starch (HES) 130/0.4 or 130/0.42** | **Modified gelatin** |
| **Mortality at 28-30 days** | VERY LOW | LOW | LOW |
| **Impairment of kidney function** | VERY LOW | LOW/VERY LOW | Not evaluated |
| **Acute pulmonary oedema** | Not evaluated | MODERATE | Not evaluated |
| **Heart failure** | Not evaluated | Not evaluated | LOW |
| **Myocardial infarction** | Not evaluated | LOW | LOW |
| **Arrhythmia** | Not evaluated | Not evaluated | Not evaluated |
| **Sepsis** | Not evaluated | LOW | Not evaluated |
| **Surgical site infection** | Not evaluated | Not evaluated | Not evaluated |
| **Pneumonia** | Not evaluated | LOW | Not evaluated |
| **Respiratory failure ARDS** | Not evaluated | Not evaluated | Not evaluated |
| **Venous thrombosis** | Not evaluated | Not evaluated | MODERATE |
| **Nausea or vomiting** | Not evaluated | Not evaluated | Not evaluated |
| **Time to start of oral intake** | Not evaluated | Not evaluated | Not evaluated |
| **Adverse effect: coagulopathy** | VERY LOW | VERY LOW | VERY LOW |
| **Adverse effects: clinical haemorrhage** | VERY LOW | Not evaluated | Not evaluated |
| **Adverse effect: hypervolaemia** | Not evaluated | Not evaluated | Not evaluated |
| **Adverse effect: pruritus** | Not evaluated | Not evaluated | Not evaluated |
| **Time on mechanical ventilation (ICU patients)** | Not evaluated | Not evaluated | Not evaluated |
| **Length of stay in ICU** | Not evaluated | LOW | Not evaluated |
| **Length of hospital stay** | Not evaluated | Not evaluated | Not evaluated |
| **Quality of life** | Not evaluated | Not evaluated | Not evaluated |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table S5 Evaluation of kidney function in the comparison between crystalloids and colloids (question 1).** | | | | | |
| **Study** | **Baseline kidney function** | | **Post-intervention kidney function** | | **Analysis/conclusion** |
| Evans60 2003 | Does not evaluate kidney function | | | | |
| Feldheiser53 2013 | Serum creatinine, neutrophil gelatinase-associated lipocalin (NGAL) and preoperative urine output reported in charts. Exact values cannot be determined from the charts. | | Serum creatinine, neutrophil gelatinase-associated lipocalin (NGAL) and postoperative urine output at 1 and 6 hours reported in charts. Exact values cannot be determined from the charts. | | Perioperative kidney function did not differ between groups in terms of perioperative urine output, creatinine or NGAL. |
| Fries62 2004 | Does not evaluate kidney function | | | | |
| Hamaji51 2012 | Ringer's lactate  Serum creatinine (mg.dL-1)  Mean (95% CI)  =0.82 (0.71-0.92) | HES 130/0.4  Serum creatinine (mg.dL-1)  Mean (95% CI)  =0.86 (0.77-0.95) | Ringer's lactate  1. Serum creatinine at 24 hours POP (mg.dL-1): Mean (95% CI) = 0.87 (0.75 to 0.99) 2. Kidney complications 0/24 (0%) | HES 130/0.4  1. Serum creatinine (mg.dL-1) 24 hours POP,Mean (95% CI) =0.86 (0.77-0.95) 2. Kidney complications 1/24 (4%) | No difference in onset of heart, respiratory or kidney complications. |
| Hung63 2012 | Does not evaluate kidney function | | | | |
| Innerhofer65 2002 | Does not evaluate kidney function | | | | |
| Jin66 2010 | Does not evaluate kidney function | | | | |
| Parker67 2004 | Does not evaluate kidney function | | | | |
| Rasmussen42 2013 | Baseline creatinine not reported | | Ringer's lactate  POP creatinine (mmol/L)  Day 1 = 88.6 (27.1) | HES 130/0.4  POP creatinine (mmol/L)  Day 1 = 75.0 (16.2) | Creatinine (mmol/L) was elevated during the first postoperative day in the HES 130/0.4 group, 75.0 (16.2) vs. 88.6 (27.1) in the Ringer's lactate group. P<0.01”. |
| Yang50 2011 | Ringer's lactate  Preoperative creatinine (mmol/L)  Mean (SD) = 77.4 (15.3) | A. HES  Preoperative creatinine (mmol/L)  Mean (SD)= 77.8 (20.0)  B. Albumin  Preoperative creatinine (mmol/L) Mean (SD) = 72.7 (11.4) | Ringer's lactate  1. Kidney failure = 0/25  2. POP creatinine (mmol/L), mean (SD)  D1= 70.6 (18.3) D3= 60.6 (17.0)  D5= 58.3 (17.9) | A. HES  1. Kidney failure = 0/26 2. POP creatinine (mmol/L), mean (SD)  D1 = 73.4 (21.6)  D3 = 66.9 (19.2)  D5= 64.4 (18.3)   B. Albumin  1. Kidney failure = 0/30 2. POP creatinine (mmol/L), mean (SD)  D1 = 66.9 (15.6)  D3 = 59.3 (10.2)  D5= 60.1 (14.3)   B. Albumin | Creatinine and BUN levels were within normal range, with no significant differences between groups. |
| Yates52 2013 | Crystalloids  Kidney failure = 1/98 (1%) | HES  Kidney failure = 1/104 (1%) | Crystalloids  Kidney failure = 0/98 (0%) | HES  Kidney failure = 4/104 (4%) | None |
| HES Hydroxyethyl starch; POP: Postoperative period; D: day; | | | | | |

**Table S6 Evidence and recommendations for the choice of colloids for volume replacement in non-cardiac surgery**

|  |  |
| --- | --- |
| **Question 2. Which colloid solution has the best safety profile for perioperative volume replacement in non-cardiac surgery?** | |
| **Recommendation** | |
| Hydroxyethyl starch (HES 130/0.42 or HES 130/0.4) or modified fluid gelatin are recommended over albumin in non-cardiac surgery patients requiring volume replacement. | ***Weak recommendation in favour*** |
| \*need for rapid fluid resuscitation not achieved with crystalloids alone. | |
| **Justification** | |
| Available studies have not shown any difference between different types of colloids and crystalloids in terms of critical outcomes such as mortality, impairment of kidney function and coagulopathy, among others (low quality of evidence). Nevertheless, the cost of albumin greatly exceeds that of other colloids. For these reasons, a weak recommendation is given in favour of hydroxyethyl starch or modified gelatin. | |
| **Research recommendations** | |
| Clinical trials of a higher methodological quality with more appropriate sample sizes are needed to investigate critical outcomes. Studies evaluating the cost-effectiveness of treatment strategies are also needed. | |
|  | |
| **From evidence to recommendation** | |
| ***Quality of the evidence*** | |
| Three different comparisons were made for each type of colloid: 1) Albumin vs Hydroxyethyl starch (HES); 2) Modified gelatin vs. HES; 3) HES 130/0.42 vs. HES 130/0,4. The overall quality of the evidence is low due to the risk of bias and the imprecision of the findings. | |
| ***Risk-benefit ratio*** | |
| Generally speaking, no significant differences were observed between the different types of colloid analysed in the context of this question (albumin, modified gelatin, hydroxyethyl starch 130/0.42 or 130/0.4) for any of the critical or important outcomes of interest analysed.  1. Albumin vs.HES:  Fluid management with albumin showed no significant difference compared with crystalloids in terms of mortality, risk of kidney failure, risk of renal replacement therapy, time on mechanical ventilation, venous thrombosis, length of stay in ICU or length of hospital stay. One study reported a trend towards reduced 24-hour bleeding in the HES group, although this difference was not sustained at 72 postoperative hours.  2. Gelatins vs.HES:  Fluid management with gelatins did not differ significantly from HES in terms of mortality, renal replacement therapy, 24-hour blood loss, onset of pruritus, length of stay in ICU or length of hospital stay.  3. Hydroxyethyl starch (HES) 130/0.42 vs. HES 130/0.4:  No differences were observed between HES 30/0.42 and HES 130/0.4 in terms of intraoperative blood loss or risk of thrombosis. No studies evaluating the remaining outcomes of interest were found. | |
| ***Importance of the outcomes of interest*** | |
| No studies on patient values and preferences were found. Nevertheless, due to the unlikelihood of undesirable effects, we do not consider this to be a determining factor in the recommendation. | |
| ***Use of resources and costs*** | |
| The cost of albumin greatly exceeds that of other colloids. | |

|  |  |
| --- | --- |
| **Summary of the evidence for effectiveness** | |
| Fourteen systematic reviews (SR) evaluating the effect of colloids on mortality, kidney function and some safety aspects in critically ill patients were found. Generally speaking, these included clinical trials in various different contexts (perioperative, sepsis, burns, intensive care)  *NB: Studies published by Joachim Boldt were excluded because they have been rejected by the scientific community following revelations of research misconduct.*  We performed an aggregate analysis of the individual studies included in the foregoing SRs. All the studies analysed had been published since 2000, and focussed on the perioperative period of non-cardiac surgery, specifically comparing different colloids in terms of the critical outcomes of interest.  One Cochrane SR published in November 2012 (Bunn 2012) compared the effect of different colloids in patients requiring volume replacement (86 studies, 5484 patients). Of these 86 studies, 28 analysed fluid management in patients undergoing non-cardiac surgery, and of these, 6 studies published after 2000 compared different types of colloids in the context of the outcomes of interest.  - Albumin vs.HES: 2 studies (Mukhtar 2009, Yang 2011)  - Modified gelatin vs. HES: 4 studies (Godet 2008, Mahmood 2007, Jin 2010, Mittermayr 2007)  Another SR (Gattas 2013) evaluated the effects of HES on mortality and kidney function (35 RCTs, 10391 patients). Of the studies included in this SR, 13 were performed in non-cardiac patients, and of these 2 fulfilled the selection criteria (Wu 2010, Zdolsek 2011).  Other SRs included studies already included in the aforementioned reviews, in addition to some new studies:  -Cochrane RS (Mutter 2013): included a study comparing albumin and HES (Yassen 2011).  -Van Der Linden, et al (2013) RS: included a study comparing albumin and HES (Kim 2009).  -Saw, et al (2012) SR: included a study (Liang 2006) comparing gelatin with HES.  Other reviews (Guilles 2013, Martin 2013, Wiedermann 2012, Groeneveld 2011, Hartog 2011 and Toomtong 2010) were excluded because the studies analysed had already been included in the aforementioned reviews.  Two additional studies published after the initial literature search were found (Staikou 2012 and Topcu 2012). However, these did not analyse the outcomes of interest related to this question.  Some SRs on colloids were excluded because they compared solutions (HES 200) or surgical interventions that were not relevant to the question (Ishihara 2013, Zarychanski 2013)  The following is a summary of the outcomes of interest for each of the colloids analysed. | |
| **1. Albumin vs. hydroxyethyl starch (HES)** | |
| **Mortality up to hospital discharge (no studies relevant to morality at 28-30 days were found)** | |
| Two RCTs (96 patients) evaluated albumin vs. HES without finding any significant reduction in mortality in either treatments. (2 RCTs, 2 events, RR: 1 95% CI 0.07 to 14.9). (Mukhtar 2009, Yang 2011). | **Quality**  **LOW** |
| **Impairment of kidney function** | |
| Impairment of kidney function was evaluated on the RIFLE (Risk, Injury, Failure, Loss, End stage kidney disease) scale in 2 studies (Yang 2011 and Yassen). However, Yang et al. did not present events, and Yassen et al. found no significant differences between the groups (2 RCTs, 4 events RR: 2.15 95% CI 0.27 to 17.02).  Mukhtar et al. found no significant differences in the risk for requiring renal replacement therapy (1 RCT, 40 patients, 2 events, RR: 1 95% CI 0.07 to 14.90). | **Quality**  **VERY LOW**  **Quality**  **VERY LOW** |
| **Adverse effect: coagulopathy (intraoperative blood loss)** |  |
| Yang et al. found no significant differences in intraoperative blood loss (1 RCT, 56 patients, difference between means 47 ml 95% CI -92.75 to 186.75 ml).  Another study (Kim 2009) described postoperative blood loss at 24 and 72 hours. Significant differences were found at 24 hours (1 RCT, 60 patients, difference between means 203 ml 95% CI 7.97 to 398.03 ml in favour of HES), but not at 72 hours (difference between means 228 ml 95% CI -49.08 to 505.08). | **Quality**  **LOW**  **Quality**  **VERY LOW** |
| **Time on ventilation (days)** |  |
| Two RCTs (100 patients) evaluated the time on mechanical ventilation, finding no significant differences between albumin and HES (2 RCTs, 100 patients, difference between means -0.18 95% CI from -1.42 to 1.06). | **Quality**  **LOW** |
| Other important but non-critical outcomes are shown at the end of this document. | |
| **2. Modified gelatin vs. hydroxyethyl starch (HES)** | |
| **Mortality at 28-30 days** | |
| Two RCTs (108 patients) evaluated albumin vs. HES without finding any significant reduction in mortality in either treatment. (2 RCTs, 2 events, RR: 2.39 95% CI 0.07 to 15.28). (Godet 2008, Mahmood 2007). | **Quality**  **LOW** |
| **Impairment of kidney function** |  |
| None of the studies comparing gelatin with HES used the RIFLE scale.  Mahmood et al. found no significant differences in the risk for requiring renal replacement therapy (1 RCT, 42 patients, 2 events, RR: 1 95% CI 0.07 to 14.95). | **Quality**  **LOW** |
| **Adverse effect: coagulopathy** |  |
| In 4 studies analysing 24-hour blood loss, no differences between gelatins and HES were observed (4 studies, 143 patients, difference between means -21.47 ml 95% CI from -68.35 to 25.41). (Jin 2010, Liang 2006, Mahmood 2007, Mittermayr 2007). | **Quality**  **LOW** |
| **3. Hydroxyethyl starch (HES) 130/0.42 vs. HES 130/0.4** | |
| **Adverse effect: coagulopathy** |  |
| Only 1 study reporting intraoperative blood loss was found. No significant differences between HES 130/0.42 and HES 130/0.4 were found (Zdolsek 2011, 40 patients, difference between means 28 ml in favour of HES 130/0.4 95% CI -188.99 to 244.99 ml). | **Quality**  **VERY LOW** |
| **Summary of evidence on the use of resources and costs** | |
| No cost-effectiveness studies relevant to this question were found. The cost of albumin greatly exceeds that of other colloids (Table 1) | |

**Table S7 Quality of the studies evaluated to determine the outcome of interest: colloids vs. hydroxyethyl starch (HES) (question 2).**

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome evaluated | **Albumin** | **HES 130/0.42 vs. HES 130/0.4** | **Modified gelatin** |
| **Mortality at 28-30 days** | LOW | Not evaluated | LOW |
| **Impairment of kidney function** | VERY LOW | Not evaluated | LOW |
| **Acute pulmonary oedema** | Not evaluated | Not evaluated | Not evaluated |
| **Heart failure** | Not evaluated | Not evaluated | Not evaluated |
| **Myocardial infarction** | Not evaluated | Not evaluated | Not evaluated |
| **Arrhythmia** | Not evaluated | Not evaluated | Not evaluated |
| **Sepsis** | Not evaluated | Not evaluated | Not evaluated |
| **Surgical site infection** | Not evaluated | Not evaluated | Not evaluated |
| **Pneumonia** | Not evaluated | Not evaluated | Not evaluated |
| **Respiratory failure ARDS** | Not evaluated | Not evaluated | Not evaluated |
| **Venous thrombosis** | Not evaluated | Not evaluated | Not evaluated |
| **Nausea or vomiting** | Not evaluated | Not evaluated | Not evaluated |
| **Time to start of oral intake** | Not evaluated | Not evaluated | Not evaluated |
| **Adverse effect: coagulopathy** | LOW/VERY LOW | VERY LOW | LOW |
| **Adverse effects: clinical haemorrhage** | Not evaluated | Not evaluated | Not evaluated |
| **Adverse effect: hypervolaemia** | Not evaluated | Not evaluated | Not evaluated |
| **Adverse effect: pruritus** | Not evaluated | Not evaluated | Not evaluated |
| **Time on mechanical ventilation (ICU patients)** | LOW | Not evaluated | Not evaluated |
| **Length of stay in ICU** | Not evaluated | Not evaluated | Not evaluated |
| **Length of hospital stay** | Not evaluated | Not evaluated | Not evaluated |
| **Quality of life** | Not evaluated | Not evaluated | Not evaluated |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S8 Evaluation of kidney function in the comparison between colloids (question 2).** | | | | | | | | | |
| **Study** | **Baseline kidney function** | | | **Post-intervention kidney function** | | | | **Analysis/conclusion** | |
| Evans60 2003 | Does not evaluate kidney function | | | | | | | | |
| Godet54 2008  NB. Study performed in patients with impaired kidney function (preoperative creatinine clearance <80mL min) | Gelatin  1. Serum creatinine Mean and range: 54.3 (30.9-76.8)  2. Impairment of kidney function: Mild (CrCl>50 mL min): 18/33  Moderate (CrCl 30 to 50 mL min): 15/33  Severe (CrCl<30 mL min): 0/33 | HES  1. Serum creatinine  Mean and range: 55.1 (22.1-79.7)  2. Impairment of kidney function: Mild (CrCl>50 mL min): 20/32  Moderate (CrCl 30 to 50 mL min): 9/32  Severe (CrCl<30 mL min): 3/32 | | Gelatin  1. Peak creatinine level (maximum changes from baseline at 6 days POP or at discharge)   Mean (SD): 36.56 (103.3 mmol L) Median (range) 4.0 (222 to 561)  2. Creatinine clearance Mean: 53.5 (25.2)  Mild (CrCl<50 mL min): 17/33  Moderate (CrCl 30 to 50 mL min):10/33  Severe (CrCl<30 mL min): 5/33  3. POP kidney dysfunction (any creatinine levels above normal range and >44.2mmol or >0.5 mg d over baseline)  7/33  4. Oliguria 4/33  5. Anuria:  1/33 | | HES  1. Peak creatinine level  Mean (SD): 26,3 (55.3 mmol) Median (range) 4.5 (247 to 222)  2. Creatinine clearance Mean: 61.1 (34.2)  Mild (CrCl<50 mL min): 17/32  Moderate (CrCl 30 to 50 mL min): 9/32  Severe (CrCl<30 mL min): 5/32  3. POP kidney dysfunction: 8/32  4. Oliguria 3/32  5. Anuria: 0/32 | | 1. Difference in peak creatinine level. Non-inferiority analysis  Non-inferiority of HES vs. gelatin was analysed using the appropriate unilateral non-parametric 95% CI for the HES - gelatin difference [-∞ to 11 mmol]  2. Difference between POP creatinine clearance means P= 0.184.  HES is not inferior to gelatin in terms of risk for kidney function impairment. | |
| Jin66 2010 | Does not evaluate kidney function | | | | | | | | |
| Kim71 2009 | Does not evaluate kidney function | | | | | | | | |
| Liang72 2006 | Does not evaluate kidney function | | | | | | | | |
| Mahmood55 2007 | No baseline kidney function parameters given | | | Gelatin  1. Need for renal replacement therapy: 3/20  2. POP serum creatinine reported in charts. Exact values cannot be determined from the charts. | | HES  1. Need for renal replacement therapy: 1/21  2. POP serum creatinine reported in charts. Exact values cannot be determined from the charts. | | Serum creatinine levels were significantly lower in the HES vs. the gelatin group on days 1, 2 and 5 (P = 0.020; P = 0.045 and P = 0.045 respectively) | |
| Mittermayr73 2007 | Does not evaluate kidney function | | | | | | | | |
| Mukhtar56 2009 | Albumin  1. Creatinine: Median and range: 77 (36-194)  2. Impairment of kidney function: Mild (CrCl>50 mL min): 15/20  Moderate (CrCl 30 to 50 mL min): 5/20  Severe (CrCl<30 mL min): 0/20 | HES  1. Creatinine: Median and range: 100 (24-129)  2. Impairment of kidney function: Mild (CrCl>50 mL min): 11/20 Moderate (CrCl 30 to 50 mL min): 6/20  Severe (CrCl<30 mL min): 3/20 | | Albumin  1. Need for renal replacement therapy: 1/20  2. POP serum creatinine reported in charts. Exact values cannot be determined from the charts  3. POP creatinine clearance reported in charts. Exact values cannot be determined from the charts. | | HES  1. Need for renal replacement therapy: 1/20  2. POP serum creatinine reported in charts. Exact values cannot be determined from the charts  3. POP creatinine clearance reported in charts. Exact values cannot be determined from the charts. | | Serum creatinine and CRCl were similar in both groups. Plasma cystatin C showed a tendency towards elevation in the HES group on days 2 and 3; this was not statistically significantly (P= 0.08). | |
| Ragaller79 2000 | Does not evaluate kidney function | | | | | | | | |
| Staikou74 2012 | Does not evaluate kidney function | | | | | | | | |
| Topcu75 2012 | Does not evaluate kidney function | | | | | | | | |
| Volta76 2007 | Does not evaluate kidney function | | | | | | | | |
| Wu57 2010 | Gelatin  Pre-incision serum creatinine Mean (SD) 728 (213) | | HES  Pre-incision serum creatinine Mean (SD) 719 (217) | | Gelatin  End-of-surgery serum creatinine Mean (SD) 91 (36) | | HES  End-of-surgery serum creatinine Mean (SD) 76 (20) | | Postoperative serum creatinine levels fell significantly in both groups, with no difference between groups. |
| Yang50 2011 | Albumin  Mean preoperative creatinine (SD) = 72.7 (11.4) | | HES  Mean preoperative creatinine (SD) = 77.8 (20.0) | | Albumin  1. Kidney failure = 0/30  2. Mean POP creatinine D1 (SD)= 66.9 (15.6) Mean POP creatinine D3 (SD)= 59.3 (10.2) Mean POP creatinine D5 (SD)= 60.1 (14.3) | | HES  Kidney failure = 0/26  2. Mean POP creatinine D1 (SD)= 73.4 (21.6) Mean POP creatinine D3 (SD)= 66.9 (19.2) Mean POP creatinine D5 (SD)= 64.4 (18.3) | | Creatinine and BUN levels were within normal range, with no differences between groups. |
| Yassen58 2011 | No baseline kidney function parameters given | | | | Albumin  RIFLE (risk or more)= 2/15 | | HES  RIFLE (risk or more)= 2/30 | | None |
| Zdolsek78 2011 | Does not evaluate kidney function | | | | | | | | |
| CrCl: Creatinine clearance; HES; Hydroxyethyl starch; POP: Postoperative period; D: day; | | | | | | | | | |