

# Safety of gelatin solutions for the priming of cardiopulmonary bypass in cardiac surgery: a systematic review and meta-analysis

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## Abstract

This systematic review and meta-analysis was conducted to evaluate the safety of gelatin versus hydroxyethyl starches (HES) and crystalloids when used for cardiopulmonary bypass (CPB)-priming in cardiac surgery. MEDLINE (Pubmed), Embase and CENTRAL were searched. We included only randomized, controlled trials comparing CPB-priming with gelatin with either crystalloids or HES-solutions of the newest generation. The primary endpoint was the blood loss during the first 24 hours. Secondary outcomes included perioperative transfusion requirements, postoperative kidney function, postoperative ventilation times and length of stay on the intensive care unit. Sixteen studies were identified, of which only ten met the inclusion criteria, representing a total of 824 adult patients: 4 studies compared gelatin with crystalloid, and 6 studies gelatin with HES priming. Only 2 of the studies comparing HES and gelatin reported postoperative blood loss after 24 hours. No significant difference in postoperative blood loss was found when results of both studies were pooled (SMD -0.12; 95% CI: -0.49, 0.25;  $P=0.52$ ). Likewise, the pooled results of 3 studies comparing gelatin and crystalloids as a priming solution could not demonstrate significant differences in postoperative bleeding after 24 hours (SMD -0.07; 95% CI: -0.40, 0.26;  $P=0.68$ ). No differences regarding any of the secondary outcomes could be identified. This systematic review suggests gelatins to have a safety profile which is non-inferior to modern-generation tetrastarches or crystalloids. However, the grade of evidence is rated low owing to the poor methodological quality of the included studies, due to inconsistent outcome reporting and lack of uniform endpoint definitions.

## Keywords

cardiopulmonary bypass; crystalloid solutions; gelatin; hydroxyethyl starch derivatives

**Trial registration number:** CRD42016033047 (<http://www.crd.york.ac.uk/PROSPERO/>)

## Introduction

In cardiac surgery, colloid solutions are frequently used as constituents of the priming fluid, attempting to abate the drop in colloid oncotic pressure (COP) that results from dilution after initiating cardiopulmonary bypass (CPB).<sup>1,2</sup> The choice for a particular colloid [albumin, hydroxyethyl starches (HES) or gelatin] seems to be based primarily on personal experience, historical beliefs and regional preferences rather than on clinical evidence.<sup>2</sup>

In critically ill patients, the use of HES for volume resuscitation is increasingly being questioned or even abandoned. While no convincing evidence exists that HES improves outcome, several clinical trials demonstrated HES solutions to significantly increase the risk of acute kidney injury, bleeding complications or even mortality.<sup>3–7</sup> These observations have driven both the

European Medicines Agency and the U.S. Food and Drug Administration to communicate warnings on these increased risks of HES solutions.<sup>8,9</sup> Data on the efficacy and safety of HES solutions for intraoperative use are inconclusive.<sup>10–13</sup> Consequently, the intraoperative use of HES decreased dramatically. Although

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reliable data are lacking, it is reasonable to assume that many cardiac surgical centers have modified their priming solutions, with a preference for gelatins. However, comparative data on gelatin safety and, more specifically, its use as CPB priming are scarce. In order to evaluate the safety profile of gelatin, randomized, controlled trials comparing the safety of gelatins, HES and crystalloids as CPB primes in elective cardiac surgery were systematically searched and reviewed. In addition, a meta-analysis on the combined results was performed.

The objective of this systematic review and meta-analysis was the assessment of gelatin safety as a constituent of CPB priming in elective cardiac surgery. Primarily, the effects of gelatin priming compared to HES solutions and crystalloids on postoperative bleeding were evaluated. Postoperative bleeding requiring transfusion is considered an independent risk factor for morbidity and mortality during cardiac surgery.<sup>14,15</sup> As secondary objectives, the effects of gelatin priming solutions on perioperative transfusion requirements, renal function, postoperative ventilation times and postoperative intensive care unit (ICU) length of stay (LOS) were evaluated.

## Methods

### *Protocol registration*

The study protocol was registered at PROSPERO, the international prospective register for systematic reviews (registration number: CRD42016033047) and is freely accessible on the website <http://www.crd.york.ac.uk/prospéro/>.

### *Inclusion criteria and eligibility*

Only published, randomized, controlled trials comparing gelatin use for CPB priming with either crystalloid or HES solutions of the newest generation (6% HES 130/0.4 or 6% HES 130/0.42) were selected. Only adult patients undergoing elective cardiac surgery were included. No language or publication date restrictions were imposed. Ethical approval was not requested as all data were extracted from published original reports.

### *Primary and secondary outcomes*

Eligible, randomized, controlled trials had to report at least postoperative blood loss or postoperative chest tube drainage. Additional outcomes were perioperative transfusion requirements: packed red blood cells (PRBC), platelets (PLT), fresh frozen plasma (FFP), postoperative renal function (estimated glomerular filtration rate, [eGFR], RIFLE [Risk, Injury, Failure, Loss of function, End stage renal disease], creatinine, urea),

postoperative ventilation times (in hours or days) and postoperative ICU LOS (hours or days).

### *Search methods*

MEDLINE (PubMed), EMBASE and CENTRAL were systematically searched on the 2nd of January 2016. Both MeSH terms and free-text terms were used to build up a search strategy for PubMed, which was subsequently translated to cover the systematic search in EMBASE (EMTREE terms) and CENTRAL. No filters were used, but the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) for PubMed and EMBASE was added as an additional concept.<sup>16</sup> Details and search terms concerning the systematic search can be found in the supplementary material. All results were gathered in a Reference Manager program (Mendeley) and duplicates were removed. All titles were screened for eligibility by two independent reviewers (IG and SR), potential eligible abstracts were read and studies for full-text reading were selected. A PRISMA flow diagram was made to summarize the study selection process. Any case of disagreement was resolved by discussion. Reference lists of eligible studies were scanned for additional manuscripts.

### *Data collection and analysis*

Included studies were scanned for relevant data and statistical analysis and processing was performed using the freely available computer program Review Manager 5.3 (Review Manager (RevMan) [Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data and study characteristics were retrieved from the included studies by two reviewers (IG and SR) in an unpiloted MS Excel® data sheet. The following information was extracted from each included study: study design, participants and participant demographics (total amount, amount in HES, gelatin and crystalloid groups), type of surgery and surgical technique, primary and secondary outcomes, type of fluids given, priming volume, perioperative fluid administration protocol and guiding volume replacement, inclusion and exclusion criteria, transfusion requirements (PRBC, PLT, FFP, cell saver) and transfusion policy, blood loss calculation, other influences on coagulation (heparin, tranexamic acid, temperature, protamine administration protocol), human albumin administration, colloid limits applied, haemodynamic and laboratory parameters measured, administration of inotropes, statistical methods and characteristics of CPB. After data extraction, all relevant data were double checked by one investigator (IG). In the case of doubt or any question regarding outcome

data, the appropriate authors were contacted to provide the additional necessary information.

### Assessment of risk of bias in included studies

The risk of bias of the included studies was assessed using the Cochrane 'risk of bias' tool.<sup>17</sup> The reviewers conducting the assessment of risk of bias were not blinded to the names of the authors, institutions, journal and results of a study when they assessed the methods (IG and SR). All included studies were searched for selection bias, performance bias, detection bias, attrition bias, reporting bias and other possible sources of bias (risk of bias tables, supplementary material). We considered study protocol differences that might have affected the outcome data of different studies and the administration of drugs that could have affected coagulation as other possible sources of bias. The PRISMA guidelines were followed, when appropriate, to guarantee the methodological quality of the systematic review and meta-analysis.<sup>18</sup>

### Statistical analysis

Results across the studies were pooled using the meta-analysis software of Review Manager 5.3. Data from studies comparing gelatin-priming solutions with HES-priming solutions were not used in the meta-analysis of studies comparing gelatin-priming solutions with crystalloid-priming solutions, nor vice-versa. Results from meta-analyses were reported to obtain the average differences between two groups (gelatins vs. HES and gelatins vs. crystalloids) for blood loss after 24 hours, perioperative transfusion requirements, postoperative kidney function, postoperative ventilation times and ICU LOS. Considered study estimates are standardized mean differences (SMD). Differences between studies reflect true variability ("heterogeneity") and sampling variability. Heterogeneity was quantified by the  $I^2$  statistic,<sup>19</sup> which is the percentage of total variation in study estimates that is due to heterogeneity and tested by the Cochran's  $\chi^2$ -test. Results were based on a fixed-effect approach unless the observed  $I^2$  exceeded 50%. In that case, the random-effects approach of DerSimonian and Laird was applied.<sup>20</sup> A funnel plot for each outcome to assess the risk of publication bias between studies was not performed because of insufficient included studies. No subgroup or sensitivity analyses were performed.

## Results

### Search results

The process of the systematic search is depicted in the PRISMA flow diagram (Figure 1). The systematic

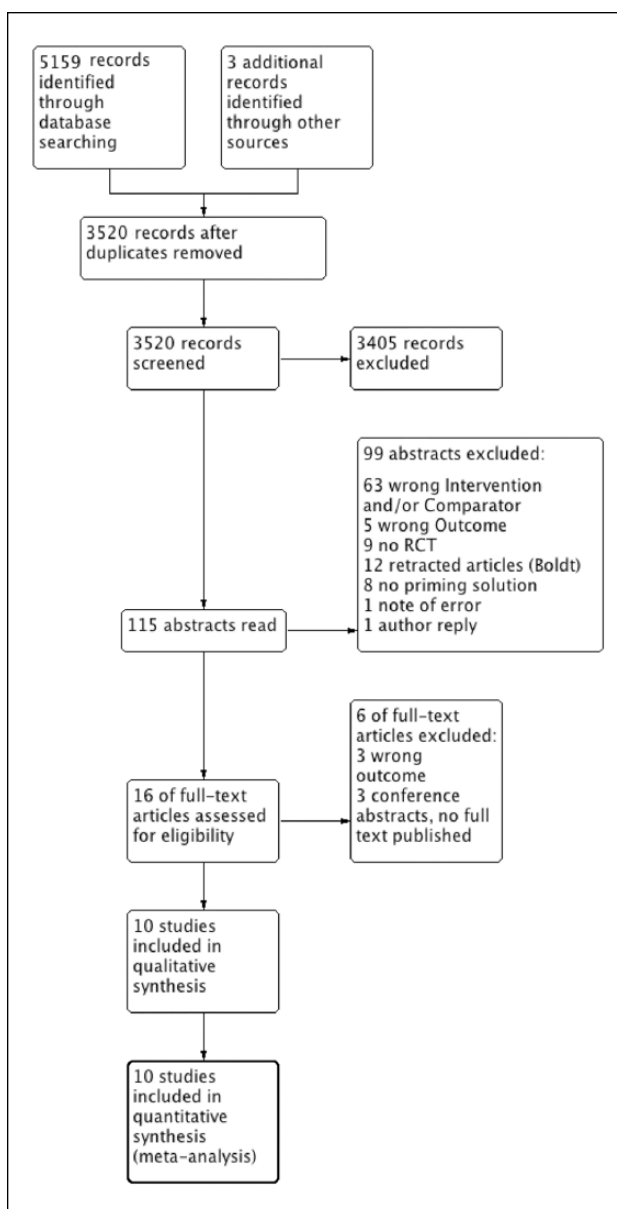


Figure 1. PRISMA flow diagram.

search yielded 3520 studies after the removal of duplicates. All studies were screened, 115 abstracts were read and 16 articles were selected for full-text reading. Six studies were excluded because they did not assess one of our pre-defined outcomes<sup>21-23</sup> or because there was no full text published.<sup>24-26</sup> Ten studies were included in our systematic review for qualitative and quantitative analysis.<sup>27-36</sup> For the comparison between gelatin and HES, 6 studies were found;<sup>27-32</sup> for the comparison between gelatin and crystalloids, 4 studies were included.<sup>33-36</sup> Study characteristic tables of all included full-text articles can be found in the supplementary material (supplementary material can be found online with this article).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1. Van der Linden 2005	+	?	-	+	+	+	-
2. Yap 2007	+	+	?	+	+	+	-
3. Boks 2007	+	?	-	?	+	+	-
4. Vanhoonacker 2009	?	?	+	?	+	+	+
5. Ooi 2009	?	?	-	?	+	+	-
6. Kimenai 2013	+	?	-	?	+	+	+
7. Scott 1995	?	?	+	?	+	+	+
8. Jansen 1996	?	?	+	?	+	+	-
9. Singh 1999	?	?	-	?	+	+	+
10. Tamayo 2008	+	?	+	?	+	+	-

**Figure 2.** Risk of bias summary.

### Risk of bias of the included studies

Judgement of the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other possible sources are shown in the risk of bias tables and risk of bias graph in the supplementary material and are summarized in Figure 2.

**Allocation (selection bias):** The randomization method was described and considered adequate in only 5 out of 10 included studies.<sup>27-29,32,36</sup> Correct allocation concealment was mentioned only in one study.<sup>28</sup>

**Blinding (performance and detection bias):** Correct blinding was not achieved in 5 out of 10 included studies.<sup>27,29,31,32,35</sup> The three studies that blinded the investigator, but not the CPB technician, were considered to have a low risk of bias.<sup>28,34,36</sup> Outcome assessment was adequately blinded in only two studies,<sup>27,28</sup> while the

other eight studies did not mention any blinding of outcome assessment.<sup>29-36</sup>

**Incomplete outcome data (attrition bias):** All studies included the pre-specified number of patients in outcome analysis or clearly mentioned dropouts. Thus, attrition bias was considered low in all studies.

**Selective reporting (reporting bias):** Reporting bias was considered low. In one study, the authors did not differentiate between primary and secondary outcomes, but reported all outcome data correctly.<sup>35</sup> Therefore, we considered the risk of selective reporting bias in this study low as well.

**Other potential sources of bias:** In three studies, drugs (e.g., tranexamic acid) were used that may have affected the primary outcome (postoperative bleeding), which can be considered a possible source of bias.<sup>27,31,36</sup> Furthermore, in different studies, the primary endpoint 'postoperative blood loss' was measured at different postoperative time points, which made an inclusion in the quantitative meta-analysis impossible for the aberrant data. Four studies lacked a clear fluid administration protocol and, thus, were considered at high risk of bias.<sup>28,29,34,36</sup> A funnel plot to assess the risk of bias across studies was not performed due to the low number of included studies.

### Outcome reporting and effects of interventions

**Gelatin versus HES.** All data can be found in Table 1.

**Blood loss.** Postoperative chest tube drainage after 24 hours was only reported in two studies, in 154 and 90 patients, respectively.<sup>30,31</sup> In one study, the postoperative blood loss in the first 24 hours after surgery was comparable in both groups (Table 1).<sup>31</sup> In the other study the measured cumulative blood loss was significantly higher in the HES group only at one hour postoperatively.<sup>30</sup> Although the average blood loss was consistently higher in consecutive hours, the results did not reach the statistical significance threshold (Table 1). No significant difference in postoperative blood loss was found when results for the comparison between gelatin and HES solutions of both studies were pooled (SMD -0.12; 95% CI, -0.49, 0.25;  $p=0.52$ ) (Figure 3a). Due to significant heterogeneity ( $I^2=51\%$ ), a random-effect model was used. Two other studies reported blood loss after 12 hours and none of these two studies could show a statistically significant difference in postoperative blood loss (Table 1).<sup>28,32</sup> Unfortunately, the results of these studies could not be pooled since the data from one study were expressed as median  $\pm$  interquartile range and it was impossible to retrieve the results expressed as mean  $\pm$  standard deviation.<sup>32</sup> Other studies reported blood loss on 22.8 hours, 20 hours and 18 hours after surgery.<sup>27,29,32</sup> None of them found significant differences in postoperative blood loss.

**Table I.** Details of included studies comparing HES and gelatin for the priming of cardiopulmonary bypass.

Source	Number of included patients	Surgical procedure	Study type	Double blinding	Hydroxyethyl starch		Gelatin		Fluid Administration Protocol	Mortality	Bleeding outcome	Perioperative Transfusion requirements	Renal outcome	Commercial support	Ventilation time (h)	ICU length of stay (h)
					Type	Dose	Type	Dose								
<b>Van der Linden 2005<sup>27</sup></b>	132	coronary surgery	Prospective, randomized, controlled trial	no	Voluven®	48.9 ± 17.2 mL/kg (intra- + postop)	Geloplasma®	48.9 ± 14.6 mL/kg (intra- + postop)	HES or GEL for intra- and postoperative volume management, max 50 mL/kg/day. Crystalloids for additional fluid requirements	HES 0/64, GEL 1/68	Total blood loss after 20h, intra- and postoperatively (mL/kg) HES 19.4 ± 12.3 GEL 19.2 ± 14.5 (p=ns)	Number of patients received: FFP/Platelets: HES 11/8 GEL 4/3 (p=ns) Units PC received (median (range)): HES 0 (0-6) GEL 0 (0-6) (p=ns)	Creatinine (mg/dl) after 20h HES 1.0 ± 0.26 (pre-op: 1.05 ± 0.23) GEL 1.04 ± 0.34 (pre-op: 1.09 ± 0.29) (p=ns)	Not reported	HES 13.1 ± 3.4 GEL 13.1 ± 3.8 (p=ns)	(median (range)) HES 24 (20-73) GEL 43 (22-100) (p=ns)
<b>Yap 2007<sup>28</sup></b>	40	CABG	Prospective, randomized, controlled trial	unclear	Voluven®	Priming solution: 1000 mL Hartmann® and 500 mL Voluven®	Gelofusine®	Priming solution: 1000 mL Hartmann's and 500 mL Gelofusine®	Not adequately reported	Not reported	Blood loss after 12h (mL) GEL 561 ± 227 HES 507 ± 183 (p=0.411)	Not reported	Urea (mmol/l) after 14h, GEL 8.11 ± 4.14 HES 6.5 ± 2.41 (p=0.142) creatinine (μmol/l) after 14h GEL 118.4 ± 50.5 HES 96.3 ± 22.6 (p=0.085)	Not reported	Not reported	Not reported
<b>Boks 2007<sup>29</sup></b>	180	Elective primary valve or CABG surgery	Prospective, randomized, controlled trial	no	Voluven®	Priming solution: 1000 mL Voluven® + 300-500 mL Ringer Lactate Solution.	Gelofusine®	Priming solution: 1300-1500 mL Gelofusine®	Not adequately reported	Not reported	Blood loss end-ICU (mL) (mean ± SE) GEL 1259 ± 57 HES 1163 ± 61 (p=ns)	Per + postoperative transfusion requirements (mL) (mean ± SE) PC GEL 582 ± 57 HES 586 ± 55 Platelets GEL 104 ± 17 HES 115 ± 19 FFP GEL 466 ± 58 HES 509 ± 70 (p=ns)	Not reported	Not reported	Not reported	(mean ± SE) HES 22.8 ± 0.7 GEL 22.9 ± 0.7 (p=ns)
<b>Vanhoonaeker 2009<sup>30</sup></b>	157	CABG	Prospective, randomized, controlled trial	yes	Voluven®	1500 mL Voluven®	Geloplasma®	1500 mL Geloplasma®	Per op only saline 0.9% max 1000ml Postop only Voluven®	Not reported	Chest tube drainage after 24h (mL) GEL 592.43 ± 347.89 (=7.79 mL/kg ± 5.04) HES 695.79 ± 368.82 (=9.42 mL/kg ± 6.09) (p=0.07)	Postoperative transfusion requirement after 24h (mL) PC GEL 251 ± 366 HES 302 ± 380 Platelets GEL 29 ± 94 HES 31 ± 79 FFP GEL 86 ± 222 HES 111 ± 268	Creatinine at arrival at the ICU and on day one, but no results depicted	Not reported	Not reported	Not reported

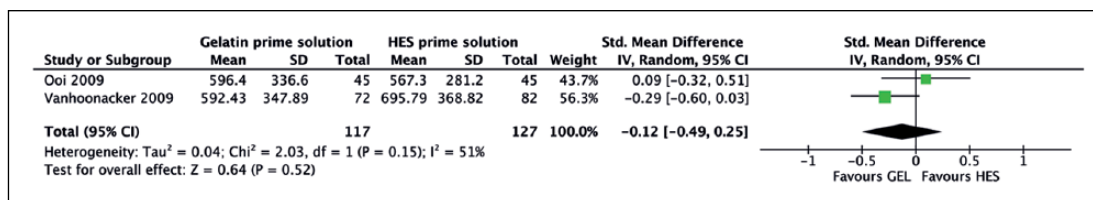
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Table 1. (Continued)

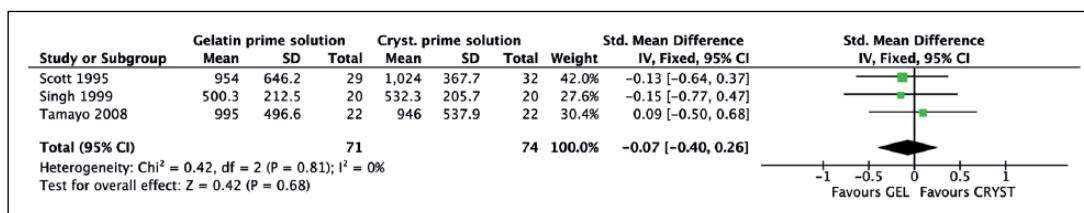
Source	Number of included patients	Surgical procedure	Study type	Double blinding	Hydroxyethyl starch		Gelatin		Fluid Administration Protocol	Mortality	Bleeding outcome	Perioperative Transfusion requirements	Renal outcome	Commercial support	Ventilation time (h)	ICU length of stay (h)
					Type	Dose	Type	Dose								
Ooi 2009 <sup>31</sup>	90	CABG	Prospective, randomized, controlled trial	no	Voluven <sup>®</sup>	Total of 1600 ml priming solution, exact amount of Voluven <sup>®</sup> not mentioned	Gelofusine <sup>®</sup>	Total of 1600 ml priming solution, exact amount of Gelofusine <sup>®</sup> with colloids not mentioned	Per-op: Ringer's lactate solution Post-op: volume replacement according to group	Not reported	Blood loss after 24h (ml) GEL 596.4 ± 336.6 HES 567.3 ± 281.2 (p=0.66)	Postoperative transfusion requirements: Patients receiving 1 unit PC GEL 42 (93.3%) HES 40 (88.9%) p=0.46 FFP GEL 24 (53.3%) HES 17 (37.8%) p=0.14 Platelets GEL 18 (40.0%) HES 18 (40.0%) (p=1.00)	eGFR (ml·min <sup>-1</sup> (1.73m <sup>2</sup> ) <sup>-1</sup> ) after 24h GEL 81.5 ± 22.2 (pre-op: 92.3 ± 21.4) HES 84.1 ± 24.7 (pre-op: 85.3 ± 15.3) (p=0.6)	Not reported	HES 7.8 ± 8.6 GEL 9.3 ± 5.9 (p=0.34)	HES 58.6 ± 32.7 GEL 62.3 ± 31.5 (p=0.59)
Kimenai 2013 <sup>32</sup>	60	CABG	Prospective, randomized, controlled trial	no	Volulyte <sup>®</sup>	550-650 ml Volulyte <sup>®</sup> lactated Ringer's solution	Gelofusine <sup>®</sup>	550-650 ml Gelofusine <sup>®</sup> lactated Ringer's solution	During CPB: group-specific fluid was administered in case of suspected hypovolemia. At reaching maximum dose of HES (50 ml/kg/24h), saline or lactated Ringer's solution was administered. At arrival at the ICU, patients received gelatin (Gelo group) or HES 130/0.4 (HES group) according to the ICU protocol	Not reported	Chest tube drainage after 12h (ml) (median ± IQR) GEL 375 ± 255 HES 425 ± 300 (p=0.56) and Chest tube drainage after 18h (ml) GEL 465 ± 390 HES 500 ± 420 (p=0.48)	Perioperative, median cumulative units transfused: PC GEL 1 ± 0 HES 1 ± 2 p=0.22 FFP GEL 0 HES 2 P=0.15 Platelets GEL 0 HES 1 p= 0.31	Not reported	No conflicts of interest	Not reported	Not reported

All data are expressed as mean ± standard deviation (SD), unless mentioned otherwise. Voluven® = 6% HES 130/0.4 (Waxy maize, Fresenius Kabi®), Volulyte® = 6% HES 130/0.4 (waxy maize), Geloplasma® = 3% modified fluid gelatin (Fresenius Kabi®); Gelofusine® = Succinylated 4% modified fluid gelatin.

ns = not significant; FFP = fresh frozen plasma; PC = packed red blood cells; SE = standard error; IQR = interquartile range.



**Figure 3a.** Forest plot of primary outcome blood loss after 24 hours for the comparison of gelatin prime solution versus HES prime solution.



**Figure 3b.** Forest plot of primary outcome blood loss after 24 hours for the comparison of gelatin prime solution versus crystalloid prime solution.

A randomized trial compared HES and modified gelatin as priming solutions in cardiac surgery patients and found, using thromboelastography, *in vitro* parameters of coagulation to be more impaired in patients with HES priming.<sup>23</sup> However, these findings were not reflected by differences in blood loss or transfusion requirements. Because of the short postoperative follow-up, inclusion of this study into our meta-analysis was impossible.

**Perioperative transfusion requirements.** Perioperative transfusion requirements were reported differently across the several included studies. One trial found the HES group to receive more FFP and PLT than the gelatin group. However, this difference did not reach statistical significance (Table 1).<sup>27</sup> Another study reported intra- and postoperative transfusion requirements independently, expressed in millilitres, while the total need for transfusion between HES and gelatin groups were comparable (Table 1).<sup>29</sup> A third study reported only postoperative transfusion requirements in millilitres and found no statistical differences between the two groups (Table 1).<sup>30</sup> A fourth study reported transfusion requirements as the number of patients receiving at least 1 unit of PC, PLT or FFP.<sup>31</sup> They found no statistical differences in outcomes (Table 1). Likewise, another study could not illustrate differences in transfusion requirements between gelatin and HES groups (Table 1).<sup>32</sup> Due to a wide variation in the reporting of perioperative transfusion requirements, statistical pooling of results was not feasible.

**Renal function.** Two studies reported postoperative creatinine serum levels 20 and 14 hours after ICU admission, respectively;<sup>27,28</sup> only one study included eGFR in the outcome reporting.<sup>31</sup> Therefore, a

quantitative pooling of results was not possible. None of the two first studies could show a statistical difference in postoperative creatinine serum levels. In the third study, eGFR deteriorated temporarily on days 1, 2 and 4 postoperatively, but improved similarly 4 weeks later in both groups.<sup>31</sup> None of the study participants required any type of renal replacement therapy (RRT) during the study period.

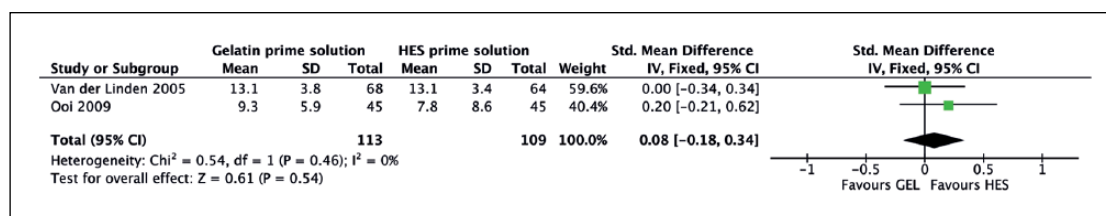
**Ventilation times.** Mean ventilation times were reported in two out of six studies and were similar in both studies.<sup>27,31</sup> Pooling of results showed no significant difference for postoperative mean ventilation times (SMD, 0.08; 95% CI, -0.18, 0.34;  $p=0.54$ ) (Figure 4a).

**Intensive care unit length of stay.** Three out of six studies reported mean ICU LOS.<sup>27,29,31</sup> Only the results of two studies could be pooled<sup>29,31</sup> since the data of the third study were expressed as median  $\pm$  range and the original data could not be retrieved (Table 1).<sup>27</sup> No significant differences were found in the postoperative ICU LOS between the gelatin and the HES groups (SMD, 0.05; 95% CI, -0.19, 0.29;  $p=0.69$ ) (Figure 4b).

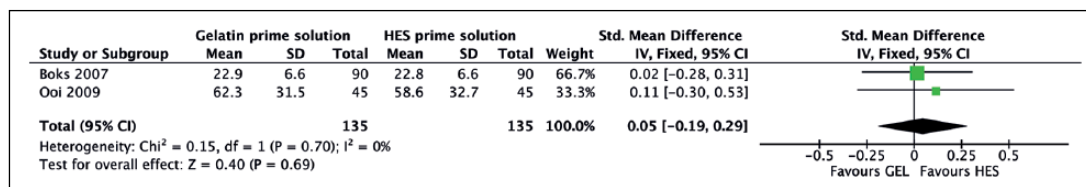
**Gelatin versus crystalloids.** All data can be found in Table 2.

**Blood loss.** One study encompassing 20 patients reported blood loss after 18 hours and could, therefore, not be included in the pooling of results.<sup>34</sup> This study was not able to show a statistical difference in postoperative blood loss between the comparator and study groups (Table 2). Three studies, including 145 patients altogether, reported postoperative bleeding after 24 hours.<sup>33,35,36</sup> None of the studies could solely demonstrate

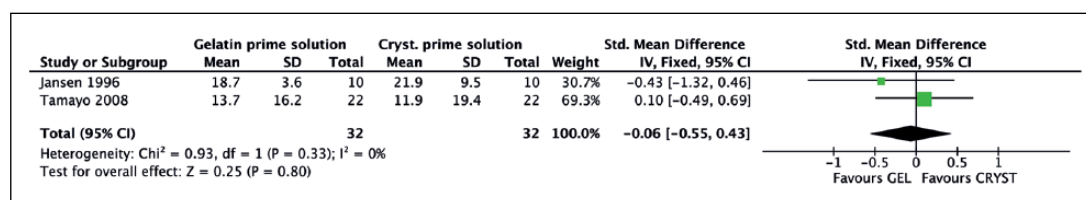




**Figure 4a.** Forest plot of secondary outcome postoperative ventilation time for the comparison of gelatin prime solution versus HES prime solution.



**Figure 4b.** Forest plot of secondary outcome postoperative ICU LOS for the comparison of gelatin prime solution versus HES prime solution.



**Figure 4c.** Forest plot of secondary outcome postoperative ventilation time for the comparison of gelatin prime solution versus crystalloid prime solution.

a statistical difference in postoperative blood loss after 24 hours, comparing gelatin as a priming solution to mere crystalloid priming solutions; neither did the pooled results of the three studies (SMD  $-0.07$ ; 95% CI,  $-0.40$ ,  $0.26$ ;  $p=0.68$ ) (Table 2, Figure 3b).

**Perioperative transfusion requirements.** One study reports homologous blood transfusion in millilitres, without any difference in transfusion requirements between the gelatin and the crystalloid groups.<sup>33</sup> Another study found no difference in the amount of received units of donor blood<sup>34</sup> while a third study showed a difference in the postoperative need for transfusion or received units of donor blood (Table 2).<sup>36</sup> Owing to a lack of reporting of the observation periods, it was impossible to pool the results of the different studies.

**Renal function.** One study measured serum creatinine and urea at 24 hours, with urea, but not creatinine, levels being significantly higher in the gelatin group at 24 hours postoperatively (Table 2).<sup>33</sup> Another study reported postoperative urea and creatinine, but failed to mention the postoperative blood sample time.<sup>36</sup>

Therefore, a meta-analysis of this secondary outcome was not possible.

**Ventilation times.** Only two studies reported postoperative ventilation times.<sup>34,36</sup> Neither of them could show any statistical difference (Table 2). Meta-analysis of the pooled results shows no significant difference for postoperative ventilation times (SMD,  $-0.06$ ; 95% CI,  $-0.55$ ,  $0.43$ ;  $p=0.80$ ) (Figure 4c).

**Intensive care unit length of stay.** ICU LOS was reported in only one study.<sup>36</sup> There was no significant difference between the postoperative ICU LOS in the gelatin-priming group compared to the crystalloid-priming group (Table 2).

## Discussion

### Summary of main results

This systematic review and meta-analysis could not demonstrate differences in postoperative blood loss comparing gelatin solutions with modern generation



**Table 2.** Details of included studies comparing crystalloids and gelatin for the priming of cardiopulmonary bypass.

Author	Number of included patients	Surgical procedure	Study type	Double blinding	Crystalloid-Priming		Gelatin-Priming		Fluid Administration Protocol	Mortality	Bleeding outcome	Perioperative transfusion requirement	Renal outcome	Commercial support	Ventilation time (h)	ICU length of stay
					Type	Dose	Type	Dose								
<b>Scott 1995<sup>33</sup></b>	61	CABG	Prospective, randomized, controlled trial	Yes	Plasmalyte <sup>®</sup> 2000ml Plasmalyte <sup>®</sup> < 60kg 1500ml Plasmalyte <sup>®</sup>		Hemaccel <sup>®</sup> (polygeline) Hemaccel <sup>®</sup> +1000ml Plasmalyte <sup>®</sup> <60kg -500ml Hemaccel <sup>®</sup>		During CPB: No colloids administered. Post CPB: fluid administration according to normal practices of the anaesthetist	Not reported	Chest tube drainage after 24 h (ml) (mean $\pm$ SE) CRYST 1024 $\pm$ 65 GEL 954 $\pm$ 120 (p=0.35)	Homologous blood transfusion (ml) (mean $\pm$ SE) CRYST 445 $\pm$ 97 GEL 419 $\pm$ 89 (p=0.97)	Serum-urea and creatinine (mmol/l) after 24 h (mean $\pm$ SE) CRYST urea 5.2 $\pm$ 0.3 (pre-CPB: 5.6 $\pm$ 0.2) GEL urea 6.4 $\pm$ 0.4 (pre-CPB: 5.7 $\pm$ 0.3) (p=0.04) CRYST creat 0.09 $\pm$ 0.003 (pre-CPB: 0.09 $\pm$ 0.002) GEL creat 0.09 $\pm$ 0.003 (pre-CPB: 0.09 $\pm$ 0.002) (p=ns)	Not reported	Not reported	Not reported
<b>Jansen 1996<sup>34</sup></b>	20	CABG	Prospective randomized controlled trial	Yes	Lactated Ringer's solution <sup>®</sup>	1500 ml	Gelofusine <sup>®</sup>	1000 ml Gelofusine <sup>®</sup> + 500ml Lactated Ringer's solution <sup>®</sup>	Pre CPB: fluid infusion before CPB consisted of MFG (500ml maximum) and 0.9% NaCl (500ml maximum) During CPB: crystalloid group: No colloids administered. Colloid group: colloids administered. Post CPB + ICU: basic intravenous fluid administration consisted of 0.9% NaCl, MFG 4% and 20% human albumin were infused if COP was less than 15 mm Hg	0%	Blood loss after 18h (litre) CRYST 0.9 $\pm$ 0.3 GEL 0.8 $\pm$ 0.3 (p=ns)	Units donor blood (median (range)) CRYST 2.5 (0-4) GEL 1 (0-3) (P=ns)	Not reported	This study was supported by a grant from B. Braun Melsungen AG and NPBI BV.	CRYST 21.9 $\pm$ 9.5 GEL 18.7 $\pm$ 3.6 (p=ns)	Not reported All but one patient discharged from ICU on first postoperative day

(Continued)

Table 2. (Continued)

Author	Number of included patients	Surgical procedure	Study type	Double blinding	Crystalloid-Priming		Gelatin-Priming		Fluid Administration Protocol	Mortality	Bleeding outcome	Perioperative transfusion requirement	Renal outcome	Commercial support	Ventilation time (h)	ICU length of stay
					Type	Dose	Type	Dose								
<b>Singh 1999<sup>35</sup></b>	40	CABG	Prospective randomized controlled trial	No	Lactated Ringer's solution <sup>®</sup>	1500 ml	Gelofusine <sup>®</sup>	1000 ml	CRYST: RL prime and no infusion of colloids during CPB and for 4 hours after shifting to the ICU GEL: 4% MFG prime GEL 500.3 ± 212.5 (p=0.63)	Not reported	Chest tube drainage after 24h (ml) CRYST 532.3 ± 205.7 GEL 500.3 ± 212.5 (p=0.63)	Not reported	Not reported	Not reported	Not reported	Not reported
<b>Tamayo 2008<sup>36</sup></b>	44	CABG	Prospective randomized controlled trial	Yes	Lactated Ringer's solution <sup>®</sup>	1500 ml	Gelofusine <sup>®</sup>	1000 ml	Intraoperative: not specified Postoperative: standard fluid regimen, not specified Pre CPB: As per requirement: CRYST max 1 L colloids before CPB	0%	Chest tube drainage after 24h (ml) CRYST 946.0 ± 537.9 GEL 995.0 ± 496.6 (p=0.76)	Postoperative need for blood transfusion [n (%)] CRYST 17 (89.5%) GEL 16 (94.1%) (p=0.412)	Serum creatinine (mg/dl) (sample time not reported) CRYST 1.22 ± 0.8 (pre-op: 1.07 ± 0.7) GEL 1.33 ± 0.5 (pre-op: 0.88 ± 0.5) (p=0.520)	Not reported	CRYST 11.9 ± 19.4 GEL 13.7 ± 16.2 (p=0.82)	CRYST 2.10 ± 1.8 days GEL 2.64 ± 2.2 days (p=0.38)

All data are expressed as mean ± standard deviation (SD), unless mentioned otherwise. Geloplasma<sup>®</sup> = 3% modified fluid gelatin (Fresenius Kabi<sup>®</sup>); Gelofusin<sup>®</sup> = Succinylated 4% modified fluid gelatin.  
 ns = not significant; SE = standard error; CPB = cardiopulmonary bypass; MFG = modified fluid gelatin; COP = colloid oncotic pressure.

HES or crystalloid solutions as part of the CPB priming. Furthermore, the review could not reveal relative safety issues for gelatin regarding postoperative kidney function, ventilation times and LOS.

### *Completeness, applicability and quality of evidence*

Methodological heterogeneity lowered the quality of the evidence in several ways. First, only 6 out of 10 included studies unambiguously reported a fluid administration protocol suitable to repeat the study.<sup>27,30–33,35</sup> As it remains unclear which type of fluid was given at which time during the study protocol of the other 4 studies, distinguishing between the effects of priming and the perioperative fluid regimen in general was not possible.<sup>28,29,34,36</sup> Therefore, we consider the evidence derived from these studies at high risk for bias. Second, outcomes were inconsistently reported, with primary and secondary endpoints being measured at different postoperative time points across the studies. Third, our systematic review suffers from a lack of uniform outcome definitions used in the included trials. For example, postoperative impairment of renal function was never assessed using modern classification systems for acute kidney injury and the reported laboratory parameters of kidney function varied widely. This made a meta-analysis impossible. Fourth, due to the low number of available studies, it is impossible to assess the comparative safety of different types of gelatins. As an example, Haemacell® (studied in one trial by Scott et al.)<sup>33</sup> contains – in contrast to Gelofusine® (as studied in the trials by Jansen, Singh, Tamayo and colleagues)<sup>34–36</sup> – calcium and might, thus, have a different effect on coagulation, the primary outcome of this meta-analysis. Unfortunately, exclusion of Scott's data will render this meta-analysis almost impossible. Further, given the paucity of available clinical trials, we were unable to assess dose-dependency of adverse effects and to evaluate safety in patient populations with low vs. high perioperative risk for bleeding or renal dysfunction. Fifth, due to a presumably low event rate, other relevant safety issues, such as anaphylactic reactions, were not reported in 8 out of 10 included trials.<sup>27,28,30,31,33–36</sup> No anaphylactic reactions occurred during the course of two of the included trials.<sup>29,32</sup> Sixth, due to the lack of reported data, we were unable to assess in-hospital mortality and long-term outcome or to evaluate long-term safety profile.

Failure to adequately describe the randomization methods and allocation concealment further downgraded the level of evidence of this review, as did the lack of double blinding in 5 out of 10 studies.<sup>27,29,31,32,35</sup> To avoid the occurrence of poor methodological reporting in future studies, we advocate the adherence to guidelines for performing randomized, controlled trials, such as the CONSORT 2010 guidelines (Consolidated

standards of reporting trials).<sup>37</sup> We believe that the systematic use of guidelines when performing randomized, controlled trials can lead to more robust evidence in subsequent systematic reviews.

### *Potential biases in the review process*

The review protocol was slightly changed, which might be considered as a possible source of bias. Nevertheless, we consider the methodological quality of this study high as we adhered closely to the Cochrane and PRISMA guidelines for performing systematic reviews and meta-analyses.<sup>18,38</sup>

### *Literature review*

*In vitro* findings suggest that gelatin colloid solutions interfere less with coagulation than HES solutions. When testing the effect of profound haemodilution with different colloid solutions on the coagulation profile measured by thromboelastography, a significant increase in clot formation time was seen in preparations treated with 6% HES, as well as a significant decrease in clot formation rate and maximum amplitude.<sup>39</sup> By contrast, these coagulation parameters were not affected by gelatin 4%.

These findings were, however, contradicted by other investigators who were unable to demonstrate significant differences for the effects of HES and gelatin on routine coagulation tests and/or thromboelastography in cardiac surgery.<sup>32,40,41</sup> Clinical evidence is also in line with the latter observations. A recent meta-analysis could not demonstrate any safety issue comparing tetrastarches with other colloidal or crystalloid solutions with respect to blood loss, transfusion requirements or hospital LOS in cardiac surgery patients.<sup>10</sup> This meta-analysis however, was not designed to assess gelatin safety compared to crystalloids nor did it specifically address CPB priming.

When analyzing clinical studies specifically addressing the use of gelatins as priming constituents, we also found gelatin not to be superior to the latest-generation HES solutions.

Of note, our findings are, at first sight, inconsistent with the findings of an observational cohort study comparing HES 130/0.4, gelatin 4% and crystalloids for perioperative fluid resuscitation in 6478 consecutive cardiac surgical patients in which the transfusion of PRBC did not differ within the groups, while significantly more patients in the HES-group received FFP and PLT.<sup>42</sup> Even more concerning, this study demonstrated an increased risk for RRT when using synthetic colloids compared to crystalloids (odds ratio, 2.29; 95% CI, 1.47–3.60,  $p < 0.001$  for HES and odds ratio, 2.75; 95% CI, 1.84–4.16,  $p < 0.001$  for gelatin) and a higher in-hospital mortality in patients treated with gelatin (odds ratio 1.72, 95% CI, [1.15, 2.58],  $p = 0.008$ ).<sup>42</sup> However, this study was not randomized and the findings are significantly confounded by the fact that

all patients in this study received CPB priming with HES, irrespective of the group allocation. Moreover, the systematic use of aprotinin was stopped about halfway during the gelatin group episode. To which degree these known confounders and, also, potential unknown confounders (due to the use of a sequential design instead of randomization) might have influenced or biased the observed outcomes cannot readily be estimated.

Comparing gelatin with crystalloid priming, the present meta-analysis could not identify any clinically significant difference indicating that gelatin is less safe than crystalloids.

This confirms the results of a previous meta-analysis which analyzed the effects of different colloidal pump-priming solutions for CPB.<sup>43</sup> When aggregating data from nine studies comparing HES, gelatin and albumin versus crystalloids, postoperative bleeding did not differ significantly ( $n=663$ ; SMD:  $-0.03$ , 95% CI:  $-0.18$  to  $0.12$ ;  $p=0.69$ ). In this study, unfortunately, a pooling of the results of secondary outcomes, including length of hospital stay, clinical scores and acid-base status, was not performed due to insufficient data. Comparably, a recent meta-analysis was also unable to detect any safety issue for the perioperative use of tetrastarches in cardiac surgery when compared to crystalloids.<sup>10</sup>

Globally, these findings suggest that gelatins and modern-generation starches have a safety profile comparable to that of crystalloids.

## Conclusion

This systematic review and meta-analysis evaluated the safety profile of gelatin-priming solutions in elective cardiac surgery. Gelatins were found to be non-inferior to modern generation tetrastarches as no significant differences could be found in postoperative blood loss or any other clinically relevant outcome. Likewise, the present study was unable to find any differences in the safety profile of gelatins compared to different crystalloid solutions. Thus, at the moment, it remains largely unclear whether or not the choice for a specific priming strategy is able to relevantly affect outcomes.

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## Contributions of authors

IG: Study design, literature search and synthesis, data extraction and first draft of the manuscript.

DH: study design and critical review of the manuscript.

SR: study design, literature search, data extraction and critical review of the manuscript.

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