6% Hydroxyethyl starch (130/0.4) vs Ringer’s lactate preloading before spinal anaesthesia for Caesarean delivery: the randomized, double-blind, multicentre CAESAR trial‡


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Editor’s key points

- Defining optimal fluid management techniques to prevent maternal hypotension is important in Caesarean section.
- This multicentre trial assessed the efficacy and safety of fluid preloading with hydroxyethyl starch (HES).
- HES with Ringer’s lactate (RL) preloading was superior to RL alone in preventing hypotension.
- For future studies, one-sided hypothesis testing should be avoided, particularly when inconsistently applied to related outcomes.

Background. Vasopressor administration is recommended to prevent hypotension during spinal anaesthesia (SA) for elective Caesarean delivery. We aimed to test the superior efficacy and ensure safety of a hydroxyethyl starch (HES) vs a Ringer’s lactate (RL) preloading, when combined with a phenylephrine-based prophylaxis.

Methods. A total of 167 healthy parturients undergoing elective Caesarean delivery under SA were included in this multicentre, randomized, double-blind study. Patients received 500 ml of 6% HES (130/0.4)+500 ml of RL (HES group) or 1000 ml of RL (RL group) i.v. before SA. After SA, i.v. phenylephrine boluses were titrated when systolic arterial pressure (SAP) was below 95% of baseline. The primary outcome was the incidence of maternal hypotension (SAP <80% of baseline).

Results. The incidence of both hypotension and symptomatic hypotension (i.e. with dizziness, nausea/vomiting, or both) was significantly lower in the HES group vs the RL group: 36.6% vs 55.3% (one-sided P = 0.025) and 3.7% vs 14.1%. There was no significant difference in total phenylephrine requirements [median (range): 350 (50–1800) vs 350 (50–1250) μg]. The decrease in maternal haemoglobin value the day after surgery was similar in the two groups [1.2 (1.0) vs 1.0 (0.9) g dl⁻¹]. There was no detectable placental transfer of HES in six umbilical cord blood samples analysed in the HES group. Neonatal outcomes were comparable between the groups.

Conclusions. Compared with a pure RL preloading, a mixed HES–RL preloading significantly improved prevention of both hypotension and symptomatic hypotension based on early phenylephrine bolus administration and did not induce adverse effects.

Clinical trial registration. NCT00694343 (http://clinicaltrials.gov).

Keywords: anaesthesia, spinal; Caesarean section; fluid therapy, hydroxyethyl starch; fluid therapy, preloading; hypotension

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Spinal anaesthesia (SA) is the technique of choice in healthy parturients undergoing elective Caesarean delivery. However, maternal hypotension is very frequent (on average 70%), exposing mother and neonate to adverse effects that may be severe (altered consciousness, Mendelson syndrome, cardiovascular collapse or arrest, and adverse neonatal sequelae). The use of vasopressors, especially phenylephrine, has become the most important strategy to prevent it. Nonetheless, the combination of an i.v. fluid loading with a phenylephrine-based prophylaxis is currently advocated.

Systematic reviews show that colloid preloading is more effective than crystalloid preloading in reducing the incidence of maternal hypotension. Among colloids, clinical studies with hydroxyethyl starches (HES), two of them using a tetra-starch (6% wt/vol. 130/0.4), have confirmed their efficacy in helping to decrease the incidence and severity of hypotension, and/or the ephedrine requirements. However, waiting until hypotension occurs and using ephedrine as first-line vasopressor—a strategy that was implemented in these studies—is no longer recommended. Thus, optimal strategies for preventing post-spinal hypotension need to be elucidated. Although phenylephrine has been shown to be effective in preventing post-spinal hypotension, it is uncertain whether combining colloid preloading with phenylephrine provides additional supplementary value in minimizing the incidence of post-spinal hypotension compared with crystalloid preloading + phenylephrine. In addition, safety information is lacking in this obstetric setting, whereas this is needed to assess the HES risk/benefit ratio.

We designed this randomized double-blind multicentre study (termed the ‘CAESAR’ study) to test the superiority of a 6% HES 130/0.4 + Ringer’s lactate (RL) preloading vs a conventional full RL preloading, when combined with a phenylephrine-based prophylaxis. The primary outcome was the incidence of maternal hypotension. We also assessed clinical and laboratory data to identify maternal and neonatal adverse outcomes which may be associated with the type of fluid preload and phenylephrine bolus injection.

**Methods**

After obtaining Ethics Committee approval (CPP Ile-de-France VII, Kremlin-Bicêtre, France) and written informed consent from all participants, 167 patients with American Society of Anesthesiology physical status I or II, undergoing elective Caesarean delivery using SA, were enrolled between July 2008 and December 2009 in 12 centres in France. Inclusion criteria were age 18 yr or older, weight ≥ 60 kg and ≤ 95 kg, and term singleton pregnancy (≥ 37 weeks’ gestation). We excluded patients with concomitant diseases (such as pregnancy-induced hypertension, diabetes mellitus, cardiovascular or cerebrovascular disease, and history of coagulation disorders), fetal complications, and contraindications to SA or HES administration. Patients in labour and those who had received intravascular fluid before admission to the operating theatre were also excluded. Patients were fasted overnight and given cimetidine or ranitidine with sodium citrate orally on arrival to the operating theatre. Standard monitors included non-invasive arterial pressure (AP) measurement, electrocardiography, and pulse oximetry.

Patients were randomly allocated in a 1:1 ratio to one of the two treatment groups according to computer-generated randomization codes by means of SAS® software, using the method of randomly permuted blocks of four patients each. Over a 15–30 min period before induction of SA, patients received study fluids via an 18 or 16 G i.v. catheter placed in a forearm vein:

- either 500 ml HES 130/0.4 (6%) (Voluven®, Fresenius Kabi, Bad Homburg, Germany) followed by 500 ml RL (Fresenius Kabi) (HES group)
- or 500 ml RL, followed by a second infusion of 500 ml RL = 1000 ml RL (RL group).

Study fluids were provided in indistinguishable 500 ml bottles in both groups with randomization code, as previously pictured. We aimed to use solely 500 ml HES in our HES group, rather than 1000 ml, because of insufficient safety data available (especially on maternal haemostasis, renal function, and placental transfer). Thus, we used in fact a mixed HES–RL regimen (as detailed above in the HES group) to ensure a reliable blinding vs the pure RL infusion regimen.

SA was performed in the sitting position. At the L2–3, L3–4, or L4–5 vertebral interspace, hyperbaric 0.5% bupivacaine 11 mg + sufentanil 3 μg + morphine 100 μg were injected slowly (=30 s) into the intrathecal space in the cephalad direction through a 27 or 25 G pencil-point needle. The upper sensory/sympathetic block level was determined by cold sensation with an alcohol swab along the medioclavicular lines, 10 min after induction of SA. I.V. fluid maintenance was done with RL solution (250 ml h⁻¹) and supplemental quick flushes were allowed only when vasopressor boluses were required (see predefined phenylephrine algorithm below).

The primary outcome variable was the incidence of maternal hypotension, defined as at least one systolic AP (SAP) recording below 80% of baseline from induction of SA until delivery (umbilical cord clamping). Baseline SAP was determined by calculating the mean of three measurements before i.v. cannulation and fluid preloading, in the left lateral tilt supine position. After induction of SA, patients were placed back to the same tilt supine position. AP and maternal heart rate (HR) were measured automatically every minute for the first 10 min and then every 2 min until delivery. Any decrease in SAP of more than 5% of baseline that occurred between induction of SA and delivery was treated with an i.v. bolus of phenylephrine according to the following predefined algorithm:

- SAP ≥ 95% baseline: no treatment;
- SAP between 94% and 80% of baseline: 50 μg (1 ml) of phenylephrine;
- SAP between 79% and 70% of baseline: 100 μg (2 ml);
- SAP < 70% of baseline: 150 μg (3 ml).

Maternal bradycardia (HR < 50 beats min⁻¹) was treated on the clinical discretion of the attending anaesthetist with atropine 0.5–1 mg i.v.
Secondary maternal outcomes recorded from induction of SA to delivery were: time of onset of maternal hypotension, symptomatic hypotension (defined as hypotension plus nausea and/or vomiting and/or dizziness), severe hypotension (SAP<70% of baseline), minimum recorded SAP, cumulative duration of hypotension, minimum HR, bradycardia, atropine use, and cumulative phenylephrine requirements. If required, patients with sustained nausea or vomiting after SA were given ondansetron (4 mg i.v.).

Before Caesarean delivery and on the first postoperative day, we performed a complete physical examination and measured the following laboratory indices: haematology, coagulation parameters, and chemistry, including haemoglobin, platelets, aPTT, INR, creatinine. Until discharge, every maternal or neonatal adverse event that occurred and appeared in the medical and/or nurse chart (data source), regardless of being related or unrelated to the study, was recorded in the Case Report Form (CRF). Similarly, every drug given to the patient was recorded. The investigator also checked this information at his systematic first postoperative morning visit and discharge visit. Apgar scores were recorded at 1 and 5 min after delivery. Umbilical venous (UV) and umbilical arterial (UA) pH were obtained from a double clamped segment of the cord. In addition, at the principal investigator’s (F.J.M.) study site, we measured plasma HES concentrations from venous blood taken from the umbilical cord in 11 patients to assess potential placental transfer. HES in plasma was precipitated using acetone; after removal of the supernatant, HES precipitate was dissolved and hydrolysed into glucose with trifluoroacetic acid; then, after drying and dissolving in buffer solution, the glucose was determined enzymatically with a glucose analyzer. The limit of detection/quantification for HES 130/0.4 was given as 0.05 mg ml⁻¹.

Statistical analysis

The sample size calculation in the study protocol was based on the assumption that the incidence of maternal hypotension would be 35% in the RL group. We estimated that the incidence of hypotension would be 20% less in the HES group compared with the RL group (absolute incidence = 15% vs 35%, respectively). To achieve a power of 80% and an overall type I error of 5% (one-sided), it was planned to enrol 79 patients per treatment group. Owing to the uncertainty regarding the true magnitude of the treatment effect, it was planned to perform one interim analysis after enrolment of 50% of the patients with the option to modify the sample size. At this interim analysis including a total of 79 patients, a trend towards superiority of HES was observed and based on these results, an increase in the sample size to 152 patients per treatment group was planned. As there was still an uncertainty about the magnitude of the treatment effect, a second interim analysis after a total of 152 patients was planned and performed. The second interim analysis revealed that no additional patients needed to be included; 167 patients were finally included in the study due to ongoing enrolments during the completion of the second interim analysis. The two interim analyses were performed by an independent statistician not involved in the conduct of the study nor in the final analysis. Type I error for the multiple analyses was adjusted as required for this adaptive study design.¹⁴ ¹⁵

The incidence of hypotension (primary efficacy criterion) was analysed by a logistic regression with the incidence of hypotension as the dependent and treatment group and medical centre as independent variables (covariates); this test was performed one-sided. The intent-to-treat (ITT) analysis was considered as the primary analysis for the primary outcome and all other parameters (Fig. 1). Data are presented as number, percentage, mean with standard deviation (sd), or median (range) as indicated. Logistic regression, analysis of variance, and Mann-Whitney U-tests were used to compare percentages, means, and medians, respectively, unless otherwise indicated. All these tests were two-sided, except for the primary outcome because the medical question there appeared one-sided (i.e. no question about whether HES preloading could be less efficacious than RL preloading). The time from induction of anaesthesia to onset of hypotension was analysed by means of the Kaplan-Meier estimate followed by the log-rank test. Longitudinal measurements of AP and HR (up to 10 min post-baseline) were analysed by a repeated measures analysis of covariance with the treatment group, the time-point, and their interaction as factors, and the baseline value as a covariate. For the haemoglobin and the creatinine values, P-values for the difference between treatment groups were calculated, based on an analysis of covariance with the treatment group and the centre as factors and the baseline value as a covariate. Statistical analysis was performed using SAS® 9.1.3 software (SAS Institute Inc., Cary, NC, USA). P<0.05 was considered significant.

Results

A total of 167 patients were randomized, 82 to the HES group and 85 to the RL group (ITT patient group). All patients completed the study and received the correct treatment; therefore, the ITT analysis was also the treatment-received (TR) analysis. The per-protocol (PP) patient group comprised 140 patients; the most frequent cause for exclusion from PP analysis was deviation from phenylephrine administration algorithm (Fig. 1). Patient, anaesthetic, and surgical characteristics were comparable between treatment groups (Table 1).

Haemodynamic changes are summarized in Table 2. Only 30 patients (36.6%) in the HES group experienced hypotension in contrast to 47 patients (55.3%) in the RL group; this represents an 18.7% absolute decrease in the incidence of maternal hypotension in the HES group, when compared with the RL group (P=0.025). The unadjusted odds ratio for hypotension was 0.47 [95% confidence interval (CI) (0.25; 0.87)] and the adjusted odds ratio was 0.45 [95% CI (0.23; 0.86)]. The difference was also significant in the PP analysis (P=0.019). There was no study centre effect for both the ITT analysis (P=0.30) and the PP analysis (P=0.14). Time from induction of SA to onset of hypotension is depicted in Figure 2. The graph shows
a significant slower onset rate and lower rate of hypotension in the HES group ($P=0.006$).

Compared with the RL group, the incidence of symptomatic hypotension was 3.5 times lower in the HES group ($P=0.028$). The minimum recorded SAP tended to be higher in the HES group, but this was significant only in the PP analysis. Cumulative duration of hypotension until delivery was similar in the two groups and lasted on average 2 min. Minimum recorded HR, incidence of bradycardia, and atropine use were comparable between the two groups (Table 2). Only one patient

| Table 1 | Patient characteristic, anaesthetic, and obstetric characteristics. Values are presented as mean (SD) or median (range), except for age [mean (range)]. BMI, body mass index; SAP, systolic arterial pressure; HR, heart rate; WG, weeks' gestation; SA, spinal anaesthesia. *One missing baseline HR value in the HES group. †Upper sensory level of anaesthesia to cold sensation 10 min after SA (for medians, $P$-value was calculated using the Mann–Whitney $U$-test) |

<table>
<thead>
<tr>
<th></th>
<th>HES group ($n=82$)</th>
<th>RL group ($n=85$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34 (22–50)</td>
<td>33 (20–44)</td>
<td>0.51</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76 (9)</td>
<td>74 (9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>162 (6)</td>
<td>163 (7)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>28.7 (3.6)</td>
<td>28.1 (3.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Gestational age (WG)</td>
<td>39.0 (0.9)</td>
<td>38.9 (0.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>SAP, baseline (mm Hg)</td>
<td>121 (11)</td>
<td>120 (11)</td>
<td>0.80</td>
</tr>
<tr>
<td>HR, baseline (beats min$^{-1}$)*</td>
<td>82 (15)</td>
<td>86 (13)</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of preloading (min)</td>
<td>23 (12–52)</td>
<td>24 (15–146)</td>
<td>0.18</td>
</tr>
<tr>
<td>End of preloading to induction of anaesthesia (min)</td>
<td>9 (0–34)</td>
<td>9 (0–55)</td>
<td>0.44</td>
</tr>
<tr>
<td>Total fluid input until cord clamping (ml)</td>
<td>1135 (81)</td>
<td>1138 (106)</td>
<td>0.95</td>
</tr>
<tr>
<td>Upper sensory level†</td>
<td>T4 (T2–T7)</td>
<td>T4 (T1–T7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Induction of anaesthesia to cord clamping (min)</td>
<td>21 (11–58)</td>
<td>22 (13–47)</td>
<td>0.97</td>
</tr>
<tr>
<td>Uterine incision to cord clamping (min)</td>
<td>2 (0–12)</td>
<td>1 (0–8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>38 (19–130)</td>
<td>37 (12–79)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
RL group) experienced reactive hypertension (162 mm Hg = 134% of baseline SAP). She had received 1 mg atropine before, due to bradycardia accompanied by a moderate decrease in AP (112 mm Hg = 93% of baseline SAP).

Serial changes in SAP and diastolic AP (DAP) during the first 10 min after induction of SA are presented in Figure 3. There were no statistically significant differences between the two groups. Serial changes in HR during this 10 min time period were also not different between the two groups (not shown).

In one patient in each group, SAP never decreased below 95% of baseline until delivery and thus no phenylephrine was administered according to our predefined vasopressor algorithm. Cumulative phenylephrine requirements until delivery were not statistically different between the two groups [median (range): 350 (50–1800) vs 350 (50–1250) μg; Table 2].

The most frequently reported adverse event was nausea/vomiting with a non-significant higher rate in the RL group (22% vs 12%, P = 0.087). Pruritus occurred only at the day of surgery, the day after, or both and in all cases, it has resolved the second day after surgery; the overall incidence was low and identical in the two groups (7%). Operative haemorrhage occurred in one case in each group (uterine hypotonia in the HES group and bleeding from hysterotomy in the RL group), and one patient (HES group) required a delayed blood transfusion of two pack red blood cells (700 ml) on the second postoperative day (her haemoglobin value had decreased from 119 to 78 dl⁻² between day 0 and day 1). Haemoglobin value variations from baseline (day 0) to first postoperative morning (day 1) are detailed in Table 3: the mean haemoglobin decrease the day after surgery was comparable in the HES and RL groups [1.2 (1.0) vs 1.0 (0.9) g dl⁻², P = 0.10]. Standard coagulation parameters (platelets, aPTT, INR) and plasma creatinine (Table 3) and other laboratory parameters (not shown) were also similar between the groups. Maternal AP and HR on the first postoperative morning and at discharge were similar between the two groups (data not shown).

Neonatal outcomes were not different between the two groups and most often in normal ranges (Table 4). HES concentration was below the limit of detection in each of the 11 umbilical cord blood samples, six of which pertained to the HES group.

**Discussion**

The randomized, double-blind, multicentre CAESAR study demonstrates that a mixed HES–RL-based preload reduces maternal hypertension compared with a pure RL-based

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**Table 2** Haemodynamic variables. All data provided in the table are from induction of spinal anaesthesia to delivery, cumulative during this time period and in ITT population unless otherwise indicated; **Incidence of hypotension (ITT and PP)**, the primary outcome, is provided with one-sided P-values (all other P-values are two-sided). ITT, intention-to-treat population; PP, per-protocol population; SAP, systolic arterial pressure; **SAP < 80% of baseline** + nausea and/or vomiting and/or dizziness; HR, heart rate; **bradycardia, HR < 50 beats min⁻¹**

<table>
<thead>
<tr>
<th></th>
<th>HES group</th>
<th></th>
<th>RL group</th>
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<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>n (%) or mean (SD) or median (range)</td>
<td>n (%) or mean (SD) or median (range)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Incidence of hypotension, ITT*</td>
<td>82 30 (37%)</td>
<td>85 47 (55%)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of hypotension, PP*</td>
<td>68 23 (34%)</td>
<td>72 40 (56%)</td>
<td>0.019</td>
<td></td>
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</tr>
<tr>
<td>Incidence of symptomatic hypotension†</td>
<td>82 3 (4%)</td>
<td>85 12 (14%)</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP &lt; 70% baseline</td>
<td>82 8 (10%)</td>
<td>85 15 (18%)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, minimum recorded ITT (mm Hg)</td>
<td>82 98 (14)</td>
<td>85 94 (14)</td>
<td>0.058</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, minimum recorded PP (mm Hg)</td>
<td>68 99 (14)</td>
<td>72 93 (14)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hypotension (min)</td>
<td>30 2.0 (0–20)</td>
<td>47 2.0 (1–10)</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, minimum recorded (beats min⁻¹)</td>
<td>82 62 (10)</td>
<td>85 61 (10)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of bradycardia‡</td>
<td>82 9 (11%)</td>
<td>85 11 (13%)</td>
<td>0.70</td>
<td></td>
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</tr>
<tr>
<td>Atropine use</td>
<td>82 8 (10%)</td>
<td>85 8 (9%)</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine requirements (μg), ITT</td>
<td>82 350 (50–1800)</td>
<td>85 350 (50–1250)</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine requirements (μg), PP</td>
<td>68 350 (50–1800)</td>
<td>72 400 (50–1250)</td>
<td>0.075</td>
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</tr>
</tbody>
</table>

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![Figure 2](https://example.com/fig2.png)

Fig 2 Kaplan–Meier curves analysing the onset of maternal hypotension after induction of SA in both treatment groups. The graph shows a significant slower onset rate and lower rate of hypotension in the HES group, when compared with the RL group (P = 0.006 by log-rank test).
preload, when combined with phenylephrine i.v. bolus administration initiated as soon as SAP decreases below 95% of baseline. In addition, it provides new maternal and neonatal peripartum safety data unavailable so far showing lack of between-group differences in outcomes. This supports a reassuring use of this third-generation HES in the obstetric setting.

The efficacy of colloid has been reported quite consistently in many studies. The last meta-analysis of the Cochrane group confirmed that colloids were more effective than crystalloids to decrease the incidence of maternal hypotension (RR 0.68, 95% CI 0.52–0.89; 11 trials, 698 women).\(^1\) However, these studies are no longer relevant to current recommended practice. First, older trials used dextrans or gelatin as colloidal solutions, whereas HES is preferred nowadays because of much lower allergic risk.\(^16\) Secondly, only two studies used a third-generation HES, that is, an iso-oncotic low molecular weight tetrastarch (6% HES 130/0.4);\(^11\)\(^12\) all other HES studies used older starches that may produce greater side-effects such as renal, coagulation, or both impairments.\(^17\) Thirdly, ephedrine was the vasopressor most commonly used, whereas phenylephrine is now well established as the first-line vasopressor treatment.\(^4\)–8 Fourthly, the vasopressor was usually administered only when maternal hypotension occurred, whereas vasopressor prophylaxis is now recommended.\(^4\)–8\(^18\)\(^19\) Fifthly, all these previous studies were single-centre trials, often of small size and none was adequately double-blinded.\(^1\) In contrast, this CAESAR trial included 167 parturients in 12 study sites and used indistinguishable 500 ml fluid bottles to ensure reliable blinding. It provides therefore robust data showing better haemodynamic control when tetrastarch preloading is combined with phenylephrine prophylaxis. Our data are consistent with a previous smaller single-site study that showed advantage of gelatin 15 ml kg\(^{-1}\) vs no preload (31% vs 64% of hypotension) when used in combination with prophylactic metaraminol (a vasopressor no longer available in most countries, which has vasoconstrictive properties close to phenylephrine).\(^20\)
As shown by the Kaplan–Meier analysis in Figure 2, the use of HES slowed down the onset and decreased the rate of maternal hypotension, thus allowing more patients to remain with an SAP above 80% of baseline. However, most of these patients in the HES group still needed phenylephrine prophylaxis (50 μg boluses), according to our phenylephrine administration algorithm. It appears that they finally received a cumulative phenylephrine dose that was not significantly lower than the one used in the RL group, in which patients received more often right away a 100 μg bolus because of hypotension (instead of repeated boluses of 50 μg only in the HES group).

In addition to this potential role of the bolus technique itself, the lack of significant difference in phenylephrine requirements between the two groups may also have been favoured by a delayed administration of the vasopressor until SAP had decreased below 95% of baseline. Of note, in our groups, the median ITT phenylephrine requirements were quite low (350 μg in each), whereas total mean or median doses are ranging from 800 to 2300 μg in phenylephrine infusion studies. A recent study confirms that patients receiving a prophylactic phenylephrine infusion ultimately receive a higher total dose than when prophylactic phenylephrine is provided by boluses. Both this delayed and bolus phenylephrine technique we used could have contributed to markedly decrease vasopressor requirements and therefore to mask potential differences between the two groups. Nonetheless, in the PP analysis, they tended to be slightly higher in the RL group than in the HES group (400 vs 350 μg; P=0.075).

HES vs crystalloid preloading studies in previous obstetric literature focused on efficacy and provided little information, if any, on maternal and/or neonatal side-effects/safety. According to the Cochrane meta-analysis, only four studies reported maternal side-effects (nausea or vomiting, or both) with no differences detected among 200 women overall. Other maternal side-effects such as pruritus, perioperative bleeding, and biological abnormalities were never systematically investigated. This is particularly of concern because HES preloading is routinely used in several institutions of many countries and positive or negative safety data reported in non-obstetric setting may not be valid in parturients undergoing Caesarean deliveries. Indeed, pregnancy is associated with considerable physiological changes, especially with regard to haemostasis and renal function, that might increase or decrease parturients’ sensitivity to HES vs crystalloid side-effects. In addition, higher HES/crystalloid volumes often used in non-obstetric perioperative setting or prolonged administration used in intensive care medicine patients might produce side-effects different from those that could occur during Caesarean delivery.

In our study, the incidence of nausea/vomiting was nearly halved in the HES group, but the trial was not powered for this secondary outcome parameter. The incidence of pruritus was low in both groups (7%) and was solely related to the administration of intrathecal morphine (all cases of pruritus had resolved the second day after surgery). Our results also indicated that the use of HES was not associated with any increased propensity to bleeding and standard coagulation parameters were unaltered; this lack of clinically significant bleeding is likely due to the very mild coagulation impairment produced by 500 ml 6% HES (130/0.4) preloading, only detectable by thromboelastography. There was no postoperative renal dysfunction in any patient, and no differences between the two groups regarding plasma creatinine variation from day 0 to day 1. This is also in accordance with recent studies showing the safety of this third-generation HES on renal function, particularly when used in an acute trauma setting with hypovolaemic risk.

As expected for these healthy young women with healthy fetuses, neonatal outcome values were most often within normal ranges and similar in the two groups. However, the present study provides new and important information: HES was not detectable in each of the six UV blood samples analysed in the HES group. In 12 non-pregnant volunteers, the maximal concentration peaked at 3.7 mg ml⁻¹ after infusion of 500 ml of the same HES product. With a 0.05 mg ml⁻¹ HES plasma limit of detection, the present study thus suggests that placental transfer of HES is insignificant (3.7:0.05, i.e. ~1% or less). To our knowledge, this information had been reported in sheep only (no placental transfer detectable too) and it is well known today that placental transfer is far different in this animal model for catecholamines at least. Thus, crystalloid coloading could appear as a better control group to document the efficacy of HES preloading, but this could not be done in a double-blind study obviously. We felt that establishing blinded safety data with HES was a priority.

We acknowledge some limitations of the present study. First, we accept that crystalloid preloading may have been a non-ideal control group. Crystalloid preloading is presumed to be less effective than crystalloid co-loading. Thus, crystalloid coloading could appear as a better control group to document the efficacy of HES preloading, but this could not be done in a double-blind study obviously. We felt that establishing blinded safety data with HES was a priority.

Another potential limitation of this study is the 500 ml HES volume chosen, with a moderate beneficial efficacy as a result. Indeed, although it produced a significant 18.7% absolute reduction in the incidence of maternal hypotension, the residual 36.6% incidence observed in the HES group remains high and actually higher than expected in the sample size calculation. This may have been favoured by the relatively low bolus dose (50 μg) we selected for the first threshold of administration in our pre-defined prophylactic phenylephrine algorithm. It could be also related to the ‘delayed prophylactic’ phenylephrine algorithm we designed, as the first vasopressor bolus was given only when SAP had started to decrease below 95% of baseline at least. In addition, the 18.7% decrease in the incidence of hypotension obtained is slightly lower than the effect size powered for in the study (i.e. 20%). This suggests that the decrease in the incidence of hypotension provided by a 500 ml HES preloading is slightly lower when given in combination with prophylactic boluses of phenylephrine (rather than when given alone), which in retrospect is not surprising. Indeed, one important novelty of this study was to assess whether the use of starch preloading still conferred a beneficial effect on AP control, when combined with vasopressor prophylaxis, and determine the magnitude of this potential beneficial effect. Ueyama and colleagues reported that increasing HES preload from 500 to 1000 ml dramatically improved its efficacy without vasopressor prophylaxis. The very reassuring safety
data provided in our study with 500 ml HES suggest that increasing the volume up to 750—or 1000 ml—of HES could be also a safe option; the expected better efficacy of this increased HES volume combined with phenylephrine prophylaxis would therefore deserve further investigation. Supplemental options for optimal haemodynamic control could be the combination of HES preloading with crystalloid coloading, more and/or earlier use of prophylactic phenylephrine boluses as discussed above and/or phenylephrine infusion.21 31

A third limitation of this study is that maternal cardiac output was not assessed, whereas this can be done now non-invasively, notably with Doppler flow technique.33 However, the increase in maternal cardiac output produced by HES preloading is well documented in previous studies,3 6 10 32 33 and it was not possible practically to implement this non-routine assessment in the 12 centres participating in our trial. This supplemental beneficial effect of HES preloading on cardiac output would be likely useful to counteract the well-documented decrease in cardiac output induced by phenylephrine administration.6 8 34 35

Finally, with hind-sight, we also acknowledge we would have better designed our study without any one-sided analysis. As the one-sided P-value we found is 0.0249, if a two-sided test would have been used in the statistical planning (which retrospectively cannot be done), it would still have been significant however (i.e. 0.0249 × 2 and therefore still < 0.05).

In conclusion, this large multicentre, randomized, double-blind study has demonstrated that a mixed 500 ml HES (130/0.4) + 500 ml RL preload significantly improved the prevention of maternal hypotension primarily based on prophylactic phenylephrine i.v. boluses during SA for elective Cesarean delivery, when compared with a pure 1000 ml RL preload. In addition, maternal and neonatal adverse events assessed systematically were not increased. Therefore, anaesthetists who are willing to use a third-generation HES preload to help prevent spinal hypotension during elective Cesarean deliveries can be today more confident in the efficacy of this convenient practice and reassured by the good safety and tolerability data observed in this study.

Authors’ contributions

F.J.M.: study concept and design, coordinating investigator for the 12 centres of the study, final data analysis and data interpretation (initial data analyses were performed by two independent statisticians, as indicated in the Statistical analysis section), enrolment of patients and data acquisition plus data verification at its own centre, initial drafting and subsequent revisions of the manuscript, and corresponding author. Each of the other 12 authors: final validation of the study design before the start of the study, principal investigator at its own centre, enrolment of patients and data acquisition plus data verification at its own site, critical review of the manuscript for important intellectual content before submission. CAESAR working group: one or two co-investigators from each centre. Contribution: assistant(s) of the principal investigator of each centre, enrolment of patients, and data acquisition at each centre.

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Declaration of interest

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