Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study


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Background Although orthotopic liver transplantation (OLT) is nowadays considered standard practice at experienced centres, it can still be affected by a significant risk of massive bleeding and its related complications. Solvent/detergent plasma (S/D Plasma) has been proposed as an alternative to fresh frozen plasma (FFP) to curtail such complications. This study aimed at evaluating the efficacy of S/D Plasma in OLT patients by comparing it to FFP.

Materials and Methods Sixty-three OLT patients were randomized into two groups depending on whether they were transfused with FFP or S/D plasma. A thromboelastography-based protocol aimed at achieving and maintaining predetermined coagulation goals was used to guide plasma transfusions. At the beginning and the end of surgery, standard laboratory coagulation tests were performed together with the assessment of the VII, VIII, V, XII factors and S protein blood levels.

Results The two study groups equally achieved the thromboelastography goals but with a reduced amount of transfusions in the S/D plasma group ($P < 0.0001$). At the end of surgery, factors V and XII and S protein blood levels were lower in the S/D plasma patients who also showed lower INR, aPTT and antithrombin III levels.

Conclusion In cirrhotic patients undergoing OLT, the use of S/D plasma associated with thromboelastography allows the same clinical results but with a significant reduction in the amount of plasma transfusions.

Key words: blood transfusion, liver transplantation, thromboelastography
Recently, the use of fresh frozen plasma (FFP) underwent a critical revision in OLT patients since evidence is available that plasma transfusions can make worse the clinical course and that its use may be associated with an increase in respiratory and infectious complications with a trend towards higher mortality [4, 10, 11]. In particular, transfusion-related acute lung injury can be very frequent (up to 29%) in cirrhotic patients undergoing surgery [12]. Moreover, FFP is widely administered to surgical and critically ill patients even if clinical evidence for its use is poor [13, 14]. It is therefore advisable to reduce its administration. To this end, some interest was directed towards solvent/detergent-treated plasma (S/D Plasma). This is a pharmaceutical product derived from pools of multiple donors undergoing a manufacturing process validated according to industrial specifications and tight quality controls. Its characteristics are a) inactivation of transfusion-transmitted pathogens, b) removal of cells and their fragmentation achieved by a double filtration and c) standardization of the content of coagulation factors and inhibitors [15, 16]. It has been reported that the solvent/detergent treatment does not reduce the haemostatic efficacy of plasma, and some evidence in medical and surgical patients confirms that its safety and efficacy are the same as those in the FFP from the blood bank [16–18]. However, nowadays only one randomized clinical trial on S/D plasma was published [18] and currently it makes difficult to set strong recommendations on its clinical use.

The primary endpoint of this study was to study the haemostatic efficacy of S/D plasma in cirrhotic patients undergoing OLT by comparing it to FFP. The second endpoint was to investigate the clinical differences between the two types of plasma.

**Materials and methods**

All patients who underwent OLT at our Centre during 15 consecutive months were enrolled. The only inclusion criterion was the need for a minimum of two units of human plasma. The administration of fibrinogen concentrate and/or recombinant factor VII activated during the surgical procedure excluded patients from the enrolment. The study was approved by our local ethical committee (n°3733).

Patients were prospectively randomized to receive either FFP or S/D plasma. FFP was obtained by apheresis at our hospital’s Blood Bank; it was packed in 550 ml bags and then frozen to −30°C within 6 h from harvest. The S/D plasma used in this study (PlasmaSafe®, Kedrion SpA, Barga, Italy) comes in 200 ml bags and derives from an industrial process involving two filtration phases (1 μ and 0.22 μ) that decrease concentrations of alpha-1 antitrypsin, alpha-2 antiplsmin and Protein S. S/D plasma manufacturing procedures also result in less (20–30%) factor VIII activity and a reduction (up to the 20%) in that of most of the other coagulation factors due to dilution, thawing and freezing [19, 20].

In all the studied patients, the anaesthetic technique and cardiovascular monitoring were the same according to the standard protocol at our Centre, and a veno-venous extracorporeal circulation was always used during the anhepatic phase, when the vascular anastomoses between the donor and the liver graft are performed [21].

The transfusion of plasma was decided by the attending anaesthesiologists according to the standard protocol at our Centre where thromboelastography is used to correct coagulopathy by achieving and maintaining predetermined goals (Table 1). For this study, we used the Sonoclot device (Sienco Inc., Morrison, CO, USA) that allows the monitoring of the viscoelastic properties of a sample of blood dynamically evaluating the whole haemostatic process from the start of fibrin formation to the retraction and lysis of the clot [22]. (Appendix)

Thromboelastography tests were performed on arterial blood samples at the following time-points: opening of the abdomen, anhepatic phase, reperfusion of the graft, end of procedure. At the start (Ts) and the end (Te) of surgery, blood samples for standard coagulation tests (INR, aPTT, fibrinogen concentration, ATIII and platelet count) were collected and sent into 3.8% sodium citrate or EDTA, as appropriate, separate tubes to our hospital’s laboratory. At the same time-points, other blood samples were drawn, centrifuged at 3572 g for 10 min at 4°C and then immediately frozen at −80°C. At the end of the study, these samples were used for the determination of coagulation Factors V, VII, VIII, XII (automated coagulation methodology, Instrumentation Laboratory Spa, Milano, Italy) and Protein S (automatic latex immunoassay methodology, Instrumentation Laboratory Spa, Milan, Italy) levels. Then, we evaluated the costs: the S/D plasma is a drug cost, while FFP is a direct cost.

**Statistical analysis**

We employed a systematic random sample. Data are reported as mean ± SD, only parameter without normal distribution is reported as median ± SD. The Shapiro–Wilk
test was used to check the normality of data distribution, and a statistical power analysis (ex post) was performed. The 1-β value was >0.8 indicating a low risk of type II error (The statistical software for power analysis was R.2.6.1).

Data analysis was performed using the SPSS software (version 17.0, SPSS Inc, Chicago, IL, USA), and the t-test, Mann–Whitney U-test, chi-square test and the two-way repeated measures ANOVA were performed as appropriate; P-values were determined with 95% confidence intervals, and the significance was set at p ≤ 0.05. Blinding of the statistician was assured by random assignment of Greek letters to the variables.

Results

During the study period, 166 OLTs in 161 patients were performed; 63 of them met the inclusion criteria and were enrolled: 30 patients received S/D plasma and 33 FFP. Two patients were excluded from the study because they received recombinant factor VII activated during the procedure.

The two study groups were homogeneous with respect to age (50–1 years ± 9.3 for S/D plasma vs. 52–1 years ± 6.9 for FFP), sex (21 men and 9 women for S/D plasma vs. 22 and 11 for FFP), type (23 cases of postviral cirrhosis and 7 of cirrhosis from other aetiologies in the S/D plasma vs. 27 and 6, respectively, in the FFP group) and severity of liver disease as measured by the Model for End–Stage Liver Disease (MELD) [23] score (13–9 ± 9.2 for S/D plasma vs. 15–7 ± 6.7 for FFP).

The amount of the intravenous fluids and blood components given during the study is reported in Table 2. The only significant difference between the two groups was the amount of plasma transfusions: 2617 ± 1297 ml in the FFP group vs. 1187 ± 560.6 ml in the S/D plasma group (P < 0.0001).

Table 2 Transfusions chart

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>S/D FFP</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC (units)</td>
<td>4.9 ± 4.4</td>
<td>4.8 ± 3.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Transfused patients (%)</td>
<td>87.9</td>
<td>93.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Plasma (FFP or S/D P, ml)</td>
<td>2617 ± 1297</td>
<td>1187 ± 560.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of plasma units</td>
<td>4 ± 5.2</td>
<td>7.5 ± 3.3</td>
<td>0.0784</td>
</tr>
<tr>
<td>Crystalloids (ml)</td>
<td>4667 ± 1461</td>
<td>4750 ± 1143</td>
<td>0.8363</td>
</tr>
<tr>
<td>Colloids (ml)</td>
<td>2045 ± 1371</td>
<td>2283 ± 827.2</td>
<td>0.7408</td>
</tr>
<tr>
<td>PLT (units)</td>
<td>4 U</td>
<td>3 U</td>
<td>0.8</td>
</tr>
<tr>
<td>Transfused patients (%)</td>
<td>12-1</td>
<td>6-6</td>
<td>0.47</td>
</tr>
</tbody>
</table>

PRBC, packed red blood cells; PLT, platelets; FFP, fresh frozen plasma; S/D P, solvent/detergent plasma.

Seven patients in the S/D Plasma group and one in the FFP group (P = 0.04) needed the administration of albumin 20% to keep their serum albumin level ≥ 2 mg/dl. At the end of the procedure, the FFP group showed a mean serum albumin of 2.3 ± 0.3 mg/dl vs. 1.9 ± 0.3 mg/dl in the S/D plasma group (P = 0.0005).

The Sonoclot parameters did not differ through the study indicating that the therapeutic goals were equally achieved in both groups (Table 3). Three cases of hyperfibrinolysis were observed in the FFP group (respectively, at the anhepatic phase, at the reperfusion and at the end of the procedure) and 4 episodes in the S/D plasma group (two at the opening of the abdomen, one at the anhepatic phase and one at the graft’s reperfusion); all of them were successfully treated by the administration of 1 g of tranexamic acid. Intraoperative body temperature, SvO2 and pH did not show any significant difference between the two groups.

As for the coagulation factors blood levels, at Ts they were similar in the two groups except for factor VII that resulted slightly, but significantly, higher in the S/D plasma group (Table 4). At Te, factor V, factor XII and Protein S concentrations were higher in the FFP group, whereas no difference was seen for the concentration of Factors VII and VIII (Table 4). Table 5 depicts the results of the standard coagulation laboratory tests in the two groups. Finally, the two groups did not differ for the need of postoperative mechanical ventilation, the rate of acute kidney injury requiring replacement therapy, the length of ICU stay and the survival at hospital discharge. The costs associated with use of S/D plasma were

Table 3 Sonoclot analysis data

<table>
<thead>
<tr>
<th></th>
<th>Sonoclot parameter</th>
<th>FFP Mean ± SD</th>
<th>S/D FFP Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening of abdomen</td>
<td>SONACT sec</td>
<td>138.6 ± 24.2</td>
<td>155.3 ± 41.1</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>RATE U/min</td>
<td>18.6 ± 5.1</td>
<td>19.7 ± 10.2</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>TIME TO PEAK min</td>
<td>21.3 ± 6.1</td>
<td>35.5 ± 21.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Anhepatic phase</td>
<td>SONACT sec</td>
<td>136.7 ± 37.9</td>
<td>146.5 ± 81.8</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>RATE U/min</td>
<td>22.3 ± 12.0</td>
<td>23.3 ± 15.0</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>TIME TO PEAK min</td>
<td>22.6 ± 7.6</td>
<td>18.6 ± 8.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Reperfusion + 15 min</td>
<td>SONACT sec</td>
<td>166.1 ± 56.7</td>
<td>215.0 ± 142.9</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>RATE U/min</td>
<td>16.8 ± 6.2</td>
<td>17.5 ± 8.1</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>TIME TO PEAK min</td>
<td>20.1 ± 4.8</td>
<td>18.8 ± 9.5</td>
<td>0.4</td>
</tr>
<tr>
<td>End of procedure</td>
<td>SONACT sec</td>
<td>150.5 ± 33.5</td>
<td>174.8 ± 83.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>RATE U/min</td>
<td>17.7 ± 7.5</td>
<td>18.3 ± 7.1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>TIME TO PEAK min</td>
<td>20.2 ± 6.1</td>
<td>19.6 ± 8.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

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Table 4  Haemostasis factors concentrations at the start (Ts) and the end (Te) of the procedure

<table>
<thead>
<tr>
<th>Factor</th>
<th>FFP Ts</th>
<th>S/D P Ts</th>
<th>FFP Te</th>
<th>S/D P Te</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII%</td>
<td>23.9 ± 11.2</td>
<td>30.2 ± 12.7*</td>
<td>31.7 ± 10.9</td>
<td>30.2 ± 9.9</td>
</tr>
<tr>
<td>VIII%</td>
<td>79.9 ± 24.6</td>
<td>90.4 ± 36.2</td>
<td>67.6 ± 26.6</td>
<td>56.8 ± 21.2</td>
</tr>
<tr>
<td>V%</td>
<td>30.1 ± 3.1</td>
<td>31.0 ± 22.5</td>
<td>24.7 ± 8.2</td>
<td>16.39 ± 8.4*</td>
</tr>
<tr>
<td>XII%</td>
<td>45.1 ± 13.8</td>
<td>50.9 ± 18.2</td>
<td>43.7 ± 11.9</td>
<td>37.4 ± 8.5*</td>
</tr>
<tr>
<td>Protein S%</td>
<td>61.7 ± 22.37</td>
<td>66.8 ± 19.1</td>
<td>42.6 ± 13.1</td>
<td>28.9 ± 9.6*</td>
</tr>
</tbody>
</table>

FFP, fresh frozen plasma; S/D P, solvent/detergent plasma.

*P = 0.049 vs. FFP.

**P = 0.001 vs. FFP (Mann–Whitney U-test).

†P = 0.02 vs. FFP.

‡P < 0.0001 vs. FFP.

*Median.

548.1 ± 259.0 € in the S/D plasma group and 842.1 ± 417.5 € in the FFP group (P < 0.001).

Discussion

In the last decade, the efficacy of S/D plasma was compared to that of FFP in both OLT and cardiac surgery patients using the standard laboratory coagulation tests as a reference [18, 24]. Thromboelastography, an established point of care methodology that is nowadays widely used in OLT patients to assess coagulation [7, 8, 25], is an interesting alternative approach to study S/D Plasma effects in this particular class of patients. In this study, we used the Sonoclot analysis that was introduced at our Centre several years ago after a careful standardization [26, 27]: nowadays it is part of our institutional protocol for the management of haemostasis in OLT patients.

Our data show that, in a population of cirrhotic patients undergoing OLT, the use of S/D Plasma guided by the Sonoclot analysis has the same efficacy of FFP with a significant reduction in the amount of the transfused plasma. Moreover, the use of thromboelastography showed that, from a clinical point of view, S/D Plasma and FFP can perform equally despite the finding that in patients receiving S/D plasma, some of the coagulation factors, namely Factors V and XII, at the end of surgery, are in lower levels than in the FFP group. This is due to the methodological differences in exploring haemostasis between the laboratory tests and thromboelastography. In fact, in the laboratory, quantitative analyses of the different actors involved in the haemostatic process are performed on plasma samples after patients’ blood is centrifuged. On the contrary, thromboelastography assesses the clot’s mechanical properties of a whole blood sample and dynamically tests how the different haemostatic factors interact regardless of their concentrations [28]. Furthermore, the process of coagulation, which normally takes place on the surface of activated platelets, is only mimicked in vitro by PT and aPTT [28], whereas thromboelastography is capable of capturing platelet function, unless they are inactivated. Finally, when the clot formation is measured, laboratory coagulation assays use turbidimetry, while thromboelastography relies on the detection of the viscoelastic properties of the sampled blood. Given these methodological differences, it would be unrealistic to suppose that the results of the various tests would yield identical results. Nonetheless, the intra-operative management of coagulation through a thromboelastography-driven protocol may allow S/D plasma to achieve a similar efficacy of FFP even with lower coagulation factors’ final concentrations also due to the standardization of its content.

In our patients, at the end of surgery, the use of S/D led to lower Protein S levels than FFP patients. This finding suggests that S/D plasma might down-regulate the haemostatic balance where it is used. Differently from

Table 5  Laboratory parameters results at the start (Ts) and the end (Te) of the procedure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FFP Ts</th>
<th>S/D FFP Ts</th>
<th>FFP Te</th>
<th>S/D FFP Te</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>1.6 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>1.59 ± 0.37</td>
<td>1.94 ± 0.51</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>48.6 ± 10.3</td>
<td>40.5 ± 12.9</td>
<td>39.5 ± 49.7*</td>
<td>51.6 ± 49.5*</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>190.3 ± 79.9</td>
<td>222.3 ± 106.8</td>
<td>162.3 ± 50.5</td>
<td>133.9 ± 70.8</td>
</tr>
<tr>
<td>ATIII%</td>
<td>40.3 ± 20.5</td>
<td>43.3 ± 16.2</td>
<td>36.7 ± 10.4</td>
<td>29.7 ± 10.4</td>
</tr>
<tr>
<td>PLT</td>
<td>56,360 ± 29,620</td>
<td>64,770 ± 40,690</td>
<td>51,030 ± 32,060</td>
<td>52,070 ± 30,500</td>
</tr>
</tbody>
</table>

*P = 0.007 vs. FFP.

**P = 0.002 vs. FFP (Mann–Whitney U-test).

†P = 0.01 vs. FFP.

*Median.
other studies where an increased incidence of hyperfibrinolysis was reported in OLT patients receiving S/D plasma [20, 29, 30], our data do not show any difference between the two groups with regard to the number of fibrinolytic episodes and the need for antifibrinolytic medications. To this end, it is necessary to highlight that the S/D Plasma used in those previous studies was characterized by the reduction in its α2-antiplasmin levels, whereas PlasmaSafe®, due to a different manufacturing process, shows higher levels of this compound [31, 32]. Finally, the previously reported concerns about the possible reduced concentrations in S/D Plasma [20] of plasmin inhibitor, Protein S and antitrypsin activity have not been subsequently confirmed in clinical studies and critical reviews [20].

Our finding about the chance to achieve through a thromboelastography-aided use of S/D plasma an haemostatic competence comparable to that of FFP but with significantly less amount of transfusions may have a clinical relevance due to the possible reduction in both fluid overload and infectious complications [3–6]. Moreover, the industrial process of pooling plasma units notably dilutes or neutralizes the anti-HLA and anti-HNA antibodies in S/D Plasma leading to a possible reduction in the transfusion-related acute lung injury risk [11, 32]. Finally, we found a remarkable difference between the two groups with regard to their total serum proteins and albumin concentrations. This finding is similar to that already reported for the use of another commercially available product [15] and can be related to the dilution and refining procedures that S/D plasma undergoes during its manufacturing, which reduces the proteins contents in the final product.

Plasma infusion is recommended for patients who are actively bleeding with multiple coagulation factor deficiencies and for the prevention of dilutional coagulopathy in patients with major trauma and/or massive haemorrhage [33, 34]. Its efficacy depends on the indication for which it is prescribed, the dose and the composition of the plasma being administered. However, very little high-quality data from randomized prospective trials addressing the questions of dosing and administrations regimes of plasma therapy is available, and evidence-based indications for this therapy remain limited [13, 35]. From this view, a possible aid to optimize in the clinical practice the administration of plasma comes from the use of point of care testing methods, such as the Sonoclot analysis. In fact, there is good evidence that these techniques can guide transfusion algorithms leading to a reduction in the perioperative needs of blood products with a reduction in the transfusion-related complications.

Our study has some limitations: a not very high numerosity of the sample population (but a power analysis confirmed the chance for a very low statistical error), the impossibility for the Sonoclot device to directly measure plasma fibrinogen concentration and the fact that studied patients were exclusively cirrhotic. However, this homogeneity may also strengthen our results with regard to this particular class of patients.

In summary, our data show that, in cirrhotic patients undergoing OLT, the use of S/D plasma in association with the monitoring of haemostasis by means of thromboelastography allows a significant reduction in the amount of plasma necessary to achieve the same therapeutic goals of FFP. This is of clinical relevance as it can reduce the risks of perioperative plasma transfusions in such a complicated class of patients. More randomized clinical trials are advisable to collect greater evidence about the efficacy and safety of S/D plasma in other patients’ population and in bleeding high-risk patients.

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Appendix

The Sonoclot analyser has a hollow, open-ended disposable plastic probe, mounted on an ultrasonic transducer. The probe vibrates vertically at a frequency of 200 Hz and is immersed in a cuvette containing a 0.4-ml sample of whole blood or plasma that exerts a viscous drag on the probe, mechanically impeding its free vibration. The drag increases as the sample clots and fibrin strands form between the probe and the wall of the cuvette. The increasing impedance to vibration of the probe is detected by the electronic circuits driving the probe and converted to an output signal, on a paper chart recorder, which reflects the viscoelastic properties of the developing clot. The Sonoclot analyzer provides information on the entire haemostasis process both in a qualitative graph, known as the Sonoclot Signature (fig. 1), and as quantitative results [22].

![Fig. 1 Sonoclot signature [35].](image-url)