A Systematic Review of Clinical, Laboratory and Safety Outcomes Associated with Use of Octaplas in Multiple Clinical Indications

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July 15th, 2007

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About this document

This is an unpublished systematic review that was commissioned by Canadian Blood Services (CBS) in 2007 and is owned by CBS. CBS has provided the Canadian Agency for Drugs and Technologies in Health (CADTH) with permission to post this document on the CADTH website. This document is part of a broad range of clinical, economic, and ethical information that CADTH’s Panel of Experts considered when developing a recommendation for the optimal use of solvent/detergent-treated human plasma (S/D plasma). For more information about CADTH’s recommendation and reports on S/D plasma, visit www.cadth.ca.
REPORT IN BRIEF

Title: A Systematic Review of Laboratory, Clinical and Safety Outcomes for use of Octaplas in Multiple Clinical Indications

Date of Publication: July 15, 2007

Target Audience: Canadian Blood Services

Technology: Octaplas is a pooled solvent/detergent-treated, virus inactivated blood product made from fresh frozen plasma (FFP), which Canadian Blood Services may distribute as an alternative product for frozen plasma (FP) or FFP.

Disease/Condition/Population: This systematic review sought to assess findings regarding the effectiveness and safety of Octaplas for all indications identified through the systematic literature search conducted. These primarily included liver diseases/transplantation, thrombotic thrombocytopenic purpura, cardiovascular surgery and coagulation disorders. Findings for each indication are summarized separately in this review.

Technology Description: Octaplas is a solvent/detergent, virus inactivated, fresh frozen plasma product prepared by Octapharma®. The solvent detergent treatment consists of 1% tri-nitro-butyl phosphate (TNBP) and 1% Triton X-100 for 4 hours at 30°C; residual solvent detergent reagents are removed through both oil extraction and reverse-phase chromatography on C18 resin, and plasma is subsequently re-frozen in 200mL aliquots to match specific blood types. This process eliminates the risk of transmitting lipid-enveloped viruses, further increasing the safety of blood product administered to patients.

Issue: To determine if Octaplas is comparable to fresh frozen plasma in terms of laboratory outcomes (changes in post-transfusion coagulation tests), clinical outcomes and safety when used for all clinical indications identified by a comprehensive survey of the literature.

Objectives(s): To assess the evidence from randomized controlled trials and observational studies in regard to the effectiveness and safety of Octaplas in relation to other alternatives including FP/FFP, and other frozen plasma products, and to provide guidance regarding its suitability as an alternative for FP/FFP including a discussion of what further research is needed.

Methods: A systematic electronic literature search of Medline, EMBASE and the Cochrane Register of Controlled Trials was conducted to identify all relevant randomized and observational studies pertaining to evaluation of the effectiveness and safety of Octaplas. Two reviewers independently reviewed all citations and performed data abstraction for all articles retained for inclusion, with disagreements being settled through discussion with a third party. Meta-analysis of findings was not feasible or appropriate based on a large degree of between-study heterogeneity in terms of clinical indications,
study design and outcomes reported, and thus indication-specific summaries of all identified research studies have been compiled.

**Health Services Impact:** Due to the limited data comparing the effectiveness and safety of Octaplas and FFP, the health services impact cannot be determined.

**Conclusions:** The findings from this systematic review suggest that Octaplas is effective in improving coagulation test results in a number of patient groups. However, there are some potentially important differences in laboratory outcomes that were identified in specific studies, which could result in clinically important outcomes that would not be detected in the included studies due to their small size. Overall, considering Octaplas as an alternative FFP/FP in the treatment of bleeding disorders may be reasonable given the poor quality of evidence for both the effectiveness of Octaplas and FFP. In TTP, where there is good evidence to support the effectiveness of FFP, the routine use of Octaplas in cannot be justified based on the included studies. The adverse event rate and safety of Octaplas appears to be similar to FFP.
EXECUTIVE SUMMARY

**Issue:** To determine if Octaplas is comparable to fresh frozen plasma in terms of coagulation factors and safety when used for all clinical indications identified by a comprehensive survey of the literature.

**Objective(s):** To assess the evidence from randomized controlled trials and observational studies in regard to the effectiveness and safety of Octaplas in relation to other alternatives such as FFP and other frozen plasma products, and to provide guidance regarding its suitability as a replacement for FFP and a discussion of what further research is needed.

**Clinical Review of Efficacy/Effectiveness**

**Methods:** A systematic electronic literature search of Medline, EMBASE and the Cochrane Register of Controlled Trials was conducted to identify all relevant randomized and observational studies pertaining to evaluation of the effectiveness and safety of Octaplas. Two reviewers independently reviewed all citations and performed data abstraction for all articles retained for inclusion, with disagreements being settled through discussion with a third party. Meta-analysis of findings was not feasible or appropriate based on a large degree of between-study heterogeneity in terms of clinical indications, study design and outcomes reported, and thus indication-specific summaries of all identified research studies have been compiled.

**Results:** Twelve studies (3 RCTs, 3 controlled observational studies and 6 one-armed studies) were included representing a total of 931 patients. The main indications for treatment were liver disease/transplantation, cardiovascular surgery, thrombotic thrombocytopenic purpura (TTP), congenital coagulation disorders, obstetric/gynaecologic emergencies, and neonatal intensive care. In liver disease/transplantation, 3 studies showed that Octaplas will improve coagulation test results. The one small RCT (n=49) showed no significant differences in laboratory or clinical outcomes in patients treated with Octaplas and FFP. A controlled cohort study reported increased markers of fibrinolysis with Octaplas as compared to FFP, but no difference in bleeding outcomes. In cardiac surgery patients, four studies examined the effectiveness of Octaplas. The one RCT (n=84) showed no differences between patients treated with Octaplas and Uniplas. A controlled cohort study of Octaplas showed similar changes in coagulation testing except for lower total protein S levels in patients treated with Octaplas; there were no differences in clinical outcomes. The only study of Octaplas in TTP reported the use of Octaplas in 7 of 8 patients with thrombotic complications. No data on the effectiveness of Octaplas or the patients without thrombotic events were reported. Two studies of Octaplas in congenital coagulation factor deficiencies reported good increments in coagulation factor levels and good hemostatic control following the administration of Octaplas. A small RCT (n=40) comparing Octaplas and FFP in acquired coagulopathies showed similar corrections in coagulation test results with Octaplas. One study demonstrated improved coagulation test results following the use of Octaplas in neonatal patients and obstetric/gynecology
patients. A final study showed improved coagulation test results in post-surgical ICU patients following the administration of Octaplas.

**Health Services Impact:** Due to the limited data comparing the effectiveness and safety of Octaplas and FFP, the health services impact cannot be determined.

**Conclusions:** The findings from this systematic review suggest that Octaplas is effective in improving coagulation test results in a number of patient groups. However, there are some potentially important differences in laboratory outcomes that were identified in specific studies, which could result in clinically important outcomes that would not be detected in the identified due to their small size. Given the poor quality of evidence for both the effectiveness of Octaplas and FFP, considering Octaplas as an alternative FFP/FP in the treatment of bleeding disorders may be reasonable. In TTP, where there is good evidence to support the effectiveness of FFP, the routine use of Octaplas in cannot be justified based on the included studies. The adverse event rate and safety of Octaplas appears to be similar to FFP.
1. INTRODUCTION:

1.1 Background/setting in Canada:
Despite the improved screening tests for infectious diseases for blood donors developed in recent years, there still remains a theoretical residual risk of transmission of transfusion-related viruses from single blood components. This is mainly from donors in the window period of infection and possibly the emergence of new pathogens. Octaplas is a virus-inactivated form of fresh frozen plasma (FFP) that, as a consequence of its means of preparation, reduces the risk of transfusion-related viral infections, thereby improving safety. Canadian Blood Services, which is the distributor of all blood products for 9 Canadian provinces and 3 territories, is considering a broadening of their product coverage to include Octaplas as an alternative to fresh frozen plasma (FFP) for certain indications. While several publications claim the in-vitro equivalence of Octaplas and FFP in terms of clotting factor activities, the clinical effectiveness of this product in the treatment of various indications is not well understood or researched. Prior to offering this alternative to FP/FFP for distribution to Canadian hospitals, a formal systematic review of the evidence of its therapeutic efficacy and its cost-effectiveness is required.

In Canada, over 200,000 units of FFP are transfused annually (personal communication, Canadian Blood Services). Given an average dose of 4 units per transfusion, this represents over 50,000 doses and represents an estimated cost in excess of $30 million dollars.

1.2 Technology Overview:
1.2.1 Octaplas Method of Preparation
Solvent/detergent virus inactivation of fresh frozen plasma is a technique that has been shown to accomplish efficient inactivation of transfusion-related viruses such as hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Octaplas is a form of solvent/detergent, virus inactivated, fresh frozen plasma prepared by Octapharma® using a solvent detergent treatment of 1% tri-nitro-butyl phosphate (TNBP) and 1% Triton X-100 for 4 hours at 30°C; residual solvent detergent reagents are removed through both oil extraction and reverse-phase chromatography on C18 resin, and plasma is subsequently re-frozen in 200mL aliquots to match specific blood types. Octaplas has been described as being associated with an improved safety profile as compared to standard FFP based on reduced rates of transfusion-associated allergic reactions, transfusion-related acute lung injury and other such outcomes.

1.2.2 Prior In-Vitro Assessments of Stability
A number of studies have been since the early 1990s that primarily sought to perform in-vitro comparisons of Octaplas with standard FFP (or other virus-inactivated products) with regard to variations of coagulation factor content, protein levels, prothrombin time (PT), activated partial thromboplastin time (aPTT), and other relevant coagulation parameters. Doyle et al. compared coagulation factor content in 16 units of Octaplas and 48 units of standard FFP using a series of standard coagulation screening tests, and noted that while all levels fell into reference ranges for all factors, Octaplas was associated with significant reductions in factor V, factor VIII and protein S. Yarranton et al. compared
levels of von Willebrand factor (VWF) antigen, von Willebrand factor-cleaving protease and protein S amongst standard FFP, cryosupernant, Octaplas and methylene blue/light treated plasma; they observed that Octaplas was associated with reduced protein S activity below the regular reference range (all other levels were normal), and indicated that while it may be an effective alternative choice to FFP for use in treatment of thrombotic thrombocytopenic purpura, it may also predispose patients to venous thromboembolism. Beck and Hellsen4 compared the stability of clotting factors, inhibitors and plasma proteins in 12 plasma pools, 12 batches of Octaplas and 12 batches of quarantined FFP, and concluded, despite respective 35% and 76% declines in activity of protein S and plasmin inhibitor, that there were no clinically important reductions of the activity of clotting factors, inhibitors or plasma proteins. Buchta et al5 compared the stability of coagulation factors in 5 units of thawed SDFFP after thawing and warming to 20°C and subsequent re-cooling and storage at 4°C for a duration of six days; they concluded that, following this pattern of storage, SDFFP continued to demonstrate adequate coagulation activity and plasma protein levels to be considered an appropriate alternative for plasma exchange. Other similar studies by Heger et al6, Zeiler et al7 and others have also been performed. However, while there is substantial data regarding the in-vitro stability of Octaplas, there still exists a large degree of uncertainty regarding its effectiveness in the clinical treatment of patients that must be addressed.

2. THE ISSUE:
Thus far, a lack of research on the clinical use Octaplas has left experts divided as to the relative balance of benefits and harms associated with this blood product. To address the issues of both effectiveness and safety, we performed a comprehensive systematic review of all randomized trials and observational studies comparing Octaplas to a relevant active therapy. Given the paucity of literature, one-armed studies were also assessed.

3. OBJECTIVE(S):
The goal of this systematic review was to determine the effectiveness of Octaplas in all identified patient populations with regard to its impact on a variety of bleeding-related and clotting-related outcomes. Safety of this product was established based on data reported in the identified body of literature.

4. CLINICAL REVIEW:
4.1 Methods:
Prior to initiation of the review process, a protocol outlining the approach to be taken for the review in terms of literature search strategy, study identification/selection, data abstraction, quality assessment, data analysis and reporting of findings was compiled by the three primary reviewers (BH, AT, DF). No deviations from this outline were required, and description of relevant methodologies is provided in the following sub-sections of the document. Recommendations of the guidelines from the Quality of Reporting of Meta-analyses (QUOROM) statement8 were followed during the conduct of this review.

4.1.1 Literature search strategy:
A broad, systematic search strategy applied to Medline (1966-June 2007), the Cochrane Register of Controlled Trials (June 2007 edition) and EMBASE (June 2007) was developed to identify randomised controlled trials and observational studies evaluating Octaplas as a mode of therapy. The strategy combined the text terms 'octaplas', 'solvent detergent', 'solvent/detergent', 'SD', 'S/D', 'viro inactivated', 'virus inactivated', 'virus-inactivated', along with the group of 'FFP' and 'frozen plasma' to locate relevant clinical studies; findings were then further refined through application of the Dickersin filter for randomized clinical trials⁹ and the Scottish Intercollegiate Guidelines Network (SIGN) filter for observational studies. An EMBASE-oriented randomized trial filter was also incorporated from SIGN. The bibliographies of all identified studies were also reviewed to identify any additional relevant reports, and expert consultation was also pursued as an additional means to identify any remaining uncovered studies.

4.1.2 Selection Criteria and Method
To be eligible, studies had to be either a randomised/non-randomised comparator controlled trial, a randomised/non-randomised non-comparator controlled trial, a crossover trial, a prospective/retrospective cohort study or a prospective/retrospective before-after study comparing Octaplas to either standard FFP or any other relevant active control. One-armed observational studies assessing effectiveness and safety of Octaplas were also included. Abstracts were excluded from this review. Case reports or case series consisting of a sample size of <5 patients were also excluded. All dosage regimens of Octaplas were considered, and no limitations were placed on clinical indication or subject age. Eligibility was not restricted by language of publication. Studies were required to report on one or more of three outcome subsets of interest, namely (1) laboratory outcome information (including pre-and post-transfusion aPTT, PT, international normalized ratio (INR), coagulation factor levels (factors I-XIII), prothrombin fragment F₁₂, fibrinogen, antithrombin-III, Von Willebrand factor antigen and cleaving protein, D-dimers, thrombin-antithrombin, plasmin-antiplasmin, α₁-antitrypsin, α₂-antiplasmin, plasmin inhibitor, plasminogen, and IgM/IgG anticoagulopin antibodies), (2) clinical outcome information (bleeding outcomes), or (3) safety outcome information (including frequency of relevant events such as death, thrombosis, pulmonary embolism, febrile transfusion reactions, hypotension, hypoxia, transfusion related acute lung injury (TRALI), seroconversions of hepatitis B/hepatitis C/human immunodeficiency virus, parvovirus B19 infections and transfusion-associated circulatory overload (TACO)) within each treatment group.

Three authors (BH, AT, DF) independently reviewed all citations retrieved from the electronic search to identify all potentially relevant trials for this review. Disagreements in choice of studies were settled by consensus amongst the group.

4.1.3 Data Abstraction Strategy
A standardised data abstraction form was developed that included the following categories: authors, source journal, country of study origin, modes of therapy compared, clinical indication, dosage and duration of treatment, FFP product preparation method, number of patients randomly assigned to each treatment group (and number analyzed),
length of follow-up, patient demographics, laboratory outcome information (see 4.1.2 for specific items), clinical outcome information (see 4.1.2 for specific items), and safety outcome information (see 4.1.2 for specific items). Patient demographic data and appropriate baseline data specific to each clinical indication considered were also recorded. Two authors (BH, AT) independently performed data abstraction using this form, with results being compared after completion of document review. Disagreements in abstracted elements were settled through involvement of a third party (DF) if the source of the disagreement could not be clarified and adjusted amongst the two reviewers. If an article claimed that no side effects/adverse events were observed without specifically listing those that were monitored, a 0 was entered for all events of interest in this review.

4.1.4 Strategy for Quality Assessment
Validated scales were used to evaluate the quality of studies included in this review. Quality of randomized controlled trials was assessed through use of the Jadad quality scale\textsuperscript{10}; this scale provides scoring for randomisation (0-2 points), double-blinding (0-2 points) and account for withdrawals (1 point), with scores ranging from 0 to 5, and a score of 3 or more being considered as indicative of a high quality trial. Observational studies were assessed through judgment of five criteria chosen by the authors of this systematic review: (1) proper ascertainment of exposure (yes/no); (2) use of a non-exposed study cohort (yes/no); (3) use of a representative sample (yes/no/somewhat); (4) maximization of group comparability via matching or analysis; (5) choice of an adequate amount of follow-up for the study’s outcome of interest. All quality findings are reported in the results section of this review. Quality assessment of single-arm studies was not performed as their methodological weaknesses are well established (e.g. lack of controls).

4.1.5 Data Analysis & Summaries
Measures of effect were to be calculated for each trial independently, and studies were to be pooled based on clinical and methodologic judgment as to its appropriateness. However, investigation and data abstraction of all studies retained for this review showed that this set of investigations was too heterogeneous in terms of patient populations, outcomes reported, dosages and durations of therapy and so forth, and thus meta-analysis of findings was not feasible. Given this limitation, summary of findings was limited to narrative description of observed results from all included studies. Consequentially, reporting of summary estimates of treatment effectiveness for each indication and formal assessment for the presence of heterogeneity are not part of this systematic review.

4.2 RESULTS:
4.2.1 Quantity of Research Available
The literature search performed for this systematic review identified a total of 142 citations: 83 from Medline, 19 from the Cochrane Register of Controlled Trials, and 40 from EMBASE. Following independent review of this collection of citations and removal of duplicates contained in more than one database, a total of 18 citations were agreed upon as being potentially relevant, and were subsequently retrieved for additional consideration. A set of 9 manuscripts were identified through review of study bibliographies (n=3) and personal communication (n=6) to increase the total of reviewed
manuscripts to 27. Appraisal of these manuscripts and subsequent discussion of their relevance amongst the three primary reviewers left a total of 13 articles that were retained for inclusion in this systematic review, which studied various aspects of effectiveness and/or safety in a total of 931 patients (173 in randomized controlled trials, 758 in observational research that included one safety study involving 343 patients). One included article contained data included in another of the retained manuscripts, meaning that the 13 articles referred to a total of 12 published studies. Figure 1 below details the process of study selection, and also provides details regarding the reasons for exclusion amongst this final collection of candidate articles. Excluded studies included 3 abstracts/letters, 4 studies with a sample size <5, 3 studies that assessed an SDFFP product other than Octaplas, 1 study that provided interim findings from an included study with final results, 1 study containing duplicate information, 1 study with a design/goal not appropriate for inclusion in this review, and 1 study that provided insufficient information.

4.2.2 Trial/Study Characteristics
Pertinent details of the 12 studies included in this review are provided in table 1, including primary author, study design, patient characteristics and documentation of various study characteristics such as inclusion/exclusion criteria, clinical indication, sample sizes enrolled and interventions (and dosages) compared. Identified research was heterogeneous in terms of study designs used, comparator groups chosen, clinical populations studied, outcomes assessed (as well as reporting/classification format of common outcomes across studies) making meta-analysis of findings infeasible in the context of this review. Clinically, Octaplas was compared amongst a number of different indications that included liver disease/transplantation, thrombotic thrombocytopenic purpura (TTP), cardiovascular surgery, thrombotic thrombocytopenic purpura (TTP), coagulation disorders, obstetric/gynaecologic emergencies, and neonatal intensive care. Standard fresh frozen plasma (FFP) served as the control therapy in 5 studies (2 RCTs), while Uniplas served as control in 1 study (RCT), and 6 studies were one-armed. Three studies were randomized controlled trials, and the remaining 9 were observational studies. Dosages of Octaplas varied notably across studies and indications (table 1). Enrolled sample sizes were consistently small, and the majority of studies did not blind treatment. Very few of the included studies reported on bleeding outcomes and correction of INR, PT and aPTT, the review’s primary outcomes of interest, suggesting a gap in the published literature.

4.2.3 Effectiveness: Summary of Findings
4.2.3.1 Liver Transplantation:
A total of 3 studies enrolling a total of 122 patients were identified from our search of the literature. One randomized trial and one observational study compared Octaplas to standard FFP, and the remaining observational study had only one arm and treated participants with Octaplas. In terms of study quality, the randomized trial was graded a Jadad score of 3, indicating high quality, while the two observational studies sufficiently met totals of 3 and 4 quality criteria, respectively (table 2). A description of study-specific findings follows.
Williamson et al\textsuperscript{12} reported findings from a randomized trial that enrolled a total of 49 patients with coagulation factor deficits due to liver disease (24 liver disease (LD), 25 liver transplantation (LT) patients) that were assigned to treatment with either Octaplas (n=25) or standard FFP (n=24). The observed changes in individual coagulation factor levels (including factors II, VII and VIII, protein C and fibrinogen) were not discernibly different for LD or LT patients receiving either FFP or Octaplas. The same was also true for the correction of INR (LD: pre-/post-change (median, IQR) Octaplas 3 (1.5-5.8) to 2.3 (1.5-3.3) versus FFP 2 (1.4-3.1) to 1.8 (1.4-2.4); LT: Octaplas 1.6 (1-3.2) to 1.8 (1-2.6) versus FFP 1.5 (0.9-3.9) to 1.6 (1.3-2.8)). With regard to safety, there were no observed seroconversions for HIV, HBV or HCV in either treatment group, while one participant in the FFP group showed seroconversion for human parvovirus B19. One individual in the FFP group and two receiving Octaplas died from underlying disease within 9 days of treatment, and 11 patients (5 FFP, 6 Octaplas) died prior to post-treatment virologic sampling. One patient in the Octaplas group experienced both nausea and pruritis, one patient in the FFP group underwent re-operation for exploration of bleeding, and two patients in the FFP group experienced low urine output.

De Jonge et al\textsuperscript{26} compared collections of 21 consecutive liver transplants using FFP to 20 consecutive liver transplants performed using Octaplas in the context of a retrospective cohort study. All patients received 10 mls/kg of Octaplas or FFP during the pre-anhepatic phase and then 1 ml for every ml of RBCs or salvaged blood transfused. Hyperfibrinolysis was observed in totals of 6/21 and 15/20 FFP and Octaplas patients, respectively (p=0.005), while intra-operative antiplasmin levels were reported to reach as low as 0.27IU/mL in the Octaplas group versus 0.58 in the standard FFP group. Assessment of standard coagulation variables by the investigators showed no statistically significant differences between treatment groups, with the exceptions of a higher PT in the anhepatic phase (mean\pm SEM 15.1\pm 0.5 seconds for FFP versus 24.0\pm 5.5 seconds for Octaplas), and higher D-dimer levels and fibrinogen degradation product levels in the anhepatic phase and after reperfusion, both in patients receiving Octaplas. Increased fibrinolysis was not associated with increased total blood loss across treatment groups, but those experiencing hyperfibrinolysis in both groups did show an association with increased blood loss. The study concluded that antifibrinolytic drugs should be used during surgeries involving Octaplas.

Chekrizova et al\textsuperscript{27} reported findings from a multi-center study that sought to evaluate both the efficacy and safety of Octaplas use in a mix of patients with varying indications, one of which was a group of 32 patients (15 children, 17 adults) with liver disease. Amongst children, clinical diagnoses included autoimmune hepatitis (n=2), cystic fibrosis (n=2), hepatoblastoma (n=2), liver injury, portal hypertension with bleeding, and leishmaniasis. Three of these individuals underwent liver surgery. A total of 33 transfusions of Octaplas were administered at a mean dose of 38.0\pm 41.5mL/kg. Investigators had complete pre-/post-transfusion data from totals of 22/33 individuals for aPTT, PT and platelets, and from 13/33 for fibrinogen, respectively. Statistically significant reductions of aPTT (61.5\pm 33.0 seconds to 47.8\pm 12.5 seconds) and PT (24.4\pm 10.0 seconds to 19.9\pm 4.2 seconds) were observed, while a non-significant improvement in fibrinogen (1.46\pm 0.75g/L to 1.66\pm 0.59g/L) was also seen. With regard to
safety, two deaths (1 congenital abnormality, one hemorrhagic death) were observed, and no other adverse events were seen. Amongst the group of seventeen adult patients with end stage liver disease either prior to or following liver transplantation, individuals received Octaplas treatment at a mean dose of 10.2±3.4ml/kg. Sources of disease amongst these subjects included alcoholic liver disease (n=4), hepatocellular carcinoma (n=4), cryptogenic cirrhosis (n=3), as well as single cases of autoimmune hepatitis, hepatitis B, hepatitis C, primary biliary cirrhosis, primary sclerosing cholangitis and eosinophilic granulomatous hepatitis. Administration of plasma was performed primarily for treatment of coagulopathy after liver transplant or prior to liver biopsy. Statistically significant reduction of both aPTT (45.1±8.9 seconds to 36.4±7.1 seconds) and PT (23.2±4.9 seconds to 18.6±2.9 seconds) were observed. In regard to safety, there were no deaths or other adverse effects observed in this sub-group.

4.2.3.2 Cardiac Surgery:
A total of four studies enrolling a total of 560 patients were identified from our search of the literature. One randomized trial compared Octaplas with Uniplas\textsuperscript{28}, one observational study compared Octaplas to standard FFP\textsuperscript{25}, one compared Octaplas to both standard FFP and no plasma\textsuperscript{31}, and the final observational study was a report of safety findings in a large group of patients\textsuperscript{30}. A fifth article associated with one of the aforementioned studies\textsuperscript{28} re-visited previously reported findings, and provided additional information on safety in the patients evaluated\textsuperscript{57}. In terms of study quality, the randomized trial was assigned a Jadad score of 2, indicative of low quality, while two observational studies sufficiently met totals of 4 quality criteria, respectively (table 2), and one one-armed study was not quality assessed. A description of study-specific findings follows.

Noddeland et al\textsuperscript{28} carried out an observer-blinded, randomized controlled trial of Octaplas and Uniplas (a universal solvent-detergent frozen plasma product) consisting of 84 adult patients undergoing open-heart surgery. Nineteen patients received Octaplas and 36 received Uniplas (1:2 randomization) either intraoperatively or up to 2 days postoperatively; the 29 patients who did not require plasma were reported separately (non-transfused group). Physicians provided plasma for treatment of coagulation disorders resulting from either blood loss or dilution, or for acute reversal of warfarin treatment. Use of warfarin was typically not stopped prior to surgery, though ASA use was discontinued to the extent possible. Both activated clotting time (ACT) and aPTT were selected as measures used to assess treatment effectiveness of hemostatic activity. The investigators observed that individuals in the non-transfused group were administered significantly less other blood products than all remaining groups; two patients in the Uniplas group and three in the Octaplas group were recipients of large amounts of transfusion (as compared to one from the non-transfused group). With regards to coagulation testing, both ACT and aPTT, specific pre- and post-transfusion values were not reported; however, there were no significant differences observed either pre-operatively, post-operatively, or within 2 days following surgery. Totals of 28/36=77.8%, 13/19=68.4% and 14/29=48.3% amongst the Uniplas, Octaplas and the non-transfused groups received RBCs, while corresponding totals of 8/36=22.2%, 4/19=21.1% and 2/29=6.9% received platelets. In regard to safety data, these findings were reported in a separate manuscript\textsuperscript{57}; the authors indicated that there were no
seroconversions to HBV, HCV, HIV, HTLA, CMV or parvovirus B19 in any treatment group. A total of 26 patients experienced one or more adverse events; in the Octaplas group, 3 patients required re-operation, 2 experienced peri-operative death, 3 experienced surgical bleeding, 2 experienced bradycardia, 1 experienced myocardial infarction, and 1 experienced atrial fibrillation. Patients receiving Uniplas experienced atrial flutter/fibrillation (n=3), surgical bleeding (n=2) and re-operation (n=1), and patients in the control group primarily suffered only atrial flutter/fibrillation (n=6).

In a prospective cohort study, Haubelt et al\textsuperscript{29} provided treatment with either Octaplas or standard FFP to a group of 75 adult patients (n=36 Octaplas, n=31 FFP, 8 late exclusions based on study ineligibility) undergoing open-heart surgery and receiving post-operative care in the ICU. Treatment was assigned to consecutive groups of five patients, and consisted of a total dose of 600mL at an established rate of 30mL/min of either of these two products. Investigators collected and compared between-group differences in terms of changes amongst pre-transfusion and 60-minute post-transfusion median levels of factor VIII, fibrinogen, prothrombin fragment\textsubscript{1+2}, antithrombin, protein C, protein S, free protein S, \textalpha\textsubscript{1}-antitrypsin activity, plasminogen, plasmin inhibitor, d-dimers, and fibrinogen degradation products, as well as both PT and aPTT. Increases in most coagulation factors and fibrinolytic proteins were seen in both groups. However, the increase in the factor VIII levels and the plasmin levels following the administration of FFP and Octaplas, respectively, were not statistically significant and the total protein S levels decreased (but not the free protein S level) in patients receiving Octaplas. Comparable levels of good (14/36=38.9\% SDFFP vs. 13/31=41.9\% FFP), satisfactory (12/36=33.3\% Octaplas vs. 11/31=35.5\% FFP) and unsatisfactory (10/36=27.8\% Octaplas vs. 7/31=22.6\%) reduction of bleeding were also reported between groups, where the level of satisfaction was based on the extent of arrest or reduction of blood loss per 30 minutes from chest tubes within a 6-hour period. Regarding safety, the authors reported that there were no side effects or adverse events observed that were associated with treatment (no other figures were reported), and that a total of 14 deaths (4 Octaplas, 10 FFP) unrelated to treatment occurred between 1-32 days following the study.

Solheim et al\textsuperscript{31} reported findings from a prospective cohort study that assessed both effectiveness and tolerability in a collection of 66 adult patients (n=20 Octaplas, 20 FFP, 26 no plasma) undergoing elective open-heart surgery. The authors reported little relevant data comparing Octaplas and FFP in terms of either laboratory or clinical outcomes of interest (authors indicated only that there were no notable differences in blood loss, postoperative coagulation test results, frequency of post-operative complications, respiratory time, circulatory support or length of hospital stay), and were also generally non-specific when providing a description of differences between those receiving Octaplas versus no plasma; comparable complement activation groups were seen in both groups, and PTs were also similar. No patients in the study were found to acquire HBV, HCV or HIV infections.

Solheim et al\textsuperscript{30} also reported in a separate article an assessment of the viral safety of Octaplas in a collection of 343 adult patients who underwent cardiac surgery with extracorporeal circulation. Patient follow-up was carried out between 6-12 months and
also 2 years following surgery, and blood sampling was performed to estimate the frequency of Hepatitis B surface antigen, and IgG antibodies against HAV, HBV, HCV, HIV, CMV and human parvovirus B19. A total of 194 patients were transfused, with 41 receiving only Octaplas, 100 receiving Octaplas and other blood components, and 53 receiving only traditional blood components; based on observed frequencies of seroconversion, the investigators indicated there were no indications of an association between use of Octaplas only and seroconversion, but noted that there were near-significant findings correlating Parvovirus B19 with use of Octaplas and cellular blood products together.

4.2.3.3 Thrombotic Thrombocytopenic Purpura:
One observational study encompassing 68 patients that assessed use of Octaplas in the treatment of thrombotic thrombocytopenic purpura (TTP) was identified from our search of the literature. This study was a one-armed study of Octaplas. Quality assessment of this study could not be performed. A description of study-specific findings follows.

Yarranton et al. performed a retrospective review of a case series consisting of 68 patients diagnosed with TTP to assess reports of an association between use of Octaplas and occurrence of venous thromboembolism (VTE); Octaplas, standard FFP and cryosupernatant were all acceptable replacement fluids. A total of 7 patients, all female, experienced an event (6 VTE, 2 pulmonary embolism (PE), with one patient >1 event), and detailed case history notes and blood results for these seven individuals were reviewed; details from the other 61 patients were not provided (including whether Octaplas was used as a replacement fluid). All 7 patients had TTP that was non-responsive to FFP or cryosupernatant. All VTEs were found to be associated with use of a central venous catheter. While other common risk factors for VTE/PE were present in multiple patients, 7 of 8 of these observed events occurred in situations where the last plasma product administered was Octaplas. The mean protein S levels (functional and free) were lower in the Octaplas unit tested (0.58 and 0.56) as compared to the FFP units (0.91 and 0.81) and the cryosupernatant units (1.02 and 1.1). The investigators concluded that administration of large volumes of Octaplas in plasma exchange may act as a risk factor in the occurrence of thrombotic events.

4.2.3.5 Coagulation Disorders:
Two studies enrolling a total of 28 patients were identified from our search of the literature that assessed the use of Octaplas in the treatment of coagulation disorders. Both were one-armed studies of Octaplas only, and thus quality assessment was not performed. A description of study-specific findings follows.

Santagostino et al. reported findings from a one-armed, prospective cohort study of Octaplas carried out in a collection of 17 patients with recessively inherited coagulation disorders (1 afibrinogenemia, 4 factor V, 6 combined factor V and factor VIII, one Factor X and 5 Factor XI deficiencies) who required replacement therapy for either a bleeding episode or for a surgical procedure. Dosing of patients was variable (table 1), and reasons for treatment were also heterogeneous and included indications such as laparoscopy/biopsies, carpal tunnel syndrome, cholecystectomy, cyst removal and
Cesarean section, amongst others. The investigators were primarily interested in assessment of pharmacokinetic data of the deficient factors as well as hemostatic efficacy, while also measuring bleeding outcomes and safety data. Investigators indicated that 13/16=81% of all treatment administrations were deemed effective (the remaining 3 were deemed partially effective), where effectiveness was defined based observation of blood less not exceeding the expected amount and no occurrence of a bleeding complication. Regarding safety, a rash was observed in one patient, as well as mild bleeding at the surgical site in three patients, excessive bleeding from drainage in 2 patients and intra-operative bleeding in one patient. No seroconversions to HAV, HBV, HCV or parvovirus B19 were noted.

Inbal et al\textsuperscript{34} reported findings from a prospective cohort study consisting of 11 patients receiving Octaplas who were diagnosed with either hereditary (8 with either a factor VII, factor X or factor XI deficiencies) or acquired coagulation disorders (3 from liver disease), and sought to assess both haemostatic and pharmacokinetic activity, as well as safety. Indications for treatment amongst patients included hip replacement, labour induction, menorrhagia, prostatectomy, right vitrectomy, plasmapheresis, closed kidney biopsy, angiography, orbital tumour biopsy, hemorrhrosis of the left knee and excision of congenital urethral cyst. Treatment with Octaplas resulted in a cessation of joint bleeding in one patient, prevented bleeding both during and after child birth in an individual with factor X deficiency, prevented bleeding in four individuals undergoing surgical procedures, and stopped menorrhagia in one patient. The 8 patients suffering from hereditary coagulopathies were noted to show increases in the levels of their respective deficient factors following Octaplas administration, and 2 patients that had coagulopathies associated with liver disease showed only minor correction of coagulation factor levels despite prevention of bleeding. In regard to safety, 1 patient experienced urticaria following plasma infusion, and another experienced a moderate anaphylactoid reaction following plasmapheresis. No evidence of HAV, HBV, HCV, HIV or CMV was observed.

\textbf{4.2.3.4 Other Indications:}
A total of 3 studies enrolling a total of 149 patients were identified from our search of the literature that assessed the use of Octaplas in the treatment of other conditions not described above. One was a randomized controlled trial comparing Octaplas to standard FFP\textsuperscript{35}, and the remaining two were one-armed studies of Octaplas only\textsuperscript{27,36}. In terms of study quality, the randomized trial was assigned a Jadad score of 2, indicative of low quality, and the two one-armed studies were not assessed. A description of study-specific findings follows.

In a randomized, controlled trial performed by Beck et al\textsuperscript{35} in 2000, Octaplas and standard FFP were compared in a total of 40 patients (17 Octaplas, 23 FFP) diagnosed with either dilutional coagulopathy, liver disease, polytrauma, extracorporeal circulation, or disseminated intravascular coagulation (DIC). Doses of 7ml/kg FFP and 6ml/kg Octaplas were infused over a one hour time period, and the authors assessed a broad range of laboratory measures of interest to this review. Given that 1 of 3 lots of Octaplas used in the study contained activated factor VII, the authors excluded the group of 5
patients receiving treatment from this lot from their statistical analysis, reducing the sample size of the Octaplus group to 12 individuals. The authors reported that differences of markers of anticoagulation in terms of pre-/post-transfusion changes generally differed insignificantly between groups, though changes in both antithrombin (Octaplus: 61.4±29% to 67.0±26% versus FFP: 62.9±29% to 64.0±32.0%) and protein C (Octaplus: 49.3±11% to 57±12% versus FFP: 59.7±25% to 62.4±31%) were significantly higher in those receiving Octaplus. No safety data were reported.

In their earlier mentioned study, Chekrizova et al\textsuperscript{27} also reported findings regarding a cohort of 41 neonates that received Octaplus. Amongst them, 25/41=61% had sepsis, 30/41=73.2% had respiratory distress syndrome, 4/41=9.8% had pulmonary hemorrhage, 7/41=17% had necrotizing enterocolitis, 22/41=53.7% had intraventricular hemorrhage, 12/41=29.3% had disseminated intravascular coagulation, 13/41=31.7% had neonatal anemia, 3/41=7.3% had congenital pneumonia, 2/41=4.9% had herpes simplex encephalitis, and 3/41=7.3% had coagulation factors deficiency. Transfusions were given primarily in this group given their risk of bleeding due to presence of a coagulopathy. Mean pre/post PT (28.7±20.3 seconds to 20.7±14.2 seconds) and pre/post aPTT (68.9±37.4 seconds to 44.0±15.6 seconds) both decreased significantly, though only 40/67 and 43/67 transfusions administered had complete data, respectively. Mean fibrinogen and platelet levels both increased. A total of nine deaths were observed: 2 associated with pulmonary hemorrhage, 3 associated with prematurity and sepsis, 2 associated with perinatal asphyxia, one associated with meningitis and one associated with a congenital echovirus infection. No adverse events were observed that were associated with Octaplus.

Chekrizova et al\textsuperscript{27} also reported details regarding a total of 26 obstetric and 12 gynecologic patients who received Octaplus at a mean dose of 15.3±7.7mL/kg. Obstetric indications consisted of antepartum hemorrhage (n=3), intrapartum hemorrhage (n=2) and postpartum hemorrhage (n=19), while gynecologic indications consisted of ruptured entopic pregnancy (n=4), miscarriage (n=2), fibroid surgery (n=2) or carcinoma surgery (n=4). Investigators had complete pre-/post-transfusion data from totals of 41/57, 42/57 and 41/57 individuals for aPTT, PT and fibrinogen, respectively. Statistically significant reductions of aPTT (50.1±18.4 seconds to 32.7±6.9 seconds) and PT (21.0±5.2 seconds to 15.6±1.9 seconds) were observed, while a significant improvement in fibrinogen (1.55±0.75g/L to 2.74±0.86g/L) was also seen. No adverse events or side effects were observed in this group of patients.

Hellstern et al\textsuperscript{36} reported findings from a prospective, one-armed study that included a set of 30 post-operative, intensive care patients with either intravascular coagulation or coagulopathy associated with blood volume dilution/loss that received a single dose of Octaplus at a mean dose of 5.2±1.1mL/kg, no less than six hours after the last administration of any form of blood product. Primary indications for surgery amongst this group were carcinoma (n=10/30) and vascular disease (n=10/30), with other diagnoses including multiple trauma, (n=2), acute abdomen (n=2), duodenal ulcer (n=1) and osteosynthesis (n=1). Significant improvements in PT (62±18% to 67±17%), fibrinogen (3.1±1.46g/L to 3.45±1.44g/L), antithrombin III (55±16U/dl to 64±18U/dl)
and systolic blood pressure (124±17mm HG to 137±21mm HG) were observed after Octaplas administration, while statistically insignificant changes in aPTT and platelets were seen. In regard to safety, the investigators reported that no side effects were observed in any patient.

5. DISCUSSION:
A total of 12 studies (3 randomized controlled trials, 9 observational studies) that enrolled a total of 931 patients were included in this systematic review. A discussion of clinical, laboratory and safety measures is provided in 5.1 below. We identified 12 clinical studies reporting on the use of Octaplas in a variety of clinical conditions. In 11 of these studies, Octaplas was used to replace coagulation factors in patients with a variety of conditions associated with bleeding or an increased risk of bleeding. The patients included liver disease and liver transplant patients, cardiac surgery patients, acquired coagulopathies, post-surgical ICU patients, neonates, obstetrical and gynecology patients, and patients with congenital coagulation factor deficiencies. In addition, there was one study that evaluated the use of Octaplas in patients with TTP.

Overall, our findings suggest that Octaplas is effective in improving coagulation factor levels. Based on this systematic review, Octaplas may be comparable to FFP in terms of correcting coagulation factor levels, important clinical outcomes and safety; however, given the paucity of rigorous research evaluating the effectiveness of Octaplas as a substitute for fresh frozen plasma firm conclusions are not possible. This lack of evidence is illustrated by both the lack of randomized trials, as well as the overall poor quality of the included studies. Among the 3 RCTs identified, only 1 achieved an acceptable score on the Jadad quality scale and all 9 observational studies had at least one major deficiency as determined by a predetermined set of key methodological quality criteria (Table 2).

5.1 Summary of Results
A total of 10 studies (3 RCTs, 7 observational studies) included in this review reported findings regarding pre- and post-administration levels of coagulation proteins in patients receiving Octaplas. Review of this data suggests that the administration of Octaplas results in improved coagulation test results. Based on the 2 RCTs and 3 observational studies which compared patients receiving Octaplas and FFP, the correction in the INR, aPTT and individuals coagulation factor levels appear similar. Control of bleeding (including re-operation for bleeding or blood loss) was examined in 4 studies. Again, there were no differences in patients receiving Octaplas as compared to FFP.

Two observational studies did note some differences in laboratory test results between patients receiving Octaplas and FFP. The first study reported smaller changes in antiplasmin levels and a second cohort study reported lower total protein S levels in patients receiving Octaplas as compared to FFP. In the first study, there was an associated increase in the markers of hyperfibrinolysis, but no evidence of increased bleeding complications. In the latter case, the free protein S levels were similar and there were no differences in thrombosis rates. However, neither study was adequately powered or designed to detect clinically important differences in clinical outcomes. Important
outcomes have not been adequately studied in the identified studies. With regards to coagulation testing, the proportion of patients in whom there was correction of the PT, aPTT or INR was not reported.

Bleeding outcomes were evaluated in eight studies, but these were often limited evaluations such as bleeding complications, or calculation of blood loss/chest tube drainage. Only four studies evaluated the hemostatic effectiveness of Octaplas or FFP, and these were subjective assessments by treating physicians. None of the included studies used a standardized or validated tool to evaluate bleeding.

The only study of patients with TTP examined the association of Octaplas with thrombotic complications. No data on the clinical effectiveness of Octaplas was presented in this study and no data on the patients who did not have a thrombotic complication were provided. As a result, no conclusions can be reached about either the effectiveness or the potential adverse effects of using Octaplas as a replacement fluid for plasma exchange in patients with TTP.

From the identified studies, there is a gap in current research with regard to these important clinical and laboratory outcomes. While Octaplas and FFP may produce similar results in terms of changes in coagulation factor assays, there are differences in the composition of the products that lead to some differences in laboratory outcomes. Based on the current evidence available, it is not possible to ascertain whether or not these would lead to differences in clinically important outcomes such as bleeding or thrombosis. Further research directly comparing FFP and Octaplas in randomized controlled trials is required to determine if there are any clinically important differences with Octaplas and FFP.

In regard to the issue of patient safety, Octaplas did not appear to be associated with an increased frequency of adverse effects (table 2). Seroconversion to hepatitis B, hepatitis C or HIV appeared similar in patients receiving Octaplas or FFP, with rates being low in both treatment groups. Frequency of death (typically unrelated to treatment) was comparable between these interventions, and frequency of minor side effects including urticaria, pruritus and febrile reactions were also similar. Based on the evidence in the literature thus far, Octaplas appears to be a safe alternative to FFP, though future research aimed at assessing Octaplas versus other comparators to establish effectiveness will also provide important information regarding the aspect of risk and adverse events associated with the administration of Octaplas and FFP.

5.2 Study Limitations
There are limitations associated with this systematic review that were noted during compilation of the evidence pertaining to the effectiveness and safety of Octaplas. First, a large degree of heterogeneity in terms of clinical indications, treatment regimens employed, outcomes reported and approach to outcome reporting made meta-analysis of study-specific findings infeasible. As mentioned above, the quality of the published reports was poor, seriously limiting the strength of the conclusions that can be derived from the included studies. The problem of heterogeneous clinical indications was
additionally compounded by the presence of consistently small sample sizes; the majority of included studies were not specifically targeted at performing formal comparisons of interventions, and were primarily hypothesis generating in nature. Lastly, a viable assessment of publication bias using funnel plots was not performed given that meta-analysis was not feasible in this systematic review, and one cannot rule out the possibility that there exists unpublished studies that may alter the conclusions of this systematic review.

5.3 Generalizability of Findings
The generalizability of the findings in this systematic review is limited by a number of factors. The included studies evaluated Octaplas in patients with a variety of disorders including patients with liver disease, cardiac surgery patients, TTP and congenital bleeding disorders. Most of the studies were small and, as a result, a small number of patients are included for each indication. Additionally important patient groups such as patients on oral anticoagulants and non-surgical critical care patients were not included in any of the studies. Even for the patient groups included in the studies, the lack of RCTs comparing Octaplas and FFP limits the generalizability of any comparisons between Octaplas and FFP. For important indications such as TTP, cardiac surgery and other surgeries, there is no evidence from RCTs comparing Octaplas and FFP. As a result, any generalization of the results from the individual studies and this systematic review must be tempered with caution.

5.4 Health Services Impact
The impact on health services on the use of Octaplas instead of FFP is difficult to assess given the limited evidence available. Based on the included studies, the effectiveness of Octaplas as compared to FFP cannot be adequately assessed to determine if there any differences in clinical effectiveness or adverse events. Further research comparing Octaplas and FFP is required to determine the potential impact of Octaplas on health services.

5.5 Knowledge Gaps
From the included studies, there are important knowledge gaps in the current evidence. As discussed previously, the lack of direct comparison between Octaplas and FFP in RCTs limits the ability to compare the effectiveness of Octaplas and FFP. Important clinical outcomes have also not been adequately addressed including the number of patients who have correction of their coagulation parameters (INR, aPTT, PT) and bleeding outcomes.

6. CONCLUSIONS:
The findings from this systematic review suggest that Octaplas is effective in improving coagulation test results in a number of patient groups. From the limited evidence, the effectiveness of Octaplas and FFP may be similar; however, there are some potentially important differences in laboratory outcomes that were identified in specific studies.
Unfortunately, despite the fact that FFP represents the standard of care for the treatment of most coagulation disorders (with the exception of isolated coagulation factor defects where specific recombinant or plasma derived factor concentrates are available), the quality of evidence supporting the use of FFP in the treatment of coagulation disorders is also poor\textsuperscript{39,40}. Therefore, while there is not sufficient clinical evidence to demonstrate that Octaplas is equivalent to FFP, considering Octaplas as an alternative FFP in the treatment of bleeding disorders may be reasonable given the poor quality of evidence for both. However, in the case of TTP, there is good quality evidence demonstrating the effectiveness of FFP\textsuperscript{41}. Due to a lack of studies evaluating the effectiveness of Octaplas in TTP, the routine use of Octaplas instead of FFP can not be justified from the included studies.

The adverse event rate and safety of Octaplas also appears to be similar to FFP. While no differences in clinical outcomes in patients receiving Octaplas and FFP were identified, the quality of the evidence in this systematic review provides limited ability to assess differences in clinically important outcomes in patients receiving Octaplas as opposed to FFP/FP. Further well designed RCTs are required to determine the effectiveness, adverse reactions and effectiveness of Octaplas as compared to FFP.
Reference List


23. Mortelmans Y, Beck KH, Kretschmer V. [Preliminary results of a prospective randomized clinical study on the comparison of solvent- and detergent-inactivated
plasma (SDP-TNBT/Triton X-100) and untreated fresh-frozen plasma]. [German]. Beitrage zur Infusionstherapie und Transfusionsmedizin.32:419-21, 1994.


APPENDIX A - Search Filters:

Dickersin RCT filter:
RANDOMIZED CONTROLLED TRIAL.pt.
CONTROLLED CLINICAL TRIAL.pt.
RANDOMIZED CONTROLLED TRIALS.sh.
RANDOM ALLOCATION.sh.
DOUBLE BLIND METHOD.sh.
SINGLE-BLIND METHOD.sh.
or/1-6
(ANIMALS not HUMAN).sh.
7 not 8
CLINICAL TRIAL.pt.
exp CLINICAL TRIALS/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
PLACEBOS.sh.
placebo$.ti,ab.
random$.ti,ab.
RESEARCH DESIGN.sh.
or/10-17
18 not 8
19 not 9
COMPARATIVE STUDY.sh.
exp EVALUATION STUDIES/
FOLLOW UP STUDIES.sh.
PROSPECTIVE STUDIES.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28

EMBASE RCT Filter:
Clinical Trial/
Randomized controlled trial/
Randomization/
Single blind procedure/
Double blind procedure/
Crossover procedure/
Placebo/
Randomized controlled trial$.tw.
Rct.tw.
Random allocation.tw.
Randomly allocated.tw.
Allocated randomly.tw.
(allocated adj2 random).tw.
Single blind$.tw.
Double blind$.tw.
Placebo$.tw.
Prospective study/
or/1-17
Case study/
Case report.tw.
Abstract report/ or letter/
or/19-21
18 not 22

**EMBASE Observational Study Filter:**
Clinical study/
Case control study.mp. or Case Control Study/
Family study/
Longitudinal study/
Retrospective study/
Prospective study/
Randomized controlled trials/
39 not 40
Cohort analysis/
(Cohort adj (study or studies)).mp.
(Case control adj (study or studies)).tw.
(follow up adj (study or studies)).tw.
(observational adj (study or studies)).tw.
(epidemiologic$ adj (study or studies)).tw.
(cross sectional adj (study or studies)).tw.
or/34-38,42-48
<table>
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<tr>
<th>Author (year)</th>
<th>Study Design</th>
<th>Indication</th>
<th>Interventions</th>
<th>Inclusion/exclusion criteria</th>
<th>Sample Sizes</th>
<th>Patient characteristics</th>
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<tbody>
<tr>
<td>Williamson (1999)</td>
<td>RCT</td>
<td>Liver disease and liver transplantation</td>
<td>OCTAPLAS, standard FFP; initial dose of 12-15ml/kg, followed by administration based on coagulation results. If fibrinogen went below &lt;1.5mg/ml, cryoprecipitate use was allowed.</td>
<td>Included if FFP clinically indicated for correction of coagulopathy prior to elective invasive procedures; excluded if pregnant/lactating, had antibodies to IgA, D-negative with preexisting anti-D present, IV drug users.</td>
<td>25 OCTAPLAS, 24 FFP</td>
<td>15M/10F; 13LD/12LT; median ages 50 years (range 30-60) amongst LD and 47 patients (range 20-60) amongst LT; median plasma doses 12ml/kg (range 11-15) amongst LD and 44ml/kg (range 25-104) amongst LT</td>
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<td>De Jonge (2002)</td>
<td>Retrospective cohort</td>
<td>Liver transplantation</td>
<td>OCTAPLAS vs. standard FFP</td>
<td>Patients undergoing orthotopic liver transplantation for end-stage cirrhosis</td>
<td>20 OCTAPLAS, 21 FFP</td>
<td>15M/5F; median age 44 (range 23-62); 6 viral hepatitis cirrhosis, 8 cholestatic liver disease, 6 other cirrhosis</td>
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<td>Chokrizevafi (2006)</td>
<td>Prospective cohort (one-armed study)</td>
<td>Child and adult patients with liver disease</td>
<td>OCTAPLAS, mean dose 30-641.5ml/kg in children, mean dose 10.2±3.4ml/kg in adults</td>
<td>None described</td>
<td>32 OCTAPLAS</td>
<td>15 children (6M/9F), 17 adults (13M/4F); age range 12 days-16 years in children and mean age 50.4±15.8 years in adults</td>
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**Cardiovascular Surgery**

<table>
<thead>
<tr>
<th>Author (year)</th>
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<th>Indication</th>
<th>Interventions</th>
<th>Inclusion/exclusion criteria</th>
<th>Sample Sizes</th>
<th>Patient characteristics</th>
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<td>Noddeland (2002)</td>
<td>RCT</td>
<td>Open heart surgery</td>
<td>UNIPLAS vs. OCTAPLAS; patients randomized to treatment if plasma transfusion was indicated during the day of surgery or the 2 following days. A starting dose of 2-3 units of plasma was used, with 2-3 units also used for reversal of warfarin when patients were weaned from extracorporeal circulation</td>
<td>Adult patients scheduled for open heart surgery, excluding those with unstable angina pectoris, hypersensitivity to blood products, exposure to viral hepatitis during the previous 6 years, pregnancy, current participation in another trial or suspected drug abuse</td>
<td>36 Uniplas, 19 OCTAPLAS, 29 non transfused</td>
<td>11M/8F; mean age 67.6±12.5 years; 15/19 NYHA III or IV; 8/19 anticoagulation</td>
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<td>Uniplas-1: 13M/12F; mean age 71±10.1 years; 22/25 NYHA III or IV; 9/25 anticoagulation</td>
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<td>Uniplas-2: 5M/6F; mean age 69.9±5.1 years; 10/11 NYHA III or IV; 3/11 anticoagulation</td>
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<td>Control: 20M/9F; mean age 65.2±10.5 years; 26/29 NYHA III or IV; 2/29 anticoagulation</td>
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<td>Haubelt (2002)</td>
<td>Prospective cohort (consecutive groups)</td>
<td>Open-heart surgery with post-op care in the ICU</td>
<td>OCTAPLAS vs. FFP; a total of 600ml at a rate of 30ml/min was given in the ICU</td>
<td>Adult patients undergoing open-heart surgery and receiving post-op care in the ICU.</td>
<td>36 OCTAPLAS, 31 FFP</td>
<td>20M/16F; median age 69.5 years (range 34-79); median plasma dose 8.5ml/L/kg (range 5.5-14.2)</td>
</tr>
<tr>
<td>Solheim (1993)</td>
<td>Prospective cohort</td>
<td>Elective open heart surgery</td>
<td>OCTAPLAS vs. FFP vs. no plasma; plasma given at either the end of surgery or during post-op care in the ICU</td>
<td>Adult patients undergoing elective open heart surgery, non-allergic to plasma proteins, not pregnant, no uremia requiring dialysis</td>
<td>20 OCTAPLAS, 20 FFP, 26 no plasma</td>
<td>17M/14F; median age 72.0 years (range 55-86); median plasma dose 8.5ml/L/kg (range 5.5-12.2)</td>
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<td>Author (year)</td>
<td>Study Design</td>
<td>Indication</td>
<td>Interventions</td>
<td>Inclusion/exclusion criteria</td>
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<td><strong>Cardiovascular surgery (continued)</strong></td>
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<td>Solheim (2000)</td>
<td>Prospective cohort (one-armed study)</td>
<td>Cardiothoracic surgery</td>
<td>Details of OCTAPLAS dosage not reported; Adult patients undergoing cardiothoracic surgery with extracorporeal circulation</td>
<td>194/343 were transfused with Octaplas and one or more other blood products, and 41/343 received OCTAPLAS only</td>
<td>219M/124F; mean age 64±12 years; 66% mean ejection fraction; 29% previous MI; 21% hypertension; 40% coronary surgery; 36% valvular surgery; 16% combined</td>
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<td><strong>Thrombotic Thrombocytopenic Purpura</strong></td>
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<td>TTP</td>
<td>OCTAPLAS 0.5-1 plasma volume exchange</td>
<td>All patients referred for primary management or a second opinion of acute TTP between May 1997-May 2002</td>
<td>68 OCTAPLAS (7 events of interest reviewed)</td>
<td>25M/43F; mean age 41 years (range 19-70)</td>
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<td><strong>Congenital Coagulation Disorders</strong></td>
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<td>Coagulation disorders</td>
<td>One-arm study; OCTAPLAS dosing varied from 9-21mL/kg, with durations varying from 1-10 days and intervals between administrations varying between patients. Reasons for treatment varied.</td>
<td>Patients with recessively inherited coagulation disorders needing replacement therapy for bleeding episodes or surgical procedures.</td>
<td>17 OCTAPLAS</td>
<td>6M/11F; median age 39 (range 13-65); 8 with severe factor deficiencies (1 fibrinogen, 4 factor V, 6 factor V+factor VIII, 1 factor X, 1 factor XI)</td>
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<td>Santiagoostino (2006)</td>
<td>Prospective cohort (one-arm study)</td>
<td>Acquired coagulation disorders (due to liver disease or hereditary factor VII, X, XI deficiencies)</td>
<td>OCTAPLAS, doses ranged from 6mL/kg to 12mL/kg.</td>
<td>Diagnosis of hereditary or acquired coagulopathy</td>
<td>11 OCTAPLAS</td>
<td>5M/6F; median range 44 years (range 20-75); 9 with prior bleeding manifestations; 3 with no past treatment with FFP or RBCs</td>
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<tr>
<td>Author (year)</td>
<td>Study Design</td>
<td>Indication</td>
<td>Interventions</td>
<td>Inclusion/exclusion criteria</td>
<td>Sample Sizes</td>
<td>Patient characteristics</td>
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<tr>
<td>Chehrizova (2006)</td>
<td>Prospective cohort (one-armed study)</td>
<td>Critically ill neonates</td>
<td>OCTAPLAS, mean dose 18.4±13.2ml/kg</td>
<td>None described</td>
<td>41 OCTAPLAS</td>
<td>22M/19F; mean gestational age 32.1±5.1 weeks; mean birth weight 1811.5±958.2g; 29 premature births</td>
</tr>
<tr>
<td>Chehrizova (2006)</td>
<td>Prospective cohort (one-armed study)</td>
<td>Obstetric/gynecologic patients</td>
<td>OCTAPLAS, mean dose 15.3±7.7ml/kg</td>
<td>None described</td>
<td>38 OCTAPLAS</td>
<td>0M/28F; mean age 34.7±12.9 years; 36 hemorrhage</td>
</tr>
<tr>
<td>Beck (2000)</td>
<td>RCT</td>
<td>Dilutional coagulopathy, liver disease, polytrauma, extracorporeal circulation or disseminated intravascular coagulation</td>
<td>OCTAPLAS, vs. standard FFP; 6ml/kg of OCTAPLAS, 7ml/kg of FFP</td>
<td>None described</td>
<td>23 FFP, 17 OCTAPLAS (only 12 analyzed due to presence of activated factor VII in 1 lot of Octaplas)</td>
<td>Baseline characteristics not reported</td>
</tr>
<tr>
<td>Hellstern (1993)</td>
<td>Prospective cohort (one-armed study)</td>
<td>Post-operative patients with disseminated intravascular coagulation and/or dilution or loss coagulopathy</td>
<td>OCTAPLAS at least 6 hours after the last administration of any blood products, using a mean dose of 5.2±1.1ml/kg</td>
<td>Admitted to ICU for treatment of disseminated intravascular coagulation and/or dilution or loss coagulopathy with plasma or plasma derivatives; conscious.</td>
<td>30 OCTAPLAS</td>
<td>20M/10F; mean age 61±11 years; 10 carcinoma, 10 vascular disease, 2 multiple trauma, 2 acute abdomen, 1 osteosynthesis, 1 duodenal ulcer</td>
</tr>
</tbody>
</table>

Abbreviations: RCT=randomized controlled trial, TTP=thrombotic thrombocytopenic purpura, FFP=fresh frozen plasma, ml=milliliters, kg=kilograms, M=Male, F=female, NYHA=New York Heart Association grading, LD=liver disease, LT=liver transplantation, ICU=intensive care unit
Table 2: Quality assessment of included cohort studies using five predetermined primary criteria to score all cohort studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure Properly Ascertained</th>
<th>Non-exposed cohort</th>
<th>Representative Sample</th>
<th>Comparability maximal by matching or analysis</th>
<th>Follow-up period adequate for outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Jonge (2002)²⁶</td>
<td>Yes</td>
<td>Yes</td>
<td>Somewhat</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chekrižova (2006)²²</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Haubelt (2002)²⁹</td>
<td>Yes</td>
<td>Yes</td>
<td>Somewhat</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Solheim (2000)²⁰</td>
<td>Yes</td>
<td>Yes</td>
<td>Somewhat</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Yarranton (2003)²²</td>
<td>Yes</td>
<td>No</td>
<td>Somewhat</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inbal (1993)²⁴</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Summary of Effectiveness</td>
<td>Summary of Safety</td>
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<tr>
<td><strong>Liver Transplantation/Disease</strong></td>
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<tr>
<td>Williamson (1999)¹²</td>
<td>Comparable correction of clotting factors and INR between FFP and Octaplas in both liver transplant and liver disease patients</td>
<td>No observed seroconversions for HIV, HBV or HCV with either FFP or Octaplas. One seroconversion for human parvovirus B19 in the FFP group. One in the FFP group and two receiving Octaplas died from underlying disease within 9 days of treatment, and 11 patients (5 FFP, 6 Octaplas) died prior to post-treatment virologic sampling. One patient in the Octaplas group experienced both nausea and pruritis, one receiving FFP underwent re-operation for exploration of bleeding, and two receiving FFP experienced low urine output.</td>
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<tr>
<td>De Jonge (2002)²⁶</td>
<td>Fibrinolysis observed in totals of 6/21 and 15/20 FFP and Octaplas patients respectively, while intra-operative antiplasmin levels were reported to reach as low as 0.27IU/mL in the Octaplas group versus 0.58 in the standard FFP group.</td>
<td>None reported</td>
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<tr>
<td>Cheleirizový (2006)²⁷</td>
<td>Statistically significant reductions of aPTT and PT were observed, while a non-significant improvement in fibrinogen was also seen amongst children. Statistically significant reduction of both aPTT and PT were observed in adults.</td>
<td>No deaths or adverse effects reported</td>
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<tr>
<td><strong>Cardiovascular Surgery</strong></td>
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<tr>
<td>Noddeland (2002)²⁸</td>
<td>No significant differences in ACT or aPTT were observed either pre-operatively, post-operatively, or within 2 days following surgery. Totals of 77.8%, 68.4% and 48.3% amongst the Uniplas, Octaplas and control groups received red cells, while corresponding totals of 22.2%, 21.1% and 6.9% received platelets.</td>
<td>(From Tollefsrud²⁵) No seroconversions to HBV, HCV, HIV, HTLA, CMV or parvovirus B19 in any treatment group. 26 patients experienced one or more adverse events: in the Octaplas group, 3 patients required re-operation, 2 experienced peri-operative death, 3 experienced surgical bleeding, 2 experienced bradycardia, 1 experienced myocardial infarction, and 1 experienced atrial fibrillation. Patients receiving Uniplas experienced atrial flutter/fibrillation (n=3), surgical bleeding (n=2) and re-operation (n=1), and patients in the control group primarily suffered only atrial flutter/fibrillation (n=6).</td>
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<tr>
<td>Haubelt (2002)²⁹</td>
<td>Correspondent increases of most clotting factors were seen, though there were observed between group-differences in regard to plasmin inhibitor, protein S and factor VIII. Comparable reductions of bleeding.</td>
<td>No side effects or adverse events observed that were associated with treatment (no other figures were reported), and that a total of 14 deaths (4 Octaplas, 10 FFP) unrelated to treatment occurred between 1-32 days following the study.</td>
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<tr>
<td>Solheim (1993)¹¹</td>
<td>No notable differences in blood loss, frequency of post-operative complications, respiratory time, circulatory support or length of hospital stay. Comparable complement activation groups were seen in both groups, and PTs were also similar</td>
<td>No patients in the study were found to acquire HBV, HCV or HIV infections.</td>
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<tr>
<td>Solheim (2000)⁰⁹</td>
<td>None reported</td>
<td>Investigators indicated there were no indications of an association between use of Octaplas only and seroconversion, but noted that there were near-significant findings correlating Parvovirus B19 with use of SDFFP and cellular blood products together.</td>
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<tr>
<td><strong>Thrombotic Thrombocytopenic Purpura</strong></td>
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<tr>
<td>Yarranton (2003)³²</td>
<td>7 of 8 observed VTEs occurred in situations where the last plasma product administered was Octaplas</td>
<td>None reported</td>
<td></td>
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</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary of Effectiveness</th>
<th>Summary of Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santagostino (2006)</td>
<td>13/16=81% of all treatment administrations were deemed effective (the remaining 3 were deemed partially effective) based on extent of blood loss</td>
<td>A rash was observed in one patient, as well as mild bleeding at the surgical site in three patients, excessive bleeding from drainage in 2 patients and intra-operative bleeding in one patient. No seroconversions to HAV, HBV, HCV or parvovirus B19 were noted.</td>
</tr>
<tr>
<td>Inbal (1993)</td>
<td>Octaplas resulted in a cessation of joint bleeding in one patient, prevented bleeding both during and after child birth in an individual with factor X deficiency, prevented bleeding in four individuals undergoing surgical procedures, and stopped menorrhagia in one patient. The 8 patients suffering from hereditary coagulopathies were noted to show increases in the levels of their respective deficient factors following Octaplas administration, and 2 patients that had coagulopathies associated with liver disease showed only minor correction of coagulation factor levels despite prevention of bleeding.</td>
<td>1 patient experienced urticaria following plasma infusion, and another experienced a moderate anaphylactoid reaction following plasmapheresis. No evidence of HAV, HBV, HCV, HIV or CMV was observed.</td>
</tr>
<tr>
<td>Other Indications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chekizova* (2006)</td>
<td>Mean pre-/post-PT (28.7±20.3 seconds to 20.7±14.2 seconds) and pre-/post-aPTT (68.9±37.4 seconds to 44.0±15.6 seconds) both decreased significantly. Mean fibrinogen and platelet levels both increased.</td>
<td>Nine deaths were observed: 2 associated with pulmonary hemorrhage, 3 associated with prematurity and sepsis, two associated with perinatal asphyxia, one associated with meningitis and one associated with a congenital echovirus infection. No adverse events were observed that were associated with Octaplas.</td>
</tr>
<tr>
<td>Chekizova* (2006)</td>
<td>Statistically significant reductions of aPTT (50.1±18.4 seconds to 32.7±6.9 seconds) and PT (21.0±5.2 seconds to 15.6±1.9 seconds) were observed, while a significant increase in fibrinogen (1.55±0.75g/L to 2.74±0.86g/L) was also seen.</td>
<td>No adverse events or side effects were observed in this group of patients.</td>
</tr>
<tr>
<td>Beck (2000)</td>
<td>Differences of markers of anticoagulation in terms of pre-/post-transfusion changes generally differed insignificantly between groups, though changes in both antithrombin and protein C were significantly higher in those receiving Octaplas</td>
<td>None Reported.</td>
</tr>
<tr>
<td>Hellstern (1993)</td>
<td>Significant improvements in PT, fibrinogen, antithrombin III and systolic blood pressure were observed after Octaplas administration, while statistically insignificant changes in aPTT and platelets were also seen.</td>
<td>No side effects were observed in any patient.</td>
</tr>
</tbody>
</table>

Abbreviations: INR=international normalised ratio, aPTT=activated partial thromboplastin time, PT=prothrombin time, FFP=fresh frozen plasma, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, VTE=venous thromboembolism.
Figure 1: Flow Chart of Selected Reports

148 citations identified from electronic search and broad screened (83 Medline, 25 Cochrane, 40 EMBASE)

110 Citations excluded from preliminary screening; an additional 21 duplicate citations excluded after identification of those appearing in multiple databases

18 Potentially relevant reports from search identified for further scrutiny; an additional 3 from the bibliographies of these reports

6 Potentially relevant reports retrieved from other sources

27 Potentially relevant reports

14 reports excluded:
* Interim results of a complete study (n=1)
* Duplicate information (n=1)
* Did not contain sufficient information (n=1)
* Study design/goal not appropriate for this review (n=1)
* Abstract/letter (n=3)
* Sample size <5 (n=4)
* Solvent-detergent plasma other than Octaplas (n=3)

13 citations identified from electronic search and broad screened