CADTH Optimal Use Report

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

May 2011

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

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May 2011

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REPORT IN BRIEF

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

May 2011

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, and Population

This systematic review sought to update findings regarding the effectiveness and safety of Octaplas for all indications identified through a systematic literature search. These primarily included acute thrombotic thrombocytopenic purpura (TTP), intensive care, thorax conditions, and mixed populations. Findings for each indication are summarized separately in this review.

Technology Description

Octaplas is a solvent/detergent-treated, virus-inactivated FFP product prepared by Octapharma. The solvent/detergent treatment consists of 1% trinitrobutyl phosphate and 1% Triton X-100 for four 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 refrozen in 200 mL 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

The goal of this systematic review was to provide an update to an earlier review, conducted in 2007. The aim was to determine whether Octaplas is comparable with FFP 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.

Objective(s)

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

Methods

A systematic electronic literature search update of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials was conducted to identify all recent 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**

Because of 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 update suggest that Octaplas is effective in improving clinical outcomes in acute TTP, although no significant difference was noted in comparison with cryoprecipitate-poor plasma (CPP). Notably, no laboratory outcomes were reported in included studies. While no differences in clinical outcomes were noted, differences could have been missed due to small sample sizes, outcome selection, lack of reporting, or inadequate safety report rate. The rate of transfusion-associated infections and other adverse events was low for Octaplas and may be similar to wet plasma, FFP, and CPP. Given the poor quality and quantity of evidence for the effectiveness of both Octaplas and comparators, Octaplas may be a reasonable alternative for the treatment of bleeding disorders. In TTP, where there is good evidence to support the effectiveness of FFP, the routine use of Octaplas cannot be justified based on the included studies. Overall, further well-designed randomized clinical trials comparing Octaplas and standard FP or FFP are required to determine whether there are any clinically important differences in effectiveness and safety between these two blood products.
EXECUTIVE SUMMARY

Issue
To determine whether Octaplas is comparable with fresh frozen plasma (FFP) 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 regarding the effectiveness and safety of Octaplas in relation to other alternatives such as FFP and other frozen plasma (FP) 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 and Effectiveness

Methods
A systematic electronic literature search update of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials was conducted to identify all recent relevant randomized and observational studies pertaining to evaluation of the effectiveness and safety of Octaplas. Two reviewers independently screened 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
Three studies were included consisting of two clinical reports (observational studies)\(^1,2\) representing 1,304 patients and one multinational hemovigilance study\(^3\) representing 947 incident reports. All studies were conducted in European countries. The main indications focused on for treatment were thrombotic thrombocytopenic purpura (TTP),\(^2\) intensive care, and thorax conditions.\(^1\) No laboratory outcome was reported.

Only limited clinical outcomes were reported in one study.\(^2\) All acute TTP patients (N = 32) responded to treatment, whether they received Octaplas or cryoprecipitate-poor plasma (CPP), with no significant difference in volume transfused to obtain remission (P = 0.06).

Safety outcomes were reported in all three studies. In a prospective cohort study (N = 1,272) that enrolled a majority of intensive care patients, frozen or wet plasma (from male donors only) resulted in a small number of mild, moderate, and severe allergic transfusion reactions, while none were observed with Octaplas.\(^1\) A retrospective cohort study (N = 33 acute TTP episodes) showed that exclusive use of Octaplas as plasma therapy led to fewer allergic reactions and to fewer citrate reactions, as compared with exclusive use of CPP.\(^2\) A multinational hemovigilance study also showed that there was no transfusion-related acute lung injury (TRALI) and fewer serious immunological reactions where Octaplas was exclusively used at a national scale, as compared with countries using FFP only.\(^3\)

One group of authors underlined the reduced industrial cost of inactivation procedures and the reduced work demands related to Octaplas production, administration, and surveillance. However, no formal cost analysis was performed.\(^1\)
Health Services Impact
Because of the limited data comparing the effectiveness and safety of Octaplas and FFP, the health services impact cannot be determined.

Conclusions
As in our previous review (June 2007), the findings from this systematic review update suggest that Octaplas is effective in clinically improving bleeding disorder episodes in TTP patients. While no differences in clinical outcomes were noted, important clinical differences could have been missed due to potential imbalances between compared groups, outcome selection, small sample size, or inadequate rates of safety reporting. The rate of transfusion-associated infections, TRALI, and other adverse events remain lower for Octaplas than for FFP. In one small observational study, no seroconversion was observed for hepatitis (A, B, or C) or human immunodeficiency virus (HIV), in either group. In one report, authors mentioned one catheter thrombosis and 22 central or peripheral line infections, but without specifying the study group in which they occurred. No data were found about other infections (e.g., parvovirus B19, West Nile virus, prions). Given the poor quality and quantity of evidence for both the effectiveness of Octaplas and FFP, Octaplas may be a reasonable alternative to FFP or FFP in the treatment of bleeding disorders. In TTP, there is good evidence to support the effectiveness of FFP. While there is no evidence to suggest worse outcomes, the routine use of Octaplas as initial treatment for TTP can still not be recommended based on our update. Overall, further well-designed randomized clinical trials comparing Octaplas and standard FP or FFP are required to determine whether there are any clinical important differences in effectiveness and safety between these two blood products.
ABBREVIATIONS

aPTT    activated partial thromboplastin time
CPP     cryoprecipitate-poor plasma
FP      frozen plasma
FFP     fresh frozen plasma
HIV     human immunodeficiency virus
INR     international normalized ratio
PLEX    plasma exchange
PRISMA  Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT      prothrombin time
RCT     randomized controlled trial
S/D     solvent/detergent
SDFFP   solvent/detergent inactivated fresh frozen plasma
SIGN    Scottish Intercollegiate Guidelines Network
TACO    transfusion-associated circulatory overload
TRALI   transfusion-related acute lung injury
TTP     acute thrombotic thrombocytopenic purpura
VWF     von Willebrand factor
1 INTRODUCTION

1.1 Background and Setting in Canada

Despite the improved screening tests developed in recent years for infectious diseases for blood donors, there still remains a theoretical residual risk of transmission of transfusion-related viruses from single blood components. This mainly relates to donors in the window period of infection and the possible 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. The Canadian Blood Services, which is the distributor of all blood products for nine Canadian provinces and three territories, has been considering a broadening of its product coverage to include Octaplas as an alternative to 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 blood product in the treatment of various indications is not well understood or researched.

In Canada, over 200,000 units of FFP are transfused annually (personal communication, Canadian Blood Services). Given an average dose of four units per transfusion, this represents over 50,000 doses and an estimated cost in excess of $30 million.4 To assess the relevance of offering Octaplas as an alternative to FP or FFP for distribution to Canadian hospitals, in 2007 we conducted a formal systematic review of the scientific literature, to synthesize evidence about its therapeutic efficacy and safety. Although some reports suggested that Octaplas was safe and effective, the body of literature analyzed was very heterogeneous, making that evidence inconclusive. The purpose of this summary report is to synthesize new evidence released since the original systematic review.

1.2 Technology Overview

1.2.1 S/D Plasma Method of Preparation

Solvent/detergent virus inactivation of FFP 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-treated, virus-inactivated FFP prepared by Octapharma, using a solvent/detergent treatment of 1% trinitrobutyl phosphate and 1% Triton X-100 for four 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 refrozen in 200 mL aliquots to match specific blood types. Octaplas has been described as being associated with an improved safety profile as compared with standard FFP, based on reduced rates of transfusion-associated allergic reactions, transfusion-related acute lung injury (TRALI), and other outcomes.

1.2.2 Prior In Vitro Assessments of Stability

Since the early 1990s, a number of studies have been conducted 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.\(^3\) 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.\(^6\) compared levels of von Willebrand factor (VWF) antigen, VWF-cleaving protease, and protein S among standard FFP, cryosupernatant, Octaplas, and methylene blue- or 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 to FFP in the treatment of thrombotic thrombocytopenic purpura (TTP), it may also predispose patients to venous thromboembolism. Beeck and Hellstern\(^7\) 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 declines of 35% and 76% in activity of protein S and plasmin inhibitor, respectively, that there were no clinically important reductions of the activity of clotting factors, inhibitors, or plasma proteins. Buchta et al.\(^8\) compared the stability of coagulation factors in five units of thawed solvent/detergent inactivated FFP (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 coagulation activity and plasma protein levels adequate for it to be considered as an appropriate alternative for plasma exchange. Other similar studies by Heger et al.,\(^9\) Zeiler et al.,\(^10\) and others have also been performed. However, while there are 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, which must be addressed.

2 THE ISSUE

Thus far, a lack of research on the clinical use of 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 update of all randomized trials and observational studies comparing Octaplas with a relevant active therapy.

3 OBJECTIVE(S)

The goal of this systematic review was to provide an update to our earlier review, conducted in 2007. The aim 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 initiating the review process, the three primary reviewers (MK, AT, DF) updated a protocol outlining the approach to be taken for the review in terms of literature search strategy, study identification and selection, data abstraction, quality assessment, data
analysis, and reporting of findings. No deviations from this outline were required, and description of relevant methodologies is provided in the following subsections of the document. Recommendations of the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed during the conduct of this review.11

4.1.1 Literature search strategy

Broad, systematic search strategies were applied to MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials respectively on December 17, 2010, with a limit set on years (2007-2010), to identify randomized controlled trials (RCTs) and observational studies evaluating Octaplas. The strategies combined text terms such as “octaplas,” “solvent detergent,” “solvent-detergent,” “solvent/detergent,” “SD,” “S/D,” “vitro inactivated,” “virus inactivated”, “virus-inactivated”, along with “FFP” and “frozen plasma,” to locate relevant clinical studies. The Dickersin filter for RCTs12 and the Scottish Intercollegiate Guidelines Network (SIGN) filter for observational studies were inserted in the search strategy for MEDLINE. An Embase-oriented randomized trial filter was also incorporated from SIGN. Google Scholar (since 2007) and google.com (first 100 hits) were also searched on January 10, 2011, using the keyword “octaplas.” The bibliographies of all included studies were also reviewed to identify any additional relevant reports.

4.1.2 Selection criteria and method

To be eligible, studies had to be a randomized/non-randomized comparator controlled trial, a randomized/non-randomized non-comparator controlled trial, a crossover trial, a prospective/retrospective cohort study, or a prospective/retrospective before-after study comparing Octaplas with 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 fewer than five 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:

- Laboratory outcome information, including pre- and post-transfusion aPTT, PT, international normalized ratio (INR), coagulation factor levels (factors I through XIII), prothrombin fragment F$_{1+2}$, fibrinogen, antithrombin-III, VWF antigen and cleaving protein, D-dimers, thrombin-antithrombin, plasmin-antiplasmin, α$_1$-antitrypsin, α$_2$-antiplasmin, plasmin inhibitor, plasminogen, and IgM/IgG anticardiolipin antibodies
- Clinical outcome information — bleeding outcomes or response rates
- Safety outcome information, including frequency of relevant events such as death, thrombosis, pulmonary embolism, febrile transfusion reactions, hypotension, hypoxia, TRALI, hepatitis B/hepatitis C virus/HIV seroconversions, parvovirus B19 infections, and transfusion-associated circulatory overload (TACO), within each treatment group.

Three authors (MK, 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 among the group.
4.1.3 Data abstraction strategy

We used a standardized data abstraction form 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 assigned to each treatment group (and number analyzed), length of follow-up, patient demographics, laboratory outcome information (see section 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 (MK, 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 between the two reviewers. If an article claimed that no side effects or adverse events were observed without specifically listing those that were monitored, a null value was entered for all events of interest in this review.

4.1.4 Strategy for quality assessment

Observational studies were assessed through judgment of five criteria chosen by the authors of this systematic review: proper ascertainment of exposure (yes/no); use of a non-exposed study cohort (yes/no); use of a representative sample (yes/no/unclear); maximization of group comparability via matching or analysis (yes/no); choice of an adequate amount of follow-up for the study’s outcome of interest (yes/no). All quality findings are reported in the Results section of this review. Quality assessment of single-armed studies was not to be performed, as their methodological weaknesses are well established (e.g., lack of controls).

4.1.5 Data analysis and summaries

Measures of effect were to be calculated for each trial independently, and studies were to be pooled based on clinical and methodological judgment as to its appropriateness. However, investigation and data abstraction of all studies retained for this review update showed that this set of investigations was too heterogeneous in terms of study designs, patient populations, outcomes reported, dosages, and durations of therapy, 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 update identified a total of 78 citations: 30 from MEDLINE, 46 from Embase, and two from the Cochrane Central Register of Controlled Trials. Following independent review of this collection of citations and removal of duplicates contained in more than one database, 62 citations were agreed upon as being
potentially relevant. Six reports were subsequently retrieved for additional consideration. One manuscript was identified through review of study bibliographies, which brought the number of full-text manuscripts reviewed to seven. Appraisal of these manuscripts and subsequent discussion of their relevance among the three primary reviewers left a total of three articles that were retained for inclusion in this systematic review update, which studied various aspects of effectiveness and/or safety in a total of 1,304 patients (1,272 in a prospective cohort study, 32 in a retrospective study) plus 947 adverse event reports from a multinational hemovigilance study. Figure 1 details the process of study selection and also provides details regarding the reasons for exclusion among this final collection of candidate articles. Excluded studies included two abstracts and letters, one case report, and one study that assessed a SDFFP product other than Octaplas.

4.2.2 Trial and study characteristics

Pertinent details of the three 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 and 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, and outcomes assessed (as well as reporting or classification format of common outcomes across studies). Clinically, Octaplas was compared among a number of different indications that included acute TTP, intensive care, and thorax conditions. Standard FFP served as the control therapy in two studies (one prospective cohort study, one hemovigilance study), while cryoprecipitate-poor plasma (CPP) served as control in one study (retrospective cohort study). Dosages of Octaplas were specified only for one study (Table 1). Included studies had moderate to large sample sizes; no masking was used. None of the included studies reported laboratory outcomes such as correction of INR, PT, and aPTT or bleeding outcomes. These results demonstrate a persistent gap in the published literature regarding the primary outcomes of interest for this review.

4.2.3 Effectiveness: Summary of findings

a) Thrombotic thrombocytopenic purpura

Scully et al. performed a retrospective review of 50 acute TTP episodes in 32 patients, in the United Kingdom. Twenty-four TTP cases were due to acute idiopathic disease, four to HIV, two to pregnancy, and one was congenital. Eleven subjects had recurrent episode(s). Investigators assessed Octaplas, as compared with CPP/cryosupernatant. CPP was used as a standard therapy and as the initial replacement fluid for plasma exchange (PLEX); 17 patients had to switch from CPP to Octaplas. Five hundred and nine PLEX procedures used Octaplas, including 21 TTP episodes (277 procedures) using this product exclusively, while 172 used CPP, including 12 TTP episodes (86 procedures) using this product exclusively. Clinical remission was obtained for all patients, with Octaplas representing 72.3% of all the plasma transfused. A subgroup analysis focusing on episodes treated exclusively with either type of plasma (n = 21 for Octaplas and n = 12 for CPP) showed similar median numbers of interventions/TTP episodes (eight with Octaplas, seven with CPP, P = 0.06), and comparable median volumes per episode (29.0 L with CPP, 34.1 L with Octaplas, P = 0.52). There was no death, TRALI, hepatitis A, B, or C seroconversion, or HIV seroconversion in either group. Compared with Octaplas, transfusion of CPP led to more allergic reactions (9.3% versus 3.1%, P = 0.001) and to more citrate reactions (18% versus 6.9%, P < 0.0001). This study sufficiently
met four of the five quality assessment criteria predetermined for this review (Table 2). Table 3 summarizes efficacy and safety data.

b) **Mixed populations**
Vaara and Nilsson prospectively collected standardized safety data for all Octaplas and FFP or wet plasma (male donors only) units delivered to their study clinic between late 2006 and December 2008, in Sweden. Their institution implemented exclusive use of Octaplas for plasma therapy for about 17 months during the study period. There were no missing data and transfusion reactions reports were analyzed for a total of 2,621 Octaplas units (811 patients) and 1,135 FFP or wet plasma units (461 patients). The distribution of patients was the same in the two study groups: intensive care patients (54% of patients), patients with thoracic conditions (40%), and other patients (6%). Nineteen FFP or wet plasma transfusions led to a transfusion reaction (eight mild, six moderate, five severe), whereas no transfusion reaction followed any Octaplas transfusion treatment. This study sufficiently met four of the five quality assessment criteria predetermined for this review (Table 2). Table 3 summarizes safety data.

Flesland reported hemovigilance data (transfusion-related adverse reactions) from five European countries, around the same period. One hundred and five cases were reported for Denmark (1999-2003), 241 for Norway (2004-2005), 60 for Sweden (2004), and 541 for the United Kingdom (2004). The total number of incidents recorded from Finland (2004-2005) was not given. Based on our review question, we focused on incidents related to Octaplas, especially when compared with FFP, but data related to red blood cells concentrates and platelet concentrates were also reported. During the study period, Norway practitioners used exclusively Octaplas for plasma replacement therapy, while only FFP was exclusively used in the other countries (with a male-donor-only policy implemented sometime in that period). A total of four incident reports (10.1/100,000 transfusions) were recorded for Octaplas, including three serious adverse events. One serious immunological reaction was attributed to Octaplas (2.5/100,000 transfusions), while 3.7 and 5.6 serious immunological reactions were reported per 100,000 transfusions of FFP for Denmark and for the United Kingdom, respectively. Although national incidence ratios were reported, there was no standardization. This study sufficiently met three of the five quality assessment criteria predetermined for this review (Table 2). Table 3 summarizes safety data.

## 5 DISCUSSION

A total of three studies (one hemovigilance study, one prospective cohort, one retrospective cohort) that represented a total of 1,304 patients in addition to a total of 941 transfusion reaction reports were included in this systematic review update. A discussion of laboratory, clinical, and safety measures is provided in section 5.1 below. The three clinical studies included reported on the use of Octaplas in a variety of clinical conditions. In one of these studies, Octaplas was used to treat acute TTP, while it was used to treat a variety of bleeding disorders in the other two studies.

Overall, our findings add little to our 2007 conclusion suggesting that Octaplas is effective in improving clinical outcomes, in bleeding disorders. Based on this systematic review update, Octaplas may be comparable with FFP in terms of treatment response and volume needed to treat acute TTP. There are still no adequately powered RCTs comparing Octaplas with other replacement fluids as the initial treatment for TTP. Our findings suggest that Octaplas may
result in fewer adverse reactions, as compared with CPP in patients with acute TTP, and as compared with FFP or FP in treatment or prevention of bleeding. However, these results are based only on observational studies. No randomized trials are available to evaluate either the clinical effectiveness or the safety of Octaplas. Given the paucity of rigorous research evaluating the effectiveness of Octaplas as a substitute for FP, firm conclusions are not possible. This lack of evidence is illustrated by the persistent lack of randomized trials, as well as the overall poor quality and quantity of the included studies. All three observational studies had at least one deficiency, as determined by a predetermined set of key methodological quality criteria (Table 2).

5.1 Summary of Results

None of the three observational studies included in this review reported findings regarding levels of coagulation proteins in patients receiving Octaplas, but some clinical data were reported on clinical evolution and safety. However, important outcomes remain inadequately studied in the studies included. Bleeding outcomes such as hemostatic effectiveness were not evaluated. In addition, none of the included studies used a standardized or validated tool to evaluate bleeding.

The only study that focused on a particular condition relates to acute TTP. Response rate was similar between Octaplas and CPP, but there were two to three times fewer allergic or citrate reactions with Octaplas than with CPP, which was highly statistically significant. Other safety outcomes were similar between study groups (no HAV/ HBV/HCV/HIV seroconversion, no TRALI, no death). The study size was small (32 patients, 50 transfusions), with a retrospective design. As a result, no definitive conclusions can be reached about either the effectiveness or the potential adverse effects of using Octaplas as an initial replacement fluid for plasma exchange in patients with TTP.

The other two studies were larger (hundreds of transfusions each), with prospective controlled designs and a focus on safety. The superior safety profile of Octaplas over FFP or wet plasma showed by a single-centre study conducted in Sweden over two years (zero adverse reactions reported) was also observed in a comparison of hemovigilance data from Norway and four other European countries (almost twice less serious immunologic reactions and no TRALI).

From the identified studies, there is still a gap in current research with regard to important clinical and laboratory outcomes. While Octaplas and FFP may produce similar results in terms of changes in safety outcomes, there are differences in the composition of the products that may lead to some differences in laboratory outcomes. Based on the current evidence available, it is not possible to ascertain whether there are differences in clinically important outcomes such as bleeding, thrombosis, infections, or other transfusion reactions. Further research directly comparing FFP and Octaplas in RCTs is required to determine whether there are any clinically important differences associated with the use of Octaplas and FFP.

5.2 Study Limitations

Limitations associated with this systematic review update were noted during compilation of the evidence pertaining to the effectiveness and safety of Octaplas. First, limited information 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. This was additionally compounded by the fact that the study designs used were hypothesis generating in nature. In addition, 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 exist unpublished studies that may alter the conclusions of this systematic review. Lastly, in both our original review (2007) and this update, we excluded studies that tested S/D plasma products other than Octaplas. As such, this report is not a review of S/D products, but specifically Octaplas. As noted in the original report, other S/D plasmas are prepared using similar processes but there can be differences in the final products. Including the studies of other S/D plasma products might better characterize current evidence for S/D plasma, but this is unlikely, given the small number of studies examining other S/D products identified in our literature searches.

5.3 Generalizability of Findings

A number of factors limit the generalizability of the findings in this systematic review. The included studies evaluated Octaplas in patients with a variety of disorders, including patients with TTP, patients requiring intensive care, patients with thorax conditions, and patients with other unspecified bleeding disorders. The one TTP-specific study was small and retrospective, and the two larger prospective studies had mixed populations, with no subgroup analysis focusing on specific conditions. Even for the patient groups identified in the studies, the lack of RCTs testing Octaplas versus 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 of 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 with FFP cannot be adequately assessed to determine whether there are 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 and safety 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), bleeding outcomes, and adverse transfusion reactions.
6 CONCLUSIONS

The findings from this updated systematic review and our previous results 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, our previous review (studies published until June 2007) showed that there were some potentially important differences in laboratory outcomes that were identified in specific studies. These were not associated with adverse clinical outcomes, but the included studies were not large enough to rule out clinically important differences. Based on the evidence available, the adverse event rate for Octaplas also appears to be low and possibly similar to FFP.

Our conclusion remains the same as in 2007. 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.\(^{17,18}\) Therefore, while there is not sufficient clinical evidence to demonstrate that Octaplas is equivalent to FFP, considering Octaplas as an alternative to 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.\(^{19}\) Because of a lack of studies evaluating the effectiveness of Octaplas in TTP, the routine use of Octaplas as initial therapy instead of FFP cannot be justified from the included studies.

While no differences in bleeding, infections, and other adverse transfusion reactions in patients receiving Octaplas and FFP were identified, the quality of the evidence in this systematic review update provides limited opportunities to assess differences in clinically important outcomes in patients receiving Octaplas as opposed to standard FP/FFP. More well-designed RCTs are required to determine the effectiveness and safety of Octaplas as compared with standard FFP.
REFERENCES


APPENDIX A: SEARCH STRATEGIES

OVERVIEW

Databases:
- Embase (2007 – December 17, 2010)
- Cochrane Central Register of Controlled Trials (2007 - 2010)

Date of Search: December 17, 2010
Study Types: Randomized controlled trials; observational studies
Limits: Date limit (2007 – December 17, 2010)

SYNTAX GUIDE

/ At the end of a phrase, searches the phrase as a subject heading
.sh At the end of a phrase, searches the phrase as a subject heading
MeSH Medical Subject Heading
? Truncation symbol for one or no characters only
ADJ Requires words are adjacent to each other (in any order)
ADJ# Adjacency within # number of words (in any order)
.ti Title
.ab Abstract
.pt Publication type
.tw Text word: searches title, abstract, captions, and full text
.mp Keyword search: includes title, abstract, name of substance word, subject

Multi-database Strategy

MEDLINE:

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIAL.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. (ANIMALS not HUMAN).sh.
9. 7 not 8
10. CLINICAL TRIAL..pt.
11. exp CLINICAL TRIAL/
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS.sh.
15. placebo$.tl,ab.
16. random$.tl,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
Addendum to a Systematic Review of Clinical, Laboratory and Safety Outcomes Associated with Use of Octaplas in Multiple Clinical Indications

20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. Octaplas.mp.
31. octapla$.mp.
32. (solvent-detergent or solvent detergent).mp. or solvent/detergent or SD.mp. or S/d [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
33. (Viro inactivate$ or Virus inactivated or Virus-inactivated).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
34. plasma.mp. or Plasma/
35. (32 or 33) and 34
36. Epidemiologic studies/
37. exp case control studies/
38. exp cohort studies/
40. (cohort adj (study or studies)).tw.
41. Cohort analy$.tw.
42. (Follow up adj (study or studies)).tw.
43. (observational adj (study or studies)).tw.
44. Longitudinal.tw.
45. Retrospective.tw.
46. Cross sectional.tw.
47. Cross-sectional studies/
48. or/36-47
49. 30 or 31 or 35
50. 29 and 49
51. (frozen plasma or ffp).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
52. (32 or 33) and 51
53. 30 or 31 or 52
54. 29 and 53
55. 48 and 53
56. limit 54 to yr="2007 -Current"
57. limit 55 to yr="2007 -Current"
58. 56 or 57

Embase:

1. Clinical trial/
2. Randomized Controlled Trial/
3. Randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomized controlled trial$tw.
11. Randomly allocated.tw.
15. Double blind$tw.
16. Placebo$tw.
17. Prospective Study/
18. or/1-17
19. Case Study/
21. Abstract report/ or letter/
22. or/19-21
23. 18 not 22
24. Octaplas.mp.
Addendum to a Systematic Review of Clinical, Laboratory and Safety Outcomes Associated with Use of Octaplas in Multiple Clinical Indications

25. octapla$.mp.
26. (solvent-detergent or solvent detergent or solvent/detergent or SD.mp. or S/d [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer])
27. (Viro inactivate$ or Virus inactivated or Virus-inactivated).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
28. plasma.mp. or Plasma/
29. (26 or 27) and 28
30. 24 or 25 or 29
31. (frozen plasma or ffp).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
32. (26 or 27) and 31
33. 24 or 25 or 32
34. Clinical study/
35. Case control study.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
36. Family study/
37. Longitudinal study/
38. Retrospective study/
39. Prospective study/
40. Randomized controlled trials/
41. 39 not 40
42. Cohort analysis/
43. (Cohort adj (study or studies)).mp.
44. (Case control adj (study or studies)).tw.
45. (follow up adj (study or studies)).tw.
46. (observational adj (study or studies)).tw.
47. (epidemiologic$ adj (study or studies)).tw.
48. (cross sectional adj (study or studies)).tw.
49. or/34-38,41-48
50. 23 and 33
51. 49 and 33
52. limit 50 to yr="2007 -Current"
53. limit 51 to yr="2007 -Current"
54. 52 or 53

Cochrane Central Register of Controlled Trials:

1. Octaplas.mp.
2. octapla$.mp.
3. (solvent-detergent or solvent detergent or ("solvent/detergent" or SD or "S/d")).mp.
4. (Viro inactivate$ or Virus inactivated or Virus-inactivated).mp.
5. (frozen plasma or ffp).mp.
6. (3 or 4) and 5
7. 1 or 2 or 6
8. limit 7 to yr="2007 - 2010"

OTHER SOURCES

Sources searched: Google Scholar
Google.com
Keywords: Octaplas
### Table 1: Characteristics of Studies Included in this Systematic Review Update

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design</th>
<th>Indication</th>
<th>Interventions</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Sample Sizes</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombotic Thrombocytopenic Purpura</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scully (2007)</td>
<td>Retrospective cohort (2-armed study)</td>
<td>Acute TTP (treated with CPP in first intention)</td>
<td>Octaplas, median dose 34.1 L/plasma volume exchange</td>
<td>Available case notes for acute TTP episodes treated at study centre between February 2003 and December 2005 (n = 32 patients, n” = 50 TTP episodes). 24 TTP cases were due to acute idiopathic disease, 4 to HIV, 2 to pregnancy, 1 was congenital. 11 subjects had recurrent episode(s)</td>
<td>509 Octaplas (277 in subgroup analysis: plasma exchange using exclusively Octaplas/21 TTP episodes)</td>
<td>Baseline characteristics not reported by group</td>
</tr>
<tr>
<td><strong>Other Indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flesland (2007)</td>
<td>Multinational hemovigilance study</td>
<td>Transfusion safety</td>
<td>Octaplas (use of male-only plasma started during reporting period)</td>
<td>All reports of transfusion complications (N = 947), at national level (Denmark, Finland, Norway, Sweden, United Kingdom)</td>
<td>5 Octaplas</td>
<td>Baseline characteristics not reported</td>
</tr>
<tr>
<td>Vaara (2010)</td>
<td>Prospective cohort (2-armed study)</td>
<td>Unclear</td>
<td>Octaplas, plasma from male donors only</td>
<td>Patients receiving FFP or S/D plasma in study clinic (N = 1,272)</td>
<td>2,621 Octaplas</td>
<td>ICU patients (54%), thorax patients (40%), unspecified others</td>
</tr>
</tbody>
</table>

CPP = cryoprecipitate-poor plasma; FFP = fresh frozen plasma; HIV = human immunodeficiency virus; ICU = intensive care unit; S/D = solvent/detergent; TTP = thrombotic thrombocytopenic purpura.
Table 2: Quality Assessment of Included Cohort Studies Using 5 Predetermined Primary Criteria

<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>Scully (2007)²</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Flesland (2007)³</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Vaara (2010)⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
### Table 3: Summaries of Effectiveness and Safety

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary of Effectiveness</th>
<th>Summary of Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombotic Thrombocytopenic Purpura</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scully (2007)²</td>
<td>No difference in percentage of patients reaching remission (100% in both groups).</td>
<td>Fewer allergic reactions with Octaplas than with CCP (3.1% versus 9.3%, ( P = 0.001 )).</td>
</tr>
<tr>
<td></td>
<td>Wider range of number of plasma exchange interventions per episode (5-30 for exclusive Octaplas treatment versus 3-14 for exclusive CCP treatment).</td>
<td>Fewer citrate reactions with Octaplas than with CCP (6.9% versus 18%, ( P &lt; 0.0001 )).</td>
</tr>
<tr>
<td></td>
<td>No statistically significant difference in median number of plasma exchange interventions (8 with IQR = 5.5-8.8 for exclusive Octaplas treatment versus 7 with IQR = 5.0-8.8 for exclusive CCP treatment, ( P = 0.06 )).</td>
<td>No observed death, TRALI, HAV/HBV/HCV/HIV seroconversion (after 3 months) occurrences (in both groups).</td>
</tr>
<tr>
<td></td>
<td>No statistically significant difference in median volume used per episode (34.1 L for exclusive Octaplas treatment versus 29.0 L for exclusive CCP treatment, ( P = 0.52 )).</td>
<td>1 catheter thrombosis and 22 central/peripheral line infections were reported, but group distribution was not specified.</td>
</tr>
<tr>
<td><strong>Other Indications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flesland (2007)³</td>
<td>No effectiveness data reported.</td>
<td>Octaplas was the object of 4/241 hemovigilance reports in Norway, where it was systematically used in lieu of FFP. 3 of those 4 reports were about serious reactions. The corresponding figure for FFP was not reported for Denmark, Finland, Sweden, and United Kingdom; FFP use is exclusive. Octaplas reportedly caused 1 serious immunological reaction (2.5/100,000 transfusions) in Norway, compared with 3.7 and 5.6/100,000 transfusions of FFP (for Denmark and the United Kingdom, respectively). No TRALI reportedly due to Octaplas transfusion, compared with 4.0 TRALIs per 100,000 FFP transfusions.</td>
</tr>
<tr>
<td>Vaara (2010)¹</td>
<td>No effectiveness data reported.</td>
<td>None of 2,621 Octaplas caused any transfusion reactions (( n = 811 ) patients) while 19/1,135 FFP/thawed plasma transfusions caused adverse reactions (8 mild, 6 moderate, and 5 severe) not due to infection (( n = 461 ) patients).</td>
</tr>
</tbody>
</table>

CCP = cryoprecipitate-poor plasma; FFP = fresh frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; TRALI = transfusion-related acute lung injury.
Table 4: Adverse Reactions Associated with Octaplas and Relevant Comparators

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Allergic Reactions</th>
<th>Death</th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HIV</th>
<th>Line Infection</th>
<th>Other Infections</th>
<th>TRALI</th>
<th>TACO</th>
<th>Thrombosis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scully (2007)¹</td>
<td>Octaplas</td>
<td>3.1%*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>1</td>
<td>Citrate reactions: 6.9%*</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>9.3%*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td></td>
<td>Citrate reactions: 18%*</td>
</tr>
<tr>
<td>Flesland (2007)¹</td>
<td>Octaplas</td>
<td>5/100,000</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>Total transfusion reactions: 10.1/100,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5-8.8/100,000</td>
<td></td>
<td>1.5-8.8/100,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FFP</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>Serious allergic reactions: 3.7-5.6/100,000</td>
</tr>
<tr>
<td>Vaara (2010)¹</td>
<td>Octaplas</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FFP or wet plasma</td>
<td>19/1,135</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant difference
CPP = cryoprecipitate poor plasma; FFP = fresh frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NR = not reported; TRALI = transfusion-related acute lung injury; TACO = transfusion-associated circulatory overload.

Shaded areas represent outcomes that were of particular interest for this review update.
Figure 1: Flow Chart of Selected Reports

78 citations identified from electronic search and broad screened (30 MEDLINE, 46 Embase, 2 Cochrane)

54 irrelevant citations excluded from preliminary screening; 18 duplicates identified within and between databases

6 potentially relevant reports from search identified for further scrutiny; 1 additional from the bibliographies of these reports

7 potentially relevant reports

3 citations identified from electronic search and broad screening

4 reports excluded:
*Abstract/letter (n = 2)
*Case report (n = 1)
*Solvent/detergent-treated plasma other than Octaplas (n = 1)

0 potentially relevant reports retrieved from other sources