Alternatives of plasma for transfusion to patients

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English

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Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Knowledge Centre is organized under The Norwegian Directorate of Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, March 2015

Key messages (English)

Plasma transfusion is used to stop or prevent bleeding. Currently, all plasma used for transfusion at Norwegian hospitals (50,000 units per year) is the plasma product Octaplas®. Each unit (200 mL) contains a mix of plasmas from around 1,000 donors, and is treated chemically using solvent-detergent to eliminate virus, bacteria and parasites (pathogens). Several alternative plasma products are available on the market, and there are concerns about the costs of purchasing Octaplas® and whether these costs are too high compared with other plasma products. Alternatives to Octaplas® may be based on plasma from only one or several donors and/or other methods of eliminating pathogens (pathogeninactivation. This is the background for the commission by the "Bestillerforum RHF" to the Norwegian Knowledge Centre for the Health Services to conduct a health technology assessment (HTA), which has compared the various alternatives for generation of plasma for transfusion purposes in terms of clinical effectiveness, safety and costs.

Main results are the following:

Clinical effectiveness

- According to availble documentation, it is not possible determine whether there are differences in terms of clinical effectiveness between the different plasma alternatives assessed.

Safety

- Based on registry data, it seems that the various types of plasma routinely used in various European countries are safe in terms of adverse events.
- Patogen inactivated plasma appears to be the safest alternative.
- There might be some indications that certain methods of pathogen inactivation may lead to more allergies than others, but the evidence is both sparse and partly inadequate.

Costs

- Fresh frozen and quarantined plasma have the lowest costs among the alternatives evaluated.
- Pathogen-inactivated plasma produced in-house represents the middle level of costs while purchase of Octaplas® incurs the highest costs.
- An important assumption in our analysis is that plasma, which is not used for transfusion, can be sold at the market price.

Title:
Alternatives of plasma for transfusion to patients

Type of publication:
Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

NOKC does not provide any recommendations in terms of which method(s) should be used in the Norwegian health care services

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Helene Arentz-Hansen, Senior Researcher, NOKC
Arna Desser, Researcher, NOKC

Executive summary (English)

Background

Plasma transfusion is used for reestablishing normal hemostasis, i.e. to stop or prevent bleeding. In Norway, currently about 50,000 units of plasma are transfused per year, and the only product in use is Octaplas®. This product is a mix of plasmas (pooled) from approx. 1 000 donors and treated with solvent-detergent to potentially eliminate virus, bacteria and parasites (pathogens), and thus avoid transfusion-transmitted infections. There are concerns about the cost of purchasing Octaplas® compared with other plasma alternatives. Other methods of pathogen inactivation of plasma are available, and these can be performed in blood banks at Norwegian hospitals. This is the background for the commission from "Bestillerforum RHF" to the Norwegian Knowledge Centre to carry out a health technology assessment (HTA) comparing the various alternatives for generation of plasma for transfusion purposes with Octaplas® in terms of clinical effectiveness, safety and costs.

Method

Clinical effectiveness

To assess clinical effectiveness and safety we have followed the methods and work processes described in the handbook issued by the Norwegian Knowledge Centre for the Health Services (NOKC). June 2014 we searched for systematic reviews, but we did not find any of high enough quality we could communicate. Therefore, we performed a literature search for prospective controlled trials, that had compared Octaplas® or SD-plasma variants with the alternatives Intercept, Mirasol, Methylene blue, quarantine plasma, fresh frozen plasma and freeze-dried plasma. The search strategy was developed based on our predefined inclusion criteria, and the literature search was carried out in all relevant and available databases. For assessing the quality of the evidence we have used the GRADE tool.

Safety

We pursued various options for assessing safety. In addition to looking at adverse events reported in the studies included to assess clinical effectiveness, we repeated the search conducted to assess clinical effectiveness, but excluded any study design

filters. Moreover, we searched for data on adverse events related to plasma transfusions from registry data (hemovigilance reports).

Costs

After a search and review of existing literature on economic evaluations of plasma products, we performed an economic evaluation from a societal perspective. Because the results of the clinical-effectiveness analysis revealed no differences in effects, we conducted a cost analysis which compares seven plasma products. We included Octaplas®, Intercept, Mirasol, Methylene blue, quarantined plasma, fresh frozen plasma and freeze-dried plasma. Freeze-dried plasma was not examined in detail since this alternative entails very high investment- and production costs. Probabilities and costs for side effects are presented separately because of high uncertainty surrounding the probabilities for side effects and incomplete information about all of the alternatives under consideration. We analysed three production strategies for coverage of the demand for plasma for transfusion in Norway. The strategies include central production at one hospital, regional production at four regional health authorities (RHF) and production at 19 health authorities. The time perspective is three years. The first year is presented separately due to investment costs. In a sensitivity analysis we have doubled the work time to investigate its impact on costs.

Results

Clinical effectiveness

Searches in the literature resulted in the inclusion of seven prospective controlled trials, where six were RCTs and one a non-randomized controlled trial. The studies were published during the period 1997-2013 and included 553 patients in total with serious liver disease as well as patients that underwent liver transplantation or open heart surgery. Outcomes assessed in the included studies that were relevant to our HTA were fibrinogen levels in the blood, various parameters for measuring coagulation and bleeding.

Except for one small study (presented as an abstract only and without providing any effect estimates), none of the included studies showed any statistically significant differences after transfusion of methylene blue plasma (MB-FFP), quarantine plasma (Q-FFP) or regular (untreated) fresh frozen plasma (FFP) as compared with Octaplas® or SD-FFP variants. None of the studies could be combined in meta-analyses since different products were used in the different comparisons performed, and since most of the data were provided as median with interquartiles range (i.e. not as mean with standard deviation). The evidence ranged from very low to low quality.

Safety

None of the studies included for assessing clinical effectiveness recorded any adverse events among their participants. We could therefore not conclude anything from these studies with regard to safety issues. Further, we included four publications which were retrospective studies based on data from hemovigilance reports from France, Greece and Finland. However, the documentation was both sparse and insufficient. They reported no significant changes in numbers of adverse events between the different types of plasma, with the exception of quarantine plasma (Q-FFP) when compared to SD-FFP in one study, and regular FFP (not pathogen inactivated) when compared to Octaplas® in another study.

Twelve hemovigilance reports from France and Norway (2007 – 2012) were also included in our HTA, as an attempt to find any indication of incidence or possible trends or differences between the plasma products in terms of adverse events. In France, several different methods of pathogen inactivation have been used, and adverse events have been thoroughly recorded as they have a comprehensive and well-organized system for hemovigilance. According to all of the reports, the incidence of adverse events related to plasma transfusion is overall very low. Data are nevertheless not sufficient to indicate whether there are any variations between the different pathogen inactivation methods, with perhaps the exception of allergies which seem to occur more often with MB-FFP compared to SD-FFP and IA-FFP (Intercept that uses amotosalen for pathogen inactivation). However, it should be noted that other countries than France have been using MB-plasma for years in routine and have not reported an increased frequency of allergic reactions (personal communication Joakim Hagvik, MacoPharma).

In Norway, only Octaplas is used, and therefore we cannot compare with other methods of pathogen inactivation. The reports issued by the hemovigilance group at NOKC do however show that, in line with the included retrospective studies, the number of adverse events is very low, and that there were no recorded incidence of TRALI. We did not perform any statistical calculations or quality assessments of the documentation on safety, as the results are based on adverse events registry data, which additionally are very few and partly inadequate.

Costs

The plasma products can be grouped into three cost levels. Fresh frozen and quarantined plasma result in the lowest costs, plasma produced by pathogen inactivation technologies is in the middle range of costs and purchase of Octaplas® incurs the highest costs. Fresh frozen plasma results in the lowest costs among the included alternatives. Among the pathogen inactivation technologies, Intercept is the least-cost alternative. Central production at one hospital results in the lowest costs but the difference in cost between central and regional production is low after the first year. The cost for Octaplas® is constant across all three perspectives, since it is purchased

by the health authorities at a negotiated unit price. Accounting for double work time has relatively little impact on the total costs for the methods using pathogen inactivation technology.

Discussion

Lack of high quality evidence prevents us from drawing any clear-cut conclusions in terms of either clinical effectiveness or safety issues. Nevertheless, it should be pinpointed that even if we can not conclude whether there are any differences, it does not mean that there *are* no differences between the different types of plasmas.

An economic evaluation can include many different models regarding ownership and strategies for the production of plasma. As alternatives to today's practice of purchasing plasma, we have compared producing plasma at a single hospital, four RHFs or 19 HFs. Other alternatives are to outsource the production to a non-profit organisation or a private enterprise. In this analysis, we have assumed that the model with the blood banks included in the RHFs remains unchanged.

Although central production results in the lowest costs for pathogen inactivated plasma for transfusion, this alternative is vulnerable. In case of a crisis, having only one central production leaves us more vulnerable as compared to having a site of production in each of the four RHFs (at regional level) or at the HF (local) level.

Today Norway has a surplus of plasma. An important assumption in our analysis is that any plasma not used for transfusion can be sold at the market price.

National self-sufficiency for blood products might be a separate goal. With all the evaluated alternatives for plasma production, except today's purchase of plasma, this goal can be achieved. Of note, we are anyway self-sufficient when it comes to plasma-derived medicaments such as immunglobulin concentrates and albumine.

Conclusion

According to availble documentation, it is not possible determine whether there are differences in terms of clinical effectiveness between the different plasma alternatives assessed.

With regard to safety issues, the documentation is both sparse and of inadequate. It seems that the various types of plasma overall are safe in terms of adverse events, and that patogen-inactivated plasmas are safer than non-pathogen-inactivacted plasmas. There might be some indications that certain methods of pathogen inactivation may lead to more allergies than others, but no conclusions can be drawn based on the insufficient evidence material.

Fresh frozen and quarantined plasma entail the lowest costs, plasma produced by pathogen inactivation technologies is on the middle cost level and purchase of Octaplas® incurs the highest costs.