Improved efficiency of plasmapheresis collection in Italy through licensed variations of current practice: a proposal

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Background. The overall production efficiency of plasmapheresis in Italy is significantly less than that indicated by international data, but can be significantly improved by slightly increasing the amount of plasma collected for each procedure, while fully respecting the current regulations.

Materials and methods. In order to compare the average plasma volumes collected by means of apheresis in Italy and other European countries, we considered data supplied by Kedrion (the only company active in Italy in the field of plasma-derived products) relating to Italy and three centres managed by Kedrion in Germany.

Results. In 2014, Kedrion received about 174,000 kg of plasma collected by means of plasmapheresis in Italy, for an average unit weight including anticoagulant of 577 g, as against the approximately 97,000 kg (average unit weight including anticoagulant 783 g) produced by the three Kedrion centres in Germany.

The net weight of the plasma (without anticoagulant) contained in a plasmapheresis unit of 577 g is about 520 g, whereas a maximum collected volume of 600 mL (permitted by current Italian legislation without the need for volume reintegration) would provide a plasma unit volume of 660 mL (600 mL of plasma plus about 60 mL of anticoagulant): i.e. 14% more than that currently provided by Italian Transfusion Centres. This would increase the total amount of plasma sent to Kedrion to 199,500 kg, without creating any major organisational difficulties (only a few minutes' increase in the length of the procedure) or additional costs, or increasing donor risk.

Discussion. It is possible to hypothesise the following donation volumes. Women weighing 50-60 kg: 550 mL (net of anticoagulant), final unit volume about 610 mL; men, and women weighing >60 kg: 600 mL net, final unit volume about 660 mL. Using recently published data relating to the plasmapheresis centre in Verona (Italy), the cost of a litre of plasma is € 283.87 if the average unit volume (including anticoagulant) is 600 mL, and € 263.46 if it is 650 mL (i.e. a net plasma yield of 585 mL): a 7.2% cost reduction simply by increasing final unit volume by 50 mL, something that is already feasible and perfectly safe, and does not require donor volume reintegration under current Italian law.

Keywords: plasmapheresis, efficiency, regulations.

Introduction

Collecting plasma by means of plasmapherisis (PP) is critical in order to guarantee a sufficient supply of plasma-derived products (albumin, coagulation factors to integrate the use of recombinant factors) necessary for clinical use, with the aim of ensuring or at least approaching (e.g. in the case of aspecific immunoglobulins) regional and national self-sufficiency.

Current data concerning the production of plasma by means of PP show that it is significantly less efficient in Italy than in other European and extra-European countries[1-3]. This is partially due to some ethical and regulatory limitations peculiar to Italy (first of all, the maximum quantity and maximum frequency of plasma donations are both clearly less than in other European countries, and the donations are voluntary and unremunerated), and specific historical choices concerning the way in which plasma collection (particularly by means of PP) is organised, which means that the plasma collection systems in Italy are generally under used.

Given these conditions, improving the efficiency of plasma donation while maintaining the principle of its gratuity and the public ownership of the donated blood components, requires making specific ethical, regulatory and organisational evaluations that are often long and complex, and cannot be rapidly applied.

However, there is one aspect of donation by means of PP that can improve production efficiency without substantially affecting costs, without making any

organisational or regulatory changes, and without any giving rise to any additional donor risk. The question is whether it is possible to increase the per procedure collection of plasma in Italy, and by how much.

Materials and methods

In order to compare the average of plasma volumes collected by means of PP in Italy and other European countries, we considered data supplied by Kedrion (Kedrion SpA, Castelvecchio Pascoli, Italy) (the only company active in Italy in the field of plasma-derived products) relating to Italy and three centres managed by Kedrion in Germany. The per procedure efficiency of the collection was evaluated taking into account the Italian laws and regulations[4,5], the Recommendations of the Council of Europe[6], and the regulations applied at Kedrion's collection centres.

It needs to be borne in mind that plasma collection in Italy is totally public and donors do not receive any direct remuneration, whereas the collection of plasma by means of PP in Germany is managed directly by the producers of plasma derivatives, and the donors' expenses are directly and immediately reimbursed (about € 20/donation).

For the sake of simplicity, the volume and weight of plasma are considered equivalent.

Results

In 2014, Kedrion received about 198,000 kg of plasma collected by means of apheresis (PP and multicomponent apheresis) in Italy in accordance to national regulations, and regional or consortial contractual agreements. Considering the three major regional and inter-regional agreements, which cover about 90% of such plasma sent to Kedrion by Italian Transfusion Centres, the average weight of a bag of plasma (including anticoagulant) was 560 g. Given that about 12% of the total amount plasma comes from multi-component collections (and therefore has an average unit weight of 400 g), the average weight of the plasma units obtained by means of PP (including anticoagulant) can be considered as being 577 g, and the overall amount of plasma obtained by means of PP about 174,500 kg.

The data from Kedrion's three plasma collection centres for the commercial production of plasma derivatives in Germany (Bayreuth, Fürth and Ingolstadt) indicate a total collection of 97,000 kg of plasma, for an average unit weight (including anticoagulant) of 783 g (Bayreuth 781, Fürth 793, and Ingolstadt 777 g).

Regulatory comparison

Current Italian regulations (particularly Ministerial Decree, 3 March 2005)[4,5]

The minimum interval between two plasma donations is 14 days, and the minimum amount of donatable plasma per session is 450 mL. The maximum donatable amount is 650 mL net of anticoagulant per session (in the absence of volume reintegration, no more than 600 mL); 1.5 L per month, and 10 L per year. The maximum number of plasma donations per year is not explicitly stated, but is theoretically 26 (one every 14 days), although this is not possible because the maximum amount of plasma that can be donated per year is 10 L which, assuming 600 mL per PP session, would mean no more than 16-17 sessions.

Forthcoming Italian regulations (Ministerial Decree in the course of publication)[7] will not change the maximum number of plasma donations per year, the minimum interval between two donations, or the maximum amount of donatable plasma per month, but will change the minimum and maximum donatable amount per session (to respectively 600 mL and 700 mL net of anticoagulant), and the maximum donatable amount per year (12 L).

Rules at Kedrion's plasmapherisis centres in Germany

Maximum number of plasma donations per year: 45; minimum interval between two donations: 48 hours; maximum donatable amount per session: 650 mL if body weight <60 kg, 750 mL if body weight 60-80 kg, and 850 mL if body weight >80 kg; maximum donatable amount per year 38.25 L (equivalent to 45 donations of 850 mL). Donations are directly reimbursed to donors.

EDQM Recommendation R(95)15, 17th edition, 2013[6]

The per session volume collected (excluding anticoagulant) should never exceed 16% of estimated total blood volume, and never exceed 750 mL in the absence of fluid reintegration; the total blood volume of every donor should therefore be estimated before every donation. Furthermore, maximum extra-corporeal volume should never exceed 20%. The minimum interval between two donations should be 48 hours, and the maximum number of donations per year 33 (equivalent to a maximum annual collected volume of 24.75 L, assuming a maximum collected volume per session of 750 mL, net of anticoagulant).

It is clearly and ethically important that the primary objective of the regulations is donor safety, which is why they establish limits for the maximum amount of plasma that can be collected by means of PP per session and per year, and therefore a maximum annual number of sessions. However, it is also clear that, by excluding profit-making collection and any form of donor remuneration even in the case of "intensive" PP programmes (and therefore emphasising the ethical

nature of the donation and respect for the person of the donor), the Italian regulations establish much lower quantities and frequencies than the European regulations or the rules in force in countries where profit-making collection is allowed. On the other hand, what is of primary interest in terms of fractionation are the characteristics of the raw material, and therefore unit volumes and, even more, the real volume of plasma per unit.

Discussion

Current possibilities of improving efficiency in Italy, with reference to the Ministerial Decree of 3 March 2005[5]

It is possible to make some calculations. As the average unit weight of the plasma obtained by means of PP and sent to Kedrion is 577 g, the weight of the plasma net of anticoagulant is about 520 g (anticoagulant accounts for about 10% of the content). Reasoning in terms of net plasma volumes, and given a maximum volume of 600 mL (allowed by the current Italian regulations for both "occasional" and "intensive" PP sessions without requiring volume reintegration), it follows that a unit of plasma including anticoagulant could become 660 mL (600 mL di plasma + circa 60 mL di anticoagulant): i.e. 14% more than the average sent to Kedrion.

Consequently, simply by modifying the amount donated per session, the same number of donations could increase the amount of plasma obtained by means of PP sent to Kedrion from 174,500 kg to 199,500 kg, without creating any major organisational difficulties (only a few minutes' increase in the length of the procedure) or additional costs, and without increasing donor risk.

An additional 25,000 kg of plasma would mean:

- at least 600,000 g of albumin (assuming a minimum yield of 24 g/L), equal to 60,000 50 mL vials of 20% albumin; an economic value of € 1,800,000 as calculated on the basis of the average purchase price of the marketed product (€ 3/g according to the ISTISAN 2012 Report)[8];
- at least 87,500 g of immunoglobulins (assuming a minimum yield of 3.5 g/L), equal to 17,500 5 g vials; an economic value of €4,375,000 as calculated on the basis of the average purchase price of the marketed product (€ 50/g according to the ISTISAN 2012 Report)[8].

Respecting the current Italian regulations and without the need for donor volume reintegration, it is possible to hypothesise the following standard donation volumes:

- women weighing 50-60 kg: 550 mL net of anticoagulant, for a final unit volume of about 610 mL;
- women weighing >60 kg: 600 mL net of anticoagulant, for a final unit volume of about 660 mL;
- men: 600 mL net of anticoagulant, for a final unit volume of about 660 mL.

Possibility of further improvement in efficiency

It is also possible to make some hypotheses of improvements in per session efficiency by applying the European and forthcoming Italian regulations.

Applying EDQM Recommendation R(95)15, which indicates a collected volume (excluding anticoagulant) of no more than 16% of estimated total blood volume, and never more than 750 mL in the absence of volume reintegration, the following standard collected volumes could be obtained:

- woman weighing 50 kg and 160 cm tall (calculated blood volume 3,370 mL): 539 mL net of anticoagulant, for a final unit volume of about 600 mL;
- woman weighing 55 kg and 165 cm tall (calculated blood volume 3,586 mL) 574 mL net of anticoagulant, for a final unit volume of about 631 mL;
- men weighing 50 kg and 170 cm tall (calculated blood volume 3,981 mL): 637 mL net of anticoagulant, for a final unit volume of about 700 mL.

Applying the forthcoming Italian regulations, and with reference to R(95)15 without volume reintegration, the possible figures are:

- women weighing 50-60 kg: 600 mL net of anticoagulant, for a final unit volume of about 660 mL;
- women weighing >60 kg: 650 mL net of anticoagulant, for a final unit volume of about 720 mL;
- men weighing 50-60 kg: 650 mL net of anticoagulant, for a final unit volume of about 720 mL;
- men weighing >60 kg: 700 mL net of anticoagulant, for a final unit volume of about 770 mL.

Using the plasma production costs at the Verona Department of Transfusion Medicine recently published by Eandi *et al.*[1], the per litre cost of plasma obtained by means of PP is € 283.87 if the average unit volume (including anticoagulant) is 600 mL, and € 263.46 if it is 650 mL (i.e. a net plasma yield of 585 mL): a 7.2% cost reduction simply by increasing final unit volume by 50 mL, something that is already feasible and perfectly safe, and does not require donor volume reintegration under current Italian law.

There are probably many reasons for which, in Italy, the amount of plasma collected from each individual plasmapheresis withdrawal procedure is significantly below the maximum approved level. But it is certainly the case that, when plasmapheresis programmes were started at the end of the 1980s/early 1990s, certain habits were formed that have since been proved to have had a strong influence on the way plasma is collected, and the collection procedures that have developed have never undergone critical revision. This, together with a

strong sense of respect for the donor, and in particular to women, may have led to an excessively cautious approach being adopted.

This is in line with national legislation that imposes strict criteria to guarantee the maximum respect for donors and to ensure their safety.

Conclusions

It would really take little to improve the efficiency of collecting plasma by means of PP. Simply by increasing the amount collected at each session, without making any changes in the current frequency of sessions or the total number of donations per year, and while fully respecting the health of the donor and the voluntary nature of the donations (no donor commitment to highly intensive programmes and no direct donor remuneration), the total annual amount of plasma could be increased by as much as 8-10% at no additional cost. And that is not to be disdained.

Disclosure of conflict of interest

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