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Review

Are all therapeutic plasma preparations the same: Is it worth assessing them in clinical trials?

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ABSTRACT

Contrary to what is generally considered, plasma for direct therapeutic use is all but "standard" and can be made using a multitude of variable processes differing from one preparation to another; in sum, those changes make the final component inhomogeneous especially within inter-blood bank comparisons. The variability is further multiplied by the donors' genetic polymorphisms. This is rarely addressed in the clinical trials and meta analyses, though this may have impact on clinical outcome in patients. This short review encompasses the variability parameters in the processing of therapeutic plasma and advocates for novel, prospective, trials to assess which type of plasma is the most beneficial to patients in need, as this type may differ depending on the patients' pathological condition.

Contents

1. Preliminary remarks

Plasma for direct therapeutic use is assumed to be restricted to a limited number of clinical indications. Recommendations usually consider plasma transfusion in situations where there is active, severe bleeding, with insufficient quantities (due to loss, excess consumption, peripheral destruction or neutralization) of clotting factors that cannot be corrected by the infusion of prothrombin complex concentrates (PCC) or fibrinogen (or other single unit clotting factors that can be made available either by plasma fractionation or bioengineering) [1]. There is one noticeable exception to this golden rule: the medical indications for therapeutic plasma exchange (TPE) [2].

TPE aims, in general, at eliminating pathogenic antibodies and/or at replacing clotting factors that may have been targeted by such pathogenic antibodies. TPE thus brings polyreactive antibodies, clotting factors and antifibrinolytic factors that restore immunological and hemostatic baselines. Contrary to red blood cell concentrate (RBCC) transfusion, which is decreasing (minus 5–10% yearly), plasma transfusion still increases in high-income countries, with an estimated rise of near 10% yearly; this increased demand merges with the increased demand for plasma derived medicines, posing high pressure on plasma collectors and fractionators to meet the demand, often at the expense of ethical issues as has been recently outlined [3].

Plasma for direct therapeutic use most frequently comes—in high-income countries—as fresh frozen plasma (FFP); some blood establishments (BEs) however have started making liquid plasma available, or increase the rate of liquid plasma readily available for trauma patients; this plasma can be made from never frozen

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plasma, and different processes and categories of this exist depending on how quickly the plasma has been separated and refrigerated after collection [4,5]; alternatively, it can consist of thawed plasma, available for a limited period only (there again, different schedules have been proposed and validated by BEs). Interestingly, liquid plasma can come as ABO matched plasma or "universal" plasma after the pooling of AB, A, B and/or O units after testing for low anti-A and anti-B "natural" antibodies and the absence of iso-antibodies [6]. Further, liquid plasma can undergo pathogen reduction technologies (PRTs), to avoid quarantine, and to secure plasma in relation to untested/emergent viruses [7]. Similarly, some presentations of lyophilized plasma are available that are very stable for a long time at room temperature and require only a couple of minutes for reconstitution with distilled water (this plasma can be universal and treated with a pathogen reduction technology [PRT] as well, as done by the French Military Transfusion Service). This is a serious improvement for battlefield conditions or civil disasters [8].

Optionally, plasma for direct therapeutic use can be secured by different processes (after the usual testing); there are basically two principles, which are either a quarantine (that varies in timeframe in the various BEs) or by a PRT. Some PRTs are applied on large to very large pools, and consist of solvent-detergent (SD) treatment, while other technologies are used on individual or minipool plasma (currently Methylene Blue [MB], Amotosalen, and Riboflavin, all needing illumination at specific wave-lengths depending on the chemical) [7]. In these situations, the distinction between blood components and "industrialized" medicines or drugs is not that clear [9]. Finally, plasma for direct therapeutic use can originate from separated whole blood (the most frequent source worldwide), or from apheresis (plasmapheresis or supernatant of cell apheresis).

Of importance to note, much effort has been made, under the auspices of international accreditation organizations and national regulatory agencies, to harmonize standards (for instance the minimum requirement in target compounds and the maximum level of undesired compounds). From the above, it should be nevertheless deduced that blood components (BCs) in general, and plasma for direct therapeutic use in particular, are not "standard" despite their name. Finally, in many countries, male only plasma (or plasma collected from females testing negative for the presence of anti-HLA antibodies [Abs] of significant titer) is allowed in order to minimize the risks associated with anti-HLA Ab positive female plasma, notably the occurrence of transfusion related acute lung injuries (TRALI) [10].

2. Therapeutic plasma preparations are not all the same—from donor to bag

Donors exhibit multiple genetic polymorphisms that affect plasma proteins such as haptogobin, gamma-globulins or apoE, with as-yet unknown physiological consequences for the majority of them. Such polymorphisms are e.g. responsible for anti-A and anti-B Antibody (Ab) titers, levels of von-Willebrand factor, and many other factors that are instrumental in the essential functions of plasma: hemostasis, blood purification and elimination of toxic/degraded/metabolized molecules, immunity, etc. Individual parameters influencing blood plasma "active" molecules start with gender: males and females display different redox potential [11], have distinct cytokine and other biological response modifier patterns, and hormones. Age is also an influent parameter, alongside with immune experience, relative e.g. to so-called polyreactive and specific Abs. Then, conditions of blood/plasma collection influence the content of essential plasma proteins such as coagulation and fibrinolytic factors: the source of blood (whole blood, apheresis), the timeframe of collection (pre- or postprandial period), the time elapsed from collection to processing, temperatures all along the process, intermediate transport conditions, filtration and leukofiltration, and deep-freezing etc. All plastic containers (most containing DEHP), filters, devices (including automats for apheresis where applicable) that are commercially available exert some effect on plasma proteins (absorption, reduction, activation and cleavage, degradation). One may keep in mind that blood in its natural form cannot be readily sampled because of immediate clotting of the outside veins: therefore, blood and BCs sampled from donors are always and necessarily transformed and anticoagulated; and anticoagulation—that can be achieved through several types of chemicals (in usually citrated solutions CPD/CPDA)—alters blood function; the objective of the plasma collection process aims at keeping this alteration as small as possible. In summary, ten to a hundred variables make a huge dispersion of the target proteins around normal or accepted ranges, with relatively unknown clinical consequences.

3. Therapeutic plasma preparations are not all the same—from bag to bench

Despite the tremendous variability within the phenotypic presentation of clotting (and antifibrinolytic) factors, quality control parameters consider less than half a dozen of them for biological activity and BEs accept a large range of activity, in general equal or above a minimum level compared to control. Of note, the study of plasma storage lesions has been largely ignored, and a limited set of sentinel proteins are evaluated to control the freezing and thawing process rather than validate the individual's plasma for its therapeutic value [12]. Factors that are essential in certain pathologies (such as ADAMTS13) are not tested for as part of the quality control or process validation.

Next, the global proteome of plasma before and after application of the chemical and/or the UV illumination has been studied by several investigators: It appears that each process induces a discrete set of protein alterations [13]. However, the extent as well as the clinical relevance of the modifications observed has not been evaluated. Further, the ultimate alteration of the proteome during the freezing and preservation has not been specifically pointed out. Frozen plasma or thawed plasma stored at 4 °C for a limited period of time also endures catabolic degradation: only sentinel proteins that are known to be largely in excess to generate thrombin or fibrin are tested for, which does not imply that other essential factors such as antifibrinolytic factors or enzymes are preserved [12]. The issue that degraded proteins may become immunogenic (e.g. by creation of neoantigens) has barely been addressed, apart from Amotosalen, which has been tested for in experimental models to pass accreditation with e.g. the French Agency, ANSM. Whether ageing of plasma favors toxic metabolites upon an extended timeframe remains grossly unquestioned.

4. Therapeutic plasma preparations are not all the same—from bag to patient

Plasma for direct therapeutic use has been evaluated for a long time; there has been accumulated evidence that fresh plasma helps restore clotting in patients presenting with hemorrhagic shock, and nearly all preparations of plasma currently licensed seem to succeed in achieving this task. The question of plasma in trauma and shock rather deals with appropriate ratios of plasma compared to RBCC and platelet component transfusion rather than with the type of plasma [14]. As outlined earlier in this essay, presentation of fresh plasma which is readily available in minutes rather than in the 30–40 min that can be required to order, thaw and transport the plasma to the operation or emergency room, is considered a serious advantage, and one would even prefer whole blood in some circum-

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