PARACHUTING PLASMAPHERESIS INTO THE EBOLA CRISIS

PARACHUTAGE DE LA PLASMAPHERÈSE DANS LA CRISE D'EBOLA

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ABSTRACT

BACKGROUND
The Safe Blood for Africa Foundation™ (SBFA) supported Blood Safety for a clinical trial on Ebola Convalescent Plasma (ECP) during the Ebola crisis in Liberia in 2014. Several technical challenges needed to be met and interaction with Ebola survivors who were willingly donors.

OBJECTIVES
To setup the first plasmapheresis and pathogen inactivation technology in West Africa to harvest Ebola Convalescent Plasma (ECP) for a clinical trial.

MATERIALS AND METHODS
An initial team of four was deployed (November 2014) to set the facility. A vehicle was pre-fitted with sophisticated equipment and airlifted to the study site (ELWA). Survivor donors were sourced via the Hospital Medical Director. Training included plasmapheresis, donor management, testing and pathogen inactivation.

RESULTS
The unit was set up in three weeks. Three Liberian technicians were trained in blood safety. Rapid declining new infections ended the trial. ECP was collected until May 2015 with 97 participants (19 – 67yr), 42% female and blood group profiles matching those for West Africa and African Americans (O Pos 57% & B Pos 20%) with only one Rh Neg unit. Eighty five full-volume units were collected with a 90.4% success rate and repeat donors contributed 39 units with no adverse effects recorded.

RESUME

CONTEXTE
La Safe Blood For Africa Foundation (SBFA) a soutenu la sécurité transfusionnelle dans un essai clinique sur le plasma convalescent pour le traitement de l'infection à Ebola (ECP) pendant la crise d'Ebola au Liberia en 2014. Plusieurs défis techniques devaient être relevés dans l'interaction avec les survivants du virus Ebola volontaires.

OBJECTIFS
Mettre en place la première technologie de plasmaphérèse et d'inactivation de pathogènes en Afrique de l'Ouest pour récolter le plasma convalescent Ebola (ECP) pour un essai clinique.

MATÉRIAUX ET MÉTHODES
Une équipe initiale de quatre personnes a été déployée (novembre 2014) pour l'installation du projet. Un véhicule a été pré-équipé avec un équipement sophistiqué et a été transporté par avion sur le site d'étude (ELWA). Les donneurs survivants étaient envoyés par le directeur médical de l'hôpital. La formation comprenait la plasmaphérèse, la gestion des donneurs, les tests et l'inactivation des agents pathogènes.

RÉSULTATS
L'unité a été créée en trois semaines. Trois techniciens libériens ont été formés à la sécurité du sang. La régression rapide de nouvelles infections a mis fin à l'essai clinique. L'ECP a été collecté jusqu'en mai 2015 avec 97 participants (19-67 ans), 42% de femmes et des groupes sanguins correspondant à ceux de l'Afrique de l'Ouest et des Afro-Américains (Pos O =57% & B Pos=20%) avec une seule unité Rh Neg. Quatre-vingt-cinq unités de plein volume ont été recueillies avec un taux de réussite de 90,4% et les donneurs réguliers ont contribué pour 39 unités sans effets indésirables enregistrés.

CONCLUSION

The conflict between expectations of the research team and realities of extreme resource constraints were overcome in the context of Ebola in a very low Human Development Index (HDI) country. Increased deployment of apheresis technology in West Africa needs consideration given 600kl of plasma is discarded in Africa each year.

CONCLUSION

Le conflit entre les attentes de l'équipe de recherche et les contraintes de ressources limitées a été surmonté dans le contexte d'Ebola dans un pays à indice de développement humain (IDH) très faible. Le déploiement accru de la technologie de l'aphérèse en Afrique de l'Ouest doit être pris en compte étant donné que 600 mille litres de plasma sont jetés en Afrique chaque année.

INTRODUCTION

'Ebola' is a viral disease that has infected over 31 000 people and killed 42% of ill cases in 35 sporadic instances since 1976[1]. By far the majority of deaths have occurred in low Human Development Index countries[2] in Central and West Africa. Prior to 2014, those few cases that have occurred out of this geographic region were in laboratory facilities in the USA, England, Italy, Russia and the Philippines. In 1996, one case was managed in South Africa for a foreign Health Care Worker (HCW) who contracted the disease in Gabon while treating patients there. He survived but the nurse treating him, who came into contact with his blood, died[3]. Removing these non-West African instances reduces the total number of EVD cases by 12 but the number of deaths by only three, nearly halving the death rate for this group of individuals (analysis of data from CDC[1]). In the post 2014 era, a similar pattern is shown whereby those treated out of the region nearly all survived. This was largely due to the additional resources and supportive high care (e.g. dialysis) at resource levels not available in the severely affected countries in West Africa or to patients in the developing world generally[4]. Despite nearly 30 'outbreaks' of the disease in Africa spanning almost 40 years[1] no effective treatment or preventive measure of the disease was known in 2014. So when West Africa was impacted by the Ebola Virus Disease (EVD) outbreak in 2014 to 2015, the world was unprepared for any effective response. Clinical services were provided by many organisations as well as the national health systems in the severely affected countries of Guinea, Liberia and Sierra Leone which were quickly overwhelmed in the initial period of the epidemic. However, in general, treatment consisted of fluid and electrolyte replacement, usually administered orally, with very limited laboratory testing for guidance on electrolyte status and renal function. To mitigate risks to health workers, oral administration of fluids was frequently preferred but less effective than intravenous administration. By mid-2014, WHO and others identified a need for a therapeutic strategy[5] and in September 2014, the World Health Organization (WHO) issued guidelines for collection and administration of Ebola Convalescent Plasma (ECP) as an experimental therapy[6,7,8]. These guidelines paved the way for several adjustments to treatments and the rapid formulation of clinical trials[4].

This paper describes the logistical process required to initiate plasmapheresis for the first time in West Africa to facilitate the research for a clinical trial in Monrovia, Liberia.

CLINICAL TRIAL OBJECTIVES AND REQUIREMENTS

The use of convalescent blood or plasma in transfusion for mass epidemics has been known for over 100 years[10]. The level of efficacy is not understood for many diseases and Ebola is no exception. During the 2014/15 crisis, most of the clinical trials sought to collect data to evaluate the efficacy of ECP as a curative therapy for EVD following prior anecdotal evidence. Specifically, eight patients were treated in Kikwit, Democratic Republic of the Congo with Convalescent Whole Blood during an outbreak in 1995 where seven patients (87.5%) survived, one of the highest ever recorded in Africa for a defined cohort[11]. However, as an uncontrolled 'study' several important data elements were not collected. Randomised clinical trials were needed to establish efficacy and in 2014, given the unprecedented scale of the epidemic, these were urgent. However, several ethical and logistical issues prevented this. The most significant was defining a statistically realistic but humane 'control' group, so three non-randomised trials were initiated[4]. Most resorted to 'historical' controls and others used the availability of compatible plasma as the determinant of inclusion in the ECP group versus the 'control' group[4,12].

In summary the objectives of the clinical trial we supported were to:

- Correlate anti-EBOV IgG (Ebola virus Immuno-globulin) in ECP with viral load in patients under treatment;
- Compare mortality in those subjects treated with ECP versus untreated controls; and
- Assess safety of treatment with and without ECP.

The protocol (EVD-001[9]) was supported by the second (EVD-002[13]) that governed the harvesting of ECP. This required the establishment (notably the first time in West Africa) of an ECP plasmapheresis unit at, ELWA hospital Monrovia, the selected location for the trial. The acronym 'ELWA' was their original radio call sign when they relied on shortwave radio for communication. This was subsequently fitted to the name "Eternal Love Winning Africa (ELWA)" (Personal communication Steve Kerj, Technical Manager ELWA Hospital, November 2014). The principle investigator for the trial was a Liberian surgeon serving as the ELWA Medical Director, Dr Jerry Brown. His tireless efforts resulted in him being justifiably recognised as one of Time Magazine's Persons of the year[14]. He developed, managed and ran the Ebola Treatment Unit (ETU), known as ELWA-II which was established on the construction site of unfinished new hospital buildings at the time. The first ETU, ELWA-I, was housed in the small hospital chapel but soon became inadequate in size and posed a risk to non-infected patients. The hospital was one of the few that stayed functioning in all departments throughout the crisis.

GETTING STARTED

In late October 2014 the Safe Blood for Africa Foundation™ (SBFA) was contracted to assist ClinicalRM (a for profit contract research organization headquartered in Hinckley, OH) with aspects of the Blood Safety Value Chain (BSVC)[15] in support of clinical trials using ECP in Liberia based on an approved protocols for clinical research[9] and for plasma harvesting[13]. At the time, apart from Côte d'Ivoire, there was no functioning apheresis capacity in West Africa that we knew of and none in general use in any of the affected countries. Separate protocols were need as the one for plasma harvesting made provision for the plasma collected to be used for humanitarian purposes as proposed in the WHO guidelines[7]. The two protocols were approved by ethics committees of the participating US academic institutions, the University of Liberia's Pacific Institute for Research and Evaluation and the Liberia Medicines and Health Products Regulatory Authority[12]. Prior to arrival it was obvious that sourcing and subsequent safe clinical use of ECP faced multiple challenges *inter alia*:

- development and ethical implementation of clinical trial designs;
- rapid harvesting and deployment of ECP in countries with limited blood collection expertise and poorly developed blood safety systems;
- the lack of local experience with apheresis;
- consistently producing safe blood components under suitable cold chain conditions;
- ensuring the principles of Good Manufacturing Practice and Quality Assurance were applied; and
- prevention of harm to or exploitation of donors.

Before arrival on site the collection equipment was specified. It was planned that donation activities would be conducted in a four-bed 'bloodmobile' (Matthews Specialty Vehicles, Greensboro, NC) as it was supposed that a mobile unit would be necessary to travel for the collection of plasma from remotely located donors. This vehicle was pre-fitted with:

- apheresis machines (PCS2, Haemonetics Corporation, Braintree, MA);
- a pathogen reduction system based on amotosalen/UV light (INTERCEPT, Cerus Corporation, Concord, CA) for plasma;
- a sterile connection (docking) device (Fresenius Compodock, Fresenius Kabi, Bad Homburg, Germany);
- a small laboratory deep freeze (Helmer Scientific, Bergen Blvd, Noblesville, IN); and
- a blood establishment computer system (BECS, provided by BBCS, Auburn, Washington).

In addition the unit included interview and laboratory space and two on-board diesel generator sets (Cummins Inc., Columbus, IN). The fitting of the vehicle was completed in the United States and airlifted to Liberia with the equipment partially commissioned by the relevant agencies but locked down to facilitate transport[12]. This meant all the equipment needed to be finally calibrated and commissioned on site. This necessitated some of the advance team to be trained to calibrate the instruments and this was carried out in the laboratories of Dr A Winkler at Emory University, Atlanta. An anticipated problem was the compatibility of the power supply. This is not insignificant as a recurring reason for equipment failure is the incompatibility with the electrical systems in Africa that are all 220 volts at 50 Hz as opposed to the US with 110 volts at 60 Hz. The equipment was mostly US configured so the vehicle's power supply was spliced into the primary hospital generators (that had dual capability), with the two back-up generators located on board the vehicle as stand-by. Furthermore, the vehicle's fuel emission control system required a fuel specification not available in Liberia and together with the incompatible power supply rendered the vehicle a static collection site. An unexpected finding was that the vibration through the unit caused by the on-board generators was not conducive to good donor experience. Having access to the hospital power grid was therefore critical. An advance party of four people from Blood Centers of America (BCA), University of North Carolina and the Safe Blood for Africa Foundation™(SBFA) arrived in late November 2014 and after considerable effort, commissioned the apheresis unit within three weeks. It is important to note that the advance team did not include a professional engineer or instrument technician and many of the initial challenges were very technical in nature. Fortunately the collective advance team had sufficient practical skills and a positive attitude to get the job done with remote support. The ELWA service division contributed considerable assistance to overcome multiple mechanical challenges within the first week. However, Monrovia's climate is challenging with heat, extreme humidity and tropical downpours causing leaks and necessitating temperature control in the unit for donor and staff comfort and to successfully operate sophisticated and sensitive instrumentation. Monrovia is the wettest capital city in the world receiving over 5100 mm of rain per annum[16]). Consequently maintaining suitable space for the plasma collection process, including work areas with climate control required for donor comfort and reliable equipment operation, was a significant challenge. The air-conditioning and climate control fitted in the vehicle was essential as were the back-up generators as frequent power cuts were experienced, often due to increased demand by other facilities responding to the Ebola crisis that were also based around the hospital.

DEVELOPING THE ABILITY TO HARVEST PLASMA

Once assembled, the three vehicle units were airlifted to Liberia, Guinea and Nigeria respectively. To all intents and purposes, these were fitted as state-of-the-art facilities in the context of the Ebola crisis. The unit at ELWA was parked at the entrance of the hospital buildings and was in stark contrast to the general surroundings. This unit was the teaching ground for the rapid training and development of competency of three Liberian laboratory technicians in procedures and processes that were entirely novel in Liberia and in the region. An important factor in the approach not to use expatriate technicians, apart from cultural sensitivity, was that in Liberia all HCWs are required to be registered and licenced by the Liberian MoH. As a consequence all aspects of the collection of ECP, care of the donor, as well as the laboratory tests had to be performed by certified Liberian health workers. Whilst this was not insurmountable there was insufficient time to complete the necessary formalities. The training model was a brief introduction to theory of the procedures followed by a Test-Teach-Test[17] approach that was then directly linked to demonstration of competency in 'wet' sessions. The international experts doing the training were successively used as live donor subjects who went through the entire work flow including counselling, informed consent, testing, needle stick and plasmapheresis – embellished by role play and simulated adverse donor events. The Liberian team demonstrated aptitude and application, despite competing demands from a hospital in the midst of a crisis.

They demonstrated sufficient knowledge, skills and competency to conduct testing, safe plasmapheresis and processing in less than 20 days. Prior to this none had any experience in aspects of the BSVC outside of drawing blood samples and testing, mostly with Rapid Determination Tests (RDT). Counselling and bedside donor care were unknown concepts for otherwise competently trained laboratory technicians. The need to master plasmapheresis, pathogen inactivation, sterile transfer, separating pathogen reduced plasma into aliquots and use of a real-time BECS contributed to a very steep and demanding learning curve. Effectively the deployment of pathogen inactivation technology for plasma in West Africa preceded approval by the US Food and Drug Administration (FDA) for plasma on 16th December 2014[18]. In keeping with experience elsewhere in West Africa, internet connectivity was often unstable in Liberia. Therefore we resorted to manual data collection and subsequently uploaded these to the US-hosted system[12]. This added to the training demands under a pressure situation as the Liberian laboratory staff had not had routine access to computers in the work place. A specific intended outcome of the trial was to leave a Blood Safety legacy capability in Liberia, so we added to the above a broader set of technical competencies such as equipment maintenance, management of the vehicle, development of Standard Operating Procedures (SOP), process and equipment validation and coping with power failures during active procedures. Critical aspects such as the apheresis and the pathogen inactivation equipment had recovery routines, provided the power was restored within a limited amount of time (<5 minutes (apheresis) and <7 minutes (pathogen inactivation). A SOP was developed for managing the vehicle that ensured the on-board power system could be activated within two minutes.

ATTRACTING AND MANAGING ECP DONORS

The management of donors for the collection of plasma from survivors was generally defined by the approved protocol known as EVD-002[12,13]. In summary the inclusion criteria for donor's eligibility were as follows:

- confirmed EVD within last 2 years;
- at least 60 days since disease onset;
- at least 28 days since discharge from an ETU;
- two negative EBOV tests by Reverse Transcription Polymerase Chain Reaction (RT-PCR);
- adult, ≥50 kg, with negative history of risk behaviour;
- Haemoglobin (Hb) ≥12.0 g/dl;
- negative pregnancy test for all female donors; and
- negative results for standard TTI tests HIV, HBV, HCV, syphilis, malaria[19].

These were to be implemented following generally accepted best practice for blood safety and donor care[20,21,22,23]. The TTI tests and blood grouping were based on RDTs and cross matching was not used. Added to these technical specifications there were several challenges anticipated regarding donor health. Importantly, in this context a potentially eligible donor was by definition an Ebola Survivor! This required greater vigilance regarding donor health and care. Most survivors were, to a variable extent, emotionally traumatized. As an illustrative example, the first donor to volunteer had lost over 25 members of their immediate family to Ebola in the preceding months. The rationale for Donor Care was to assume that as the donors would be relatively early in their convalescence there may still be residual or ongoing metabolic affects that accompanies overwhelming, severe inflammatory states (JD van Hasselt, personal communication, April 2016). Therefore, the challenges that were anticipated for donors were:

- ongoing convalescence;
- unrecognized target organ damage and uncertain metabolic status;
- chronic debility (nutritional, chronic parasitaemia, other infectious diseases, etc.);
- environmental factors such as extreme heat and humidity; and
- Post-Traumatic Stress Disorder in survivors compounded by ongoing stigma, grief and social isolation.

Most of this was speculative as collectively the clinical experts around the globe, despite those in the advance team having significant experience in Blood Safety in Africa, had no experience of Ebola survivors as donors. To address these, all donors were subjected to a thorough physical examination by trained clinicians from ELWA. If adequately fit, they were retested for EBOV by PCR.

Once selected, based on the criteria above, a standard 650 ml plasmaphersis draw followed:

- a simple meal prior to the procedure;
- medical evaluation (Hb, weight, blood pressure etc.);
- donor counselling to affirm their willingness to participate including written informed consent;
- pre-hydration with 500 ml of calcium enriched drink; and then
- volume replacement with 500 ml saline IV infusion after the plasma draw was completed.

The anticipated challenges in recruiting plasma donors was successfully addressed by Dr Brown who had already made considerable headway due to his personal relationship with survivors and his reliable contact information. In addition, during our interviews with them they stated that their experience with the disease and their survival motivated many survivors to willingly give back. Donors were also compensated for the cost of participation (travel, etc.)[12].

SOME RESULTS

As documented by van Griensven *et al*[4], all the trials were prematurely ended due the rapid decline in the number of victims in all affected countries in late February. However, the collection of plasma at ELWA continued until May 2015. The results are summarised as follows (see Brown *et al*[12] for greater details):

- 97 participants were enrolled as donors;
- 42% were females;
- Donors were O Pos (57%), B Pos (20%), A Pos (16%), AB Pos (6%), and A Neg (1%);
- 85 full-volume ECP units were collected;
- 90.4% successful collection rate;
- 39 units from repeat donors;
- <4% donated more than twice;
- average age was 33.8 ± 8.6 years (19 to 67);
- mean weight 69.3 ± 11.4 kg (50 to 112);
- average Hb13.83 ± 1.26 g/dl (11.6 to 17.1);
- mean donation interval of 47 ± 20 days (28 to 118 days); and
- no adverse effects were recorded.

As far as is known at the time of writing, the harvested plasma remains in dedicated plasma deepfreeze storage housed in the hospital laboratory at ELWA at -18 °C. The breakdown of ABO-grouping follows similar pattern to that for West Africa (Cameroon) and the ECP donor panel interestingly was also similar to those of African Americans (Table 1).

Table 1: Distribution of ABO Groups among Survivor Donors compared with other West African data and African Americans.

	O Pos	B Pos	A Pos	AB Pos	A Neg
ECP Donors	56.6	20.2	16.1	6.1	1.0
West Africa[a]	46.6	15.3	31.1	4.3	1.0
African American[b]	47.0	18.0	24.0	4.0	2.0

Data from:

a. C. Tayou Tagny, V. Fongué Fongué et D. Mbanya 2009. Rev Med Brux – 2009; and
b. http://www .redcrossblood.org/learn-about-blood/blood-types. Accessed 18 August 2016

PROMOTING PLASMAPHERESIS AND PATHOGEN INACTIVATION IN RESOURCE CONSTRAINED SETTINGS IN AFRICA – *quo vadis*?

The cost of producing a unit of whole blood and any blood components in Africa is not well characterized[24,25]. Figures determined from the WHO's 2006 data are highly variable ranging from US$ 10 to US$ 225 for whole blood[24]. Mafirakureva[25] argues that these and more recent figures are likely to be an underestimation due to the complex nature of the process[26] and poor or inappropriate application of several costing methods. In 2010, the 43 countries in Africa reporting to the WHO's Global Data Base for Blood Safety indicated that out of 1397 Blood Centres reporting, 32% were preparing blood components while only 20% prepared paediatric units[27]. The volume this represents is not stated but Red Cell Concentrate (RCC) is the dominant component produced. The only known large scale fractionation capability on the continent is in South Africa so the fate of most of the plasma separated from whole blood elsewhere is not clear. In most African countries, perhaps with the exception of South Africa, use of blood for transfusion is mainly for complications of pregnancy, births and anaemia in children under five years because of malaria[28]. In the context of the burden of diseases most commonly encountered in hospital settings in the region, there are relatively few clinical indications for plasma. The advent of pathogen reduction, in all its forms, has the potential to be a step change for blood safety in many developing countries especially for whole blood or RCC. However, as many African countries are challenged in delivering essential health services and depend substantially on foreign-funding to bolster health care, the affordability and scale of benefit of sophisticated technology being sustainably deployed in challenging and generally under resourced environments needs to be very carefully assessed. There remains a dependency in some countries on President's Emergency Plan for AIDS Relief (PEPFAR) funds for many Blood Safety activities[29] but it is clear these funds are declining based on a review of SBFA Notice of Awards 2010 to 2016. One potentially positive legacy from the Ebola crisis is that the capacity to harvest and store plasma in significant volumes has now been established in the countries where the technology was parachuted in and rapidly deployed in the crisis. How this technology will be integrated into the normal operations of the National Blood Services is not known, as few national plans or blood safety strategies are in the public domain. There are also some unintended consequences. It has been reported that the ECP donors in Liberia were compensated for the "cost of participation". Across the trials published to date, this was in the order of US$ 100 per donation visit whether successful or not[4,12]. A careful review of the potential for this to have served as an incentive to donate needs consideration. Liberia's per capita income at the time of the crisis was reported as US$ 370 pa (Atlas method[30]) therefore a single donation represented 27 % of the average annual income. Under the circumstances and where the stigma that many survivors reported prevented reintegration into normal economic life, this may be both morally and economically justifiable. However, the consequences of paid plasma donation undermining attempts at increasing Voluntary Non-Remunerated Blood Donors (VNRBD) in Liberia and other countries as they begin to build their National Blood Service should also be considered. A further hidden consequence is the juxtaposition of introducing a global plasma industry philosophy, driven by a profit motive, on efforts to ensure sustainability of a Safe Blood supply in Africa via VNRBD. However, if surplus plasma harvested in Africa, which is estimated at 600 kl and worth USD 30 million (R Reddy, personal communication, May 2016) and currently discarded, could be channelled into the global plasma industry, the compensation the National Blood Services would receive could go a long way to overcome the challenges of sustainability and cost recovery[24,25,29]. A critical condition for success of such a development will be that the funds generated are only channelled back to the improvement and development of blood safety. In addition, the cost of deploying this technology under the conditions described here, that are not that far from the norm in many developing countries, will have to be considerably reduced to ensure the development of Blood Safety activities gains maximum benefit.

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