Journal of Infection (2017) 74, 302—309

BIAM British Infection Association

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Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone

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Accepted 11 November 2016
Available online 17 November 2016

KEYWORDS
Convalescent whole blood;
EVD;
Treatment;
Sierra Leone

Summary *Background:* Convalescent blood therapy has been a promising form of treatment for Ebola Virus Disease (EVD), but less attention has been focused on it for treatment.
Method: We assessed the effectiveness of convalescent whole blood (CWB) in the treatment of consented EVD patients. We recruited 69 subjects in December 2014 up to April 2015, at the 34 Military Hospital in Wilberforce and the PTS 1 Ebola Treatment Unit in Hastings, Freetown. Forty-four were given CWB, and 25 who consented but preferred to be exempted from the CWB treatment were used to compare clinical outcomes. All were given routine treatment used at the Ebola Treatment Unit.
Results: One of 44 subjects treated with CWB dropped out of the study and 31 recovered while 12 succumbed to the disease with a case fatality rate of 27.9%. For the group that was given routine treatment without CWB, 11 died with a case fatality rate of 44%. There was a significant difference between admission viral load and viral load after the first 24 h of treatment with convalescent whole blood ($P < 0.01$). The odds ratio for survival with CWB was 2.3 (95% CI, 0.8—6.5).

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http://dx.doi.org/10.1016/j.jinf.2016.11.009

Conclusion: CWB is promising for treating EVD in resource-poor settings, especially in the early phases of outbreaks when resource-mobilization is done. Even though our sample size was small and the evaluation was not randomised, our results contribute to existing evidence that convalescent whole blood could be considered as a useful candidate for treating EVD. Further studies that are randomised will be required to further assess the efficacy of CWB as treatment option during any EVD outbreak.

Background

Convalescent blood therapy has been seeming readily available and a potent form of therapy for Ebola, since the first outbreak of the Ebola Virus Disease (EVD) in 1976, but less attention has been focussed on it for treatment. Early signs of the value of convalescent blood therapy against Ebola were revealed by the recovery of a British laboratory worker in 1977, with occupational exposure to EVD, after treatment with convalescent serum and human interferon[1] and by 1979 convalescent plasma was considered a 'specific treatment' for Ebola.[2] Further evidence of the value of convalescent blood therapy (CBT) was provided by Mupapa and colleagues in 1995[3] after treating eight subjects with CWB, and only one of them died. The treated patients may have already developed antibodies for EVD and the recovery of the patients was not wholly attributable to the CWB, but it could not also be ruled out as the primary cause of the recovery.

Subsequently, doubts were cast on passive immunotherapy with whole blood when in 1999, Sadek and colleagues[4] proved statistically that there was no survival benefit of transfusion of blood from convalescent patients. However, statistical significance does not always correlate with clinical significance. Also, an experiment was conducted to test the effectiveness of convalescent whole blood on naïve monkeys that had been infected with EVD, but it did not lead to recovery,[5] creating further doubt on the efficacy of CWB. Again, the volume of CWB used (6 ml/kg) may not have been sufficient enough to cause a recovery in the monkeys and the blood used was obtained after 30 days of reinfection of convalescent monkeys with 1000 pfu of the EVD virus.

Despite the critiques, especially for treating EVD, convalescent blood therapy remains plausible for dealing with hard-to-treat or emerging infectious diseases and is a mode of treatment that existed and was proven before EVD and before the advent of "modern" pharmaceuticals in the 1950s.[6] Human-derived and animal-derived convalescent blood were the standard of care for treatment of many pathogen-mediated and toxin-mediated diseases such as influenza in 1918[6], polio[7] and herpes zoster.[8] In recent times, convalescent blood products have been used against hard-to-treat infectious diseases such as severe acute respiratory syndrome or SARS[9,10] and the Middle East Respiratory Syndrome corona virus infection (MERS-CoV)[11] with successful outcomes. Additionally, severe pandemic influenza A (H1N1) 2009 virus infection[12] and even Ebola[13,14] have benefitted from CWB during their onsets, but no recent report on CWB for Ebola has been reported.

The distinct forms of convalescent blood therapy are: CWB which was used in this study, convalescent blood plasma (CBP) or convalescent blood serum (CWS) which was recently used for treating EVD in Guinea[13] and in other studies.[15] Blood serum and blood plasma have the same features, except that serum lacks blood clotting factors while plasma has blood clotting factors, but they perform the same function in passive immunotherapy against EVD.[16] Additional CBT are pooled human immunoglobulin (Ig) which is an intravenous immunoglobulin preparation mostly for immunomodulation[17]; recombinantly produced monoclonal antibodies (mABs) such as ZMapp[18] and polyclonal antibodies (pABs)[19]; the difference between the two is that mABs are produced by a single clone of B lymphocytes, while pABs are secreted by a mixture of B lymphocyte clones. CWB is easier to use and adaptable for application in resource-poor settings with limited kits and burden of hard-to-treat diseases such as EVD. The blood may only require screening for transfusion transmissible infections (TTIs) such as viral hepatitis and HIV and to ensure that the blood is safe and matching the ABO blood groups of recipients. In the case of convalescent plasma, its use may require plasmapheresis, which is the separation of blood cells from the liquid plasma, before use. Also, the IgG in plasma could be enriched by fractionation.[15]

In resource-poor environments, lacking basic amenities and prone to diseases such as Ebola, the use of CWB is important. In recognition of this fact, the World Health Organisation (WHO) in September 2014, provided interim guidance for the evaluation of CWB and CBP for the treatment of EVD.[20]

However, little research has been done on CBT, and the few studies done had a small sample size. In this study, we assessed the effectiveness of CWB in the treatment of infected patients using a non-randomised study design.

Methods

Study location

The study was carried out at the 34th Regiment Military Hospital in Wilberforce, Freetown, and the PTS 1 Ebola Treatment Centre in Hastings Freetown. Both treatment centres were established through partnership of the Sierra Leone MOHS, Ministry of Defence and WHO. Both treatment units were operated mainly by Sierra Leoneans. The Hastings unit had earlier recorded a case fatality rate of 31.5% resulting from treating 581 EVD patients with IV fluids, IM vitamin K, IM artemether, IV ceftriaxone, IV metronidazole, Ringer's Lactate, dextrose saline, Ibuprofen tablets, Immunoboost nutrition supplement, zinc sulphate tablets, artesunate—lumefantrine combination therapy tablets, oral rehydration salts and other drugs.[21]