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Techniques and Procedures

COMMENTARY ON RECONSTITUTING FIBRINOGEN CONCENTRATE TO MAINTAIN BLINDING IN A DOUBLE-BLIND, RANDOMIZED TRIAL IN AN EMERGENCY SETTING

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☐ **Abstract—Background: The gold standard of trial design is the double-blind, placebo-controlled, randomized trial. Intravenous medication, which needs reconstitution by the attending clinician in an emergency situation, can be challenging to incorporate into a suitably blinded study. Discussion: We have developed a method of blindly reconstituting and administering fibrinogen concentrate (presented as a lyophilized powder), where the placebo is normal saline. Fibrinogen concentrate is increasingly being used early in the treatment of major hemorrhage. Our methodology was designed for a multicenter study investigating the role of fibrinogen concentrate in the treatment of the coagulopathy associated with major obstetric hemorrhage. The method has been verified by a stand-alone pharmaceutical manufacturing unit with an investigational medicinal products license, and to date has successfully been applied 45 times in four study centers. There have been no difficulties in reconstitution and no related adverse events reported. Conclusion: We feel our method is simple to perform and maintains blinding throughout, making it potentially suitable for use in other trials conducted in psychologically high-pressure environments. Although fibrinogen concentrate was the focus of our study, it is likely that the method is applicable to other lyophilized medication with limited shelf life (e.g., antibiotics).**

☐ **Keywords—fibrinogen; double-blind method; postpartum hemorrhage**

INTRODUCTION

The double-blind placebo-controlled randomized trial is the gold-standard trial design. It is therefore crucial that in medicinal-based studies, the active drug or placebo (investigative medicinal product [IMP]) is stored and administered in a way that prevents the clinician involved knowing what is being given to the patient. The administration of intravenous IMP that has a limited shelf life once reconstituted usually requires a pharmacist or clinician who is not directly involved in the trial to mix the product or provide a saline substitute in a covered syringe. This ensures adequate mixing and exclusion of air in the syringe while maintaining blinding within the trial to the clinician.

There are an increasing number of registered trials where reconstitution of the IMP is required in the emergency setting, and due to the trial design, researchers may have to recruit out of hours. Depending on the frequency of the intervention, it may be possible to have ready prepared IMP or employ staff to cover the out-of-hours service, but if the IMP has a short shelf life once mixed, or the

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intervention is relatively infrequent, this approach could be very wasteful and be prohibitively expensive.

There are a number of registered trials where fibrinogen concentrate (RiaSTAP, CSL Behring, Marburg, Germany) is being compared to placebo (saline) in the emergency setting of obstetric and traumatic hemorrhage (1–3). It is essential within these trial settings that the IMP can be administered quickly, without safety concerns, and without un-blinding. In the study, fibrinogen concentrate vs. placebo for treatment of postpartum hemorrhage: a multicenter, prospective, double-blind, randomized control trial; Ref: 13/SS/0008 (ISRCTN4629339); recruitment has required that over 500 clinicians be trained to mix and administer the IMP, but due to the rarity of the clinical situation, only 45 patients have been randomized over a 2-year period (4). The end-point of the trial is the number of blood-products used, and un-blinding could influence decision-making and trial outcome. The mixing method had to be easy to teach, easy to remember, and the final product quick and easy to administer.

DISCUSSION

Outline of Blinding Methodology (Detailed Description, with Step-by-Step Guide, Appendix 1)

Fibrinogen concentrate is presented as a white hydrophilic powder containing 1 g of human fibrinogen per glass vial. It can be stored at room temperature (<25°C) for 5 years. Manufacturer's reconstitution instructions recommend adding 50 mL of water for injection and gently agitating for 5 to 10 min (may require 15 min) until the powder is fully reconstituted. The resulting solution may vary in appearance from almost colorless to yellowish, clear to slightly opalescent, but always looks slightly viscous (5). In our experience, this process can cause frothing, especially if a narrow-bore needle is used to transfer the water and draw up the medication in haste. Once reconstituted, it is stable at room temperature for 8 h. The placebo in our study was 0.9% saline for injection, and although similar in volume, looks different due to the clarity, viscosity, and the propensity of the fibrinogen product to form bubbles. By covering the bottles with cardboard jackets, using a series of wide-bore decanting and drawing-up spikes, using black (completely opaque) syringes and expelling air that was drawn up into the syringe into a gelatin intravenous product, we successfully designed a system that fulfilled the requirements for the trial. The crucial final step of expelling the air, which is inevitably drawn into the opaque syringe, by injecting into an inverted bag of gelatin for intravenous use, ensured that all air has been safely expelled and blinding was not lost.

The mixing process was verified by the St Mary's Pharmaceutical Unit (SMPU), a stand-alone pharmaceutical manufacturing unit with an investigational medicinal products license [MIA(IMP)]. They verified that by decanting water under gravity through a wide-bore double-ended spike into a bottle of fibrinogen concentrate power and then leaving the contents of the bottle to stand rather than be agitated as described in the manufacturer's insert, the fibrinogen concentrate had completely dissolved by the time the solution had been drawn into a clear 50-mL syringe. This was repeated 16 times and overseen by an SMPU pharmacist. SMPU also investigated the perception of the force required to fill the syringe with the mixed fibrinogen concentrate and the perception of the force required to expel the air/bubbles into the gelatin product. After covering the 50-mL syringes, they concluded that there was no difference between the reconstituted fibrinogen and saline. The process was performed eight times for each solution.

To date, this mixing procedure has been performed 45 times across four centers. There have been no reported problems.

Our method outlines a reliable method for mixing and administering two dissimilar intravenous medications in the setting of a randomized, placebo-controlled, double-blinded study. It is simple to perform, making it suitable for use in a psychologically high-pressure environment and maintains blinding throughout.

Strengths

This method of reconstitution improves on current guidelines. The use of wide-bore transfer devices and dispensing pins enhances the procedure by speeding up fluid transfer, reducing frothing, improving mixing, and reducing the risk of needle-stick injury. The use of black syringes is uncommon in clinical practice, but has worked without safety concerns in this trial. A rapid method of reconstituting fibrinogen has been described by Karri et al. (6). In this method, 50 mL of sterile water was forcibly injected into the bottle containing the fibrinogen concentrate. The mixture was then vigorously shaken for 30 s prior to being aspirated into a syringe. Despite producing excess foaming, the dissolved fibrinogen solution was as effective at raising plasma fibrinogen levels as fibrinogen solution prepared using the conventional method. This protocol was not part of a blinded study, so has limited application when the IMP is being drawn into an opaque syringe.

Limitations

The method is robust if followed, however, there are opportunities for un-blinding: handling or shaking the