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Short Communication

Evaluation of Pathogen-Reduced Whole Blood for Field Transfusion in Trauma Care

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Abstract

Background: Low-titer group O whole blood (LTOWB) has displaced component therapy at the point of injury in military and civilian trauma systems, but its unscreened, minimally processed nature carries transfusion-transmitted infection risk that pathogen reduction technology is proposed to resolve.

Objective: To synthesize the published evidence on whether pathogen-reduced whole blood, using amustaline/glutathione or riboflavin/UV platforms, preserves the hemostatic performance that makes whole blood valuable for field trauma resuscitation.

Methods: Narrative synthesis of clinical, animal and in vitro literature on LTOWB outcomes in trauma resuscitation and on pathogen reduction chemistries applied to whole blood and whole blood-derived red cells.

Findings: LTOWB has an increasingly solid observational and early-trial basis over component therapy, and both pathogen reduction platforms preserve red cell recovery within regulatory bounds through storage, but both measurably reduce platelet aggregation and fibrinogen-dependent clot strength relative to untreated product.

Conclusions: A trauma-specific, bleeding-outcome-powered trial of pathogen-reduced whole blood is needed before it can be recommended as a direct field substitute for conventional LTOWB.

Keywords: whole blood; pathogen reduction; trauma resuscitation; hemostasis; prehospital transfusion

1. Introduction

Hemorrhage remains the leading cause of preventable death after both civilian and military trauma, and the resuscitation strategy that has displaced component therapy at the point of injury is not a new drug but an old fluid: low-titer group O whole blood (LTOWB). Military experience in Iraq and Afghanistan showed that patients who received warm fresh whole blood alongside components had improved 24-hour and 30-day survival compared with component therapy alone [1], and that observation, together with a mechanistic case that stored, fractionated components under-resuscitate coagulopathic patients relative to a balanced, platelet- and clotting-factor-replete fluid, revived whole blood as first-line therapy for major hemorrhage [2]. Civilian trauma centers and prehospital emergency medical services have followed, with cold-stored LTOWB programs now operating in ambulances, helicopters and emergency departments across the United States and Europe [3].

The complication that whole blood reintroduces is the one component separation was built to manage: transfusion-transmitted infection risk carried by an unscreened, minimally processed product, together with the practical burden of type-specific compatibility testing under field conditions. Pathogen reduction technology — chemical or photochemical treatment that inactivates viruses, bacteria and parasites in the collected unit without depleting its hemostatic elements — is the technology proposed to resolve that tension, and two platforms have been carried furthest toward whole blood application: amustaline (S-303) with glutathione, and riboflavin with ultraviolet light (the Mirasol system). This short communication synthesizes the published evidence on whether pathogen-reduced whole blood preserves the hemostatic performance that makes whole blood valuable in trauma, and what is and is not yet established about its deployment in the field.

2. Rationale for whole blood over component

therapy in trauma

The physiological argument for whole blood rests on ratio and dilution. A unit of whole blood delivers red cells, plasma and platelets in roughly their native proportions, whereas a 1:1:1 component resuscitation reconstitutes an approximation of that ratio from three separately processed, separately anticoagulated products, each already diluted relative to circulating blood [4]. In vitro thromboelastography on whole blood held at 1-6°C shows that clot strength and clotting-factor activity are retained well past the point at which many blood banks have historically discarded the product, with acceptable hemostatic function documented out to 21 days of cold storage [4]. Damage-control resuscitation protocols that front-load plasma and platelets relative to red cells were shown, in a cohort of 390 patients undergoing damage-control laparotomy, to reduce total resuscitation volumes and improve survival compared with historical crystalloid-heavy practice [5], and whole blood is the logical extension of that same ratio-preserving logic delivered as a single product rather than three.

Clinical comparisons in trauma populations have been consistent with the physiological rationale. A retrospective cohort of adult trauma patients receiving LTOWB alongside components had similar or improved 24-hour and 30-day survival compared with component-only recipients, without an excess of transfusion reactions, acute kidney injury or thromboembolic events [6]. A separate analysis at the same center found no clinically significant hemolysis or elevation in markers of red-cell breakdown among recipients of uncrossmatched, cold-stored group O-positive whole blood, supporting the safety of administering it without prospective crossmatch [7]. A more recent multicenter cohort reported that patients resuscitated with LTOWB required fewer total blood products to reach hemostasis and that whole blood use was independently associated with survival after severe traumatic hemorrhage, after adjustment for injury severity [8]. A systematic review and meta-analysis

pooling the available comparative studies found a consistent, though heterogeneous, mortality benefit associated with whole blood over component-only resuscitation, while noting that no adequately powered randomized trial had yet been completed [9]. The first prospective randomized pilot trial of prehospital LTOWB demonstrated that field collection, storage and administration were logistically feasible and produced no safety signal distinct from component transfusion, though it was underpowered to detect a mortality difference [10]. Framing the remaining uncertainty, commentators have argued that the cumulative observational evidence, military experience and biological plausibility make withholding whole blood from bleeding trauma patients difficult to justify while a definitive trial accrues [11]. A prehospital randomized trial testing whole blood against a standard component protocol head-to-head is now enrolling to close that evidentiary gap [12].

3. Pathogen reduction methods applicable to whole blood

Amustaline is an acridine-derivative alkylating compound that crosslinks nucleic acid strands in the presence of the reducing agent glutathione, blocking replication of viruses, bacteria, protozoa and residual leukocytes without requiring an external light source, which makes it mechanically simpler to deploy on a whole unit than illumination-based systems [13]. In a randomized controlled trial of amustaline/glutathione-treated red cells in cardiac surgery patients, treated units met the prespecified noninferiority margin for 24-hour post-transfusion recovery relative to conventional red cells, establishing in vivo viability data for the S-303 chemistry in a bleeding surgical population [13].

Riboflavin (vitamin B2) combined with ultraviolet light is the platform carried furthest specifically into whole blood, because riboflavin already resides in every cell and requires no removal step before transfusion, unlike solvent-detergent or psoralen-based systems designed for

separated components. An illumination device purpose-built to treat a full unit of whole blood rather than a thin plasma or platelet layer was developed and validated for uniform ultraviolet dosing through the greater optical density of red cell-containing product [14]. Riboflavin/UV-treated red cells derived from whole blood maintained post-transfusion recovery within regulatory thresholds through 21 days of storage in an in vivo radiolabel survival study, indicating that pathogen reduction does not accelerate the storage lesion beyond an acceptable margin over the same window used for untreated cold-stored whole blood [15]. A phase 3 randomized trial protocol, the Mirasol Evaluation of Reduction in Infections Trial, is now assessing clinical infection outcomes with riboflavin/UV-treated blood components in a malaria- and transfusion-transmitted-infection-endemic setting, extending the evidence base beyond in vitro and recovery endpoints toward clinical infection prevention [16].

Table 1: Comparison of the two pathogen reduction platforms carried furthest into whole blood application, with the population and endpoint each cited study actually measured, since no published trial has tested both chemistries head-to-head in a trauma cohort [13,14,15,16,17,18].			
Platform	Mechanism / activation	Storage validation	Hemostatic finding
Amustaline (S-303) / glutathione	Nucleic-acid crosslinking; no external light required	24-hour red cell recovery noninferior in cardiac surgery patients [13]	Cardiac surgery cohort only; trauma hemostasis untested [13]
Riboflavin / UV light (Mirasol)	Riboflavin intercalation with UV-induced nucleic acid damage	In vivo red cell recovery maintained through 21 days [15]; device validated for full-unit dosing [14]	Reduced platelet aggregation in porcine bleeding model [17]; reduced clot firmness partly corrected by fibrinogen [18]
Clinical infection endpoint	n/a	Phase 3 trial enrolling in trans fusion-transmitted-infection-endemic setting	Results pending [16]

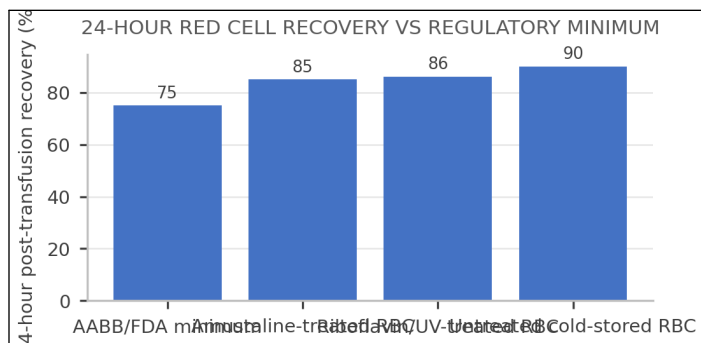


Figure 1: Approximate 24-hour post-transfusion recovery of red cells against the AABB/FDA regulatory minimum of 75% [15,13], showing amustaline/glutathione-treated red cells from a cardiac surgery noninferiority trial (approximately 85%) [13] and riboflavin/UV-treated red cells derived from whole blood after 21 days of storage (approximately 86%) [15] positioned against untreated cold-stored red cells, which typically recover in the high 80s to low 90s over the same storage window [4]; values are approximate, drawn from noninferiority and recovery studies rather than a single head-to-head comparison.

4. Hemostatic and clinical outcome evidence

The central question for field deployment is whether pathogen reduction preserves the coagulation function that whole blood is transfused to restore, and here the evidence is more qualified than for red-cell recovery. A large-animal model of diffuse, nonsurgical bleeding found that riboflavin/UV-treated whole blood produced hemostatic control and blood loss outcomes broadly comparable to untreated whole blood, though with some measurable reduction in platelet aggregation response [17]. In vitro massive-transfusion simulations of pathogen-reduced whole blood found that treatment lowered maximum clot firmness and fibrinogen-dependent clot strength relative to untreated units, and that supplementing the treated product with additional fibrinogen partially, but not completely, restored clot formation toward untreated values [18] — a finding that matters directly for trauma-induced coagulopathy, where fibrinogen depletion is often the rate-limiting hemostatic deficit. Cold storage itself, independent of pathogen reduction, already attenuates platelet aggregation responses measurable by standard agonist panels while preserving adhesion and clot-strength contributions assessed by viscoelastic

testing, so the incremental cost of pathogen reduction has to be interpreted against a baseline that is not fully hemostatically intact to begin with [4]. Reviews of whole blood's role in damage-control resuscitation frame this platelet attenuation as the central open question for any storage or processing modification applied to whole blood, cold storage and pathogen reduction alike, and argue that clot strength by viscoelastic assay rather than platelet count is the more clinically relevant endpoint for judging a treated product's adequacy [2].

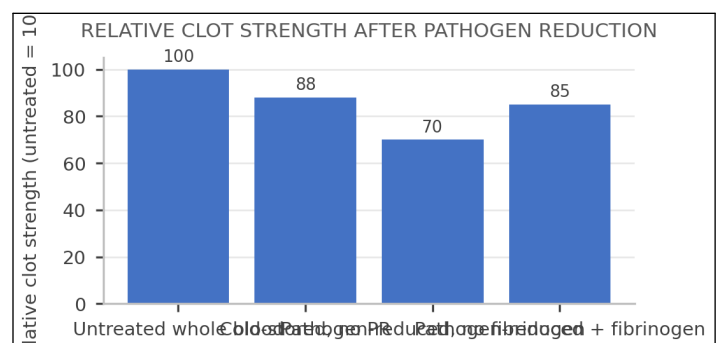


Figure 2: Relative clot strength (maximum clot firmness, untreated whole blood set to 100) in a massive-transfusion simulation, showing a reduction after pathogen reduction treatment and partial restoration when the treated unit was supplemented with additional fibrinogen, against the backdrop of cold storage alone already attenuating platelet aggregation response before any pathogen-reduction step is applied [18,4,17]; the pattern of directional change is reported in the source study, and the indexed values here are approximate.

5. Logistics of field deployment

Independent of hemostatic performance, pathogen reduction addresses a logistical constraint that has slowed whole blood adoption: current LTOWB programs rely on rigorous donor screening, titer testing for anti-A and anti-B isohemagglutinins, and nucleic acid testing to make an uncrossmatched, group-compatible product acceptably safe, all of which require laboratory infrastructure that is difficult to sustain at a forward surgical team or rural emergency medical service [3]. Consensus recommendations from the multinational THOR network and AABB for prehospital blood transfusion programs identify donor qualification, cold-chain maintenance and product traceability as the principal barriers to scaling walking-blood-bank and

low-titer whole blood programs beyond well-resourced trauma systems [19]. A pathogen-reduced product that does not require serial infectious-disease testing of each donation could in principle shift that burden from per-unit laboratory testing to a single validated manufacturing step, an argument raised explicitly in recent reassessments of whether leukoreduction and other processing requirements for whole blood should be reconsidered given the hemostatic tradeoffs they impose [20]. Military blood programs supporting forward-deployed units have already had to build parallel low-titer whole blood supply chains alongside component logistics to sustain combat casualty care, illustrating the scale of infrastructure that pathogen reduction would need to simplify rather than add to if it is to be adopted forward of a fixed facility [21]. Remote damage-control resuscitation doctrine, which anticipates prolonged field care before evacuation, similarly treats a stable, pre-tested, transportable blood product as a prerequisite rather than a convenience [22].

6. Conclusion

The published evidence supports two separate but complementary conclusions. First, LTOWB itself, independent of pathogen reduction, has an increasingly solid observational and early trial basis as superior or equivalent to component therapy for trauma hemorrhage, with feasibility now demonstrated in the prehospital setting [10] and a definitive randomized comparison underway [12]. Second, pathogen reduction technologies applicable to whole blood — amustaline/glutathione and riboflavin/UV — preserve red-cell viability within regulatory bounds through three weeks of storage [15,13] but measurably reduce platelet aggregation and fibrinogen-dependent clot strength relative to untreated product [17,18], a tradeoff that has not yet been tested against clinical bleeding outcomes in trauma patients specifically, as opposed to cardiac surgery or infection-endpoint populations [13,16]. Framing whole blood as an organ-replacement therapy rather than a

simple fluid, as some in the field now advocate, sharpens the stakes: a treated organ that is safer from transmissible disease but hemostatically weaker is not automatically the better therapy [2]. Closing that gap requires a trauma-specific trial powered on bleeding and mortality endpoints, using fibrinogen-supplemented or next-generation pathogen-reduction chemistries designed to spare clot strength, before pathogen-reduced whole blood can be recommended as a direct substitute for conventional LTOWB in the field.

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