FREEZE-DRYED PLASMA FOR MAJOR TRAUMA – SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND:
Treatment of acute trauma coagulopathy has shifted toward rapid replacement of coagulation factors with frozen plasma (FP). There are logistic difficulties in providing FP. Freeze-dried plasma (FDP) may have logistic advantages including easier storage and rapid preparation time. This review assesses the feasibility, efficacy, and safety of FDP in trauma.

STUDY DESIGN AND METHODS:
Studies were searched from Medline, Embase, Cochrane Controlled Trials Register, ClinicalTrials.gov, and Google Scholar. Observational and randomized controlled trials (RCTs) assessing FDP use in trauma were included. Trauma animal models addressing FDP use were also included. Bias was assessed using validated tools. Primary outcome was efficacy, and secondary outcomes were feasibility and safety. Meta-analyses were conducted using random-effect models. Evidence was graded using Grading of Recommendations Assessment, Development, and Evaluation profile.

RESULTS:
Twelve human studies (RCT, 1; observational, 11) and 15 animal studies were included. Overall, studies demonstrated moderate risk of bias. Data from two studies (n = 119) were combined for meta-analyses for mortality and transfusion of allogeneic blood products (ABPs). For both outcomes, no difference was identified. For mortality, pooled odds ratio was 0.66 (95% confidence interval, 0.29–1.49), with I² = 0%. Use of FDP is feasible, and no adverse events were reported. Animal data suggest similar results for coagulation and anti-inflammatory profiles for FP and FDP.

CONCLUSION:
Human data assessing FDP use in trauma report no difference in mortality and transfusion of ABPs in patients receiving FDP compared with FP. Data from animal trauma studies report no difference in coagulation factor and anti-inflammatory profiles between FP and FDP. Results should be interpreted with caution because most studies were observational and have heterogeneous population (military and civilian trauma) and a moderate risk of bias. Well-designed prospective observational studies or, preferentially, RCTs are warranted to answer FDP’s effect on laboratory (coagulation factor levels), transfusion (number of ABPs), and clinical outcomes (organ dysfunction, length of stay, and mortality). (J Trauma Acute Care Surg. 2021;90: 589–602. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.)

LEVEL OF EVIDENCE:
Systematic review and meta-analysis, level IV.

KEY WORDS:
Freeze-dried plasma; acute trauma coagulopathy; hemostatic resuscitation; blood component therapy.

Trauma is the leading cause of mortality in individuals younger than 35 years and is responsible for approximately 10% of deaths worldwide.1,2 The most common cause of preventable death from trauma is acute hemorrhage.3,4 Bleeding in trauma may be worsened by acute trauma coagulopathy (ATC), which is present even before resuscitation in approximately 25% of trauma patients.5,6 In patients with ATC, there has been a shift away from providing crystalloids if blood products are available and a shift away from using red blood cells (RBCs) alone.7 An emphasis has developed toward achieving a ratio of plasma-to-RBC of 1:1 to 1:2. One concern with crystalloid-based resuscitation and use of RBCs alone is their contributions to hemodilution because these do not provide clotting factors that are lost during acute hemorrhage. Because clotting factors are necessary to help combat ATC (hemostatic resuscitation), trauma resuscitation has focused on a more balanced strategy, where clotting factors are replaced in addition to RBCs. Currently, hemostatic resuscitation is provided in a fixed ratio of RBC/plasma (fresh frozen plasma or liquid plasma)/platelets (PLTs).8–10 In addition, several trauma centers in the United States have also been using...
whole blood,\textsuperscript{11,12} thawed plasma, and liquid plasma.\textsuperscript{13} Furthermore, in Europe and the United States, trauma centers have been using a more goal-directed therapy with thromboelastography (TEG) or rotational thrombelastometry (ROTEM).\textsuperscript{14–16} Finally, other concentrate of clotting factors, such as prothrombin complex concentrate (PCC), fibrinogen concentrate (FC), or cryoprecipitate, have also been implemented worldwide and are part of the management of the hemostatic impairments of ATC.\textsuperscript{11,12}

Plasma has logistical challenges with storage and reconstitution. Frozen plasma must be stored at $-18^\circ C$ and thawed before use. The thawing, labeling, and issuing process take approximately 30 minutes. After thawing, FP must be transfused immediately or refrigerated and used within 5 days.\textsuperscript{17} This presents many logistical challenges and results in a significant delay in receiving FP. In the United States, plasma is available in the form of FP, liquid plasma, thawed plasma, and type A plasma and are in widespread use.\textsuperscript{18} However, in Canada, only FP is available, and it is currently limited to in-hospital settings and commenced only 30 to 60 minutes after hospital arrival.

In addition to FP, thawed plasma (5-day shelf life),\textsuperscript{13,19,20} and liquid plasma (range from 26- to 40-day shelf life),\textsuperscript{13,20} freeze-dried plasma (FDP) may also be an option. Freeze-dried plasma is manufactured by freeze drying or spray drying a large batch of plasma units and can be stored at room temperature for 2 years without losing its hemostatic capabilities, as evidenced by maintained coagulation factor profiles.\textsuperscript{21} Furthermore, FDP is easily reconstituted with 200 to 250 mL of sterile water (SW), is not affected by forceful shaking during reconstitution, and can be used within minutes, making it practical in theprehospital and early hospital settings where FP is unavailable.\textsuperscript{22,23} The utility of FDP is not a novel concept; it has been used in the military setting since World War II in the treatment of hemorrhagic shock. However, concerns regarding disease transmission, including hepatitis, with the use of pooled FDP, led to the cessation of large-scale production.\textsuperscript{24} The need for FDP remained in the military setting, and with significant improvement in donor screening, testing procedures, and pathogen reduction technology, the French military produced French lyophilized plasma (FLyP).\textsuperscript{25} Since then, FDP has also been manufactured and transfused in countries such as Germany and South Africa.\textsuperscript{25,26} However, the overall safety and efficacy of FDP are still unknown because of the absence of large, randomized controlled trials (RCTs) comparing FDP with current standard of care, FP. Furthermore, the effect of FDP on host inflammatory response is also unknown. We sought to review the current evidence assessing feasibility, efficacy, and safety of FDP use in patients with traumatic injury and in animal models of traumatic injury.

PATIENTS AND METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.\textsuperscript{27}

Studies

This review included human prospective and retrospective cohort studies with or without a control group (e.g., observational studies comparing FDP vs. FP and/or observational studies assessing FDP alone) and RCTs. The review also included animal and laboratory (in vitro, ex vivo) studies with or without a control group. To be included, studies had to report at least one outcome of interest. We excluded case reports, conference proceedings, and studies assessing nontrauma patients.

Participants

Studies were included if they were conducted in adult bleeding trauma patients (≥16 years old) in whom FDP was used for resuscitation. For inclusion, we required the studies to include patients who received at least 1 U of FDP within the first 24 hours of assessment. Animal studies were included if they used bleeding trauma animal models (e.g., swine and mice) and administered FDP with or without a control group.

Interventions and Controls

The intervention we studied was use of FDP for resuscitation of adult trauma patients and trauma animal models. Controlled studies usually compared FDP with other resuscitation strategies including plasma, factor concentrates, or goal-directed therapy (laboratory guided, TEG, or ROTEM).

Outcome Measures

We considered mortality as the primary outcome. Secondary outcomes were as follows: (1) efficacy—effect on levels of coagulation factors; effect on ATC parameters represented by international normalized ratio (INR), fibrinogen levels, and TEG/ROTEM parameters; effect on the use of allogeneic blood products (ABPs); and effect on activity/levels of markers of inflammation; (2) feasibility of use of FDP; and (3) safety—adverse events attributed to FDP use compared with the control population (where applicable).

Search Methods

We searched Medline (from 1946 to March 31, 2020), Embase (1947 to March 31, 2020), Cochrane Controlled Trials Register (from inception to March 31, 2020), ClinicalTrials.gov (http://www.clinicaltrials.gov), and Google Scholar (first 200 hits). The search was not restricted by date, language, or publication status. Search terms were defined a priori and by reviewing the Medical Subject Headings terms of articles identified in preliminary literature searches. The search strategy was based on the Medline search strategy and was modified as necessary for the other databases. A sensitive search strategy combining Medical Subject Headings (MeSH) headings and the keywords “plasma,” “lyophilized plasma,” “frozen plasma,” and “trauma/injury” was used.

Data Abstraction

Two review authors (G.M., M.W.K.), not blinded to the journal, institutions, or authors, independently examined all titles and abstracts identified by the search and determined if they should undergo a full text review. Full texts with questionable eligibility or considered eligible were retrieved for evaluation. References within each included full text were also searched for additional citations. Disagreements were resolved by consensus or with another review author (L.T.d.L. or R.H.). Only published data were included. Investigators were not contacted to obtain further data. Data were also collected independently by two review authors (G.M., R.H.).

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Risk of Bias Assessment and GRADE Profile

Risk of bias for human and animal studies was assessed in duplicate (G.M., R.H.) for each included study. Disagreements were resolved through discussion and consensus with a third author (L.T.d.L.). Human RCTs were assessed using the Cochrane Collaboration’s tool, which assesses bias by describing the risks (low risk, high risk, and unclear risk) in the domains of sequence generation, allocation concealment, blinding of outcomes, incomplete outcome data, selective outcome reporting, and baseline imbalances.28 Observational cohort studies were assessed using the Newcastle-Ottawa Scale (NOS).29 This tool defines patient groups as comparable in either the design or analysis when the effect of the exposure is adjusted for confounders. The NOS assesses the following domains: selection of exposed and nonexposed cohorts, comparability of cohorts, assessment of outcomes, and adequacy of follow-up. Using NOS, a score of ≤3 was considered high risk of bias; 4 to 6, moderate risk of bias; and >7, low risk of bias. For animal studies, we assessed risk of bias by using the tool proposed by Krauth et al.,30 which includes domains of randomization, allocation concealment, blinding, sample size, ethical compliance, statistical methods, outcome assessment, and follow-up. Quality of evidence for mortality and exposure to ABPs was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, which included evaluation of each outcome for five domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias. It was classified as high, moderate, low, or very low (www.gradepro.org, version 3.6.1; McMaster University, 2014).

Analyses

Studies were combined in meta-analyses if there was enough clinical and methodological homogeneity. Studies were analyzed separately according to their design (observational or randomized). Clinical and methodological heterogeneity across the studies was assessed by examining the details of the subjects, the baseline data, the interventions, and the outcomes, to determine whether the studies were sufficiently similar. Statistical heterogeneity was determined using the $I^2$ statistic and the $\chi^2$ test. High values of both tests ($I^2 > 40\%$, a nonsignificant $\chi^2 [p < 0.05]$, respectively) demonstrate high levels of inconsistency and heterogeneity. Heterogeneity was further investigated observing the variations in the effect sizes across studies and overlapping of confidence intervals, which were used while performing the GRADE profile. Pooling of overall estimates was performed using generic inverse variance weighting methods. Using these methods, each study estimate of the relative treatment is given a weight that is equal to the inverse of the variance of the effect estimate (i.e., one divided by the standard error squared). Studies were grouped according to the data reported

![Flow diagram of the screening process](image-url)

**Figure 1.** Flow diagram of the screening process.
| Author and Year | Study Design | Population; Age, Mean/Median (±SD/IQR), y | Sample Size, Male, n (%) | Injury Type | Control Group(s) | Intervention; Dose, Mean/Median (±SD/IQR) | Intervention (Other) | Outcome(s) Measured |
|-----------------|--------------|------------------------------------------|--------------------------|-------------|------------------|------------------------------------------|----------------------|---------------------|
| Martinaud et al., 2011 | Prospective | Military; median, 23 (1–60) | 87 (60.9) | GSW, blunt, explosions | None | FDP; 3 (3.5 ± 2.3) U RBC, 2 (2.6 ± 2.1) U FVIIa, 2 (2.3 ± 2) mg | 1. Mortality 2. PT 3. FDP feasibility | 1. Mortality 2. PT 3. FDP feasibility |
| Sailliol et al., 2014 | Prospective observational | Military; 37 (16–84) | 269 (57) | Explosion, blunt, penetrating, other/not specified | None | FLYP; mean/median, NR | None reported | 1. Hemostasis before and after FLYP 2. Adverse events 3. Feasibility |
| Sunde et al., 2015 | Retrospective | Civilian; median, 36 (1–60) | 16 (88) | Penetrating, blunt | None | FDP (n = 16); 200 mL (IQR, NR) | None reported | 1. Adverse effects 2. 30-d mortality 3. Feasibility |
| Benov et al., 2016 | Retrospective | Military; median, 21 (20–22) | 704 (98) | Penetrating, blunt, burns, inhalation | None | FDP (n = 25); total, 29 U; TXA (dose, NR) | None reported | 1. Adverse effects 2. Feasibility |
| Shliaifer et al., 2017 | Retrospective | Military; median, NR (18–35) | 109 (96.3) | Penetrating, blunt, burns, blast, combination | None | FDP; 1 U (83.4%); 2 U (12.8%); 3 U (4.6%); mean/median, NR TXA, 1 g (n = 80, 73.4%); mean/median, NR RBC (n = 9, 8.2%); mean/median, NR PLTs (n = 3, 18.8%); mean/median, NR | None reported | 1. Feasibility 2. Safety, adverse reactions 3. Adherence to CPG |
| Vitalis et al., 2017 | Prospective observational | Military; median, 28 (23–39) | 28 (96) | Explosion, GSW, other | None | FLYP | TXA (dose, NR) RBC (dose, NR) Whole blood (dose, NR) | None reported | 1. Time to transfusion 2. Safety, complications 3. Mortality at 24 h |
| Nguyen et al., 2018 | Retrospective before and after | Civilian; median, 43 (31–68) | FlyP, 43 (79) FP, 29 (79) | Penetrating, blunt | FP | FLYP; mean/median, NR TXA (dose, NR) FLYP (n = 42, 98%); FP (n = 27, 93%) | None reported | 1. Time to first FP 2. Time to FP/RBC of 1:1 3. RBC, FP, PLT, Fib use in 24 h 4. MT protocol 5. 24-h hospital mortality 6. Hemorrhage-related mortality |
| Garrigue et al., 2018 | Randomized open-label trial | Civilian; FlyP, mean, 48.0 ± 16.5 Civilian; FP, mean, 38.0 ± 15.6 FlyP, 23 (82.6) FP, 24 (66.7) | Penetrating, blunt | FlyP (4 U); mean/median, NR | TXA (dose, NR) FLYP (n = 19, 82.6%); vs. FP (n = 22, 91.7%) | None reported | 1. Fibrinogen level 45 min after randomization 2. % Fibrinogen level >1.5 g/L at 45 min 3. Changes in hemostatic parameters (45 min, 6 h, 12 h, 24 h) 4. Time to transfusion 5. FC used over 24 h 6. 30-d mortality |
| Oakeshott et al., 2019 | Retrospective | Civilian; mean, 46 (4–90) | 216 (73) | Penetrating, blunt | Before FLYP availability; RBCs only | FLYP; mean/median, NR RBC alone | None reported | 1. Feasibility 2. Prehospital RBCs 3. Adverse effects |
on mortality and transfusion of ABPs (RBC, plasma, PLT, and FC), for conducting meta-analyses.

Review Manager 5.3 software (RevMan 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark; 2015) was used to carry out quantitative analyses. A random-effects model was used because this approach accommodates clinical and statistical variations. Heterogeneity was explored. Odds ratio and 95% confidence intervals were used as statistical measures for mortality as a dichotomous outcome. Mean and SD were the statistical measure used to describe exposure to ABPs. In studies that reported transfusion data in medians and interquartile ranges (IQRs), mean and SD were estimated using the sample size in each study arm, medians, and the first and third IQRs as demonstrated in the method published by Wan et al.31

RESULTS

Included Studies

The electronic search identified 15,785 potentially relevant studies, of which 67 were selected for full-text review, and from these, 27 studies (12, human; 15, animal) met the inclusion criteria (Fig. 1).22,32–57 The mean ± SD age of patients across all human studies was 33.4 ± 9.55 years; most patients were male. The majority of subjects in the animal studies were female. There was an excellent agreement between the reviewers for study inclusion (Cohen κ = 0.86).58

Clinical Characteristics

One RCT in humans was included (n = 47 patients).35 This study was an open-label trial comparing FLyP with FP conducted in civilian trauma patients with blunt or penetrating mechanism. Most patients (74.5%) were male and had a mean ± SD age of 48.0 ± 16.5 years in the FLyP group and 38.0 ± 15.6 in the FP group. Eleven observational studies were conducted in humans (n = 3,994 patients).22,32–34,36–39,55–57 Three were prospective studies (FDP vs. no control32,56,57), whereas eight were retrospective studies (FDP vs. no control22,33,34,39,55 FLYp vs. FP ,36 FLYp vs. before FLyP availability/RBCs only37 FDP vs. Hartmann solution38). Seven studies were conducted in the military setting,22,32,34,38,55–57 and five studies were conducted in a nonmilitary/civilian trauma population.33,35–37,39

Fifteen animal studies were included40–54 with 13 being conducted in swine (n = 367)40–50,52,53 and 2 conducted in mice (n = not reported).51,54 Of the swine studies, 10 induced ATC with a trauma model of extremity fractures, controlled hemorrhage, hypothermia, and organ injury (liver, spleen).40–43,45–48,52,53 Three swine studies performed trauma models of brain injury.44,49,50 In the mice studies, ATC was induced by undergoing controlled hemorrhage (Tables 1 and 2).51,54

Interventions

The only human RCT assessed FLyP versus plasma in blunt and penetrating civilian trauma.35 Across the 11 observational cohort studies22,32–34,36–39,55–57 8 used FDP but did not have a control group.22,32–34,39,55–57 Nguyen et al.53 assessed FLyP and compared with FP, and Shlaifer et al.55 assessed prehospital FDP versus no prehospital FDP (Hartmann solution

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| Reference          | Animal Model       | Sample Size | Injury Type                                                                 | Control Group (s) | Intervention (FDP) | Intervention (Other) | Outcome(s)Measured                                                                 |
|--------------------|--------------------|-------------|-------------------------------------------------------------------------------|-------------------|-------------------|---------------------|----------------------------------------------------------------------------------|
| Shuja et al., 2008 | Female Yorkshire swine | 24          | Extremity fracture, hemorrhage, hypothermia, liver injury                      | FP FWB            | FDP               | CaCl                | 1. In vitro clotting factors and coagulation parameters measurements  |
| Spoerke et al., 2009 | Yorkshire crossbred swine | 32          | Extremity fracture, hemorrhage, liver laceration, acidosis, hypothermia       | FP FP/RBCs (1:1)  | FDP               | None                | 1. Residual clotting activity  |
|                    |                    |             |                                                                                |                    | FDP/RBCs (1:1)    |                     | 2. Mortality                      |
|                    |                    |             |                                                                                |                    |                   |                     | 3. Hemodynamic measures              |
|                    |                    |             |                                                                                |                    |                   |                     | 4. Total blood loss                     |
|                    |                    |             |                                                                                |                    |                   |                     | 5. Coagulation profiles               |
|                    |                    |             |                                                                                |                    |                   |                     | 6. Inflammatory measures          |
| Hamilton et al., 2011 | Female Yorkshire swine | 30          | Extremity fracture, hemorrhage, liver laceration, hypothermia                 | FDP + CA          | FDP + AA          | None                | 1. Cytokine serum concentration         |
| Alam et al., 2011  | Female Yorkshire swine | 27          | Rib fracture, soft-tissue injury, hemorrhage, liver laceration, splenic injury | Hetastarch FWB    | SDP               | None                | 1. 7-d mortality                     |
| Van et al., 2011   | Swine              | 30          | Extremity fracture, hemorrhage, liver laceration, hypothermia                 | FDP + CA          | FDP + AA          | None                | 2. Organ dysfunction                 |
| Imam et al., 2013  | Female Yorkshire swine | 15          | Traumatic brain injury, hemorrhage                                            | NS FP             | FDP               | None                | 1. IL-6 at 2 h and 6 h               |
| Lee et al., 2013   | Juvenile female Yorkshire swine | 20          | Extremity fracture, hemorrhage, hypothermia, liver injury                     | 100% FDP          | 50% FDP           | None                | 2. 8-OH-2-deoxyguanosine level at 4 h  |
| Lee et al., 2013   | Juvenile female Yorkshire swine | 40          | Extremity fracture, hemorrhage, hypothermia, liver injury                     | FDP + NS          | FDP + SW          | None                | 3. Physiologic parameters, blood loss, and coagulation markers                |
| Lee et al., 2013   | Juvenile Yorkshire swine | 32          | Extremity fracture, hemorrhage, hypothermia, liver injury                     | FDP FDP           | FDP + RBC         | None                | 1. Measurement of coagulation factors                          |
| McCully et al., 2015 | Juvenile female Yorkshire swine | 40          | Extremity fracture, hemorrhage, liver injury                                 | LP − RL           | LP − SW           | None                | 2. Mortality                              |
| McCully et al., 2015 | Female Yorkshire swine | 52          | Extremity fracture, hemorrhage, hypothermia, liver injury                     | Operative and FDP + AA (low, nonoperative FDP + medium, high)   | None                | 3. Blood loss                          |
| Potter et al., 2015 | Male mice          | 55          | Hemorrhagic shock                                                            | FP RL             | SDP               | Dextran Phosphate-buffered saline | 4. Inflammatory markers               |
| Halaweish et al., 2016 | Female Yorkshire swine | 10          | Traumatic brain injury, hemorrhage                                            | FP FDP            | None                | None                | 1. Inflammation, DNA damage at baseline, 2 h, 4 h  |
|                    |                    |             |                                                                                |                    |                     |                     | 2. IL-6, IL-10, plasma C-reactive protein, 8-hydroxy-2-deoxyguanosine concentrations |
|                    |                    |             |                                                                                |                    |                     |                     | 3. Lung inflammatory markers            |

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given if no FDP available). Oakeshott et al.54 performed a before and after study of FDP implementation.

Across the 15 animal studies,40–54 8 compared FDP with FP.40,44,47,49–52,54 Four studies compared different FDP reconstructions with compounds such as Ringer lactate (RL), normal saline (NS), SW, ascorbic acid (AA), citric acid (CA), hydrochloric acid (HCl), and/or Hextend starch (Hx).41–43,46 One study compared 100% FDP versus 50% FDP.45 Two studies compared FDP with FWB (Tables 1 and 2).42,52

Outcomes — Human Studies

Mortality

The only RCT in humans reported no difference in 30-day all-cause mortality between the FLyP group compared with the FP group (relative risk, 22% vs. 29%, \( p = 0.56 \)).35 In the observational cohorts, seven studies reported mortality as an outcome.32,33,36,38,39,55,56 However, only two studies reported a control group.36,38 One study (n = 72) assessed FLyP compared with FP and reported no difference in 24-hour in-hospital mortality (relative risk, 21% vs. 31%, \( p = 0.59 \)), hemorrhage-related mortality (7% vs. 17%, \( p = 0.29 \)), and 28-day mortality (26% vs. 34%, \( p = 0.70 \)).36 Another study (n = 96) assessed prehospital FDP compared with no prehospital FDP (Hartmann solution given if no FDP available) and reported no difference in mortality between the two groups (8.5% vs. 6.2%, \( p = 0.17 \)) (Table 3).38

Use of Blood Products

The RCT conducted by Garrigue et al.52 reported that patients who received FDP did not have significantly less use of FC compared with those who received FP (FDP median, 2 g [IQR, 0–3 g] vs. FP median, 3 g [IQR, 2–4 g], \( p = 0.05 \)). Three observational cohorts reported comparisons between the numbers of units of RBCs transfused in the FDP versus FP,36,37 and Hartmann solution,38 respectively. Of these, two studies (n = 72, n = 216) reported that patients in the FDP group received significantly less RBCs compared with the FP group.36,37 One study (n = 96) reported no significant difference in RBC transfusions between FDP versus Hartmann solution (Table 3).38

Effect on Coagulopathy

Garrigue et al.52 reported higher mean fibrinogen levels at 45 minutes in the FDP group compared with the FP group (1.57 ± 0.78 vs. 1.05 ± 0.51 g/L, \( p = 0.006 \)). They also found an association between FDP and improvement in all coagulation parameters (PT, factor II, factor V) within 45 minutes (\( p < 0.001 \)), compared with the FP group.35 Four observational cohorts assessed the effect of FDP on coagulation parameters.22,32,36,57 Martinaud et al.52 reported a decrease in PT by 3.3 seconds (\( p < 0.01 \)) after administration of FDP, without a control group. Sailliol et al.53 assessed change in PT after FLyP administration (44.8 vs. 48.7 seconds, \( p = NR \)) but did not include a \( p \) value. Shlaifer et al.55 reported a decrease in INR using FDP compared with a Hartmann solution (median, 1.1 vs. 1.2; \( p = 0.04 \)). Nguyen et al.53 reported no difference in fibrinogen level using FDP compared with FP upon admission, and after 3 and 24 hours following admission (Table 3).
Adverse Events, Ease, and Feasibility of Use

Eight observational cohort studies assessed adverse events and feasibility of FDP use (Table 3).22,32,34,37,39,56,57 Most studies reported feasibility of use and no adverse events. Shlaifer et al.22 reported one adverse event (1 of 109 patients, 0.9%; 1 patient developed chills/rigors while receiving FDP) and difficulty with administration of FDP (5 of 109 patients, 4.6%; reported no flow or very slow rates). Sailliol et al.25 reported four cases of transient erythema (4 of 269 patients, 1.4%) that resolved spontaneously.57 Vitalis et al.39 reported difficulties with reconstitution secondary to user misunderstanding of the guide (2 of 28 patients, 7.1%).

Outcomes — Animal Studies

Measurement of Clotting Factors

Three studies assessed clotting factor profiles in FDP compared with FP.40,47,52 Two studies reported an average of 14% decrease in clotting factors with FDP compared with FP when undergoing lyophilization (p = NR).40,47 One study reported no significant differences between FDP and FP in clotting factor profile (Table 4).52

Measurement of Coagulation Parameters

Eight studies assessed coagulation profiles (PTT, INR, and/or TEG parameters) when FDP was administered to Yorkshire swine.40,43,45–49,52 Four of these studies compared FDP to FP (n = 32,47 n = 10,49 n = 24,52 n = 32,46), of which one reported decreased PTT in the FDP group compared with other groups (FP, FP + RBC, FDP + RBC; n = 32; value, NR; p < 0.05),40 and one reported improved activated clotting time and reaction time in swine that received RBC + FDP compared with FP, FDP, and FDP + RBC groups (n = 32; value, NR; p < 0.05).57 The other two studies found no difference in coagulation profiles between groups.49,52 Three studies assessed coagulation profiles of FDP when reconstituted with various mediums (HCl, CA, AA, NS, RL, SW, and/or Hx).34,45,46. Of these studies, one reported

| Reference | Summary of Findings in FDP Use in Human Studies |
|-----------|-----------------------------------------------|
| Martinaud et al., 2011 | 1. After FDP administration, PT decreased by 3.3 s, p < 0.01 |
| Sailliol et al., 2014 | 1. PT, 48.72 ± 17.94 after FLyP administration; p = NR |
| Nguyen et al., 2019 | 1. Faster first unit of plasma received in patients given FLyP compared with FP, 3. FDP users reported no difficulty in reconstitution |
| Sunde et al., 2015 | 1. FDP users reported no transfusion reactions or complications |
| Vitalis et al., 2017 | 1. No difference in transfusion time before and after implementation of battlefield transfusion program (204 min vs. 151 min, p = 0.07) |
| Shlaifer et al., 2017 | 1. FDP users reported 5 (4.6%)/109 instances of difficulty with administration; reported very slow or no flow upon administration |
| Martinaud et al., 2011 | 1. PT decreased by 3.3 s, p < 0.01 |
| Vitalis et al., 2017 | 1. No difference in transfusion time before and after implementation of battlefield transfusion program (204 min vs. 151 min, p = 0.07) |
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| Vitalis et al., 2017 | 1. No difference in transfusion time before and after implementation of battlefield transfusion program (204 min vs. 151 min, p = 0.07) |
TABLE 4. Summary of Findings in the Included Animal Studies

| Reference | Summary of Findings in FDP Use in Animal Studies |
|-----------|--------------------------------------------------|
| Shuja et al., 200845 | 1. No difference in clotting factors and coagulation patterns in FDP compared with FP group |
|  | 2. Similar PTT, INR, and TEG parameters between FDP and FP group |
| Spoerke et al., 200957 | 1. Clotting factors decreased 14% in FDP group compared with freezing/thawing FP group |
|  | 2. No difference in mortality between FDP, FDP + RBC, FP, and FP + RBC groups |
|  | 3. Lower MAP in the FP group compared with FDP, FDP + RBCs, and FP + RBC groups, p < 0.05 |
|  | 4. Less blood loss in the FDP-RBC group compared with FDP, FP, and FP + RBC groups, p < 0.05 |
|  | 5. Decreased PTT in FDP group compared with FDP + RBC, FP, and FP + RBC groups, p < 0.05 |
|  | 6. Decreased inflammatory markers in FDP group compared with FDP + RBC, FP, and FP + RBC groups, p < 0.05 |
| Hamilton et al., 201133 | 1. Decreased IL-6 in AA vs. HCl and CA groups, p < 0.05 |
| Alam et al., 201134 | 1. Improved mortality in SDP (83%) and FWB (100%) groups compared with hetastarch and valproic acid, p < 0.05 |
|  | 2. No organ dysfunction noted in survivors |
| Van et al., 201135 | 1. Increased IL-6 among all groups, but lowest increase in FDP vs. AA compared with FDP + CA and FDP + HCl (median, 113 ng/mL vs. 181 ng/mL vs. 192 ng/mL, p > 0.03) |
|  | 2. Increased oxidative damage in HCl and CA groups at 4 h, but not in AA group |
|  | 3. No difference in physiologic parameters, blood loss, or coagulation markers among groups |
| Imam et al., 201336 | 1. Decrease brain injury size (51%) and brain swelling in FDP vs. saline group, p < 0.05 |
|  | 2. No difference in brain injury size and brain swelling in FDP vs. FP group |
| Lee et al., 201337 | 1. No difference in MAP or HR in 50% FDP vs. 100% FDP group |
|  | 2. No difference in blood loss in 50% FDP vs. 100% FDP group |
|  | 3. Higher coagulation factor activity per unit volume in 50% FDP vs. 100% FDP group |
|  | 4. No difference in coagulation and TEG parameters |
| Lee et al., 201338 | 1. Less blood loss in FDP + SW and FDP + RL compared with FDP + NS and FDP + Hx groups, p < 0.05 |
|  | 2. Less coagulopathic TEG changes in FDP + SW compared with FDP + NS, FDP + RL, and FDP + Hx groups, p < 0.05 |
|  | 3. Decreased IL-6 at 4 h in FDP + SW vs. FDP + NS group, p < 0.05 |
| Lee et al., 201339 | 1. 86% of coagulation factors retained in full volume FDP |
|  | 2. Hypertonic FDP (50% original plasma volume) had higher coagulation factor concentrations, well tolerated in swine, and equally effective compared with 100% FDP |
|  | 3. No difference in mortality between FDP, FDP + RBC, FP, and FP + RBC groups |
|  | 4. Decreased blood loss in group receiving 1:1 FDP: RBC vs. FDP, FP, and FP + RBC groups, p < 0.03 |
|  | 5. Decreased IL-6 in animals receiving FDP compared with FP, p < 0.05 |
| McCully et al., 201540 | 1. No difference in cytokine profile, DNA damage, or lung inflammatory markers in LP – SW, LP – RL, LP – NS, and LP – Hx groups |
| McCully et al., 201541 | 1. No difference in hemodynamic measures between FDP + AA (low, medium, high), FDP + HCl, operative control sham, and baseline control sham groups |
|  | 2. Elevated IL-6 and TNF-α, and similar CRP levels in all groups |
|  | 3. Elevated IL-10 in low-AA group at 4 h, p < 0.017 |
|  | 4. No difference in TEG parameters among all groups |
|  | 5. Procoagulant activity not diminished by AA |
| Potter et al., 201542 | 1. Similar modulate pulmonary vascular integrity, permeability, and lung inflammation in vitro and in vivo between FP and SDP groups |
|  | 2. MAP and base excess both corrected in FP and SDP groups |
| Halaweish et al., 201643 | 1. Return to baseline at 7 d in both FDP and FP groups |
|  | 2. No difference in cognitive function between FDP and FP groups |
|  | 3. Decreased brain lesion size in FDP vs. FP at day 3 (485 ± 85 vs. 219 ± 20 mm3, p < 0.05) |
|  | 4. No difference in TEG parameters between FDP vs. FP group |
| Georgoff et al., 201744 | 1. Lower neurologic severity score postinjury days 1 and 7 in the FDP and FP groups compared with NS, p < 0.05 |
|  | 2. Faster time to complete neurological recovery in FP vs. NS groups (5 ± 0.71 vs. 9.9 ± 3.8, p = 0.036) |
|  | 3. No difference in time to complete neurological recovery in FDP vs. NS group (6.2 ± 2.2 vs. 9.6 ± 3.8, p = 0.13) |
|  | 4. No difference in brain lesion size between FDP, FP, and NS groups |
|  | 5. FDP treatment tolerated well; similar to FP |
| Pati et al., 201845 | 1. Decreased endothelial permeability, decreased endothelial cell-leukocyte binding, and restoration of adherens junctions integrity in both FDP and FP groups |
|  | 2. Decreased pulmonary vascular permeability, edema, and inflammation in FDP and FP groups |
|  | 3. Similar in vitro and in vivo findings between FDP and FP groups |

FWB, fresh whole blood; IL, interleukin; MAP, mean arterial pressure; SDP, spray dried plasma; TNR-α, tumor necrosis factor α.

(n = 32) that FDP + SW had significantly less coagulopathic TEG changes compared with other groups, and FP + Hx had a significantly higher INR compared with other groups.46 The other studies reported no significant differences in coagulation profiles depending on reconstitution medium (n = 3043 n = 2026). One study compared 100% FDP (reconstitution to original plasma volume) versus 50% FDP (reconstitution to half the original plasma volume) and reported no significant differences in TEG parameters.45 The authors also reported that 50% FDP had higher coagulation activity per unit volume compared with 100% FDP45

Measurement of Inflammatory Markers

Nine studies assessed inflammatory markers in animals receiving FDP (n = 3140,41,43,46–48,53,54; n = NR51). Seven of
these studies were performed in swine,\textsuperscript{40,41,43,46–48,53} whereas two were performed in mice.\textsuperscript{51,54} Overall, when compared with FP, FDP had similar inflammatory markers reported. Five studies compared inflammatory markers in animals that received FDP reconstituted with various mediums (HCl, CA, AA, NS, RL, SW, and/or Hx)\textsuperscript{41,43,46,48,53} Two studies reported significantly less inflammatory markers in the FDP + AA group compared with FDP + HCl and/or FDP + CA groups,\textsuperscript{41,43} whereas one study reported similar levels of inflammation regardless of levels of AA used (low vs. medium vs. high groups).\textsuperscript{53} When FDP + SW was compared with FDP + RL, FDP + NS, and FDP + Hx groups, one study reported decreased interleukin 6 in the FDP + SW group\textsuperscript{46} whereas another study reported no difference in inflammatory markers based on fluid used for reconstitution.\textsuperscript{53}

**Mortality**

Three animal studies assessed mortality (n = 91).\textsuperscript{40,42,47} When FDP ± RBCs was compared with FP ± RBCs, there were no differences in mortality reported.\textsuperscript{40,47} In one study, FDP and FWB significantly improved mortality compared with swine that received Hetastarch and valproic acid.\textsuperscript{42}

**Neurologic Injury**

Three studies assessed brain bleed size in swine that received FDP compared with FP and/or NS and showed mixed results (n = 40).\textsuperscript{44,49,50} There were two studies that assessed neurologic recovery.\textsuperscript{49,50} One study reported faster return to baseline and cognitive function in the FDP and FP group compared with NS.\textsuperscript{50} When FDP was compared with FP, there were no differences reported in cognitive function of the animals.\textsuperscript{50}

**Risk of Bias**

The RCT conducted in humans had a high risk of bias in two of the domains assessed (attrition bias, other bias—single center, small sample size, surrogate endpoints) (Supplemental Digital Content, Supplementary Tables 1 to 3, http://links.lww.com/TA/B835).\textsuperscript{35} We did not penalize the study because of lack of blinding, as this was not feasible in this setting. Overall, using the NOS tool, two observational cohort studies had high risk of bias,\textsuperscript{55,56} eight studies had moderate risk of bias,\textsuperscript{22,32–34,36,37,39,57} and one study with low risk of bias.\textsuperscript{58} Using the tool proposed by Krauth et al.,\textsuperscript{30} for animal studies, 2 studies received a score between 10 and 13,\textsuperscript{48,53} 11 studies between 7 and 9,\textsuperscript{40,42,44–47,49–52,54} and 2 studies ≤6.\textsuperscript{41,43}

**Meta-analyses**

Studies addressing mortality and exposure to ABPs were combined for the purpose of meta-analyses (Fig. 2; Supplemental Digital Content, Supplementary Figs. 1 to 4, http://links.lww.com/TA/B835). Publication bias was not assessed with funnel plots because only two studies (n = 66) were used for quantitative analyses. There was no difference in the cumulative number of units of each ABP transfused at 24 hours. The 30-day mortality in the two studies was not significantly different as demonstrated in the Forrest plot.

**GRADE Evidence Profile**

Overall, the evidence was of low quality for both mortality and exposure to ABPs (see details for each item addressed in Supplemental Digital Content (Supplementary Table 4, http://links.lww.com/TA/B835).

**DISCUSSION**

**Main Findings**

This systematic review summarizes the evidence for the use of FDP in bleeding trauma patients and in bleeding trauma animal models. The evidence is represented by 12 human studies (RCT, 1; observational, 11) and 15 animal studies (13 in swine and 2 in mice). Overall, low- to moderate-quality randomized and observational data reported no difference in mortality between patients who received FDP compared with FP. Furthermore, low- to moderate-quality evidence suggests no difference in ABP utilization in patients receiving FDP compared with FP. Moderate quality observational data also show ease of reconstitution with few adverse events noted, which suggests that FDP may have a similar safety profile to plasma. Most adverse events were mild (e.g., shivering, erythema) and self-limiting. Difficulties with reconstitution were primarily secondary to user error, which likely can be mitigated with appropriate training. Furthermore, laboratory measures of coagulopathy (INR, PT, and/or TEG/ROTEM) in human and animal studies reported similar improvement in coagulation parameters when FDP was transfused compared with FP, suggesting retained coagulation profiles in preparation and reconstitution. However, compared with FP, low-quality evidence suggests that FDP may improve coagulation parameters more rapidly. In small animal studies, laboratory results suggest that FDP with AA may be less inflammatory compared with plasma and that SW is the better medium for reconstitution compared with NS and RL. Lastly, animal data assessing neurologic injury size and cognitive recovery show inconsistent results in subjects receiving FDP.

![Figure 2. Thirty-day mortality.](image_url)
Over the past two decades, there have been considerable changes in the management of hemorrhagic shock in trauma patients. The use of whole blood, FP, liquid plasma, PCC, FC, tranexamic acid (TXA), and massive transfusion protocols including higher ratios of plasma to RBCs has replaced crystalloid or packed red blood cells (pRBC)-only resuscitation.7-9,11,12,59 The benefits of preemptive coagulation factor replacement include avoiding hemodilution of coagulation factors necessary for hemostasis and the replacement of these factors to treat ATC, including hyperfibrinolysis.3,60 However, providing plasma early for patients is difficult because of the time required for thawing of FP and the logistical complexities of administering in the prehospital setting.17 In the military setting, limited observational data show FDP as a potential solution to achieve a higher plasma/RBC ratio in patients with hemorrhagic shock.21,24 There were previously concerns with disease transmission, but this has improved with better screening and the use of pathogen reduction strategies.25 The use of FP in trauma resuscitation has been studied in the prehospital setting with two RCTs.19,61 The Control of Major Bleeding After Trauma (COMBAT) trial, an individual patient randomized trial, showed that prehospital use of FP was not associated with improved survival during ground transport compared with saline.61 The Prehospital Air Medical Plasma (PAMPer) trial, a cluster randomized trial, found that patients who were administered plasma in the prehospital setting had a lower 30-day mortality compared with standard-care resuscitation.19 The discrepancy is likely due to the shorter prehospital transportation time in the Control of Major Bleeding After Trauma trial than in the Prehospital Air Medical Plasma trial. However, the widespread utilization of FP is limited by a short half-life once thawed and the need to use universal AB plasma donors.17 It is not clear whether FP is available in Canada. Some European countries also provide clotting factor concentrates in various preparations including PCC, FC, and other coagulation factors.15,62,63 In a retrospective study, PCC and FC have been associated with decreased ABP transfusion and decreased multiple organ failure but no survival benefit compared with FP.62 However, there have been no studies to date comparing PCC and/or FC with FDP. There are also ongoing studies assessing the transfusion of cold-stored and frozen PLTs,63 FC administration,12,15,62,66 cryoprecipitate,12,15,62,66 and the use of antifibrinolytic drugs such as TXA.12,15,62,67,68

More recently, a targeted goal-directed approach has been used by physicians for patients with ATC. This approach includes guidance of transfusion with viscoelastic methods such as TEG, and/or ROTEM.14-16 Thromboelastography and ROTEM can identify the specific coagulation defects that can be targeted to guide and personalize the hemostatic resuscitation.15,16 To date, there are no studies that have assessed the effect of FDP on TEG and/or ROTEM parameters in trauma patients, which should be investigated in future research.

CONCLUSIONS

The evidence on feasibility, efficacy, and safety of the use of FDP in trauma has low to moderate quality, which precludes any definitive conclusions. Most evidence is represented by nonrandomized studies that have shown no difference in transfusion requirements or mortality in patients receiving FDP compared with FP. Observational data have reported improvement in coagulation parameters with FDP use, without statistically significant differences when compared with FP. Freeze-dried

Strengths and Weaknesses of This Review and Future Research

This is the first systematic review that assesses the use of FDP for hemorrhage in trauma for both human and animal trauma models. Feuerstein et al.69 conducted a systematic review that assessed FDP use, which included studies conducted in humans. Their review included a study by Glassberg et al.,70 but this was excluded from our review because it shared the same cohort with another study.39 The strength of this review stems from the robust search algorithm, which included relevant animal and human studies, and the quantitative analysis. The main limitation of this review is that most human data came from observational studies, with only one RCT included. As such, survival bias and detectable and nondetectable confounding variables are unavoidable. Furthermore, some studies conducted in the military setting had incomplete data collection, which was attributed to difficulties in the chaotic environment of military medicine. Studies with missing data are reflected in the risk of bias analysis and in the supplementary summary tables (http://links.lww.com/TA/B835). Furthermore, because the population in military studies is predominantly young males suffering severe mechanisms, this may be different than what is commonly seen in civilian trauma. Moreover, there is heterogeneity among the populations included across the studies, in the amount of FDP received, and a variety of comparators. Future research is strongly warranted, including RCTs or well-designed prospective trials, to provide more data on the impact of FDP on hemostatic laboratory measures, transfusion requirements, clinical outcomes, and mortality. Specifically, future research should focus on comparing the use of FDP to FP in trauma. In addition, studies comparing FDP as source of clotting factors should be conducted comparing with the current standard of care (RBC + FP + PLT + TXA, and FC administered if low levels are identified), in bleeding trauma patients. Furthermore, clinical evidence on the use of other concentrates of clotting factors such as PCC and FC should be compared with FDP, for example. These studies should assess meaningful clinical outcomes addressing efficacy, such as mortality, transfusion of ABPs, and improvement of coagulopathy. Safety outcomes such as acute lung injury, multiorgan failure, and thromboembolic phenomena should also be investigated. Future studies should also consider the impact of FDP on resource allocation (e.g., economic costs, blood product utilization, hospital length of stay). Furthermore, evaluation of use in the prehospital setting should be studied, including challenges to implementation, use, and time to administration. Currently, there are trials underway assessing the use of FDP in civilian trauma in United States, France, Great Britain, and Norway.71-74
plasma seems to be safe to use, easy to store and reconstitute, and can be given earlier to patients compared with FP, which may be advantageous for patient care. However, because the evidence in this area is represented by animal studies, non-randomized human studies, and there is a lack of clinical trials, the results should be interpreted with caution. Large, prospective, controlled trials are needed to determine efficacy and safety of FDP in severely bleeding trauma.

AUTHORSHIP

L.T.d.L. and G.M. conceived and designed the study. G.M. led the production of the systematic across the different phases, supervised by L.T.d.L., who is the methodology expert and senior author. G.M., R.H., M.W.K., and D.P. conducted the whole screening process, data retrieving, and approved the final article. G.M. takes responsibility for the article authors contributed to the revision of the article. All authors have seen and approved the final article. G.M. takes responsibility for the article as a whole.

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DISCLOSURE

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