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SCIENCE AND TECHNOLOGY: CHALLENGES, PROSPECTS AND INNOVATIONS

PROCEEDINGS OF X INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE MAY 22-24, 2025

OSAKA 2025

PHARMACEUTICAL SCIENCES

PHARMACEUTICAL SCIENCES

UDC: 615.275:355.721

DATABASE ANALYSIS OF COMPLETED CLINICAL TRIALS INVESTIGATING HEMOSTATIC AGENTS: IMPLICATIONS FOR MILITARY TRAUMA CARE

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Annotation. This database analysis examined 365 completed clinical trials investigating hemostatic agents retrieved from ClinicalTrials.gov to characterize evidence for military trauma applications. Investigation revealed substantial clinical research activity with 183 studies addressing bleeding control and 148 studies involving surgical applications. Tranexamic acid emerged as the most extensively studied intervention with 49 trials encompassing 10,526 participants, followed by topical hemostatic matrices including TachoSil (11 studies, 5,095 participants), Floseal (13 studies, 1,845 participants), and Surgicel (12 studies, 1,400 participants). Topical matrices and sealants (58 studies, 15.9%) were identified as the predominant category, followed by antifibrinolytic agents (50 studies, 13.7%). Geographic distribution demonstrated United States leadership with 110 studies (30.1%) across 47 participating countries. Critical assessment revealed only one study conducted in military settings. This represents a fundamental disconnection between civilian

clinical validation and battlefield operational requirements. The absence of battlefield-validated protocols and austere environment testing constitutes critical limitations in evidence translation to combat casualty care. Future research priorities must emphasize studies conducted under combat-relevant conditions to bridge the civilian-military evidence gap.

Keywords. clinical trials; evidence-based medicine; hemostatic agents; military medicine; war-related trauma.

Introduction. Hemostatic agents represent critical therapeutic interventions in military trauma care, where rapid bleeding control can determine survival outcomes in combat casualties. The development and clinical validation of hemostatic technologies have evolved from traditional battlefield medicine practices to sophisticated pharmaceutical and bioengineering approaches targeting specific coagulation pathways [1,2]. Current military protocols emphasize both systemic antifibrinolytic therapy and topical hemostatic interventions, yet gaps remain between civilian clinical research and military operational requirements [3, 4].

The heterogeneous nature of war-related trauma – encompassing penetrating injuries, blast-related hemorrhage, and polytrauma scenarios – demands comprehensive evaluation of available hemostatic evidence [5]. Systematic analysis of clinical trial databases [6] provides essential insight into the breadth of investigated interventions, their mechanisms of action, and the robustness of supporting evidence. Such analysis facilitates evidence-based protocol development and identifies critical research priorities for military medical applications [7].

This analysis examines completed clinical trials investigating hemostatic agents registered in ClinicalTrials.gov [8], with particular focus on interventions relevant to war-related trauma scenarios. The objective was to characterize the landscape of hemostatic research, identify evidence strengths, and delineate gaps requiring targeted investigation for military medical applications.

Materials and methods. *Data source and search strategy*. Clinical trial data were systematically retrieved from ClinicalTrials.gov [8], a comprehensive registry

maintained by the National Library of Medicine. The database search was conducted on May 14, 2025, utilizing the intervention parameter "hemostatic agent" with a filtering criterion restricted to completed studies. The search query employed the following parameters: intervention term "hemostatic agent" and study status filter "completed studies".

Data collection and verification. The systematic search yielded 365 completed clinical trials investigating hemostatic agents. All retrieved records were verified to maintain completed status, confirming the consistency of the applied search filters. The dataset encompassed comprehensive study metadata including National Clinical Trial (NCT) numbers, study titles, brief summaries, intervention descriptions, study designs, participant demographics, enrollment figures, sponsoring organizations, and completion dates.

Analytical framework. The compiled dataset contained standardized variables extracted directly from the ClinicalTrials.gov registry. Data elements included study identification parameters (NCT numbers, titles, URLs), methodological characteristics (study type, design, phases), participant demographics (sex, age categories), intervention specifications, primary conditions addressed, completion status, and institutional affiliations. This standardized extraction protocol ensured methodological consistency across the analyzed studies.

Quality assurance. All studies included in the analysis demonstrated completed status as verified through the ClinicalTrials.gov registry system. The data extraction process-maintained fidelity to the original registry entries, preserving the integrity of institutional classifications and study descriptors as provided by the submitting investigators. No additional inclusion or exclusion criteria were applied beyond the completion status requirement, ensuring comprehensive representation of hemostatic agent research within the specified timeframe.

Results. The systematic search of ClinicalTrials.gov yielded 365 completed clinical trials investigating hemostatic agents. Among these, 183 (50.1%) were bleeding/hemorrhage-related and 148 (40.5%) involved surgical applications, demonstrating the broad clinical scope of hemostatic research (Table 1). The

distribution across clinical domains shows significant potential applicability to trauma medicine, with surgical and bleeding control applications comprising the largest categories.

Table 1

Study characteristics and clinical application distribution

Parameter	n	%	Parameter	n	%
Studies with identifiable clinical applications			Study design characteristics		
			Randomized trials	257	70.4
Bleeding/hemorrhage	183	50.1	Observational studies	108	29.6
Surgical	148	40.5			
Cardiac/cardiovascular	49	13.4	Geographic distribution		
Trauma/emergency	46	12.6	With location data	340	93.2
Orthopedic	18	4.9	Without location data	25	6.8

Analysis of hemostatic mechanisms revealed the topical matrices and sealants as the most extensively studied category, suggesting continued interest in locally-applied hemostatic solutions suitable for field deployment (Table 2). Antifibrinolytic agents represented the second-largest category, reflecting the established efficacy of tranexamic acid in trauma protocols.

Table 2

Hemostatic mechanisms and agent categories

Mechanism category	Studies, n	%	Leading examples
Specific hemostatic agents identified			
Tranexamic acid	49	13.4	Tranexamic acid, TXA
Thrombin-based products	25	6.8	Thrombin, thrombin matrix
Floseal	13	3.6	Floseal hemostatic matrix
Fibrinogen products	13	3.6	Fibrinogen concentrate
Surgicel	12	3.3	Surgicel hemostatic agent
TachoSil	11	3.0	TachoSil fibrin sealant patch
Broad mechanism categories			
Topical matrices/sealants	58	15.9	Floseal, TachoSil, Surgicel, fibrin sealants
Antifibrinolytic agents	50	13.7	Tranexamic acid, aminocaproic acid
Coagulation factors	37	10.1	Fibrinogen, Factor VIIa, thrombin
Anticoagulant reversal	29	7.9	Protamine, vitamin K, reversal agents
Other hemostatic agents*	242	66.3	Various agents and combinations

*Other category includes diverse hemostatic interventions, novel agents, and studies not clearly fitting standard categories

It worth noting, that Table 1 and 2 employ a prevalence-based reporting system rather, than mutually exclusive categorization.

Detailed analysis of the leading hemostatic agents demonstrated varying levels of clinical investigation intensity and evidence quality (Table 3). Tranexamic acid emerged as the most extensively studied agent with 49 studies and 10,526 participants, while topical agents such as TachoSil, Floseal, and Surgicel showed substantial clinical investigations.

Table 3

Leading hemostatic agents: clinical investigation results

Agent	Studies, n	Total enrollment	Largest study	Key applications
Tranexamic acid	49	10,526	NCT03431805 (4,574)	Postpartum hemorrhage, surgical bleeding, trauma
TachoSil	11	5,095	NCT00285623 (3,000)	Surgical hemostasis, liver surgery
Fibrinogen	13	4,807	NCT00285623 (3,000)	Coagulation factor replacement, surgical bleeding
Floseal	13	1,845	NCT03243344 (571)	Surgical hemostasis, otolaryngology procedures
Surgicel	12	1,400	NCT01192022 (253)	Local bleeding control, surgical procedures
Thrombin products	25	2,156	NCT00652314 (350)	Topical hemostasis, surgical bleeding
Factor VIII	8	4,936	NCT03431805 (4,574)	Hemophilia treatment, bleeding disorders
Factor VIIa	4	100	NCT01359202 (50)	Hemophilia with inhibitors, bleeding disorders

Enrollment data across all 365 hemostatic studies revealed substantial participant recruitment, with 363 studies (99.5%) providing enrollment data. The analysis shows considerable variation in study scope, with individual studies ranging from small-scale investigations to large multi-center trials, reflecting the diverse research approaches in hemostatic agent development.

The technology profile analysis presented in Table 4 represents a characterization of the leading hemostatic agents based on their pharmaceutical development characteristics, manufacturing requirements, and clinical deployment strategies. This systematic categorization facilitates understanding of the diverse technological approaches underlying contemporary hemostatic interventions and provides essential insights for technology transfer and military medicine applications.

Table 4

Comprehensive technology profile of leading hemostatic agents in clinical development

Agent	Drug classification	Molecular technology	Delivery system	Mechanism of action	Manufacturing technology
Tranexamic acid	antifibrinolytic	small molecule synthetic	IV/oral/ topical	plasmin inhibitor	chemical synthesis
Thrombin (recombinant)	coagulation factor	recombinant protein	topical/ injectable	enzymatic coagulation	rDNA expression system
Floseal matrix	hemostatic composite	gelatin-thrombin biomaterial	topical application	dual mechanical-biological	bioengineering technology
Fibrinogen concentrate	coagulation factor	plasma-derived protein	intravenous infusion	clot formation substrate	plasma fractionation
Surgicel	absorbable hemostat	oxidized cellulose	topical application	mechanical hemostasis	chemical modification
Tachosil patch	fibrin sealant system	collagen-fibrinogen matrix	direct application	fibrin network formation	biotechnology manufacturing
Arista powder	plant-based hemostat	microporous polysaccharide	topical powder	rapid absorption/ swelling	natural product processing
Hemopatch	advanced hemostatic pad	collagen-NHS77 technology	flexible patch system	protein cross-linking	biomaterial engineering

The technology profile reveals distinct developmental pathways and manufacturing complexities across leading hemostatic agents. Small molecule synthetics, exemplified by tranexamic acid, demonstrate the most mature technology

platform with established chemical synthesis protocols and broad regulatory approval pathways. These agents benefit from straightforward manufacturing processes and multiple delivery route options, contributing to their extensive clinical adoption with 49 documented studies.

Recombinant protein technologies, particularly thrombin-based products, represent sophisticated biotechnology manufacturing requiring specialized rDNA expression systems and stringent quality control protocols. Despite manufacturing complexity, these agents demonstrate substantial clinical investigation with 25 studies, reflecting their targeted therapeutic efficacy in enzymatic coagulation enhancement.

Composite biomaterial systems, including Floseal matrix and TachoSil patches, exemplify advanced bioengineering approaches combining multiple active components with controlled-release mechanisms. These technologies require specialized manufacturing capabilities integrating biological and synthetic components, yet demonstrate significant clinical validation with combined investigation across 24 studies.

The technology spectrum from natural product processing (Arista) to biomaterial engineering (Hemopatch) illustrates the diversity of approaches addressing hemostatic challenges. Each technology category presents distinct advantages: chemical synthesis offers scalability and cost-effectiveness, biotechnology provides targeted biological activity, and biomaterial engineering enables localized delivery with mechanical properties suited for surgical applications.

Geographic analysis (Table 5) demonstrated United States leadership with 110 studies (30.1% of total), followed by diverse global participation including substantial contributions from European countries (United Kingdom: 21 studies, Germany: 20 studies, France: 16 studies), Asian centers (China: 18 studies, South Korea: 14 studies), and other regions.

Table 5

Temporal and geographic distribution among trials

Geographic distribution	Studies, n	Percentage	Geographic distribution	Studies, n	Percentage
Leading countries			Other contributing countries		
United States	110	30.1%	India	5	1.4%
United Kingdom	21	5.8%	Taiwan	5	1.4%
Germany	20	5.5%	Netherlands	5	1.4%
China	18	4.9%	Switzerland	4	1.1%
France	16	4.4%	Brazil	4	1.1%
South Korea	14	3.8%	Czech Republic	3	0.8%
Egypt	14	3.8%	Indonesia	3	0.8%
Canada	11	3.0%	Austria	3	0.8%
Denmark	10	2.7%	Greece	3	0.8%
Turkey	8	2.2%	Thailand	2	0.5%
Italy	8	2.2%	russia	2	0.5%
Spain	7	1.9%	Pakistan	2	0.5%
Mexico	6	1.6%	Japan	2	0.5%
Belgium	6	1.6%	Single-study countries*	13	3.6%
Israel	6	1.6%	Other countries**	4	1.1%
Iraq	6	1.6%	-		

*Single-study countries include: Ireland, Singapore, Australia, Croatia, Serbia, Norway, Poland, Chile, Argentina, Sweden, Romania, Bulgaria, and New Zealand
**Other countries with identified locations not matching standard country names

Investigation revealed substantial research gaps in military-specific applications, with only 1 study conducted in a military setting (Table 6). While others are focused on trauma hemostasis and addressed surgical bleeding control with potential military relevance.

Table 6

Analysis of hemostatic research relevant to military/trauma applications

Research area	Representative studies	Assessment
Clearly military-specific studies	NCT00517166 (Combat Support Hospital tourniquet survey, United States Army Institute of Surgical Research)	Battlefield-specific research
Trauma hemostasis	NCT01990768 (TBI), NCT00945542 (trauma coagulopathy), NCT02477774, NCT05273775	General trauma applications with potential military

		relevance
Surgical bleeding control	NCT02133378 (cardiac surgery), NCT00279383 (surgical hemostasis), NCT04058665 (spine surgery)	Standard surgical hemostasis with broad applicability
Tranexamic acid studies	NCT03280849, NCT06301204, NCT05434533, NCT05273775	Well-established agent with protocols
Hemostatic device evaluation	NCT02534571 (TC-325 powder), NCT04100447, NCT03711916	Novel devices requiring field validation
General hemostasis research	NCT01857466 (ovarian), NCT04302584 (septic shock), NCT02633670	Standard medical applications

Critically, the analysis reveals, that despite sophisticated civilian technology development, limited translation to military-specific applications persists. The absence of battlefield-validated formulations and austere environment testing protocols represents a significant technology transfer gap requiring targeted research investment and development priorities specifically addressing combat casualty care operational requirements.

Conclusions. This analysis of 365 completed clinical trials demonstrates the maturation of hemostatic intervention research within civilian medical contexts, yet simultaneously exposes critical deficiencies in military-specific evidence development. The predominance of surgical applications and hemorrhage management studies reflects established clinical priorities, while the concentration of research activity around tranexamic acid indicates consensus regarding antifibrinolytic efficacy in trauma protocols. The technology landscape reveals sophisticated pharmaceutical development spanning multiple technological paradigms, from chemical synthesis platforms to complex biotechnology manufacturing systems. The progression from traditional hemostatic approaches to advanced biomaterial composites demonstrates significant innovation capacity within the pharmaceutical industry. However, this technological sophistication has not translated proportionally to military operational contexts.

The geographic distribution of research activity, concentrated primarily in developed nations with advanced medical infrastructure, suggests potential limitations in the external validity of findings for austere operational environments

characteristic of military deployments. The underrepresentation of battlefield-specific research constitutes a fundamental evidence gap that undermines the translation of civilian clinical validation to combat casualty care protocols.

Critical analysis reveals, that current hemostatic research paradigms prioritize controlled clinical environments over operational military requirements. The absence of studies addressing logistical constraints, environmental extremes, personnel training limitations, and evacuation timeline pressures represents substantial limitations in evidence applicability to combat scenarios. The disconnect between civilian clinical research excellence and military operational needs necessitates targeted research investment in battlefield-validated hemostatic protocols. Future investigations must prioritize operational relevance through simulation of combat conditions, integration with military evacuation procedures, and validation under resource-constrained environments. Additionally, research addressing the training requirements for non-medical military personnel in hemostatic intervention deployment represents an essential component of comprehensive combat casualty care preparedness.

The establishment of dedicated military hemostatic research programs, incorporating both technological innovation and operational validation, emerges as a critical priority for enhancing combat medical readiness and reducing preventable battlefield mortality from hemorrhagic complications.

Acknowledgements. Authors gratefully acknowledge Armed Forces of Ukraine with Territorial Defense Forces of the Armed Forces of Ukraine for preparing this paper in the safe conditions of Zaporizhzhia, Ukraine; and assistance of large language model Claude 3.7 by Anthropic during manuscript preparation in English language.

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