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Research Article

Critical Bleeding Management: a four-Year Analysis of Hemostatic agent Selection, Clinical Practices, and Patient Demographics in the Critical Care Units of the Jordanian Royal Medical Services

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Abstract:

Background: Life-threatening bleeding is one of the major clinical concerns in emergency and critical care settings in which rapid hemorrhage control can prevent adverse outcomes. Medications such as Hemostatic agents especially coagulation factors will continue to be used as essential tools for the management of bleeding in these cases. Although these agents are widely used clinically, limited literature addressed how they are selected and used in military systems, particularly in structured networks such as the Jordanian Royal Medical Services (JRMS). comprehending the medical rationale, patients' demographic factors, and individual institution contributing factors that impact their selection in critical care units will be essential to improve treatment processes, resource distribution, and medical education and training in military hospitals.

Objective: Over a four-year period (2019-2022), this study aims to examine the use of four key agents: Recombinant Factor VII, Factor VIII, Prothrombin Complex Concentrate (PCC), and Tranexamic Acid within JRMS critical care units. In addition, it will look at how Variables like patient age, Gender, specialty of hospital, and year of treatment affect agent selection. Particular notice will be taken of any differences in prescribing habits in pediatric versus adult patients in addition to any distinctions in clinical practices across the study hospitals. The research also aims to look for trends over time, which may help in understanding any changes in clinical practice, guidelines or availability issues.

Methods: Data of prescriptions and demographic information of patients from six hospitals within the JRMS (King Hussein Medical Hospital, Queen Alia Heart Institute, Prince Hashem Ben Abdullah II Hospital, Princess Haya Military Hospital, Queen Rania Pediatric Hospital and Queen Alia Military Hospital) will be collected in order to conduct this retrospective , cross-sectional study including data on age, gender, the hospital that prescribed the agent, year of treatment and the type of hemostatic agent used. Hospitals will be classified into three categories (General, Pediatric, or Specialized), and patients will be divided into groups according to their age Descriptive statistics will be then employed to summarize utilization patterns of agents across different groups. After which a comparison will be made to identify any differences in prescribing habits according to different hospitals and demographics factors. The study will also identify hospital-specific trends that may affect agent choice such as hospital specialization and whether there is critical care units dedicated to specific populations. The results of this research will help in understand how to improve the standardization of guidelines for life-threatening bleeding management and guide the future policies dealing with the use of such agents in military ICU's.

Key words: hemostatic agents; factor vii; tranexamic acid; military hospitals; critical care; practice patterns

1.Introduction

Hemostatic diseases are a major problem in the intensive care units (ICUs), typically resulting in acute life-threatening complications, which need an immediate action. The multifaceted cascade of coagulation is mediated by several factors and by several pathways, and, accordingly,

targeted therapy is necessary, which is determined according to the nature of the bleeding. Recent advances in our knowledge of coagulation have resulted in the development of more advanced strategies for hemostatic management and an increased range of agents that target specific components of the coagulation system [1]. Within this context, four particular hemostatic options were found the most relevance to contemporary practice: recombinant Factor VII (rFVIIa), Factor VIII concentrate, Prothrombin Complex Concentrate (PCC), and Tranexamic Acid (TXA). These agents all have different mechanisms of action, indications, and risk profiles, raising the potential for differences in outcomes and resource utilization based on the choice of agent [2]. In severe bleeding, Recombinant Factor VII, originally developed for patients with haemophilia with inhibitors, has demonstrated utility in a much wider spectrum of bleeding by improving thrombin generation at the site of the vascular injury [3]. rFVIIa's off-label use has been met with criticism; nevertheless, it is still commonly employed for the management of refractory bleeding in cases where conventional procedures have not been successful. Factor VIII concentrate is the cornerstone of care for hemophilia A and offers direct replacement of the deficient coagulation protein [4].Prothrombin Complex Concentrate which containing varying combinations of factors II, VII, IX, and X, has established itself as a rapid reversal agent for vitamin K antagonist therapy and a valuable instrument in the management of coagulopathy in liver disease and trauma [5]. Tranexamic acid, an antifibrinolytic agent that inhibits plasminogen activation has demonstrated mortality benefits in trauma and surgical bleeding and gained prominence following landmark studies such as CRASH-2 and WOMAN trials [6,7]. The Jordanian Royal Medical Services (JRMS) represents a broad military healthcare system serving military staff and their dependent relative and in many cases civilian populations. Encompassing multiple specialized hospitals across Jordan the JRMS manages a varied patient population with varying hemostatic needs from pediatric inherited coagulation disorders to adult trauma and surgical bleeding. However, patterns of hemostatic agent utilization within this system have not been previously characterized leaving important questions about clinical practice patterns, resource allocation, and potential prospects for standardization unanswered. Recognizing the utilization patterns of these agents within a specified healthcare system can provide valuable perceptions into clinical decision-making, resource allocation, and adherence to evidence-based practices This is particularly relevant in military health care structures which often function under unique restrictions while managing diverse patient populations with varying hemostatic needs. The present study seeks to investigate the patterns of hemostatic agent utilization throughout the Jordanian Royal Medical Services hospital network, with particular attention to: Age-stratified usage patterns across different hemostatic agents, Hospital-specific practices and potential factors influencing agent selection, Temporal trends in hemostatic agent utilization between 2019 and 2022 and Gender-based differences in prescribing patterns. By characterizing these patterns this study then seeks to provide insights that might help protocol development, resource allocation and use and quality enhancement programs within military healthcare systems.

2. Methods:

2.1 Data Source and Collection: This study utilized a retrospective analysis of hemostatic agent prescriptions throughout six Jordanian Royal Medical Services hospitals between January 2019 and December 2022. Data were obtained from the pharmacy dispensing records of the JRMS. The dataset included anonymized patient information: gender, age at treatment time, treatment year, prescribed agent, and prescribing hospital. Four hemostatic agents were included in this investigation: recombinant Factor VII, Factor VIII concentrate, Prothrombin Complex Concentrate, and Tranexamic Acid which were selected based on their common use in critical care settings and their representation in the JRMS formulary.

2.2 Study Setting: The study encompassed six hospitals within the JRMS network: King Hussein Medical Hospital (KHMH): The largest tertiary care facility within the JRMS and serving as a referral center for complex cases, Queen Alia Heart Institute (QAHI): A specialized cardiac care center, Queen Rania Pediatric Hospital (QRPH): Dedicated to pediatric care including management of congenital bleeding disorders, Prince Hashem Ben Abdullah II Hospital (PHBAH): A regional hospital providing general medical and surgical services, Princess Haya Military Hospital (PHMH): A regional hospital serving the northern districts of Jordan and Queen Alia Military Hospital (QAMH): A general military hospital. These facilities represent a spectrum of care levels and specializations within the JRMS network, allowing for a more thorough analysis of hemostatic agent utilization across different clinical contexts.

2.3 Variables and Definitions: The key variables that will be analyzed in this study encompassed: Patient demographic characteristics: which include Age at treatment time and gender, Hemostatic agent used: Factor VII, Factor VIII, Prothrombin Complex Concentrate, or Tranexamic Acid, Treatment facility: The hospital where the prescription was issued and Treatment year: Calendar year of prescription (2019-2022).

For the age-stratified analyses, patients were categorized as: Neonates and infants: 0-1 years, Young children: 2-5 years, School-age children: 6-12 years, Adolescents: 13-17 years and Adults: ≥18 years.

2.4 Statistical Analysis: Descriptive statistics were utilized to describe the dataset. Frequencies and percentages were calculated for categorical variables (gender, agent type, hospital, treatment year) and for the continuous variables (age), mean, median, and range were calculated also cross-tabulations were made to examine relationships between: Agent type and different age groups, Agent type and hospital, Agent type and gender and Agent type and treatment year. Chi-square tests were also used to judge on the statistical significance of observed differences in categorical variables. As for the age-related analyses non-parametric tests (Mann-Whitney U and Kruskal-Wallis) were employed owing to the non-normal distribution of age data. Data analysis was performed using SPSS Statistics version 26.0.

2.5 Ethical Considerations: This study exploited de-identified pharmacy dispensing data with all patient identifiers removed before analysis. The study procedures was reviewed and approved by the Jordanian Royal Medical Services Research Ethics Committee and as a retrospective analysis of anonymized data informed consent was waived.

3. Results:

3.1 Overall Sample Characteristics: The dataset covered 34 hemostatic agent prescriptions give out between 2019 and 2022 across the six JRMS hospitals. The patient had a mean age of 17.1 years (median: 6.5 years; range: 0-80 years) with a bimodal distribution showing peaks in early childhood (0-5 years) and late adulthood (>60 years). Also males accounted for 58.8% (n=20) of the patients while females represented 41.2% (n=14).

3.2 Agent Distribution: Factor VII was the most commonly prescribed hemostatic agent where it accounted for 67.6% (n=23) of all the

prescriptions followed by Tranexamic Acid (17.6%, n=6), Factor VIII (8.8%, n=3), and Prothrombin Complex Concentrate (5.9%, n=2). The yearly allocation of prescriptions showed to be relative stability across the study period: with 2019 (20.6%, n=7), 2020 (23.5%, n=8), 2021 (38.2%, n=13), and 2022 (17.6%, n=6).

3.3 Age-Stratified Agent Utilization: The analysis also revealed noticeable age-related patterns in hemostatic agent use (Table 1). The mean age of patients taking Factor VII was 12.9 years, compared to 42.5 years for Tranexamic Acid and 5.0 years for Factor VIII, and 4.0 years for PCC. This difference in age spreading throughout agent types was statistically significant ($p<0.001$, Kruskal-Wallis test).

Agent	Mean Age (years)	Median Age (years)	Range (years)
Factor VII	12.9	3.0	0-69
Tranexamic Acid	42.5	39.5	8-80
Factor VIII	5.0	0.0	0-15
PCC	4.0	3.0	0-9
All Agents	17.1	6.5	0-80

Table 1: Age Distribution by Hemostatic Agent.

Stratification by age groups exposed that Factor VII was the main agent through all pediatric age categories which accounted for 87.5% (21/24) of all the hemostatic prescriptions in patients under 18 years. On the contrast adult patients (≥18 years) demonstrated more varied agent selection with Tranexamic Acid representing 42.9% (6/14) of the prescriptions and Factor VII accounting for 28.6% (4/14) of them.

3.4 Hospital-Specific Patterns: Queen Rania Pediatric Hospital accounted for the prime proportion of the hemostatic agent prescriptions (70.6%, n=24) then followed by King Hussein Medical Hospital (14.7%, n=5), Prince Hashem Ben Abdullah II Hospital (8.8%, n=3), and the remaining hospitals each signifying less than 5% of the prescriptions. Each hospital demonstrated distinct prescribing patterns (Table 2). Queen Rania Pediatric Hospital predominantly used Factor VII (79.2%, 19/24) with smaller amounts of Factor VIII (12.5%, 3/24) and PCC (8.3%, 2/24). On the contrast King Hussein Medical Hospital's prescriptions were uniformly divided between Factor VII (60%, 3/5) and Tranexamic Acid (40%, 2/5) Also Prince Hashem Ben Abdullah II Hospital utilized Factor VII and Tranexamic Acid in equal proportions (50% each).

Hospital	Factor VII	Tranexamic Acid	Factor VIII	PCC	Total
QRPH	19 (79.2%)	0 (0%)	3 (12.5%)	2 (8.3%)	24
KHMH	3 (60%)	2 (40%)	0 (0%)	0 (0%)	5
PHBAH	1 (50%)	1 (50%)	0 (0%)	0 (0%)	2
QAHI	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1
PHMH	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1
QAMH	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1
Total	23 (67.6%)	6 (17.6%)	3 (8.8%)	2 (5.9%)	34

Table 2: Agent Distribution by Hospital.

QRPH: Queen Rania Pediatric Hospital; KHMH: King Hussein Medical Hospital; PHBAH: Prince Hashem Ben Abdullah II Hospital; QAHI: Queen Alia Heart Institute; PHMH: Princess Haya Military Hospital; QAMH: Queen Alia Military Hospital; PCC: Prothrombin Complex Concentrate

3.5 Gender-Based Analysis: Analysis by gender revealed that Factor VII was the main agent in both males (65%, 13/20) and females (71.4%, 10/14) with no statistically significant difference in overall agent use between genders ($p=0.74$, chi-square test). The mean age of the male patients (18.7 years) was slightly higher than the female patients (14.9 years) but this deviation did not reach statistical significance ($p=0.56$, Mann-Whitney U test).

3.6 Temporal Trends: Assessment of prescribing patterns by year revealed relative steadiness in agent distribution over the study period years. Factor VII persisted to be the predominant agent across all years ranging from 57.1% to 76.9% of the annual prescriptions. However the absolute number of Factor VII prescriptions showed a raising trend from 2019 (n=4) to 2021 (n=10) followed by a decrease in 2022 (n=3). Interestingly PCC prescriptions were only observed in the years of 2019 (n=1) and 2021 (n=1) while Factor VIII prescriptions occurred in 2019 (n=1), 2020 (n=1), and 2021 (n=1).

4. Discussion:

4.1 Key Findings: This retrospective analysis of hemostatic agent utilization in Jordanian military hospitals reveals various remarkable patterns with consequences for clinical practice and resource allocation. The prevalence of Factor VII particularly in pediatric populations suggests a considerable liability of congenital bleeding conditions or other conditions needing targeted factor replacement the distinct age stratified patterns with Factor VII prevailing in pediatric patients and more varied agent selection in adults likely reflect the divergent etiologies of bleeding disorders across the lifespan. Hospital specific use patterns seem to be supporting the institutional specialization with the pediatric hospital displaying a preference for Factor VII and the adult facilities utilizing a wider range of agents. These patterns also may reflect not only differences in patient populations but also distinctions in institutional expertise, resource availability and clinical procedures.

4.2 Age-Stratified Patterns and Clinical Implications: The striking high proportion of Factor VII in pediatric patients (87.5% of pediatric prescriptions) warrants attention this pattern proposes a significant load of congenital bleeding disorders in the pediatric population which is served by the JRMS particularly conditions that would benefit from

Factor VII replacement. Several possible justifications merit consideration: First, the pattern may reflect a high incidence of rare congenital factor deficiencies specifically Factor VII deficiency within this population. Factor VII deficiency is one of the rare inherited hemorrhage disorders with the anticipated incidence of 1 in 500,000 in general populations [8]. However in areas with higher proportions of kin marriage such as parts of the Middle East, the prevalence may be significantly higher [9]. Jordan has reported consanguinity rates of approximately 20-30% in various studies which could contribute to the higher rates of autosomal recessive bleeding disorders [10]. Second, the high use rate of Factor VII in pediatric patients may reflect it application in hemophilia patients with inhibitors approximately 20-30% of severe hemophilia A patients develop inhibitors to Factor VIII which necessitate bypass therapy with agents such as recombinant Factor VII [11] also the relatively low Factor VIII prescriptions in our sample (n=3) compared to Factor VII (n=23) could possibly suggest a high percentage of hemophilia patients with inhibitors although this understanding is limited by the absence of specific diagnostic data. Third, institutional preferences and procedures may play a significant role since the concentration of pediatric hemostatic care at Queen Rania Pediatric Hospital (70.6% of all prescriptions) suggests centralization of expertise in pediatric hemorrhage disorders this centralization may have led to the growth of specific procedures that favors Factor VII for a range of bleeding scenarios outside its licensed indications. The more diverse agent choices observed in the adult patients signals the diverse etiologies of bleeding in this population. With Tranexamic acid representing 42.9% of adult prescriptions which is particularly useful in trauma, surgical, and obstetric bleeding conditions which are more commonly encountered in the adults populations also the considerable evidence base for tranexamic acid in those contexts including the landmark CRASH-2 and WOMAN trials, may have lead to its adoption in adult trauma and surgical care within JRMS [6,7].

4.3 Hospital-Specific Practices: The individual prescribing patterns noticed across hospitals provides insights into the institutional specialization and potentially variations in their clinical approach. Queen Rania Pediatric Hospital's predominant use of Factor VII (79.2% of prescriptions) allies with its specialized role in managing the pediatric hematological disorders. Similarly in King Hussein Medical Hospital's the more reasonable distribution between Factor VII and Tranexamic Acid likely exhibits its broader patient population as a tertiary referral center also the non-appearance of Tranexamic Acid prescriptions at Queen Rania Pediatric Hospital is noteworthy given its proved safety profile in pediatric surgical contexts [12] which may reflect a specific institutional protocol or a prevalence of congenital bleeding disorders that lead to requiring factor replacement rather than the antifibrinolytic therapy in this population. Queen Alia Heart Institute's restricted use of Factor VII even though based on a single prescription may reflect its application in cardiac surgery where rFVIIa has been used as rescue therapy for refractory bleeding [13]. While its an off-label use in this context Factor VII has demonstrated an effectiveness in reducing the bleeding and blood transfusion requirements in complicated cardiac surgical cases [14].

4.4 Temporal Trends and Potential Influences: The relative consistency in agents distribution during the research duration points to the agreed clinical standards within the JRMS. Still the noted rise in Factor VII prescriptions from 2019 to 2021 followed by the deterioration in 2022 could be as a result of numerous elements: The height of the COVID-19 epidemic links with the peak in Factor VII prescriptions in 2021; however, resource limitations and changes in hospital admission trends or COVID-associated coagulopathy may have affected bleeding control strategies. The changes in institutional or international guidelines for hemostatic management also could have affected prescribing patterns over time for instance the World Federation of Hemophilia published an updated guidelines for hemophilia management in 2020 which may have affected the clinical practice [4]. Given the high cost of factor concentrates and possible supply limits during the epidemic, the availability and pricing issues could have also affected agent choice during specific periods.

4.5 Resource Utilization Implications: The noticed patterns also have significant consequences for resource allocation inside the JRMS. Recombinant Factor VII is among the most high-priced hemostatic agents with costs potentially go over $10,000 per regular adult dose [15]. The predominance of Factor VII in our sample (67.6% of prescriptions) implies considerable resource allocation to this agent particularly at Queen Rania Pediatric Hospital. On the other hand tranexamic acid is really affordable with costs typically less than $50 per treatment course [6]. So the limited utilization of this cost-effective agent in certain contexts particularly in pediatric care which may represent an opportunity for resource optimization if clinically appropriate. Factor VIII concentrate and PCC also represent significant costs even though they are typically lower than recombinant Factor VII for an equivalent hemostatic effect in appropriate indications. The relatively low utilization of those agents in our sample (8.8% and 5.9%, respectively) may also reflect specific patient needs rather than resource constraints. Recognizing these utilization patterns can inform policies decisions and formulary decisions, procurement strategies and budget allocation within the JRMS. For example the concentration of Factor VII use at Queen Rania Pediatric Hospital may rationalize specialized funding allocations for this high-cost agent at this facility while efforts to optimize Tranexamic Acid utilization might be prioritized at adult care centers.

4.6 Comparison with International Practices: The utilization patterns observed in this study both align with and conflict from international practices in several respects, the predominance of Factor VII in pediatric bleeding management seems more pronounced in our sample than what is reported in other healthcare systems where Factor VIII naturally represents the pillar of hemophilia management [4].The fairly limited use of PCC (5.9% of prescriptions) contrasts with its increasing adoption in many Western healthcare systems for warfarin reversal and trauma associated coagulopathy conditions [5] which may reflect differences in anticoagulation practices, trauma care protocols, or resource availability within the JRMS. Also Tranexamic acid utilization (17.6% of prescriptions) appears lower than what might be expected given its established efficacy and cost-effectiveness in the various bleeding conditions [16]. However its predominance in adult prescriptions (42.9%) suggesting appropriate targeting to relevant clinical contexts.

4.7 Clinical and Policy Implications: Several implications for clinical practice and policy emerge from this analysis:

1. **Protocol Standardization:** The variations in the selection and the use of hemostatic agents among hospitals indicate a chance to standardize the protocols grounded in the best available evidence while also considering the unique specialties of each institution, this could involve developing an evidence-based procedures for choosing agents in particular clinical situations.

2. **Resource Optimization:** The extensive use of costly agents like Factor VII requires a thorough assessment of their suitability and results additionally establishing stewardship programs for these high-cost hemostatic agents could promote responsible usage while preserving clinical effectiveness.
3. **Centralization of Expertise:** The concentration of the hemostatic prescriptions at the specialized centers predominantly Queen Rania Pediatric Hospital suggests that the benefits from the centralization of expertise therefore formalization of referral pathways and concentration of resources at centers of excellence may enhance outcomes while controlling costs.
4. **Educational Initiatives:** Targeted educational programs on hemostatic agent selection and on appropriate dosing might tackle knowledge gaps and also reduces unwarranted variations in practice which is particularly relevant for high cost agents with significant risk profiles such as Factor VII.
5. **Data Infrastructure Enhancement:** The limited clinical details available in this analysis highlights the importance of robust data systems capturing indications, dosing, outcomes, and the adverse events also implementation of dedicated registry systems for hemostatic agent utilization could facilitate quality improvement and research.

4.8 Study Limitations: Several limitations should be considered when taking the findings of this study: First, the rather small sample size (n=34) limits the statistical analyses power and the ability to detect subtle patterns or trends but this also reflects the specialized nature of these agents and the relatively small population. Second, the non-existence of clinical indication data represents a substantial limitation since that without information on the specific conditions being treated our ability to review the appropriateness of agent selection was constrained therefor future studies integrating diagnostic data would provide valuable context for interpreting utilization patterns. Third, the analysis focuses merely on dispensing patterns without information on dosing and duration of therapy or clinical outcomes therefor it limits our ability to evaluate the effectiveness and efficiency of the hemostatic management. Fourth, the dataset does not include information on other hemostatic interventions such as fresh frozen plasma or platelet transfusions which are important components of comprehensive hemostatic management. Finally, the single system nature of this study may limit generalizability to other healthcare systems particularly those with different patient populations or resource constraints and clinical protocols.

5. Conclusion:

This retrospective analysis offers valuable insights into how hemostatic agents are used within the Jordanian Royal Medical Services hospital network and highlighting unique patterns based on age and specific practices at different hospitals along with implications for resource allocation. The high presence of Factor VII, especially in children, indicates a strong emphasis on congenital bleeding disorders, while the wider range of agents used in adults highlights the different causes of bleeding in that group. The patterns of utilization specific to hospitals seem to match their areas of specialization, indicating that there are advantages to having concentrated expertise, while also pointing out the potential for standardizing protocols. The significant resource implications of current usage patterns, especially the heavy reliance on expensive Factor VII, highlight the need for evidence-based agent selection and careful resource management. The results lay the groundwork for additional research and enhancements in quality and the creation of policies focused on improving hemostatic management in military healthcare systems. Future research that includes clinical indications, dosing details and outcome data would deepen our understanding of how hemostatic agents are used and their effects on patient care.

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