REVISTA ERR01 ISSN: 2595-1378

CURRENT ASPECTS OF FLUID RESUSCITATION IN TRAUMA PATIENTS

ASPECTOS ATUAIS DA RESSUSCITAÇÃO VOLÊMICA EM PACIENTES TRAUMATIZADOS

ASPECTOS ACTUALES DE LA REANIMACIÓN CON FLUIDOS EN PACIENTES TRAUMATIZADOS

10.56238/ERR01v10n7-055

Victor Miguel dos Santos Silva[1], Calyanne Ingrid Gomes Lima[2], Gabriel Batista de Siqueira Gomes[3], Paula Daiane Nunes Viana[4], Renata Gabriela Santos Dantas[5], Maria Clara Ramos Câmara[6], Danilo Monteiro Falcão[7], Martinho Dinoá Medeiros Júnior[8]

ABSTRACT

Introduction: Hemorrhage is one of the leading preventable causes of death in polytrauma patients, making fluid resuscitation a critical component in the management of hemorrhagic shock. Traditional strategies using large volumes of crystalloids have been questioned due to the risks of coagulopathy, hypothermia, and organ dysfunction. New approaches, such as permissive hypotension, early use of blood products, and adjuvant therapies—like BTK inhibitors and conjugated steroids—have shown promising results. This article discusses recent advances and ongoing challenges in fluid resuscitation in trauma, based on experimental and clinical evidence.

Objective: To analyze the current advances and challenges of fluid resuscitation in trauma patients, with a focus on evidence-based strategies aimed at improving clinical outcomes.

Methodology: This study is an integrative literature review conducted in stages, including topic definition, inclusion and exclusion criteria, selection of descriptors, and article screening and evaluation. The guiding question was: “What are the current aspects of fluid resuscitation in trauma patients?” Searches were performed in the BVS and LILACS databases using the descriptors “multiple trauma,” “shock hemorrhagic,” and “hypovolemia,” combined with the

[1] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: victor.miguelsilva@gmail.com
[2] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: calyanne.gomes@ufpe.br
[3] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: gabriel.batistag@ufpe.br
[4] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: paulaviana2815@hotmail.com
[5] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: renata.sdantas@ufpe.br
[6] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: maria.ramosc@ufpe.br
[7] Undergraduate student. Universidade de Pernambuco. Pernambuco, Brazil.
E-mail: E-mail:danilomfalcao87@gmail.com
[8] Professor. Universidade de Pernambuco. Pernambuco, Brazil. E-mail: martinho.medeirosjr@ufpe.br

Boolean operators “AND” and “OR.” Inclusion criteria were full scientific articles, in Portuguese or English, published between 2020 and 2025. Excluded were non-scientific and unavailable texts. Of the 4,930 articles found, 63 were selected for the review.

Results: The results show that excessive use of 0.9% saline is associated with hyperchloremia, acidosis, kidney injury, and increased mortality, especially in children with severe trauma. Strategies such as permissive hypovolemia proved effective in reducing mortality and complications. In addition, early interventions, such as the use of type O whole blood and monitoring with ROTEM, contributed to better outcomes. At the molecular level, changes in ADORA3, NOS3, and extracellular vesicles suggest good prognostic value. Thus, individualized fluid resuscitation stands out as an essential approach to optimize clinical outcomes.

Conclusion: Fluid resuscitation in trauma patients should follow an integrated, individualized, and evidence-based approach. Proper selection of fluid type and volume, early administration of blood products, use of strategies such as hypotensive resuscitation, and implementation of balanced solutions contribute to improved clinical outcomes. Moreover, the use of biomarkers and adjuvant therapies, such as BTK inhibitors and conjugated steroids, points to a more precise and effective therapeutic future. The implementation of these practices requires well-structured protocols, trained teams, and adequate resources, both in pre-hospital and hospital settings, aiming to reduce mortality and improve the quality of care for polytrauma patients.

Keywords: Multiple Trauma. Hemorrhagic Shock. Hypovolemia.

RESUMO

Introdução: A hemorragia é uma das principais causas evitáveis de morte em pacientes politraumatizados, tornando a ressuscitação volêmica um componente crítico no manejo do choque hemorrágico. As estratégias tradicionais baseadas no uso de grandes volumes de cristaloides têm sido questionadas devido aos riscos de coagulopatia, hipotermia e disfunção orgânica. Novas abordagens, como a hipotensão permissiva, o uso precoce de hemocomponentes e terapias adjuvantes — como inibidores de BTK e esteroides conjugados — têm demonstrado resultados promissores. Este artigo discute os avanços recentes e os desafios atuais da ressuscitação volêmica no trauma, com base em evidências experimentais e clínicas.

Objetivo: Analisar os avanços e desafios atuais da ressuscitação volêmica em pacientes vítimas de trauma, com foco em estratégias baseadas em evidências voltadas à melhoria dos desfechos clínicos.

Metodologia: Trata-se de uma revisão integrativa da literatura, conduzida em etapas, incluindo definição do tema, critérios de inclusão e exclusão, seleção de descritores e triagem e avaliação dos artigos. A questão norteadora foi: “Quais são os aspectos atuais da ressuscitação volêmica em pacientes traumatizados?”. As buscas foram realizadas nas bases de dados BVS e LILACS, utilizando os descritores “multiple trauma”, “shock hemorrhagic” e “hypovolemia”, combinados com os operadores booleanos “AND” e “OR”. Foram incluídos artigos científicos completos, em português ou inglês, publicados entre 2020 e 2025. Foram excluídos textos não científicos e indisponíveis. Dos 4.930 artigos encontrados, 63 foram selecionados para compor a revisão.

Resultados: Os resultados demonstram que o uso excessivo de solução salina a 0,9% está associado à hipercloremia, acidose, lesão renal e aumento da mortalidade, especialmente em crianças com trauma grave. Estratégias como a hipovolemia permissiva mostraram-se eficazes na redução da mortalidade e das complicações. Além disso, intervenções precoces, como o uso de sangue total tipo O e o monitoramento por ROTEM, contribuíram para melhores desfechos. Em nível molecular, alterações em ADORA3, NOS3 e vesículas extracelulares sugerem bom valor prognóstico. Assim, a ressuscitação volêmica individualizada destaca-se como abordagem essencial para otimizar os resultados clínicos.

Conclusão: A ressuscitação volêmica em pacientes traumatizados deve seguir uma abordagem integrada, individualizada e baseada em evidências. A adequada seleção do tipo e volume de fluidos, a administração precoce de hemocomponentes, o uso de estratégias como a ressuscitação hipotensiva e a implementação de soluções balanceadas contribuem para melhores desfechos clínicos. Ademais, o uso de biomarcadores e terapias adjuvantes, como inibidores de BTK e esteroides conjugados, aponta para um futuro terapêutico mais preciso e eficaz. A implementação dessas práticas exige protocolos bem estruturados, equipes treinadas e recursos adequados, tanto no ambiente pré-hospitalar quanto hospitalar, com o objetivo de reduzir a mortalidade e melhorar a qualidade do cuidado aos pacientes politraumatizados.

Palavras-chave: Trauma Múltiplo. Choque Hemorrágico. Hipovolemia.

RESUMEN

Introducción: La hemorragia es una de las principales causas prevenibles de muerte en pacientes politraumatizados, lo que convierte a la reanimación con fluidos en un componente crítico del manejo del choque hemorrágico. Las estrategias tradicionales basadas en el uso de grandes volúmenes de cristaloides han sido cuestionadas debido a los riesgos de coagulopatía, hipotermia y disfunción orgánica. Nuevos enfoques, como la hipotensión permisiva, el uso precoz de hemoderivados y las terapias adyuvantes —como los inhibidores de BTK y los esteroides conjugados— han mostrado resultados prometedores. Este artículo analiza los avances recientes y los desafíos actuales de la reanimación con fluidos en el trauma, con base en evidencias experimentales y clínicas.

Objetivo: Analizar los avances y desafíos actuales de la reanimación con fluidos en pacientes traumatizados, con énfasis en estrategias basadas en la evidencia orientadas a mejorar los resultados clínicos.

Metodología: Se realizó una revisión integradora de la literatura, desarrollada por etapas que incluyeron la definición del tema, los criterios de inclusión y exclusión, la selección de descriptores y la búsqueda, selección y evaluación de los artículos. La pregunta guía fue: “¿Cuáles son los aspectos actuales de la reanimación con fluidos en pacientes traumatizados?”. Las búsquedas se realizaron en las bases de datos BVS y LILACS, utilizando los descriptores “multiple trauma”, “shock hemorrhagic” e “hypovolemia”, combinados con los operadores booleanos “AND” y “OR”. Se incluyeron artículos científicos completos, en portugués o inglés, publicados entre 2020 y 2025. Se excluyeron textos no científicos y no disponibles. De los 4.930 artículos encontrados, 63 fueron seleccionados para la revisión.

Resultados: Los resultados muestran que el uso excesivo de solución salina al 0,9% se asocia con hipercloremia, acidosis, lesión renal y aumento de la mortalidad, especialmente

ISSN: 2595-1378

en niños con trauma grave. Estrategias como la hipovolemia permisiva demostraron ser eficaces para reducir la mortalidad y las complicaciones. Además, intervenciones tempranas, como el uso de sangre total tipo O y la monitorización mediante ROTEM, contribuyeron a mejores resultados clínicos. A nivel molecular, los cambios en ADORA3, NOS3 y las vesículas extracelulares sugieren un buen valor pronóstico. De este modo, la reanimación con fluidos individualizada se destaca como un enfoque esencial para optimizar los resultados clínicos.

Conclusión: La reanimación con fluidos en pacientes traumatizados debe seguir un enfoque integrado, individualizado y basado en la evidencia. La adecuada selección del tipo y volumen de fluidos, la administración temprana de hemoderivados, el uso de estrategias como la reanimación hipotensiva y la implementación de soluciones balanceadas contribuyen a mejorar los resultados clínicos. Asimismo, el uso de biomarcadores y terapias adyuvantes, como los inhibidores de BTK y los esteroides conjugados, apunta hacia un futuro terapéutico más preciso y eficaz. La implementación de estas prácticas requiere protocolos bien estructurados, equipos capacitados y recursos adecuados, tanto en el ámbito prehospitalario como hospitalario, con el objetivo de reducir la mortalidad y mejorar la calidad de la atención a los pacientes politraumatizados.

Palabras clave: Trauma Múltiple. Choque Hemorrágico. Hipovolemia.

1 INTRODUCTION

Trauma remains one of the leading causes of death worldwide, particularly among individuals under 40 years of age, accounting for approximately six million deaths annually (1). Among the lethal mechanisms associated with trauma, hemorrhage is the most significant and preventable factor, responsible for up to 40 % of deaths in polytrauma patients (2,3). Early and effective volume replacement is a cornerstone in the management of hemorrhagic shock, aiming to restore tissue perfusion and prevent multiple organ dysfunction syndrome (MODS).

Over recent decades, increasing evidence has highlighted the risks of traditional resuscitation strategies using large volumes of crystalloids, which may worsen coagulopathy, acidosis, and hypothermia—the so-called “lethal triad” of trauma (4). Conversely, newer approaches such as permissive hypotension and early balanced blood-product administration have shown significant reductions in mortality and complications (4).

Beyond fluid strategies, adjuvant pharmacological therapies are under investigation. Bruton’s tyrosine kinase (BTK) inhibitors, including acalabrutinib and fenebrutinib, have been shown to reduce activation of inflammatory pathways such as NF-κB and NLRP3, attenuating organ dysfunction in experimental hemorrhagic shock (2,3). In a complementary swine blast-injury model, investigators demonstrated marked systemic inflammatory activation mediated by HMGB1 and the complement cascade, reinforcing the therapeutic potential of immune modulation (2).

Another innovative avenue involves conjugated steroids. Ethinyl estradiol sulfate, for example, produced cardioprotective and anti-inflammatory effects in severe hemorrhage without volume replacement through rapid estrogen-receptor–mediated nongenomic signaling (5).

The landscape remains complex and heterogeneous. Literature reveals inconsistencies in the definition of “multiple trauma” in clinical trials, hindering the standardization of interventions and the comparison of study results (6). Animal experimental models have helped elucidate pathophysiological mechanisms and test emerging interventions, such as prolonged damage-control strategies and aortic occlusion with different resuscitation fluids (7).

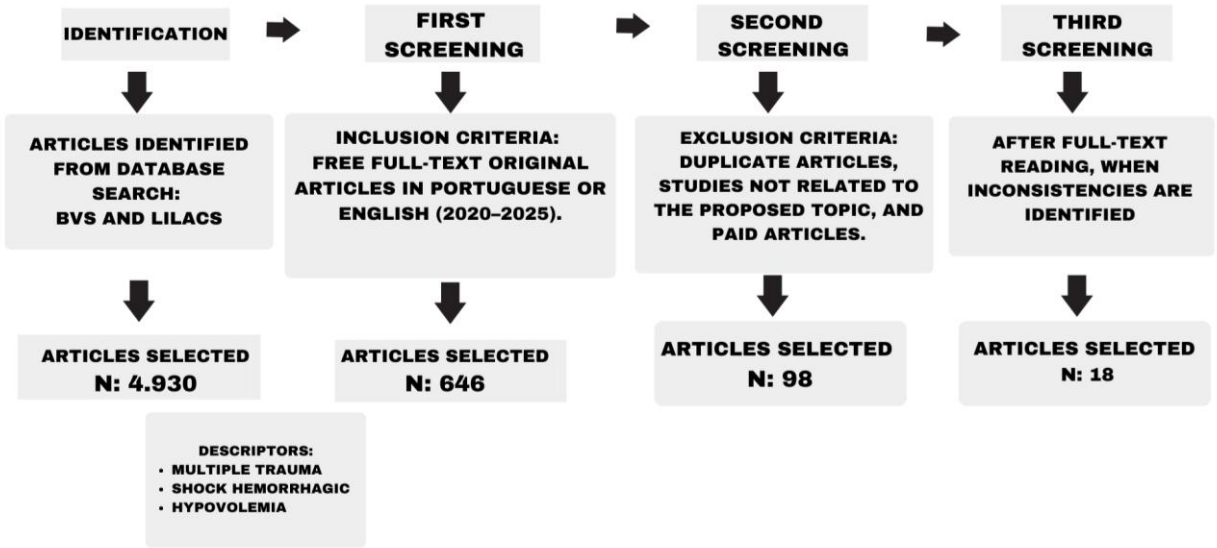
Within this context, the present article reviews contemporary aspects of volume resuscitation in trauma victims, highlighting the most promising strategies, clinical challenges, and advances in pathophysiological understanding that are shaping resuscitation practices in both pre-hospital and in-hospital settings.

2 MATERIAL AND METHOD

This study is a literature review, developed through the following steps: definition of the topic and formulation of the guiding question, establishment of inclusion and exclusion criteria, definition of the descriptors, pre-selection of articles, evaluation of the included studies, interpretation of the results, and elaboration of the review. The article selection was guided by the following question: "What are the current aspects of volume replacement in trauma victims?" The searches were conducted in the BVS (Virtual Health Library) and LILACS databases, using the descriptors "multiple trauma", "hemorrhagic shock", and "hypovolemia", combined with the Boolean operators "AND" and "OR". The inclusion criteria considered were: being a scientific article, published between 2020 and 2025, written in Portuguese or English, and available in full free of charge. The following were excluded: theses, dissertations, conference abstracts, proceedings, editorials, comments, opinions, review articles, and those that were not available. The search resulted in 4,930 articles. After reading the pre-selected studies and careful evaluation according to the established criteria, 18 articles were selected to comprise this review.

Figure 1

Flowchart



3 RESULT

Crystalloid solutions have been widely used for more than 100 years in the treatment of patients with shock, sepsis, or trauma. However, these solutions are not free from significant adverse effects. A relevant shift has been observed in the approach to volume replacement in trauma patients, focusing on patient safety, individualized therapy, and the

restriction of excessive crystalloid infusion. The indiscriminate use of 0.9% saline (NaCl) should be carefully reconsidered, since its composition does not reflect plasma and it has been associated with hyperchloremic metabolic acidosis, renal dysfunction, and worse clinical outcomes. In contrast, balanced solutions, such as lactated Ringer's and Plasma-Lyte 148®, have demonstrated greater safety and better results in most patients, especially in cases of sepsis and shock, as their acid–base profiles are associated with reduced morbidity and mortality (9).

Individual patient profile and tailored therapeutic strategies should always be considered in trauma resuscitation. Among the factors associated with poor outcomes, hyperchloremia has emerged as an independent predictor of mortality in severely injured pediatric patients. This finding correlated with total infused fluid volume within the first 48 hours, base deficit, and Injury Severity Score (ISS). In a retrospective study, all patients had normal serum chloride levels at admission; however, hyperchloremia developed more frequently among non-survivors after fluid therapy initiation. Serum chloride >110 mmol/L was observed in 75% of non-survivors compared to 22.5% of survivors, a statistically significant difference. Multivariate analysis confirmed hyperchloremia, high ISS, and infused fluid volume as independent risk factors for 28-day hospital mortality. Moreover, infusion of chloride-rich solutions, such as 0.9% saline (154 mmol/L of chloride) and 3% hypertonic solution (513 mmol/L), was identified as the main cause of serum chloride elevation in the intensive care setting, strongly associated with acute kidney injury, reduced cortical renal blood flow, hyperchloremic metabolic acidosis, and impaired immune function due to neutrophil dysfunction and reduced hypochlorous acid production (10).

Excessive crystalloid infusion has also been associated with adverse metabolic and coagulation effects. In patients with femoral fractures, infusion of 1–2 liters of crystalloids resulted in worsening pH, increased base deficit, reduced mean arterial pressure, impaired coagulation, and decreased hemoglobin levels. These findings support the recommendation to limit crystalloid infusion to no more than 1 liter, prioritizing vasopressors and blood products in more severe cases (11).

A meta-analysis including 4,503 patients demonstrated that hypotensive resuscitation significantly reduced blood loss, mortality (12.5% vs. 21.4%), and adverse events (10.8% vs. 13.4%) compared to conventional resuscitation. Patients managed with this strategy required significantly lower fluid volumes, although the incidence of anemia, thrombocytopenia, and acute kidney injury was slightly higher (4).

In adults, early hemostatic interventions should be initiated as soon as possible, ideally pre-hospital or within 3 hours after injury, maximizing survival. In pediatric patients, evidence

is more limited. A study including 207 children reported a median time to hemorrhagic death of 2.9 hours, and children with hemorrhagic shock and coagulopathy had up to four times higher risk of death compared to adults (12). Permissive hypovolemia, targeting systolic blood pressure between 80–90 mmHg, is recommended as the standard approach for hemorrhagic shock, except in traumatic brain injury, where cerebral perfusion must be preserved (13). Moreover, blood type has been linked to hemostatic response: patients with blood group B showed lower early mortality (7% vs. 16%), possibly due to higher coagulation factor levels, although with increased risk of late complications (14). Additional strategies include early administration of low-titer O whole blood (LTOWB), which has shown benefits in severely injured children, such as reduced transfusion requirements, fewer complications, and improved survival at 72 hours (12).

At the molecular level, significant associations were identified between vascular biomarkers and hemorrhagic shock severity in polytrauma patients. Gene expression and serum levels of ADORA3 and NOS3 were analyzed. ADORA3 gene expression was significantly increased at hospital discharge compared to healthy controls ($p < 0.05$), while its serum levels remained reduced throughout all clinical phases (admission, 24h, discharge). Conversely, NOS3 gene expression showed no significant changes, though serum levels were markedly decreased at admission and after 24h ($p < 0.05$), indicating early endothelial dysfunction (15). Complementarily, alterations in plasma extracellular vesicles and surface epitopes such as CD44 and CD31 were also associated with hemorrhagic shock severity and early mortality (16).

Early evaluation, bleeding control, warmed fluid administration, continuous monitoring of vital and laboratory parameters, permissive hypotension, whole blood use, and rapid intraosseous access have also shown improved outcomes in severely injured patients. Additionally, new diagnostic tools, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), have contributed to early recognition of coagulopathy and better therapeutic targeting. Biochemical markers such as serum lactate and base deficit have proven useful in detecting tissue hypoperfusion even when vital signs appear normal. Collectively, these findings reinforce the importance of early detection and aggressive management of hemorrhagic shock to reduce trauma-associated morbidity and mortality (17).

4 DISCUSSION

The evolution of fluid resuscitation strategies in trauma patients reflects a paradigm shift supported by robust scientific evidence. For decades, the infusion of large volumes of crystalloids, especially 0.9% normal saline, was considered standard practice for

hemodynamic stabilization in hemorrhagic shock. However, recent studies have shown that this approach may be associated with several metabolic and clinical complications, such as hyperchloremic acidosis, acute kidney injury, and dilutional coagulopathy. Hyperchloremia, often underestimated, has been identified as an independent risk factor for hospital mortality, particularly in severely injured pediatric patients, highlighting the importance of electrolyte monitoring and careful fluid selection (10).

In this context, balanced solutions such as lactated Ringer's and Plasma-Lyte 148® have gained prominence due to their electrolyte composition being closer to plasma, leading to less impact on acid–base balance and fewer metabolic complications. These solutions have proven effective in reducing morbidity and mortality in patients with sepsis and shock, while preserving renal function and vascular integrity (9). Fluid selection should therefore consider clinical status, injury severity, base deficit, required fluid volume, and the risks inherent to each solution type.

Permissive hypotension has also emerged as a promising strategy, particularly in patients with hemorrhagic shock not associated with traumatic brain injury. This approach aims to maintain systolic blood pressure between 80–90 mmHg, reducing blood loss and the risk of complications from excessive fluid replacement. A meta-analysis including more than 4,500 patients demonstrated that permissive hypotension significantly decreased mortality and adverse events, although some complications such as anemia and acute kidney injury were reported (4). These findings reinforce the need for individualized, evidence-based resuscitation strategies.

Another important development is the early use of balanced blood components and low-titer group O whole blood (LTOWB), particularly in prehospital and military settings. These blood products, used in ratios of red cells, platelets, and plasma, improve coagulopathy correction and outcomes in polytrauma patients. In pediatric trauma, LTOWB has been associated with reduced transfusion volume, fewer complications, and higher 72-hour survival rates (12).

At the molecular level, the expression of biomarkers such as ADORA3 and NOS3 has been linked to the severity of hemorrhagic shock and early endothelial dysfunction. Reduced serum NOS3, combined with elevated ADORA3 expression at discharge, suggests a compensatory mechanism in response to vascular stress and tissue hypoperfusion (15). Changes in extracellular vesicles such as CD31 and CD44 have also been correlated with shock severity and early mortality (16). These findings open new perspectives for diagnostic and therapeutic approaches, where biomarkers could guide risk stratification and personalized resuscitation.

Additionally, adjuvant pharmacological therapies have shown promise in attenuating the exaggerated inflammatory response of severe trauma. Bruton's tyrosine kinase (BTK) inhibitors, such as acalabrutinib, were effective in experimental models, reducing the activation of inflammatory pathways such as NF-κB and NLRP3, and protecting against organ dysfunction (1). Likewise, conjugated steroids such as ethinyl estradiol-3-sulfate demonstrated cardioprotective effects even in the absence of fluid resuscitation, possibly mediated through non-genomic estrogen receptors (5,17).

Early diagnosis and continuous monitoring are also critical. Tools such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been successfully applied to rapidly detect coagulopathies, enabling targeted interventions. Laboratory markers such as serum lactate and base deficit remain sensitive indicators of tissue hypoperfusion, even when vital signs appear stable (18). Therefore, the management of hemorrhagic shock should integrate hemodynamic, immunomodulatory, and pharmacological strategies into a multidisciplinary intensive care approach.

5 CONCLUSION

Fluid resuscitation in severe trauma victims is a continuously evolving field, driven by scientific advances that challenge traditional practices and promote safer, more effective, and individualized approaches. The progressive replacement of isotonic saline with balanced solutions, combined with judicious use of crystalloids, blood products, and whole blood, marks a turning point in the care of polytrauma patients. This shift is justified by the proven reduction in morbidity, mortality, and fluid-related complications.

Moreover, integrating strategies such as permissive hypotension, early hemorrhage control, warmed fluid administration, and the use of biochemical and molecular markers for monitoring and clinical decision-making has significantly improved outcomes in hemorrhagic shock. Adjuvant pharmacological therapies, including BTK inhibitors and conjugated steroids, are also emerging as promising interventions, broadening therapeutic possibilities for trauma care.

However, effective implementation of these strategies requires overcoming structural, logistical, and educational challenges. Continuous professional training, access to updated evidence-based protocols, and standardization of diagnostic criteria—particularly regarding the concept of "multiple trauma"—are essential to optimize clinical practice. Incorporating early monitoring technologies further enhances the ability to provide timely, targeted interventions.

In summary, contemporary fluid resuscitation should adopt a multidimensional approach that considers not only the type and volume of fluids administered, but also inflammatory modulation, individual clinical profiles, laboratory findings, and therapeutic innovations. Such an integrated, evidence-based model is vital to improving patient safety, outcomes, and survival in trauma care.

ACKNOWLEDGMENT

We thank the Federal University of Pernambuco (UFPE) and the Department of Clinical and Preventive Dentistry for institutional support. Our gratitude goes to Professor Martinho Dinoá Medeiros Júnior for his essential guidance and contributions. We also acknowledge colleagues, collaborators, scientific databases, and our families and friends for their valuable support throughout this study.

REFERENCES

1. Patel NM, Xiao Y, Han W, Ren Y, Zhang J, Yang S, et al. Inhibition of Bruton's tyrosine kinase activity attenuates hemorrhagic shock-induced multiple organ dysfunction. Ann Surg. 2023;277(3):e624-35. doi:10.1097/SLA.0000000000005357.

2. Simovic MO, Akca O, Bertram MJ, Bowman JL, Lassiter DG, Hou X, et al. Immunopathological alterations after blast injury and hemorrhage in a swine model of prolonged damage control resuscitation. Int J Mol Sci. 2023;24(8):7494. doi:10.3390/ijms24087494.

3. Patel NM, Zhang J, Liu S, Yang S, Hubbard WJ, Wang P. Inhibition of the JAK/STAT pathway with baricitinib reduces multiple organ dysfunction caused by hemorrhagic shock. Ann Surg. 2023;278(1):e137-48. doi:10.1097/SLA.0000000000005571.

4. Safiejko K, Smereka J, Filipiak KJ, Szarpak A, Dabrowski M, Ladny JR, et al. Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock: a systematic review and meta-analysis. Cardiol J. 2022;29(3):463-71. doi:10.5603/CJ.a2020.0096.

5. Hubbard WJ, Yang S, Chaudry IH. Ethinyl estradiol sulfate acts without fluid resuscitation to protect the cardiovascular system from severe hemorrhage. J Trauma Acute Care Surg. 2021;90(2). doi:10.1097/TA.0000000000002978.

6. Jeanmougin T, Chambrin M, Lazorthes F, Soubeyran P, Pellissier E. Heterogeneity in defining multiple trauma: a systematic review of randomized controlled trials. Crit Care. 2023;27:363. doi:10.1186/s13054-023-04637-w.
7. Schechtman DW, Kauvar DS, De Guzman R, Polykratis IA, Prince MD, Kheirabadi BS, et al. Differing resuscitation with aortic occlusion in a swine junctional hemorrhage polytrauma model. J Surg Res. 2020;248:90-7. doi:10.1016/j.jss.2019.11.036.

8. Aloird J, de Montgolfier S, Koszinowski J, Larroque B, Dufour T. First transfusion of cold-stored low-titer group O whole blood in the French armed forces. Transfusion. 2022. doi:10.1111/trf.16897.

9. Fernández-Sarmiento J, Casas-Certain C, Ferro-Jackaman S, Solano-Vargas FH, Domínguez-Rojas JÁ, Pilar-Orive FJ. A brief history of crystalloids: the origin of the controversy. Front Pediatr. 2023;11. doi:10.3389/fped.2023.1202805.

10. Çeleğen K, Çeleğen M. Effect of hyperchloremia on mortality of pediatric trauma patients: a retrospective cohort study. Sao Paulo Med J. 2022. doi:10.1590/1516-3180.2022.0370.R2.010923.

11. Ghahramani M. Resuscitating victims of femoral fracture: experience from Shiraz, Iran. Chin J Traumatol. 2020;24:30-3.

12. Morgan KM, Kline DD, Kaplan LJ, Davis R, Andrews S, Ramesh M, et al. Resuscitative practices and the use of low-titer group O whole blood in pediatric trauma. J Trauma Acute Care Surg. 2023;94 Suppl 1:S57-65. doi:10.1097/TA.0000000000003801.

13. Holcomb JB, Wade CE, McDaniel MR, Cohn SM, French D, Morsch CM, et al. Evidence-based and clinically relevant outcomes for hemorrhage control trauma trials. Ann Surg. 2021;273(3):452-62. doi:10.1097/SLA.0000000000004563.

14. Schofield H, Shi J, Ford JB, Smith AJ, Ray JZ, Rutherford EJ, et al. Group B or not group B? An association between ABO, early mortality, and organ dysfunction in major trauma patients with shock. J Thromb Haemost. 2023. doi:10.1016/j.jtha.2023.11.018.

15. Öztas Y, Çelik G, Karadag H. Role of adenosine A3 receptor and eNOS in traumatic hemorrhagic shock. Eur J Trauma Emerg Surg. 2025;51:167. doi:10.1007/s00068-025-02853-3.

16. Weber B, Sturm R, Henrich D, Marzi I, Leppik L. CD44+ and CD31+ extracellular vesicles are significantly reduced in polytraumatized patients with hemorrhagic shock. Front Immunol. 2023;14. doi:10.3389/fimmu.2023.1196241.

17. Mayer AR, Sharma A, Kang C, Nagaraj V, Nelson RJ. 17α-Ethinyl estradiol-3-sulfate increases survival in TBI + HS model. Crit Care. 2021;25:428. doi:10.1186/s13054-021-03844-7.

18. Caldwell NW, Martin PJ, Clark HT, Reynolds AS, Davis KJ. Trauma-related hemorrhagic shock: a clinical review. Am J Nurs. 2020;120(9).