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REVIEW ARTICLE

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ACUTE NORMOVOLEMIC HEMODILUTION: A STATE-OF-ART REVIEW

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ABSTRACT

Allogeneic blood transfusion is a widely used traditional procedure but still represents a scarce and expensive resource in healthcare. It is also associated with complications such as transmission of infectious diseases, unfavorable outcomes and increased mortality rates. The COVID-19 pandemic worsened blood scarcity and revealed the need for alternatives such as patient blood management – a patient-centered approach that aims to improve clinical results by managing and preserving the patient's own blood. Among the patient blood management techniques, acute normovolemic hemodilution stands out due to its benefits in surgeries with high potential for significant blood loss. The present study is a systematized review of the literature that presents the state-of-art acute normovolemic hemodilution surveyed on MEDLINE, Cochrane and LILACS bases. The initial search found 14,775 articles, out of which 23 were included in the review. The articles were also analyzed using the QuADS (Quality Assessment with Diverse Studies) criteria. Patient blood management and acute normovolemic hemodilution are promising strategies to reduce allogeneic transfusions, thus improving clinical and economic outcomes. Implementation of multidisciplinary patient blood management programs and standardization of the acute normovolemic hemodilution technique are essential to maximize their benefits. Tools such as the application developed by the author of the current review (hna.app.br) may favor the adoption of such techniques in the clinical practice for promoting efficient management of autologous blood and reducing perioperative complications.

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INTRODUCTION

Allogeneic blood transfusion, defined as interindividual transfusion, is a traditional and widely used procedure. However, it is still considered a scarce and expensive resource in the health area, besides being related to possible complications such as transmission of infectious diseases, unfavorable short and long-term outcomes, increased hospital care period and higher mortality rates, compared to patients who did not receive blood transfusion (SHANDER *et al.*, 2020; BARILE *et al.*, 2017; HOPEWELL *et al.*, 2013; MARIK & CORWIN., 2008; MURRAY, 2004). Rigorous infection screening of blood bags has decreased the risks but increased the costs (SHANDER *et al.*, 2020). Furthermore, the use of materials from autologous blood banks is susceptible to diverse logistical errors, including those associated with blood collection, inspection, identification and storage (MURRAY, 2004). The pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) placed blood

banks in a difficult situation due to the lack of stocks and faulty logistics. This resulted from the reduced number of donors, transportation restrictions, closing of factories, and production deficit (CHIAM *et al.*, 2021)⁶. Considering the hazards originated from blood transfusions, the concept of Patient Blood Management (PBM) has been strengthened. This systematic, evidence-based, patient-centered approach focuses on improving the patients' outcomes by managing and preserving the patient's own blood, in addition to promoting patient safety and empowerment (MONTANO-PEDROSO *et al.*, 2020; SHANDER *et al.*, 2022). The PBM program consists in the combination of a series of medication, equipment and/or surgical techniques, encompassing the following factors: 1) increased hematopoiesis (formation of blood cells); 2) blood loss control, and 3) maximized tolerance to anemia. Among the available PBM options, Acute Normovolemic Hemodilution (ANH) has been studied over the last decades due to its benefits for patients at risk of blood loss during surgery (BAYTER-MARIN *et al.*, 2021;

SHANDER *et al.*, 2016; GOODNOUGH & SHANDER, 2012; GOODNOUGH *et al.*, 2003). The ANH technique alone can be considered a good option to reduce the need for blood transfusion. After the induction of anesthesia and before heparin administration, a predetermined blood volume is withdrawn from the patient and temporarily stored near the bed. At the same time, it is substituted with sufficient volumes of crystalloid or colloid solutions to keep the intravascular volume. Hemodilution reduces the patient's hemoglobin concentration during surgery, thus resulting in a smaller number of red blood cells during intraoperative hemorrhage. The autologous blood, which had been temporarily separated from the circulatory system and is rich in red blood cells, platelets and coagulation factors, is returned to the patient after hemostasis (BARILE *et al.*, 2017; MURRAY, 2004). Although ANH is safe, efficient and cost-effective, it is not a well-known procedure and thus not widely adopted in medical practice (SHANDER *et al.*, 2020). Therefore, the current study aimed to present an updated review of this technique.

MATERIALS AND METHODS

This is a systematized review of the medical literature (SATALOFF *et al.*, 2021), approved by the Unifesp Research Ethics Committee via *Plataforma Brasil*, technical opinion number 5,556,610. The search was carried out from March 2023 to June 2024 on the databases MEDLINE, Cochrane and LILACS without date restrictions. The used descriptors (DeCS/MeSHs), in Portuguese (and in English), were: *hemodiluição* (hemodilution); *transfusão de sangue autóloga* (autologous blood transfusion); *preservação de sangue* (blood conservation); *procedimentos médicos e cirúrgicos sem sangue* (blood conservation strategies), and *tecnologia* (technology). The following search strategy was adopted after evaluation and revision by a Bireme librarian: ("Hemodilution" OR "acute normovolemic hemodilution" OR "intraoperative anemia" OR "intraoperative autologous blood donation" OR "blood conservation" OR "blood conservation strategies" OR "autologous blood transfusion" OR "patient blood management"). The included articles addressed ANH, hemodilution autologous blood transfusion, and patient blood management, written in Portuguese, English and Spanish. Studies involving animals, *in vitro* studies, letters and editorials were not included. The exclusion criteria included articles without correlation with PBM and ANH, duplicates, or articles that were retracted. To evaluate the methodological quality of the studies, the QuADS (Quality Assessment with diverse studies) criteria were also used for analysis (HARRISON *et al.*, 2021).

RESULTS

The initial literature survey found 14,775 articles which, after removal of duplicates and application of the exclusion criteria, resulted in 23 articles (Figure 1). All of them were on the Pubmed/MEDLINE, LILACS and Cochrane databases. Nine articles addressed ANH specifically, five articles focused on PBM, six investigated blood transfer, and one had related topics. The analysis according to QuADS is presented on Table 1. Since it is a systematized review, the major results are highlighted in the Discussion section to allow the synthesis of the most relevant findings, which are contextualized within the study field.

DISCUSSION

PBM Importance: Despite its widespread and traditional use, allogeneic blood transfusion has been associated with several drawbacks reported in the literature. These include perioperative complications, prolonged hospital care, intensive use of hospital resources, increased mortality rates, errors and transfusion incompatibility, in addition to adverse effects such as cardiac and pulmonary malfunction, neurological damage, renal failure, infections and immunological effects (MARIK & CORWIN, 2008; LI *et al.*, 2020; BENNETT *et al.*, 2006; SHANDER & RIJHWANI, 2004). In this context, PBM is reinforced as a patient-centered, interdisciplinary

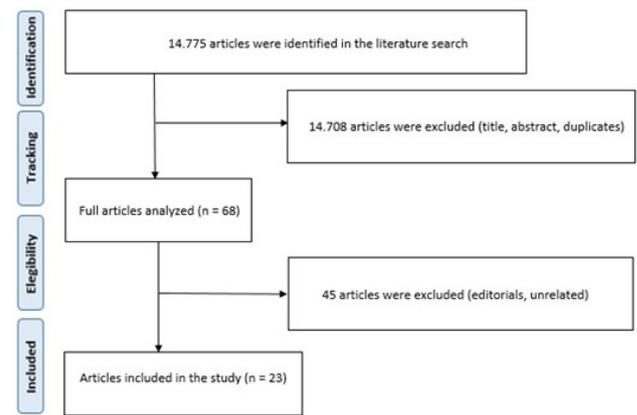


Figure 1. Flowchart of searching articles on databases

approach, which applies evidence-based measures for each selected case, managing and preserving the patient's own blood. A natural consequence is the reduction in the adoption of allogeneic blood transfusion (BAYTER-MARIN *et al.*, 2021). The PBM approach involves a set of pre, intra and postoperative strategies such as identification and treatment of pre-operative anemia, reduction in blood loss during surgery, and optimization of postoperative tolerance to anemia. These strategies also include suspension of medications that may affect coagulation, hemostasis optimization, hypothermia reduction, intraoperative hemodilution, and the use of antifibrinolytic agents (BAYTER-MARIN *et al.*, 2021). The World Health Organization (WHO) has published a document warning about the urgent need for PBM implementation worldwide (WHO, 2021).

Evidence and Benefits of ANH: Introduced in the surgical practice in the 1970s, ANH aims to reduce the use of allogeneic transfusions for presenting benefits such as increased tissue oxygenation, lower exposure to pathogens, total blood use, cost reduction, and decreased transfusion reactions (LI *et al.*, 2020; SHANDER & RIJHWANI, 2004; SEGAL *et al.*, 2004; NOBRE & GARCIA, 2020). This technique is considered a viable option for patients with contraindications to receiving allogeneic transfusions, members of the Jehovah's Witnesses community, and blood scarcity periods, such as in the COVID-19 pandemic (CHIEM *et al.*, 2021). Well-known studies have indicated that ANH significantly reduces blood transfusions, resulting in economic and logistical advantages, such as elimination of the need for blood tests and storage (BARILE *et al.*, 2017; SHANDER & RIJHWANI, 2004). This technique is also efficient in maintaining acceptable hemoglobin and hematocrit levels without prolonging the surgical-anesthetic period or the hospital stay. Systematic reviews and meta-analyses have confirmed these benefits, emphasizing that ANH is a practical and low-cost approach aimed at blood preservation (LI *et al.*, 2020; BRYSON *et al.*, 1998).

Comparison between ANH and PAD: Preoperative autologous donation (PAD) and ANH are strategies adopted to minimize the need for allogeneic transfusions. However, ANH presents advantages over PAD, such as the absence of deleterious effects associated with prolonged blood storage, decreased 2,3-diphosphoglycerate and ATP, and biomechanical and morphological alterations that occur in frozen red cells (SHANDER *et al.*, 2020; BARILE *et al.*, 2017; LI *et al.*, 2020). In addition, ANH does not predispose the patient to preoperative anemia, which may occur due to PAD and paradoxically increase the risk of allogeneic perioperative transfusions. The ANH technique is also associated with lower costs, compared to PAD (HENRY *et al.*, 2002).

QuADS Analysis: The Quality Assessment with diverse studies (QuADS) was applied based on 13 criteria, which could score from 0 to 3 points each according to the relevance, dimensionality and robustness of each item of the analyzed study, so that the score ascribed to each article could range between 0 and 39 points (HARRISON *et al.*, 2021). The evaluated criteria were "limitations

Title	Main author	Year	Design	Sample	Results	Comments	QuADS
<i>Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis</i>	Bryson GL.	1998	Systematic review with meta-analysis	24 studies	The use of acute normovolemic hemodilution reduced drastically the need for transfusion of hemocomponents.		33
<i>Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (Review)</i>	Henry D.	2001	Systematic review	46 studies	Although the acute normovolemic hemodilution was evidenced to reduce the need for allogeneic blood, the methodological quality of the clinical trials was not satisfactory and the general transfusion rates were high.		30
<i>Transfusion medicine: looking to the future</i>	Goodnough LT.	2003	Narrative review	101 studies	To obtain better results and patient safety, transfusion medicine needs to advance with new technologies, strategies and policies, while assessments should continue to refine evidence-based transfusion practices.		29
<i>Acute normovolemic hemodilution</i>	Shander A.	2004	Literature review	49 articles	Acute normovolemic hemodilution was associated with lower loss of total intra and postoperative blood and was effective in reducing the need for allogeneic transfusion in major surgeries.	This article provides essential technical information for the understanding of acute normovolemic hemodilution, showing physiological outcomes in the different body systems.	29
<i>Acute normovolemic hemodilution</i>	Murray D.	2004	Literature review	15 studies	Acute normovolemic hemodilution allowed patients to stand moderate degrees of blood loss without requiring allogeneic blood.		33
<i>Preoperative acute normovolemic hemodilution: a meta-analysis</i>	Segal JB.	2004	Systematic review and meta-analysis	42 studies	The literature only evidenced modest benefits of preoperative acute normovolemic hemodilution. The procedure did not have its safety confirmed and its generalized adoption cannot be incentivized.	The article reports that acute normovolemic hemodilution may be safely applied to patients presenting a variety of conditions provided that some specific selection criteria are followed, such as the absence of active ischemic cardiac diseases and coagulopathies.	34
<i>Acute normovolemic hemodilution in moderate blood loss surgery: a randomized controlled trial.</i>	Bennett J.	2006	Randomized and controlled clinical trial	155 patients	Despite the need for allogeneic red blood cell transfusion in hip surgeries, acute normovolemic hemodilution reduced postoperative complications.		33
<i>Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature.</i>	Marik PE.	2008	Systematic review	45 studies	Despite the limitations inherent in cohort study analyses, the findings suggest that, in adult patients in intensive care, trauma and surgical units, red blood cell transfusions are associated with increased morbidity-mortality. Therefore, current transfusion practices must be reassessed.		37

Continue

<i>Patient blood management</i>	Goodnough LT.	2012	Non-systematic literature review	84 articles	Blood transfusions represent risks, are expensive, and the blood supply is limited. Therefore, the logistics of this type of transfusion must be re-evaluated by health institutions to reduce blood use.		30
<i>A systematic review of the effect of red blood cell transfusion on mortality: evidence from large-scale observational studies published between 2006 and 2010.</i>	Hopewell S.	2013	Systematic review	32 studies	Consistency was found in the adverse effects of red blood cell concentrate transfusion and in mortality rates. However, it is still uncertain whether this is a real effect, since even the best-conducted adjustments may not fully eliminate the impact of confusing factors in this analysis.		35
<i>Patient blood management: the global view</i>	Shander A.	2016	Non-systematic literature review	71 articles	The findings demonstrated that the implementation of patient blood management, including the optimization of preoperative hemoglobin levels and the adoption of techniques to minimize blood loss during the procedure, resulted in a significant reduction in intraoperative bleeding.		29
<i>Acute Normovolemic Hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials.</i>	Barile L.	2017	Systematic review and meta-analysis	29 studies	The technique reduced the number of transfusions of red blood cell concentrates, the rate of patients receiving allogeneic red blood cell transfusion, and bleeding.	This study reported that acute normovolemic hemodilution is efficient in reducing the number of transfused allogeneic blood units, the rate of transfusions and the volume of blood loss in cardiac surgeries. Based on a robust meta-analysis of 29 randomized clinical trials, the results reinforced the relevance of acute normovolemic hemodilution as an invaluable strategy to preserve blood in high-risk surgical contexts.	37
<i>Effect of acute normovolemic hemodilution on coronary artery bypass grafting: a systematic review and meta-analysis of 22 randomized trials.</i>	Li S.	2020	Systematic review and meta-analysis	22 studies	Acute normovolemic hemodilution can reduce the number of allogeneic red blood cell concentrates in myocardial revascularization surgeries; it can also reduce the estimated total blood loss in those patients.	The employed methodological approach is the strongest point of this study, demonstrating scientific rigor, which increases the reliability of the findings.	38
<i>Standards and best practice for acute normovolemic hemodilution: evidence-based consensus recommendations.</i>	Shander A.	2020	Combined and Modified RAND-Delphi Method	8 professionals	Eighteen manuscripts were reviewed by relevant peers. The consensus building process was used to evaluate 39 statements, including 26 contraindications to preoperative blood autotransfusion and 10 variables of patients with extracorporeal circulation. Twenty-two statements were accepted or modified for the second round of scores.	Emphasis was placed on the need for careful monitoring of the cardiopulmonary parameters during acute normovolemic hemodilution to ensure that physiological compensatory mechanisms maintain proper tissue oxygenation, indicating the importance of a multidisciplinary approach.	35
<i>Papel da hemodiluição aguda na taxa de transfusão sanguínea em pacientes submetidos a tratamento cirúrgico de escoliose: estudo observacional retrospectivo (Acute hemodilution role in the blood transfusion rate in patients subjected to scoliosis surgical treatment: a retrospective observational study)</i>	Nobre LV.	2020	Retrospective Observations Epidemiological study of the case-control type	33 medical records	Acute normovolemic hemodilution in scoliosis correction surgeries reduces the blood transfusion rate, thus satisfying the patient's needs without increasing adverse effects and infection rates.	The authors made a relevant contribution to the theme by including a deeper discussion about the clinical and practical implications of the findings.	31

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<i>Gerenciamento de Sangue do Paciente (Patient Blood Management - PBM): uma maneira eficaz, segura, custo-efetiva e baseada em evidências para prover tratamento médico diante da escassez das bolsas de sangue causada pela pandemia de COVID-19. (Patient Blood Management-PBM: an efficient, safe, cost-effective alternative based on evidence to provide medical treatment in the lack of blood bags caused by the COVID-19 pandemic)</i>	Pedroso JCM.	2020	Non-systematic literature review	91 studies	Patient blood management was efficient, safe and cost-effective, promoting reduction in blood transfusions, improvement of clinical outcomes, and economy of financial resources. These characteristics made it relevant when the health system was overloaded due to the COVID-19 pandemic.		30
<i>Patient blood management strategies to avoid transfusions in body contouring operations: controlled clinical trial.</i>	Bayter-Marín JE.	2021	Controlled clinical trial	409 patients	Patient blood management strategies, such as increase in hematimetric parameters before surgery, and strategies to minimize blood loss during surgeries were seen to be efficient in reducing bleeding during body contouring surgery, besides reducing the need for postoperative blood transfusions.	The article relevance is increased by the inclusion of a considerable number of participants and the diversity of the group investigated, thus guaranteeing more cohesive and reliable results to be applied to other populations.	28
<i>The urgent need to implement patient blood management: policy brief</i>	World Health Organization	2021	Narrative review	229 studies	Regional differences in the prevalence and etiology of anemia, blood loss, coagulopathies, along with differences in the health structure and socioeconomic determinants, require specific strategies and policies for patient blood management according to the needs and possibilities of each region.		25
<i>Systematic and other reviews: Criteria and complexities</i>	Sataloff RT.	2021	Literature review	8 studies	Systematic reviews and meta-analyses provide readers with greater confidence that rigorous efforts were made to eliminate bias and guarantee the validity of a study. However, there are limitations based on the strengths and weaknesses of the evaluated literature and the skills and objectivity of the authors.		27
<i>The impact of COVID-19 on blood transfusion services: a systematic review and meta-analysis.</i>	Chiem C.	2022	Systematic review and meta-analysis	38 studies	The review evidenced that blood centers must focus on launching initiatives and policies to increase blood supply in their countries since the coronavirus did not represent a direct threat to blood safety.	The relevance of this study is evident for offering a high-quality analysis and proposing new directions for the research.	36
<i>A global definition of patient blood management.</i>	Shander A.	2022	Non-systematic literature review	128 studies	Patient blood management is a patient-focused, evidence-based systematic approach to improve the patient's results. It proposes the management and preservation of the patient's own blood and the promotion of patient safety and empowerment.		32

and positive points critically analyzed”; “evidence that the parties interested in the research were considered in the research design or conducting”; “suitable analysis method to respond to the research objectives”; “justification of the used analytical method”; “recruitment data provided”; “description of the data collection procedure”; “suitable format and content of the data collection instrument to approach the research objectives”; “justification of the choice of data collection instruments”; “suitable sampling to approach the research objectives”; “suitable study design to approach the research objectives”; “clear description of the research environment and target population”; “clear presentation of the research objectives”, and “research theoretical or conceptual background”. The detailed evaluation can be seen on Table 1.

Limitations: The current study is a systematized review of the literature, which does not completely follow the strict criteria of a systematic literature review. Despite showing more limitations than systematic reviews, systematized reviews contribute to the initial assessment of a topic that may in the future become the object of different and rigorous systematic reviews (SATALOFF *et al.*, 2021).

The ANH technique still requires standardization since it presents variations in hemodilution volumes, reposition solutions, and hematimetric indices, which may limit its uniform application (SHANDER & RIJHWANI, 2004). Standardization and recognition are essential to the diffusion and efficient implementation of ANH in the clinical practice. Thus, the authors of the current review elaborated a web application, according to the design thinking methodology, to present all steps for conducting the ANH technique. The app can be accessed for free at: www.hna.app.br.

CONCLUSION

Both PBM and ANH offer promising approaches to reducing allogeneic transfusions, thus improving clinical and economic outcomes. The implementation of multidisciplinary and multimodal PBM programs using different strategies and techniques, such as ANH, may result in a more efficient management of autologous blood, thus reducing mortality, perioperative complications, and hospital costs. However, to maximize such benefits, the barriers of knowledge and standardization of these techniques should be overcome, together with the development of instruments, such as the www.hna.app.br, which have the potential to become useful in broader applications that are consistent with these strategies in the clinical practice.

AUTHOR CONTRIBUTIONS

Eduardo de Souza Tolentino and Juan Carlos Montano-Pedroso contributed to the study’s conceptualization, project elaboration, methodology, formal analysis, writing and review; Juan Carlos Montano-Pedroso contributed to the study’s supervision; Luis Vicente Garcia contributed to the study’s methodology, review and formal analysis; Felício de Freitas Netto and Paulo Rogério Quierregatto do Espírito Santo contributed to the study’s review and formal analysis.

*This study was approved by the Unifesp Research Ethics Committee via the *Plataforma Brasil*, with technical opinion number 5,556,610.

The authors declare no conflicts of interest.

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