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Hemolysis following Intravenous Immunoglobulin Therapy - Adverse effect to remember about

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Abstract

Intravenous immunoglobulin (IVIG) therapy has become a cornerstone in the treatment of various immunological and neurological disorders. Its origins trace back to the pioneering work of Emil Adolf von Behring and Shibasaburo Kitasato in the late 19th century.[1][2] Over time, advancements in immunoglobulin preparation techniques and the shift from animal-derived to human-derived serum have significantly improved IVIG safety and efficacy.[1][3] By the late 20th century, IVIG was recognized as a standard therapy for conditions such as primary immunodeficiencies (PID) and Kawasaki disease.[4]

Today, IVIG is widely used for PID, secondary immunodeficiencies, primary immune thrombocytopenia, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and post-transplant immunomodulation. [5][6][7][8][9][10]

Despite its therapeutic advantages, IVIG can cause adverse effects, including flu-like symptoms, dermatological reactions, thromboembolic events, neurological disturbances, renal impairment, and hematological disorders like hemolysis.[11] Hemolysis, though often overlooked, can lead

to unnecessary concern and treatment modifications. Its pathophysiology involves both intravascular and extravascular mechanisms, influenced by factors such as blood group, IVIG dosage, and manufacturing processes.[11]

While severe hemolysis is rare, mild cases are more common and may prolong hospitalizations.[12] Raising awareness of IVIG-related hemolysis can improve patient management and therapeutic decision-making, ultimately optimizing clinical outcomes.

Keywords: IVIG, Hemolysis, Adverse effects

Introduction

Historical Perspective

Contemporary IVIG therapy has its place in the treatment algorithms of various diseases. The history of this therapeutic approach is intrinsically linked to the groundbreaking work of Emil Adolf von Behring, the first Nobel Laureate in Physiology or Medicine, and his collaborator Shibasaburo Kitasato. In 1890, they described the use of curative serum to immunize rabbits against tetanus using serum from animals immunized with tetanus toxin. [1][2][13]. These were not intravenous preparations due to the inefficiencies in serum purification methods of the time. Intravenous administration was associated with severe adverse reactions due to complement cascade activation. Instead, intramuscular administration was employed, which, while avoiding severe complications, still caused side effects such as muscle irritation and proteolytic reactions at the injection site. [3]

In 1907, convalescent plasma was used for measles prevention, an approach reminiscent of its recent application during the COVID-19 pandemic. This method, though debated regarding its effectiveness in improving hospitalization outcomes during the pandemic,

highlights how seemingly outdated techniques with over a century of history can still find relevance in modern medicine. [3][14][15][16]

The second and third decades of the 20th century marked a shift from animal-derived serum to human-derived serum due to reduced adverse effects. During this period, pepsin was introduced to lower the reactogenicity of animal sera. [3]

In 1952, Ogden Bruton made a pivotal discovery by describing agammaglobulinemia, a PID. [17] Bruton observed a deficiency of specific proteins in a patient's serum, which he identified as immunoglobulins through electrophoresis.[1][17] His patient was treated with subcutaneous gammaglobulins; as a result of the treatment, the previously recurrent episodes of sepsis and other severe infections subsided. After starting the treatment, the patient continued to suffer from infections more often than patients without immunodeficiencies, but he managed to fight the infections. [1]

Advancements in IVIG preparation techniques continued throughout the 20th century. Initial methods were enzymatic, later supplemented by chemical methods, including the use of ethanol and pH adjustments. [1]

The story of IVIG therapy intersects again with Nobel accolades in 1984, when Niels K. Jerne, Georges J.F. Köhler, and César Milstein received the Nobel Prize in Physiology or Medicine "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"[18].

In the early 1990s, the National Institutes of Health (NIH) released a consensus document summarizing the applications, mechanisms, and efficacy of immunoglobulin preparations while outlining future research directions. This document established IVIG as a standard therapy for conditions such as PID and Kawasaki syndrome. It also documented the most common side effects, ranging from mild symptoms like fever, headaches, and muscle aches to severe reactions such as anaphylaxis. Adverse effects included fever, chills, dizziness, nausea and/or vomiting, blood pressure changes, tachycardia, dyspnea, chest tightness, and anaphylactic reactions. The document also confirmed that IVIG products available in the U.S. did not carry risks of HIV or HBV transmission. [4]

This NIH consensus document laid the foundation for subsequent developments in IVIG therapy. Although significant progress has since been made in understanding IVIG’s

mechanisms, applications, and side effects, this foundational document remains a pivotal milestone in the evolution of knowledge about IVIG.

Current therapies utilizing IVIG

In contemporary clinical practice, IVIG are increasingly utilized and have found applications in the treatment of various conditions, including PID with impaired antibody production [5], secondary immunodeficiencies [6], primary immune thrombocytopenia [7], Guillain–Barré syndrome [8], Kawasaki disease [19], chronic inflammatory demyelinating polyneuropathy [9], multifocal motor neuropathy [20], and lymphoproliferative disorders such as chronic lymphocytic leukemia [21]. IVIG are also employed in patients following allogeneic hematopoietic cell transplantation [22] and solid organ transplantation, including kidney transplantation [10].

Furthermore, IVIG administration is being considered for patients with sepsis. Emerging studies suggest a potential reduction in mortality rates among these patients; however, further research is required to confirm these findings [23].

Adverse effects of IVIG therapy

Adverse effects of IVIG therapy can be categorized into those occurring immediately after administration and those with a delayed onset. The first group includes flu-like symptoms, dermatological reactions (ranging from local injection site reactions to epidermolysis), arrhythmias, hypotension, and transfusion-related acute lung injury. Delayed adverse effects include thromboembolic events (e.g., stroke, myocardial infarction, pulmonary embolism), neurological complications (e.g., headache, aseptic meningitis, seizures), renal impairment, electrolyte disturbances, and hematological disorders (e.g., neutropenia, hemolysis) [11].

Although these adverse effects are rare, their occurrence can cause significant concern for both patients and physicians. Therefore, we have chosen to focus on hemolysis, which, in our view, remains an overlooked potential side effect. As a result, it may lead to unnecessary anxiety and unwarranted modifications in therapy.

Pathophysiology

Hemolysis following IVIG administration is categorized as autoimmune hemolytic anemia (AIHA) and results from the transfer of antibodies against erythrocytes present in the IVIG concentrate despite purification processes.[24] Likewise any other hemolysis there are two primary mechanisms of hemolysis that are recognized:

1. **Intravascular Hemolysis**
   Mediated by IgM, which activates complement, this mechanism is relatively rare due to the low concentration of IgM in IVIG products. However, there is evidence suggesting that IgG molecules, when densely bound to erythrocytes, can activate the complement system nearly as effectively as IgM.[25]
2. **Extravascular Hemolysis**
   This is more common and results from erythrocyte opsonization by IgG antibodies, leading to phagocytosis in the spleen. Extravascular hemolysis is particularly prevalent when IVIG products contain anti-ABO antibodies, especially in cases where high doses of IVIG are administered.[26]

The distinction between these mechanisms is clinically significant, as intravascular hemolysis leads to a much more rapid decline in hemoglobin levels due to the destruction of red blood cells occurring at a rate approximately ten times higher than extravascular hemolysis. This makes intravascular hemolysis a more immediate clinical concern, often necessitating blood transfusions to manage severe anemia.

A less common mechanism involves complement complexes attacking the erythrocyte membrane, potentially contributing to hemolysis.[26][27]

Risk Factors

1. **Blood Group**
   Blood group is a key risk factor, with group AB being the most susceptible, followed by groups A and B.[27][28][29] This likely arises from the presence of autoantibodies in donor serum used for IVIG production, targeting A and B antigens on recipient erythrocytes. Group O individuals are the least affected, with hemolysis in these cases

potentially attributable to complement protein complexes and free light chains present in IVIG.[27]

2. **IVIG Dosage**

   The likelihood of hemolysis increases significantly with higher IVIG doses (1–2 g/kg) used for immunomodulation for example in neurological disease like chronic inflammatory demyelinating polyradiculoneuropathy or guillain-barré syndrome[30] compared to lower replacement doses (0.4 g/kg) used in primary or secondary immunodeficiency.[31][32] This is likely due to the cumulative effect of transfused autoantibodies.

3. **Manufacturing and Purification Processes**

   Differences in IVIG manufacturing processes, which are highly dependent on the specific product and manufacturer, including the implementation of immunoaffinity chromatography, have been shown to significantly reduce the prevalence of hemolytic complications compared to standard donor screening methods. Additionally, other techniques designed to remove isoagglutinins from the final product have been associated with a notable decrease in adverse events.[29][33][34]

Discussion

Severe hemolysis following IVIG administration, leading to marked clinical deterioration, is rare.[35][36][37] However, mild hemolysis resulting in laboratory evidence of anemia without clinical symptoms is likely more common.

It is critical to consider hemolysis as a potential cause of deteriorating laboratory results, particularly in patients with risk factors. Severe cases often prolong hospitalization and necessitate further diagnostic evaluations, frequently involving non-hematology or non-internal medicine departments unfamiliar with managing hemolysis.[12] This contributes to additional consultations and healthcare costs.

Patients should be informed about the possibility of hemolysis as an adverse effect of IVIG, including symptoms such as jaundice, which might cause undue concern. Educating patients and medical personnel about these potential side effects can reduce stress and improve overall management. This awareness enables clinicians to make informed therapeutic decisions

and facilitates better communication with patients, ensuring a more transparent and reassuring approach to IVIG therapy.

Given these variations, in patients experiencing non-severe hemolysis who might still benefit from continued IVIG therapy, it is possible to switch to a different IVIG product rather than discontinuing the therapy altogether. However, at the current stage, there is no clear consensus or established guidelines for the management of such patients. Therefore, this approach should be considered on a case-by-case basis, depending on the potential benefits, and the patient's condition should be continuously monitored..[30][34]

This summary provides insight into the mechanisms, risk factors, and clinical considerations of hemolysis related to IVIG use, aiming to enhance awareness and improve patient care.

Disclosures

Author's contribution

Conceptualization - Sebastian Iwaniuk and Ignacy Maciejewski; methodology - Jakub Skiba; software ,- Kinga Tylczyńska and Ignacy Maciejewski; check - Szymon Szypulski, Natalia Tylczyńska; formal analysis -Zuzanna Skiba and Kinga Kowalik; investigation - Maria Michalska; resources - Zuzanna Skiba; data curation - Aleksandra Zielińska and Maria Michalska; writing - rough preparation - Sebastian Iwaniuk and Kinga Tylczyńska; writing - review and editing, Ignacy Maciejewski and Sebastian Iwaniuk; visualization, Kinga Kowalik; supervision - Jakub Skiba; project administration – Aleksandra Zielińska; receiving funding not applicable, All authors have read and agreed with the published version of the manuscript.

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