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DESMOPRESSIN APPLICABILITY IN THE MANAGEMENT OF CONGENITAL COAGULOPATHIES: A LITERATURE REVIEW

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Abstract: Blood clotting is a complex process that, when disturbed, can result in coagulopathies, making individuals more prone to excessive bleeding. In this scenario, desmopressin has emerged as a valuable therapeutic tool. This article reviews the applicability of desmopressin in the management of coagulopathies, focusing on the main conditions in which this medication has demonstrated efficacy. Von Willebrand disease (vWD), an inherited coagulopathy, is characterized by deficiency or dysfunction of von Willebrand factor (vWF). Clinical studies have shown that desmopressin is capable of temporarily increasing vWF levels in plasma, resulting in significant improvements in hemostasis. This makes it an effective treatment option for the prophylaxis and treatment of bleeding in patients with VWD. Furthermore, desmopressin also shows promise in the treatment of some thrombocytopathies, such as Bernard-Soulier syndrome and thrombocytopathy associated with von Willebrand disease. These conditions are characterized by abnormalities in blood platelets. Studies have shown that desmopressin can stimulate platelet adhesion and improve platelet function in certain cases of thrombocytopathies, offering an additional therapeutic approach. However, it is critical to recognize that the effectiveness of desmopressin may vary between patients and that its use requires careful monitoring. Furthermore, accurate identification of the type of coagulopathy and the individual response to desmopressin are critical to determining the most appropriate treatment. In conclusion, desmopressin represents an important therapeutic option in the treatment arsenal of coagulopathies, offering hope and relief to those suffering from these complex conditions.

INTRODUCTION

Congenital coagulopathies (CC) constitute a heterogeneous group of hereditary blood clotting disorders that affect the body's ability to form effective clots. These conditions are of significant clinical importance as they can predispose patients to excessive bleeding, spontaneous hematomas, joint bleeding and, in severe cases, pose a threat to life.[1,2] In addition to hemophilia, von Willebrand disease and other rare conditions have substantial clinical importance due to the impact they have on patients' quality of life and the challenges they present to healthcare professionals.[3]

The fundamental characteristic of CC is the tendency to excessive bleeding. This can range from easy bleeding gums to severe bleeding in the joints or internal organs, and these episodes can be debilitating and even fatal.[2,4,5] Especially in hemophilia, repeated joint bleeding can lead to chronic complications, such as hemophilic arthropathy, which results in pain, deformities and joint dysfunction.[6]

In many cases, the management of CC requires a multidisciplinary approach, involving hematologists, physiotherapists, nurses and other healthcare professionals. This adds complexity to clinical management. Furthermore, constant concern about the risk of bleeding can significantly affect the quality of life of patients and their families. Anxiety and stress related to the possibility of frequent bleeding can be challenging.[6,7]

In order to mitigate the negative impact of these pathologies, ongoing research into advanced therapies, including gene therapy and new medications, are opening new perspectives for treating these conditions and improving patients' quality of life. Among these drugs, Desmopressin has been shown to be effective in managing and reducing severe conditions.[8]

HISTORICAL CONTEXT

In 1772, William Hewson observed that blood clots quickly in stressful situations, which triggered subsequent research. Studies carried out in the early 20th century showed that increased blood clotting under stress was related to the release of adrenaline into the plasma. In 1957, Marciniak observed a temporary increase in clotting factor VIII after injecting adrenaline into rabbits, and later studies confirmed a similar increase in humans. These discoveries stimulated the search for agents that increase factor VIII without the side effects of adrenaline.[8,9,10,11]

Desmopressin, a synthetic analogue of vasopressin, has been identified as effective in this increase without causing significant side effects. The clinical use of desmopressin proved to be effective in preventing and treating bleeding in patients with mild hemophilia or von Willebrand disease, allowing surgeries without the need for blood products and effectively replacing deficient blood factors in patients.[11]

DESMOPRESSIN MECHANISM OF ACTION

Despite 20 years of clinical use of desmopressin, its mechanisms of action are still not completely understood. Desmopressin increases plasma levels of factor VIII and VWF, not only in deficient patients, but also in healthy individuals and patients with already elevated levels of these factors.[12] Desmopressin shortens clotting time and bleeding time, probably due to an increase in factor VIII and vWF, which play a role in clotting.[12,13]

Desmopressin does not affect platelet count or aggregation, but increases platelet adhesion to the vessel wall. Furthermore, it causes the release of significant amounts of tissue plasminogen activator into the plasma. However, the majority of plasmin generated

is rapidly inactivated. Desmopressin appears to act by releasing factor VIII and vWF from storage sites, probably from vascular endothelial cells. [12,14]

The precise location of these storage sites and the interaction between the released factors are not completely understood. Although there is evidence that vascular endothelial cells are the main source of VWF, there are still uncertainties regarding this process. An important point is that desmopressin is effective in bleeding disorders other than hemophilia and von Willebrand disease, even in patients with normal or elevated levels of factor VIII and VWF, due to several mechanisms, including improving platelet adhesion, increasing coagulability and production of ultra-large vWF multimers, among others. [12,13,14]

DESMOPRESSIN IN HEMOPHILIA A

Hemophilia A is an X-linked hereditary condition that results in a deficiency or dysfunction of clotting factor VIII (FVIII). This deficiency compromises the blood's ability to clot and increases the risk of prolonged and spontaneous bleeding. Its pathophysiology follows a sequence of events. Firstly, there is a genetic deficiency in FVIII, which plays a key role in the formation of stable blood clots. When FVIII is absent or does not function properly, the activation of clotting factor X (FX) is impaired. [15]

During blood clot formation, FVIII acts as a crucial intermediate. In hemophilia A, the inability to form effective blood clots results in fragile, unstable clots. This leads to prolonged bleeding after injuries, surgeries or even for no apparent reason, increasing the risk of serious complications such as bleeding in joints, muscles and internal organs.[15,16]

It is important to highlight that the severity of hemophilia A can vary, depending on the levels of FVIII in the body. Some patients may have low but detectable levels of the factor and experience less severe symptoms, while others may have an almost complete deficiency, resulting in more severe symptoms.

An international cohort study evaluating 248 patients demonstrated that 73% of all patients with mild hemophilia A achieved a maximum FVIII level ≥ 30 IU/dl after desmopressin. This is in line with previous literature reporting similar response rates at 66%–76%. [17,18,19]. In moderate hemophilia, it was observed that 25% of patients showed an increase in FVIII to ≥30 IU/dl in the desmopressin test. This is lower than that reported by the largest study to date on moderate hemophilia, which showed that 40% had an adequate response.[20]. This may be explained by its approach in which only patients tested or treated with desmopressin were included, which may have led to the exclusion of patients with low expected response.

Furthermore, a much higher response rate was observed in moderate patients undergoing desmopressin testing (55%) and the majority of these patients had factor levels ≥3–5 IU/dl. Desmopressin test results were shown to be missing in half of the study population with moderate hemophilia and in 22% of patients with mild hemophilia. Therefore, further testing is needed to identify a potential response and facilitate optimal use of desmopressin, especially in patients with factor levels ≥3 IU/dl. Regarding age, a younger median age was reported in patients with partial response compared to those with complete response (14 years vs. 25 years).[18,19]

DESMOPRESSIN IN VON WILLEBRAND DISEASE

Von Willebrand disease (VWD) was first identified in 1926 by Dr. Erik Adolf von Willebrand, when he described a family line with severe bleeding problems. This condition has affected members of several generations, with symptoms such as recurrent mucosal bleeding. However, diagnostic methods at that time were nonspecific and complicated. Coagulation factor VIII (FVIII:C) deficiency has also been erroneously associated with VWD, causing confusion. Only in the 1970s, with the von Willebrand factor (vWF) antigen test, was it possible to accurately diagnose VWD. Since then, several diagnostic assays have been developed, but each has its own limitations. (3.11)

VWD can arise due to deficiencies in VWF, either in quantity (quantitative deficiency) or in quality (qualitative deficiency). This condition is subdivided into types based on the type of underlying defect. Types 1 and 3 are examples of quantitative defects, where Type 1 is characterized by a partial VWF deficiency, while Type 3 results in a complete VWF deficiency. Additionally, Type 1 includes subtype 1C, which is defined by rapid removal of VWF from the blood. Type 2 encompasses qualitative defects and is divided into several subtypes. Type 2A, for example, occurs due to problems in multimer formation, while types 2B, 2N, and 2M result from abnormal binding of VWF, including increased affinity for GPIb, defective binding with FVIII, and defective binding with normal multimers, respectively. (3,11,21)

In many patients with type 1 and type 2 VWD, desmopressin can be used to increase VWF levels without VWF replacement and is the most widely used medication in VWD. It is available in intravenous (IV), subcutaneous (SC) and intranasal (IN) preparations. The recommended IV and SC dosage is 0.3 μg per kilogram of body weight (up to 20 mcg), and the IN dosage is 150 μg (one spray) in patients <50 kg or 300 μg (2 sprays) in patients > 50 kg. Subcutaneous and intravenous formulations increase VWF and FVIII levels 2 to 4 times baseline within 30 to 60 minutes after administration and may be repeated every 12 to 24 hours. (11.21)

Tachyphylaxis (reduced response to successive doses) occurs after 2–3 days. The intranasal formulation has variable absorption and results in a more modest increase in levels, but not all patients with VWD will respond to desmopressin. Given its mechanism of action, it requires a pool of endogenous VWF and is therefore neither effective nor recommended in type 3 VWD. Desmopressin is generally contraindicated in patients with type 2B VWD, as increased defective VWF can lead to increased binding of VWF and platelets, worsening thrombocytopenia. Although many patients with type 2A and 2M VWD may experience improvement in minor symptoms with desmopressin, VWF levels typically do not increase sufficiently with desmopressin to permit its use in surgery or major bleeding. (11,21,22)

Adverse effects of desmopressin are generally mild (tachycardia, flushing, headache) but occur frequently. Due to its antidiuretic effect, there is a risk of hyponatremia and fluid overload. As this risk is greater in younger children, its use is not recommended in children under 2 years of age (23). For all others, fluid restriction and electrolyte monitoring are recommended when repeated doses are administered. Desmopressin is not recommended for use in patients with active cardiovascular disease, seizure disorders, women with preeclampsia, and patients with VWD type 1C in situations requiring a sustained response (11,22).

CONCLUSION

In conclusion, Desmopressin proved to be an effective therapeutic option in the treatment of hemophilia type A and VWD, two hereditary bleeding conditions. In hemophilia type A, DDAVP is particularly useful in patients with mild and moderate forms of the disease, inducing an increase in plasma levels of factor VIII (FVIII) and improving hemostasis. Furthermore, Desmopressin is often used for the prevention and treatment of bleeding in minor surgical procedures. Furthermore, in VDW, Desmopressin is the therapy of choice for patients with type 1 VDW, as it can stimulate the release of VWF stored in endothelial cells, relieving bleeding symptoms. However, it is important to highlight that DDAVP is not effective in all cases, especially in patients with severe forms of these conditions. Additionally, individual response to DDAVP may vary, and it is critical to perform response testing prior to treatment to determine potential efficacy.

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