Use of Desmopressin in Children With Inherited Platelet Dysfunctions Undergoing Adenotonsillar Procedures

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Abstract
Introduction and goals: Adenotonsillar surgery represents a major haemostatic challenge in paediatric patients with mild inherited platelet dysfunction. While there are recommendations for perioperative haemostatic management, there are no reports of the outcomes with the different recommendations in these children when undergoing adenotonsillectomy. Our objective was to evaluate the management of perioperative bleeding with desmopressin in children with mild platelet dysfunctions who underwent adenotonsillar surgery in our hospital.

Methods: We performed a retrospective study aimed at determining the perioperative bleeding and complication rate in children with mild inherited platelet dysfunction in whom desmopressin was used while undergoing adenotonsillar procedures.

Results: Between 2004 and 2010, 27 children with mild inherited platelet dysfunction underwent adenotonsillar procedures in our hospital and were treated with desmopressin. One patient developed perioperative bleeding (3.7%) and there was 1 child (3.7%) who presented transitory hypotension as a side effect of desmopressin.

Conclusions: The use of desmopressin allowed adequate perioperative bleeding prophylaxis management in children with mild inherited platelet dysfunction who underwent adenotonsillar procedures without presenting severe complications.

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KEYWORDS
Adenoidectomy; Tonsillectomy; Platelet function disorders; Surgical haemorrhage; Children

PALABRAS CLAVE
Adenoidectomía; Amigdalectomía; Disfunciones plaquetarias;

Uso de desmopresina en niños con disfunción plaquetaria congénita sometidos a adeno y/o amigdalectomía

Resumen
Introducción y objetivos: La cirugía de adenoides y/o amigdalas representa un desafío hemostático importante en pacientes pediátricos con disfunción plaquetaria congénita leve.


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Hemorragia quirúrgica; Niños

Sí bien existen recomendaciones para el manejo perioperatorio de la hemostasia en estos pacientes, no hay informes de resultados del manejo con las distintas recomendaciones en niños sometidos a cirugía adenoamigdalina. Nuestro objetivo es evaluar el uso de desmopresina para la prevención de la hemorragia perioperatoria en niños con disfunción plaquetaria congénita leve sometidos a adeno y/o amigdalectomía en nuestro centro.

Métodos: Estudio retrospectivo descriptivo dirigido a determinar la tasa de hemorragia perioperatoria y complicaciones en niños con disfunción plaquetaria congénita leve en quienes se utilizó desmopresina cuando fueron sometidos a adeno y/o amigdalectomía.

Resultados: Entre los años 2004 y 2010, 27 niños con disfunción plaquetaria congénita leve fueron sometidos a cirugía de adenoides y/o amigdalas y recibieron desmopresina. Un paciente (3,7%) desarrolló hemorragia perioperatoria. Se registró un caso (3,7%) de hipotensión transitoria como efecto adverso atribuible a la desmopresina.

Conclusiones: El uso de desmopresina permitió un buen manejo preventivo de la hemorragia perioperatoria en pacientes con disfunción plaquetaria congénita leve sometidos a adenoamigdalectomía, sin presentar complicaciones graves.

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Introduction

Congenital platelet dysfunctions include various abnormalities of one or more functions of platelet response during primary haemostasis. They comprise a heterogeneous group of diseases which in most cases represent a diagnostic and characterisation challenge and are probably significantly underdiagnosed. Locally, it is estimated that mild forms are at least as prevalent as von Willebrand disease (vWD) and may even coexist in the same patient.¹

From a clinical standpoint, the haemorrhagic symptoms are similar, regardless of the type of dysfunction, and include mucocutaneous haemorrhage (ecchymosis, epistaxis, bleeding in the oral cavity, menometrorrhagia and bleeding following ingestion of NSAIDs), and abnormal bleeding after injuries, tooth extractions or other invasive procedures. Platelet dysfunctions can be divided into mild or severe according to their clinical behaviour. In the latter, haemorrhagic manifestations are severe, usually spontaneous and present from early childhood, and have standardised diagnostic criteria and management guidelines (e.g. Glanzmann’s thrombasthenia, Bernard-Soulier syndrome). By contrast, most platelet dysfunctions can be classified as mild (MPD), with haemorrhagic symptoms occurring later in life and going unnoticed until patients are subjected to a haemostatic challenge, such as surgery or severe trauma, which brings out the condition.²,³

On the other hand, adenotonsillectomy (AT) is one of the most common surgeries performed on children, with more than 500,000 procedures performed annually in the United States⁴ and about 500 at our service. Perioperative haemorrhage (POH) is the most feared complication and its estimated prevalence in patients younger than 15 years without known haemostatic pathology is between 2% and 5%, with no clear relation to the type of surgical technique employed.⁴,⁶ POH may be primary if it occurs during the first 24 h after surgery or secondary if it occurs after this period. The latter is more common, attributed to the premature fall of crusts and occurs between 5 and 10 days after the intervention.⁴ Since surgery, especially in areas of high fibrinolytic activity (oronasal mucosa, adenoids and tonsils⁵), is one of the greatest haemostatic challenges for patients with primary haemostasis disorders, some type of action is required to facilitate haemostatic processes, in order to avoid POH.

Due to the low prevalence and heterogeneity of MPD, management guidelines for the treatment and prophylaxis of haemorrhage in these patients are based on case series and the opinions of experts and committees.⁸ At present, platelet transfusion is recommended in cases of severe bleeding and as prophylaxis in major surgery. The risks associated with transfusion of blood derivatives (alloimmunisation, resistance/refractoriness in future transfusions, anaphylaxis, infections, etc.), especially in patients with congenital disorders who will, potentially, require multiple adjuvant therapies to prevent and/or treat haemorrhagic episodes, has generated controversy and led to the search for new therapeutic options. In this regard, desmopressin (DDAVP) stands out as a well-tolerated and inexpensive drug which avoids the use of blood derivatives.

DDAVP, an analogue of the antidiuretic hormone L-arginine vasopressin, acts on V2 receptors and induces an increase in plasma levels of factor VIII and von Willebrand factor, in the absence of other effects of natural vasopressin derived from the stimulation of V1 receptors in smooth muscles. In 1977, Mannucci et al. presented the first report on the use of DDAVP to prevent bleeding in patients suffering moderate or mild haemophilia A and vWD.⁹ Since then, it has been used for the prevention of POH in these patients.¹⁰ As of 1980, its use was described in other acquired haemostasis disorders, such as uraemia or liver failure, and in congenital abnormalities of platelet function.¹¹-¹³ Currently, there are several studies showing the effect of DDAVP on platelet function¹⁴-¹⁶; however, the manner in which this phenomenon occurs and how to measure its effect have not yet been clarified.¹

DDAVP can be administered as a subcutaneous injection, through nasal inhalation (it can be self-administered) and intravenously.¹ The latter form is the most common and the one used for the prophylactic management of haemorrhage during surgery, administered in doses of 0.3 μg/kg, with a maximum of 15 μg, diluted in 50–100 cm³ of saline
serum and with a slow infusion (30–45 min) to avoid possible adverse effects. The most common side effects are mild and include facial flushing, headache, hypotension and fluid retention.\textsuperscript{17,18} Severe adverse reactions, such as symptomatic hyponatraemia and secondary seizures, have been associated with an age younger than 2 years, lack of fluid restriction and repeated administration within a short period.\textsuperscript{19} In POH prophylaxis it is generally used in conjunction with an antifibrinolytic agent as adjuvant therapy.\textsuperscript{8}

We present the experience at our centre with the prophylactic management of POH using DDAVP in paediatric patients suffering MPD who underwent AT between 2004 and 2010.

Materials and Methods

This retrospective and descriptive analysis was approved by the Ethics Committee of our hospital.

We included patients with a diagnosis of MPD, aged 18 years or less, who underwent AT between January 1st, 2004 and December 31st, 2010. We excluded children under 2 years, in whom DDAVP was not used.

All patients were diagnosed with haemostasis at the general consultation and managed by the same specialist, following an institutional protocol (Table 1). Referral from general consultation to the ENT service was due to presenting altered levels in general coagulation examination (haemorrhage time [HT], prothrombin time and partial activated thromboplastin time) or a personal and/or family history of mucocutaneous haemorrhage.

We reviewed the diagnoses of coagulation disorders according to the criteria defined in our laboratory.\textsuperscript{2} We considered platelet function to be impaired when the aggregability and/or secretion with C serotonin was abnormal with 2 or more agonists, or with the 2 concentrations of adenosine diphosphate (ADP) or collagen. The combined defect of 10 μM epinephrine and low concentrations of ADP was not considered abnormal.\textsuperscript{20}

We reviewed the records of all patients to obtain general demographic data, such as gender and age at surgery, postoperative adverse effects such as pain, nausea, vomiting, hypotension, convulsions, symptomatic hyponatraemia or fever, and the occurrence of POH.

POH was defined as any striking haemorrhage which was considered significant enough to take action as prescribed in the clinical record. In addition, we also used objective markers of POH occurrence, such as hospitalisation time, the need for red blood cell transfusion and the need for reoperation or rehospitalisation.

We also reviewed surgical protocols, seeking data such as date of surgery, indication, surgical technique, haemostatic technique and estimation of intraoperative blood loss.

Data analysis was performed using Microsoft Excel 2007 software. We calculated 95% confidence intervals for binominal proportions.

Results

We found 32 patients who underwent AT between 2004 and 2010, who were under 18 years and suffered MPD. We excluded 2 children in whom the diagnosis took place after surgery, 2 children in whom DDAVP was not used due to a history of seizures and 1 other child because no data were available on the surgery or protocol employed. The mean age of the children included in the study was 5.8 years (median 4.7; range 2.4–17.1 years). Three children (11%) presented a diagnosis of vWD and MPD, simultaneously.

Diagnostic Suspicion

Of the 27 children, 19 (70.4%) were referred due to altered HT. In the remaining cases, diagnostic suspicion only took place through information obtained during anamnisis.

Diagnosis of Mild Platelet Dysfunction

In the 27 patients, the diagnosis was confirmed by a study of platelet aggregability and secretion. The most frequently altered aggregability tests with agonists were collagen 1 μg/mL and ADP 8 μM.

Surgery

The surgeries performed were: AT in 81.5% of children, only adenoidecotomy in 11% of cases and only tonsillectomy in 7.4% of cases. The most common indication for surgery was obstructive sleep apnoea in 77.8% of cases, presence of persistent otitis media with effusion in 29.6% and recurrent bacterial tonsillitis in 3.7%. In total, 11% of the children suffered 2 simultaneous causes. All patients underwent adenoidecotomy with an adenotome according to the classical technique. The cold technique (scalpel, scissors and/or handle) was the most commonly used for tonsillectomy, in 95.8% of patients. In the remaining cases we used electrocautery.

Local haemostasis management in AT interventions was carried out with bismuth subgallate within a gauze packing. In addition, for tonsillectomy we used electrocautery and suture to the surgical site in 74.1% and 18.5% of cases, respectively.

Haemorrhagic Complications

No patients required red blood cell transfusion, reoperation or rehospitalisation. Only 1 patient (3.7%, 95% confidence interval between 0.0009% and 19%) suffered secondary tonsillar haemorrhage associated with severe coughing, on the second day after surgery. The child presented a concurrent diagnosis of vWD and MPD and was managed at the emergency service with an intravenous dose of DDAVP, with a good response.

Postoperative Adverse Effects

Adverse effects detected were nausea in 7 cases (25.9%), vomiting in 2 cases (7.4%) and 1 case (3.7%) of transient hypotension which responded to the administration of saline solution. There were no cases of seizures or symptomatic hyponatraemia.
**Table 1** Haemostasis Protocol Used at Our Centre for Children With Mild Platelet Dysfunction Undergoing Surgical Procedures.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>DDAVP</td>
<td>0.3 µg/kg (maximum 15 µg) diluted in 50 cm³ saline serum, to be passed in 30–45 min, 1–2 h prior to surgery</td>
</tr>
<tr>
<td>Trasexamic acid</td>
<td>10–15 mg/kg, once, orally, the night before surgery</td>
</tr>
<tr>
<td>NSAID suspension</td>
<td>Intravenously every 8 h the day after surgery</td>
</tr>
<tr>
<td>Observation for 1 night (control of fluid intake, observation of bleeding)</td>
<td>Orally every 8 h for 10 days after surgery</td>
</tr>
<tr>
<td></td>
<td>1 week before and after surgery</td>
</tr>
</tbody>
</table>

DDAVP: desmopressin; NSAID: non-steroidal anti-inflammatory drugs.

**Postoperative Pain**

The use of non-steroidal anti-inflammatory drugs was restricted in our patients, so the management of postoperative pain was done with paracetamol 10–15 mg/kg/8 h. A total of 8 children (29.6%) required support with codeine and in 1 case hospitalisation was extended 1 day due to pain management.

**Discussion**

POH is the most important complication of AT, with a fatality rate of approximately 1 case per 20,000 and an increased prevalence in patients with primary haemostasis disorders. The published experience of 30 years using DDAVP for the management and prophylaxis of haemorrhage in vWD shows that this drug is safe and well-tolerated.

Publications on the use of DDAVP in MPD are more recent, its mode of action is less clear and there is an underdiagnosis which makes treatment more difficult. For this reason, and as long as the response to DDAVP cannot be predicted objectively, platelet transfusion is safer in these patients when faced with surgery in which bleeding may be immediately life-threatening. Alternatives should be considered for other surgeries, and DDAVP should be included among them.

In 2010, Dunn and Cox reviewed the use of DDAVP in patients with mild haemostasis disorders who underwent AT, finding no prospective, randomised studies. They reported a considerable variability between studies in terms of dosage and frequency of DDAVP administration and antifibrolytic agents used. They found 15% of POH (primary and secondary in the same proportion), 47% of hyponatraemia and 6 cases (4%) of convulsions. The POH rate was higher than in the general population, with the primary type being predominant, and reported cases of seizures were associated with repeated doses of DDAVP and younger ages, in agreement with other publications. More recently, Davidson et al. reviewed the incidence of hyponatraemia following the use of a single dose of DDAVP in children with vWD undergoing AT and found 74.6% of cases (9.5% with Na<130 mmol/L) although none were symptomatic. This shows that hyponatraemia could be more common than previously reported, but would not represent a severe adverse event. It should also be noted that these authors included children under 2 years in their study.

Among our patients we found a POH rate of 3% (secondary), which was similar to that reported for the general population undergoing AT, but higher than the POH rate obtained at our centre (0.7%). Our patients did not present severe adverse reactions, such as symptomatic hyponatraemia and seizures. This could be explained by the characteristics of our protocol, which specifies a single dose of DDAVP and excludes children under 2 years and those with a history of seizures.

Although we believe our results are encouraging and can generate hypotheses and further developments, we must consider the retrospective nature of our study, as well as the limitations and potential confounding variables (haemostatic and surgical technique, surgeon, etc.). At present, it seems prudent to consider each case on an individual basis, with close cooperation between the otolaryngologist and the haematologist in the best interest of patients, and considering DDAVP as a tool to be used in these cases.

Regarding diagnosis of MPD, we believe it is important to note that 35% of patients presented a normal HT and were only referred due to their anaemia. This is consistent with the literature, in which we found that HT has low sensitivity and specificity for the diagnosis of primary coagulation disorders, although it supports the diagnosis when it is prolonged. The definitive diagnosis of MPD is obtained through the study of platelet aggregability-secretion by aggregometry. However, this test is costly and scarcely available in our environment.

**Conclusions**

We believe that the use of DDAVP may be considered as an alternative in the preventive management of POH in patients with MPD undergoing AT, and that it should be considered as a therapeutic option in other surgeries. However, in order to consider the widespread use of this drug in the prophylaxis of POH it is necessary to find methods to predict the haemostatic effect of DDAVP in such patients.

Future studies should be prospective and focus on the standardisation of the dosage and duration of DDAVP and antifibrolytic agent used, as well as the use of fluid restriction to minimise the risk of adverse effects.

**Conflict of Interests**

The authors have no conflicts of interest to declare.
References


