Hyponatremia After Desmopressin (DDAVP) Use in Pediatric Patients With Bleeding Disorders Undergoing Surgeries

Ruchika Sharma, MD* and Dagmar Stein, MD, PhD*

Summary: Desmopressin (DDAVP) 1-deamino-8-arginine vasopressin is used in patients with bleeding disorders, including mild factor VIII deficiency, types 1 and 2 von Willebrand disease, and platelet function defects, undergoing surgeries to help control bleeding. We conducted a retrospective chart review of bleeding disorder patients undergoing inpatient surgery at Toledo Children’s Hospital, OH, from 2005 to 2009. Our study population included 107 patients aged 2 to 19 years with platelet function defects and von Willebrand disease. Our study aimed to evaluate the extent of hyponatremia caused by DDAVP and to propose a safe and effective treatment regimen for these patients. The mean change in sodium level before and after DDAVP was statistically significant within each age group. Thirteen patients had second dose of DDAVP withheld, and 11 patients had postoperative sodium levels ≤130 mEq/L. There were 2 patients with significant complications: a 6-year-old with postoperative bleeding and a 2-year-old with post-DDAVP tonic-clonic seizures. We conclude that DDAVP causes significant hyponatremia, despite appropriate fluid restrictions. On the basis of our analysis, we recommend monitoring sodium levels before each dose of DDAVP and fluid restriction. These patients should be observed in the hospital setting after DDAVP administration for complications such as seizures and postoperative bleeding.

Key Words: hyponatremia, DDAVP/desmopressin, platelet function defects

ORIGINAL ARTICLE

Desmopressin (DDAVP) 1-deamino-8-arginine vasopressin is a synthetic vasopressin analog that is used to help control bleeding in patients with mild factor VIII deficiency, types 1 and 2 von Willebrand disease, and platelet function defects, undergoing surgeries to help control bleeding. We conducted a retrospective chart review of bleeding disorder patients undergoing inpatient surgery at Toledo Children’s Hospital, OH, from 2005 to 2009. Our study population included 107 patients aged 2 to 19 years with platelet function defects and von Willebrand disease. Our study aimed to evaluate the extent of hyponatremia caused by DDAVP and to propose a safe and effective treatment regimen for these patients. The mean change in sodium level before and after DDAVP was statistically significant within each age group. Thirteen patients had second dose of DDAVP withheld, and 11 patients had postoperative sodium levels ≤130 mEq/L. There were 2 patients with significant complications: a 6-year-old with postoperative bleeding and a 2-year-old with post-DDAVP tonic-clonic seizures. We conclude that DDAVP causes significant hyponatremia, despite appropriate fluid restrictions. On the basis of our analysis, we recommend monitoring sodium levels before each dose of DDAVP and fluid restriction. These patients should be observed in the hospital setting after DDAVP administration for complications such as seizures and postoperative bleeding.

Key Words: hyponatremia, DDAVP/desmopressin, platelet function defects

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The authors declare no conflict of interest.

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MATERIALS AND METHODS

We conducted a retrospective chart review of bleeding disorder patients undergoing surgery at Toledo Children’s Hospital (Toledo, OH) between the years 2005 and 2009. We reviewed 249 charts, and 107 patients ranging in age from 2 to 19 years met the inclusion criteria for our study. Patients included were those with bleeding disorders consisting of platelet function defects (primarily storage pool deficiency), mild FVIII deficiency, and type 1 and 2 VWD. Patients below 2 years of age and those who did not receive DDAVP were excluded from the study, as it is general practice not to administer DDAVP in patients below 2 years of age. Diagnosis of platelet function defects was made by platelet aggregometry (using collagen, ADP, ristocetin, and epinephrine) and electron microscopy for dense granules. Diagnosis of VWD was made by plasma assays for von Willebrand factor (factor VIII: von Willebrand factor) and ristocetin cofactor activity testing (factor VIII: RCoF).

Data collected included age of the patients, specific diagnoses, weight of the patient, specific surgical procedure that the patient underwent, medications that the patient received, DDAVP dose, intravenous and oral fluids, preoperative and postoperative sodium levels, and any complications. Institutional review board approval was obtained before starting chart review.
Confidentiality was maintained per HIPAA regulations.

As demonstrated in Figure 1, patients received doses of DDAVP, 0.3 μg/kg IV over 30 minutes, 1 to 1½ hours before surgery, and then 12 hours after the first DDAVP administration. The maintenance fluid requirements of the patients were calculated according to weight by the Holli-day-Segar method. Isotonic fluids were used and oral and IV fluids were restricted to a total of two third maintenance rate. A serum sodium level was checked before surgery and 2 hours before the second dose of DDAVP. If the sodium level was ≥135 mEq/L, the second dose of DDAVP was administered. Most patients also received aminocaproic acid, 100 mg/kg/dose (maximum 3 g) IV, or PO every 6 hours. All patients were monitored in the hospital setting for 12 to 24 hours in the postoperative period for any bleeding or hyponatremia complications. Any complications in these patients including seizures due to low sodium levels or postoperative hemorrhage were recorded.

Statistical Analysis
Continuous variables are described with mean, SD, median, and 95% confidence interval (CI). Categorical variables are described with frequency, percentage, and 95% CIs. Results were considered statistically significant if the confidence interval for the change did not contain 0 and paired t test yielded a P-value <0.05. To assess differences between the age groups, the CI was examined; CIs that do not overlap are significantly different. Analysis of variance was used to compare the mean change between the age groups.

RESULTS
Data from 107 patients were collected. In our study, 101 patients were found to have platelet function defect (83%), 11 patients had VWD (11%), and 4 patients had both VWD and platelet function defects. None of our patients had any significant concomitant disorders or drugs that would contribute to postoperative sodium abnormalities. Figure 2 shows the distribution of postoperative sodium levels according to different age groups with the top and the bottom of the box representing 25th and 75th percentiles, respectively.

Table 1 compares preoperative and postoperative sodium levels and demonstrates the overall sodium drop with DDAVP administration. There was a statistically significant (P-value <0.01) drop in the mean sodium level of 4.9 mEq/L. Eleven patients (10.3%) experienced drops in sodium to <130 mEq/L, and the second dose of DDAVP was held in 13 patients (12.3%).

These results demonstrate that DDAVP causes significant hyponatremia, despite fluid restriction, and careful monitoring is warranted while using this medication in patients with platelet function defects before surgeries.

Table 2 shows the change in sodium levels with DDAVP among our age cohorts. The mean change in sodium was statistically significant (P-value <0.001) within each age group

**FIGURE 1.** Institutional Protocol for DDAVP Administration. IVF indicates intravenous fluids; MD, doctor; Na, sodium.

**FIGURE 2.** Box plots showing distribution of the sodium levels. (median - line in middle, 25th and 75th percentiles - top and bottom lines.)
The mean change in Na before to after DDAVP was statistically significant within each age group (none of the CIs contained 0 and each of the paired t-tests had \( P \)-value < 0.001). There was no difference in the mean changes between age groups (the CIs of the age groups overlap each other and ANOVA \( P \)-value = 0.4). Table 2 also demonstrates the number of patients who had significant hyponatremia and required second dose of DDAVP withhold, according to age. More patients younger than 13 years of age had significant hyponatremia (sodium levels ≤130 mEq/L) as compared with the patients older than 13 years of age. As a result, more patients younger than 13 years of age had second dose of DDAVP withheld. However, this result did not achieve statistical significance as there were considerably fewer patients older than 13 years of age to base these observations. There was also no difference in serious hyponatremia when the incidence in the age groups 2 to 6 years and 6 to 13 years was compared. The same was true when comparing number of patients requiring second dose of DDAVP withhold between these 2 age groups. These observations demonstrate that the risk for DDAVP-induced hyponatremia is not significantly higher in children between 2 and 6 years of age contrary to prior reports.7

There were 2 patients with significant complications. The first patient was a 2-year-old with platelet storage pool deficiency. His preoperative sodium after the first dose of DDAVP was 133 mEq/L, second dose of DDAVP was withheld and fluids were restricted. Sodium levels dropped to 124 mEq/L, and the patient subsequently had 2 episodes of generalized tonic-clonic seizures. He was treated with 3% sodium chloride. The second patient was a 6-year-old with platelet storage pool defect who received 2 doses of DDAVP perioperatively and underwent a tonsillectomy and adenoidectomy. His postoperative sodium level was 139 mEq/L. The patient was discharged after observation and returned 48 hours later with postoperative bleeding. Both patients recovered fully after adequate treatment.

The surgical procedures primarily consisted of tonsillectomies and adenoidectomies with myringotomy tube placements, wisdom teeth extractions, minor orthopedic procedures, and laparoscopic abdominal surgeries. None of the surgeries had any major complications reported and all patients recovered completely after these procedures.

### DISCUSSION

DDAVP has been used to improve hemostasis in many patients with bleeding disorders including mild factor VIII deficiency, VWD, and platelet function defects.8 In 1989, Weinstein et al9 reported severe hyponatremia in 3 children (3 to 15 y) with underlying bleeding disorders who were treated with DDAVP before surgical procedures to improve hemostasis. Each received multiple doses of DDAVP (3 to 22) and were given intravenous hydration with hypotonic fluids. They developed significant hyponatremia (118 to 121 mmol/L). Two of the 3 patients experienced seizures and 1 patient had altered mental status. All our patients were fluid restricted with isotonic fluids, and multiple doses of DDAVP were avoided. We demonstrate that DDAVP can cause significant hyponatremia, despite fluid restriction, and must be given with caution and careful monitoring.

Previous reports have demonstrated that young children appear particularly predisposed to hyponatremia after the administration of DDAVP.7,10 The increased risk of hyponatremia in young children is likely related to their small size and large fluid intake in relation to total plasma volume compared with adults. The risk is increased by the intake of intravenous or oral hypoosmolar fluids in the context of an inability to excrete free water. In addition, infants have a lower glomerular filtration rate, irrespective of DDAVP, hindering their ability to eliminate excess water.7,10

Smith et al7 described 4 children under the age of 2 years who became hyponatremic (sodium levels, 114 to 123 [meq/l] after the administration of intravenous DDAVP; of the 4 children, 3 developed seizures. These 3 children also had other associated risk factors such as renal tubular acidosis and liver disease. In 2005, Das et al11 described 3 children under 3 years of age who developed hyponatremia (sodium levels, 124 to 126) after intravenous administration of DDAVP for hemostasis (meq/l) is, and 2 of them also developed seizures. In all these patients, the

### TABLE 1. Change in Sodium With DDAVP and Patients Needing Second Dose Withheld

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative Na ≤130</td>
<td>11 (10.3)</td>
<td>4.5%, 16.0%</td>
</tr>
<tr>
<td>Postoperative Na ≤135</td>
<td>78 (72.0)</td>
<td>64.5%, 81.3%</td>
</tr>
<tr>
<td>Second dose withheld</td>
<td>13 (12.1)</td>
<td>6.0%, 18.3%</td>
</tr>
</tbody>
</table>

*Assumed denominator of 107. Twelve percent of the patients had a second dose withheld with confidence interval ranging from 6% to 18%. The mean change in Na before to after DDAVP (mean drop of 4.9; 95% confidence interval, 4.3 to 5.4) was statistically significant (paired t test \( P \)-value = 0.001).

### TABLE 2. Change in Sodium and Patients Needing Second Dose Withheld According to Age

<table>
<thead>
<tr>
<th>Age 2-6 (n = 49)</th>
<th>Age 7-13 (n = 47)</th>
<th>Age &gt;13 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Na (pre minus post)</td>
<td>4.5± 2.0 (3.8, 5.2)</td>
<td>5.2± 2.4 (4.3, 6.1)</td>
</tr>
<tr>
<td>Postoperative Na ≤130 (mEq/L)</td>
<td>4 (8.2) (0.1%, 15.8%)</td>
<td>7 (14.9) (4.7%, 25.1%)</td>
</tr>
<tr>
<td>Postoperative Na ≤135 (mEq/L)</td>
<td>38 (77.6) (65.9%, 89.2%)</td>
<td>35 (74.5) (62.0%, 86.9%)</td>
</tr>
<tr>
<td>Second dose withheld</td>
<td>7 (14.3) (4.5%, 24.1%)</td>
<td>6 (12.8) (3.2%, 22.3%)</td>
</tr>
</tbody>
</table>

The mean change in Na before to after DDAVP was statistically significant within each age group (none of the CIs contained 0 and each of the paired t tests had \( P \)-value < 0.001). There was no difference in the mean changes between age groups (the CIs of the age groups overlap each other and ANOVA \( P \)-value = 0.4).

More of the younger patients had second dose withheld (14.3% of patients aged 2 to 6 years and 12.8% of patients aged 7 to 13 years) as compared with the older patients (0%).

*Statistical significance.

ANOVA indicates analysis of variance; CI, confidence interval.
factors contributing to hyponatremia included the administration of hypotonic fluids and the patients’ small sizes (weights of 10, 10.4, and 14 kg). We did not demonstrate any statistically significant difference in DDAVP-induced hyponatremia in younger age groups of our study; however, none of our patients were below 2 years of age and none had concomitant risk factors. Interestingly, our patient who had a seizure after hyponatremia was only 2 years old.

A recent retrospective chart review conducted by Davidson and colleagues aimed to analyze the incidence and severity of hyponatremia caused by DDAVP in patients with VWD who underwent otolaryngological procedures. All patients in this study received 1 dose of IV DDAVP and sodium levels were monitored every 6 to 8 hours during the first 24 hours. Of 63 patients, 47 patients developed some degree of hyponatremia (Na < 136), 6 developed extreme hyponatremia (Na < 130), and no serious adverse events were noted. The degree of hyponatremia was significantly associated with the volume of perioperative fluids administered. Davidson et al12 recommended half maintenance normotonic fluids in intraoperative setting with no planned postoperative intravenous fluid administration.

In addition to these reports of hyponatremia and seizure activity following the use of intravenous DDAVP, there are reports of similar occurrences following the use of intranasal DDAVP. Koskimies et al13 identified 3 children (aged 1, 7, and 13 mo) who within 10 to 15 hours of receiving intranasal DDAVP developed serum sodium levels of 118, 123, and 120 mmol/L, respectively. Receiving intranasal DDAVP developed serum sodium levels of 118, 123, and 120 mmol/L, respectively. In a recent retrospective chart review conducted by Koskimies et al13, a child aged 1 year who within 10 to 15 hours of receiving intranasal DDAVP developed serum sodium levels of 118, 123, and 120 mmol/L, respectively.

Risk factors for hyponatremia after DDAVP use may include stress, surgery, anesthesia, and narcotics, which can cause release of endogenous antidiuretic hormone. Other risk factors described are concomitant liver disease, which may hinder DDAVP metabolism, renal tubular acidosis, postoperative syndrome of inappropriate antidiuretic hormone secretion (SIADH), vomiting with loss of sodium, and administration of multiple doses of DDAVP.14,15 None of our patients had significant underlying risk factors, but stress, surgery, and anesthesia may have been factors predisposing them to DDAVP-induced hyponatremia.

Postoperative hyponatremia has also been identified in pediatric patients who do not have underlying bleeding disorders. Au et al16 conducted a retrospective observational study of postoperative children admitted to the intensive care unit to compare the incidence of hyponatremia in children receiving hypotonic and isotonic fluids. In their study16 of 145 (11%) children were hyponatremic, with no difference between the 2 groups. Choong et al17 conducted a randomized, controlled trial comparing isotonic with hypotonic maintenance fluids in postoperative pediatric patients between 6 months and 14 years of age. Of the total number of patients, 40.8% patients in the hypotonic saline group and 22.7% in the isotonic saline group developed hyponatremia (sodium ≤134 mEq/L). Eight patients (6.2%) developed severe hyponatremia (sodium ≤129 mEq/L) following hypotonic fluids, compared with 1 patient (0.8%) in the isotonic fluids group. However, in our study, we observed an increase in incidence of hyponatremia with DDAVP use in patients with underlying bleeding disorders as compared with these historic controls who did not receive this medication.

Our study has limitations as it is a retrospective study design. Our experience may not be entirely reflective of all institutions as we use 12-hour DDAVP dosing, whereas some institutions may use 24-hour DDAVP dosing schedule. A strength of our study is the relatively large number of patients reviewed and the availability of preoperative and postoperative serum sodium levels as this has been our standard practice to obtain this level of monitoring. We also have collected data about total fluids administered including intravenous and oral fluids as well as fluids administered during surgery. This has not been obtained in prior studies. We propose a protocol to check sodium levels before each dose of DDAVP for safe and effective administration of DDAVP to these patients. Many institutions do not check for hyponatremia in this setting.

CONCLUSIONS

We conclude that DDAVP is associated with a significant risk for postoperative hyponatremia with the potential for adverse events including seizures, despite fluid restrictions. We recommend close monitoring of sodium levels and fluid balance in patients with platelet function defects during hospitalization in the postoperative period. We recommend checking sodium levels on admission and before each subsequent dose of DDAVP. Intravenous and oral fluid should be restricted to two third maintenance or less, hypooplastic fluids should be avoided, and patients should be carefully observed in the hospital setting for at least 20 to 24 hours for any complications including seizures and bleeding complications. Discussing the side effects of DDAVP with the family and other physicians is advisable. In addition, multiple doses of DDAVP should be avoided. Particular sensitivity of younger patients with DDAVP was not demonstrated, but DDAVP should be avoided in children below 2 years of age. Further studies are required to evaluate the extent of DDAVP-induced hyponatremia in various age ranges.

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