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ORIGINAL PAPER

Immunoglobulin preparations affect hyponatremia in Kawasaki disease

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Abstract Hyponatremia frequently occurs in Kawasaki disease (KD). The aim of this study was to investigate the effect of Na content of the intravenous immunoglobulin (IVIG) preparation on serum Na levels in KD. Seventy-eight subjects, of whom 27 had hyponatremia, were split up into two groups: group A receiving IVIG preparations containing high Na (0.9%) and group B receiving IVIG preparations containing trace Na. While the data before IVIG therapy revealed no significant differences in the median serum Na between the groups, an administration of IVIG preparations increased the serum levels of Na in group A ($P<0.01$) but not in group B ($P>0.05$). Furthermore, the median serum Na level was significantly higher in group A than that in group B (139.0 vs 137.0 mEq/L, respectively, $P<0.01$). No significant difference was found in the prevalence of coronary artery lesions between the groups. In conclusion, we should keep it in mind that the IVIG products without Na have an adverse affect on hyponatremia in KD though their efficacy seems to be equivalent to those containing high Na.

Keywords Hyponatremia · Intravenous immunoglobulin · Kawasaki disease · Sodium content

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Introduction

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology that predominantly affects children younger than 5 years [1]. Because KD is systemic vasculitis, multiple organ involvement can develop, including coronary artery lesions (CALs), carditis, arthritis, hepatitis, and central nervous system disease [1]. In addition, hyponatremia (serum Na <135 mEq/L) frequently occurs in KD [4, 6, 9] though the precise mechanism remains unknown.

Recently, an iatrogenic hyponatremia, which is commonly seen in hospitalized children and is caused by the administration of hypotonic intravenous fluids, has brought our notice [2, 3, 5, 6].

We wonder whether the Na content in the intravenous immunoglobulin (IVIG) preparations administered to patients with KD might influence their serum Na levels because Na content in IVIG preparations vary considerably ranging from trace to 0.9% (154 mEq/L). This study was undertaken to investigate the impact of Na contained in the IVIG preparations on serum Na concentrations in patients with KD.

Materials and methods

The medical records of 78 patients with KD admitted to the Department of Pediatrics, Kansai Medical University

Hospital and its affiliated hospitals between December 2005 and June 2008 were retrospectively investigated. Charts were reviewed for clinical characteristics, such as patient age, gender, or development of CALs during the courses of acute illnesses. Laboratory data were also reviewed for serum levels of Na and C-reactive protein (CRP). Blood sampling was performed at least twice, both at a median of 36.0 h prior to IVIG administration (range 1–120 h) and at a median of 22.0 h after IVIG administration (range 6–24 h).

Soon after initial blood sampling, all patients received intravenous administration of commercially available hypotonic fluid (Na 35 mEq/L, K 20 mEq/L, Cl 35 mEq/L, lactate 20 mEq/L, glucose 4.3%) since their admission because of poor oral water intake: Parenteral fluid therapy was continued until defervescence except the period of IVIG administration (12–24 h), and totally, median volume of 66.36 mL/kg (range 0 to 390.4 mL/kg) of hypotonic solution was infused to the patients.

KD was diagnosed according to the diagnostic guidelines by Burns and Glodé [1], and CALs were assessed by echocardiography and were defined by either (1) an internal diameter of the coronary artery lumen >3 mm in a child <5 years or >4 mm in a child ≥5 years, (2) the internal diameter of a segment's being at least 1.5 times as large as that of an adjacent segment, or (3) when the lumen was clearly irregular [10]. Hyponatremia was defined as serum Na level <135 mEq/L [4, 7, 10].

Subjects were split up into two groups: group A, patients with KD receiving IVIG preparations containing high Na (Kenketsu Venilon-I® (Na 154 mEq/L) or Kenketsu Glovenin-I-Nichiyaku® (Na 154 mEq/L)), and group B, patients with KD receiving IVIG preparations containing trace amount of Na (Nisseki Polyglobin-N Injection 5%® (Na 0.09 mEq/L) or Kenketsu venoglobulin-IH YOSHITOMI® (Na 2.60 mEq/L)). Clinical characteristics, serum levels of Na, and CRP both before and after IVIG therapy in addition to the prevalence of CALs were compared between group A and group B.

Because the numerical data in the current study distributed nonparametrically, they were expressed in median and range. For statistical analysis, Wilcoxon *T* test, Mann–Whitney *U* test, and chi-square test were used for paired numerical data, unpaired numerical data, and categorical variables, respec-

Table 1 Summary of the results

	Group A	Group B	*P* value
	High-Na IVIG	Trace-Na IVIG	
	(*N*=48)	(*N*=30)	
Male/female	29:19	18:12	>0.05
Median age (years; range)	1.85 (0.47–8.81)	2.74 (0.26–8.00)	>0.05
Data before IVIG			
Median serum sodium (mEq/L; range)	135.5 (128.0–140.0)	135.0 (130.0–141.0)	>0.05
Prevalence of hyponatremia[a] (%)	16 (33.3%)	11 (36.7%)	>0.05
Median CRP level (mg/dL; range)	6.69 (0.74–15.24)	9.91 (2.70–18.10)	<0.05
Amount of parenteral administration of water and sodium during IVIG			
Fluid volume (mL/kg)	40.00 (31.58–44.87)	40.13 (34.48–45.56)	>0.05
Amount of sodium (mEq/L; range)	62.83 (36.96–154.00)	0.91 (0.03–1.82)	<0.01
Data and administered water volume after IVIG			
Median serum sodium (mEq/L; range)	139.0 (133.0–142.0)	137.0 (129.0–143.0)	<0.01
Prevalence of hyponatremia[b] (%)	5 (10.4%)	8 (26.7%)	>0.05
Administered fluid volume (mL/kg)	720 (120–960)	400 (0–920)	<0.01
Correlation between serum sodium and administered fluid volume	r_s=0.17	r_s=0.26	>0.05
Median CRP level (mg/dL; range)	3.85 (0.10–11.56)	6.18 (1.10–14.83)	>0.05
Prevalence of CALs (%) [details]	6 (12.5%) [mild[c] in 6, transient[a] in 3]	6 (20.0%) [mild[c] in 6, transient[a] in 1]	>0.05

IVIG intravenous immunoglobulin, *High-Na IVIG* IVIG preparations containing 154 mEq/L of sodium, *Trace-Na IVIG* IVIG preparations containing 0.09–2.60 mEq/L of sodium, *CRP* C-reactive protein, *CALs* coronary artery lesions

[a] CALs normalized within 1 month from the onset

[b] Defined as serum Na <135 mEq/L

[c] CALs of an internal diameter of the coronary artery lumen between 3 and 4 mm

tively. A level of $P<0.05$ by two-tailed analysis was accepted as statistically significant.

To analyze the relationship between the two groups of data, Spearman rank correlation test was applied.

Results

Table 1 summarizes the results. Group A consists of 48 patients with KD while group B consists of 30 patients with KD. There were no significant differences in male-to-female ratio and the median age. The data obtained before IVIG therapy revealed no significant differences in the median serum Na level and the prevalence of hyponatremia between the groups. The median CRP level in group A was lower than that in group B ($P<0.05$). Whereas infused fluid volume during IVIG therapy were similar between the groups, amount of administered Na was significantly higher in group A than that in group B reflecting the Na content of used IVIG preparations as shown in the Table 1.

On the contrary, the data obtained after IVIG therapy demonstrated that the median serum Na level was significantly higher in group A than that in group B (139.0 vs 137.0 mEq/L, respectively, $P<0.01$) and an administration of IVIG preparations significantly increased the serum level of Na only in group A ($P<0.01$; Fig. 1) and that serum Na level in group B remained low even after IVIG ($P<0.01$; Table 1; Fig. 1).

Prevalence of hyponatremia was also lower in group A (five out of 48) than that in group B (eight out of 30) though it did not reach statistically significant level ($P>0.05$; Table 1). There was a significant difference in administered fluid volume between the groups ($P<0.01$): Group A (median 720 mL/kg, range 120–960) received more hypotonic fluid than group B (median 400 mL/kg, range 0–920) after IVIG administration although the correlation coefficient between serum Na level and administered fluid volume did not reach statistically significant level ($P>0.05$, r_s 0.17 in group A and r_s 0.26 in group B, respectively).

No significant differences were found in the median level of CRP after IVIG therapy and the prevalence of CALs between the groups.

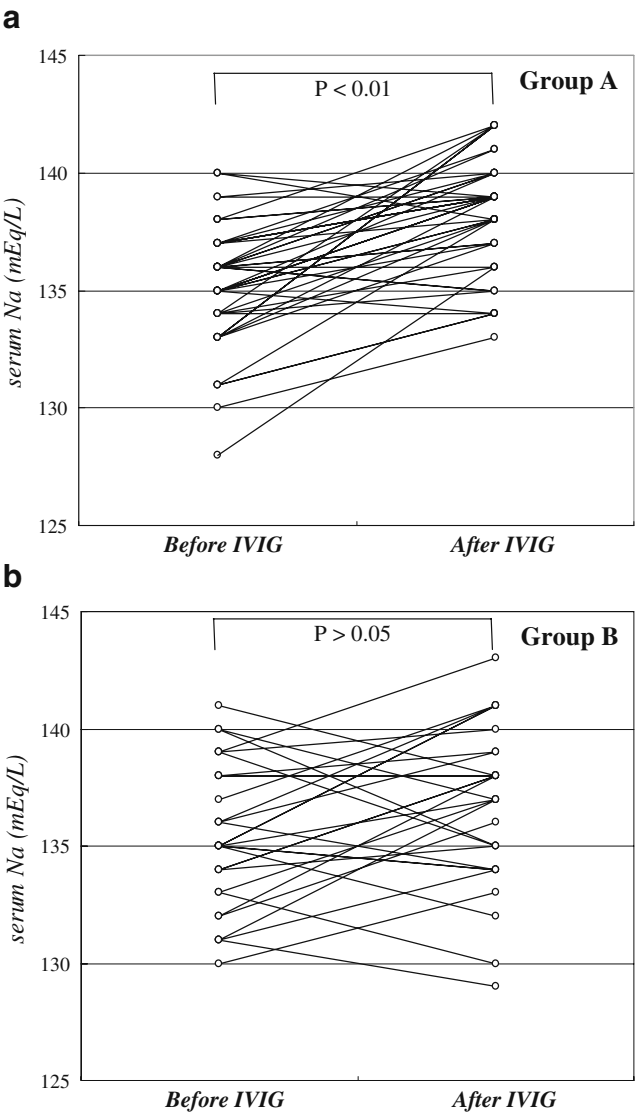

Fig. 1 Changes in serum Na levels before and after IVIG administration. Administration of IVIG preparations significantly increased the serum Na level only in group A ($P<0.01$) but not in group B ($P>0.05$, statistics by two-tailed Wilcoxon T test). **a** Group A, patients receiving IVIG containing high Na; **b** group B, patients receiving IVIG containing trace amount of Na

Discussion

It is known that patients with KD also frequently develop hyponatremia [4, 7, 10]. Our present study disclosed that the prevalence of hyponatremia is nearly one third of the patients with KD, which is in agreement with the previous reports [4, 10]. It has been proposed that mechanisms for hyponatremia in KD are associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatremic dehydration, and ingestion of fluid that is hypo-osmolar relative to the fluid loss [4, 8, 10].

Though clarifying the precise etiology in hyponatremia in KD beyond the scope of the present study, analysis of correlation between the serum Na value and CRP level before IVIG revealed significant relationship ($n=78$, $r_s=0.40$, $P<0.01$): the higher the CRP, the lower the serum Na level. This finding suggests that increased inflammatory cytokines may induce SIADH and also have direct tubular effects causing natriuresis as suggested by several authors [8, 10].

SIADH, hyponatremic dehydration, and ingestion of fluid that is hypo-osmolar relative to the fluid loss can be aggravated

by an excessive free water load. The Na content of available IVIG products ranges from trace amounts to 154 mEq/L (0.9%) [9]. While high Na content may be inappropriate for patients with heart failure or renal dysfunction, excessive free water load to young infants with hyponatremia raises the risk of deleterious change. The product's concentration of protein also affects the amount that must be administered: For a 10-kg patient to receive 2 g/kg of IVIG preparations, 400 mL of fluid volume must be delivered as the IVIG products used in Japan have protein concentrations of 5%. The situation is similar to the Western countries as the protein concentrations of the IVIG products used in those countries range from 3% to 12% [9].

Given the aggravating hyponatremia by excessive free water in patients with KD, we wonder whether the Na content in IVIG preparations may affect hyponatremia, which can be lethal [5, 6]. Our study for the first time shows that certain IVIG products with trace amount of Na slow the recovery from hyponatremia, which is seen in one third of children with KD.

An efficacy of IVIG preparations to suppress the inflammatory response seems not to be influenced by their Na content because no significant differences in change in CRP and the prevalence of CALs were found among the patients receiving IVIG products containing different amounts of Na.

There are, however, several limitations in the present study because of its retrospective nature: First, there was a difference in administered hypotonic fluid volume between the groups as shown in Table 1. Hypotonic fluid infused to the patients with KD may lower the serum Na level as hyponatremia has been increasingly reported in children receiving hypotonic fluids. However, the difference in administered hypotonic fluid volume did not seem to influence directly on the present result as there was no significant correlation between serum Na level and administered fluid volume as shown in the Table 1. Furthermore, the finding that group A which received more hypotonic fluid after IVIG than group B suggests a little effect of administered hypotonic fluid volume on the serum Na level; second, there was a significant difference in CRP level between the groups as shown in Table 1: Group B showed higher CRP level than group A, and this might lead to the biased result. Similar prevalence of hyponatremia in the two groups, however, made this possibility less likely.

In conclusion, whatever the mechanism is involved, we should keep it in mind that the IVIG products without Na have an adverse affect on hyponatremia in KD though their efficacy seems to be equivalent to those containing high Na. We had better choose IVIG preparations containing high Na (154 mEq/L, 0.9%) if the patients with KD show hyponatremia before IVIG therapy. The management of hyponatremia in KD should also include the use of isotonic fluid, such as sodium chloride 0.9% (Na 154 mEq/L) or Hartmann's solution (Na 131 mEq/L) for maintenance fluid therapy as the National Patient Safety Agency of UK has recently issued the recommendation not to use hypotonic fluid for children with nonosmotic secretion of antidiuretic hormone, such as pain, anxiety, the postoperative state, nausea, vomiting, certain drugs, pyrexia, sepsis, reduced circulating volume, respiratory disorders, central nervous system infections, and metabolic and endocrine disorders in order to reduce the risk of hyponatremia.

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Conflict of interest None to declare.

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