Plasma therapy for severe hemolytic-uremic syndrome in children in Atlantic Canada

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Clinical reports have suggested that therapy with fresh frozen plasma is a useful adjunct in the management of the hemolytic-uremic syndrome (HUS). We reviewed the charts of 36 children with severe HUS who were treated at the Izaac Walton Killam Hospital for Children, Halifax, over 10 years to assess the effectiveness of plasma therapy. All children who required specific supportive therapy for renal dysfunction, hemolysis or serious extrarenal complications were included. We compared the outcome of 18 children who received plasma therapy from 1982 to 1987 with that of 18 children who did not. The two groups were similar with regard to the severity of HUS, the length of hospital stay, the duration of renal dysfunction and the incidence of disease-related complications, such as seizures, enterocolitis and cardiomyopathy. At discharge the prevalence of hypertension was higher in the plasma therapy group than in the control group. Plasma therapy did not demonstrate any benefit that would outweigh the risk of fluid overload, hyperproteinemia and transmission of viral infection.

D'après des rapports cliniques, la thérapie au plasma frais congelé aide à traiter le syndrome hémolytique et urémique (SHU). Nous avons examiné le dossier de 36 enfants victimes de SHU grave qui ont été traités, sur un période de 10 ans, à l'Hôpital pour enfants Izaac Walton Killam de Halifax pour évaluer l'efficacité de la plasmathérapie. Tous les enfants qui avaient besoin d'une thérapie de soutien précise à cause d'un dysfonctionnement rénal, d'une hémolyse ou de complications extra-rénales graves ont été inclus à l'étude. Nous avons comparé l'état de 18 enfants qui ont reçu une plasmathérapie entre 1982 et 1987 à celui de 18 enfants qui n'en ont pas reçu. La gravité du SHU, la durée du séjour à l'hôpital, la durée du dysfonctionnement rénal et l'incidence de complications liées à la maladie, comme les crises cérébrales, l'entérocolite et la myocardiopathie, étaient les mêmes dans les deux groupes. Au moment de la libération, l'incidence d'hypertension était plus élevée chez les sujets qui avaient reçu de la plasmathérapie que chez le groupe témoin. La plasmathérapie n'a démontré aucun avantage qui l'emporterait sur le risque de surcharge liquidienne, d'hyperprotéinémie et d'infection virale.

A number of reports have suggested that abnormalities of prostanoid metabolism are factors in the loss of endothelial integrity and platelet dysfunction that are features of the hemolytic-uremic syndrome (HUS).[1-5] However, no consistent abnormality has been identified. Therapy with fresh frozen plasma would seem to be potentially beneficial among children with HUS, but recent prospective trials have yielded conflicting results.[6,7]

We reviewed the symptoms and complications of severe "classic" HUS in children treated over 10 years. To determine whether plasma therapy was beneficial we compared the outcome of those who received plasma therapy and those who did not.

Methods

We reviewed the records of 61 patients with

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HUS admitted to the Izaak Walton Killam Hospital for Children, Halifax, from Jan. 1, 1979, to Dec. 31, 1988. The review and publication of the data were approved by the Medical Records Committee of the hospital. HUS was diagnosed if microangiopathic hemolytic anemia, hematuria and thrombocytopenia were present.

We excluded 21 patients because their renal impairment was mild and did not necessitate fluid restriction or dialysis, they needed only one transfusion of packed erythrocytes for hemolysis, or they had no extrarenal complications. We also excluded four adolescents with atypical disease reminiscent of adult thrombotic thrombocytopenia (TTP); two died, one of myocardial infarction and the other of pulmonary embolism after severe hemorrhage at multiple sites. The symptoms in the 36 remaining patients satisfied the description of "classic" HUS and were severe enough to warrant hemodialysis and other forms of intensive therapy.

At the beginning of the study period hemodialysis was used to treat HUS because trained personnel were available for that technique rather than for peritoneal dialysis. As the early results were somewhat better than those in the literature at that time hemodialysis remained as part of a consistent care approach. Patients underwent the procedure for 90 to 150 minutes daily or every other day.

From 1982 to 1987 it was departmental policy to give fresh frozen plasma, 20 mL/kg daily, to all children with HUS in addition to other therapy. Of the 36 patients 18 (case subjects) received such therapy for 4 to 26 (mean 14) days. The infusion volume had to be adjusted to 10 mL/kg daily in three cases to maintain a strict fluid balance and normal plasma protein levels. Plasma therapy was continued until normal urine volumes were established and platelet counts were within normal limits.

The remaining 18 patients (control subjects) were treated with hemodialysis alone either before 1982 or after 1987, when an internal clinical audit suggested that plasma therapy not be used for HUS.

Information was obtained from each chart on patient age, length of prodrome, residence, length of hospital stay, duration of hemodialysis therapy, number of plasma exchange transfusions and any complications of disease or therapy. Follow-up information on the patient's current health, renal function and blood pressure was sought from the chart and, if necessary, from the family physician by mail.

Statistical analysis was done through the independent-groups Student's t-test or the Pearson χ^2 test with the use of Systat (version 2.0) (Systat Inc., Evanston, Ill.).

Results

None of the patient characteristics differed significantly between the two groups (Table 1). Complications of treatment were quite common, localized inflammation, hemorrhage and blockage of temporary vascular access cannulas being the most frequent (Table 2). The disease-related complications included cardiomyopathy, as indicated by cardiac failure despite strict fluid balance and confirmed through real-time echocardiography, seizures, which were part of the presenting illness and preceded therapy in all cases, and enterocolitis, which manifested as bloody diarrhea and was usually associated with nonobstructive ileus (Table 2). The frequency of the disease-related complications was comparable in the two groups.

Table 1: Characteristics of 36 children with severe hemolytic–uremic syndrome (HUS) who received hemodialysis and plasma therapy (treatment group) or who underwent hemodialysis alone (control group)

Characteristic	Group; mean (and standard deviation)	
	Control (n = 18)	Treatment (n = 18)
Age, yr	2.7 (1.7)	2.3 (1.6)
Values on admission		
Hemoglobin level, g/L	91 (24)	80 (22)
Platelet count, $\times 10^9$/L	47 (22)	51 (41)
Serum creatinine level, μmol/L	344 (170)	291 (185)
No. of hemodialysis treatments	5.5 (3.0)	4.7 (2.9)
No. of exchange transfusions of whole blood	2.4 (1.8)	2.8 (1.8)
Duration of anuria, d	3.6 (4.6)	2.5 (3.4)
Duration of hospital stay, d*	27 (17)	23 (8)
Duration of follow-up, mo	27	24

*One patient was in hospital for 88 days because of pre-existing malnutrition.

Hypertension, defined as three or more blood pressure readings in excess of the standards recommended by the Task Force on Blood Pressure Control in Children,[8] was more common among the case subjects than among the control subjects. The mean duration of plasma therapy was 15.3 (standard deviation [SD] 3.3) days among the patients with hypertension; this was slightly longer than the mean duration of 13.0 (SD 7.8) days among the normotensive patients. There was no significant difference between the hypertensive and normotensive plasma recipients in the hemoglobin level, platelet count or serum creatinine level on admission, the amount of dialysis or the number of exchange transfusions. All of the patients with hypertension were weaned from antihypertensive therapy within 1 year after the onset of illness.

Cutaneous urticaria without airway obstruction, bronchospasm or anaphylaxis developed in four plasma recipients. This reaction was related to individual units of plasma and did not recur with subsequent infusions. Specific treatment was not necessary.

None of the patients have died or had chronic renal failure to date.

Discussion

The use of plasma therapy for HUS and TTP has enjoyed a modest, albeit controversial, advocacy since the first reports of successful outcome with this treatment.[9,10] Various abnormalities of prostaglandin activity in the blood of certain patients with HUS have provided some basis for plasma therapy: decreased prostacyclin-generating activity, increased serum prostaglandin $F_{2\alpha}$ and thromboxane B_2 levels and accelerated prostaglandin degradation.[1-5,11] Unfortunately no abnormality has been identified with sufficient consistency to be considered pathognomonic; thus, the evaluation of plasma therapy at a biochemical level is difficult. Our results also cast doubt on whether plasma therapy is useful.

Although our study was retrospective all of the patients were managed according to a standard approach by one clinical group in the same institution. The number of patients treated thus exceeded the number from any individual institution entered in multicentre trials. Our measures of acute illness were objective. None of the patients died or suffered chronic renal failure.

The apparent increase in the prevalence of hypertension among the plasma recipients may have simply reflected an increased awareness by physicians of this aspect of care after 1982. A strict fluid balance was maintained in all of the patients, so that a simple volume effect was unlikely. Although the hypertensive patients were given slightly more plasma than the normotensive ones there was little evidence that they had more severe HUS. Plasmapheresis may help to regulate the plasma volume during exchange therapy;[9] however, such data in a pediatric population with HUS are unavailable. Another factor that may have contributed to the increased prevalence of hypertension was the more careful monitoring of blood pressure in the patients given blood products daily than in the other patients. Loirat and collaborators[7] reported fatal hypertension in one patient who received plasma, although they excluded this patient from their study.

Clinical evaluation of plasma therapy has been attempted in two recent prospective multicentre trials.[6,7] In one, involving 32 patients with severe HUS, Rizzoni and associates[6] detected no short-term or long-term clinical benefits. The prevalence of subtle vascular damage during the recovery phase was higher among the 15 control subjects than among the plasma recipients, but this was observed only at an ultrastructural level. The investigators found no abnormalities or differences in the plasma prostacyclin-generating activity between the two groups. They recommended against the routine use of plasma therapy for childhood HUS.

Table 2: Complications of HUS and treatment

Complication	Group; no. (and %) of patients	
	Control	Treatment
Disease-related		
Residual hypertension	4 (22)	9 (50)
Acute cardiomyopathy	3 (17)	3 (17)
Seizures	2 (11)	1 (6)
Enterocolitis	1 (6)	4 (22)
Treatment-related		
Infection at access site	6 (33)	5 (28)
Hemorrhage at access site	2 (11)	2 (11)
Urinary tract infection	3 (17)	1 (6)
Urticaria	–	4 (22)

Loirat and collaborators,[7] in a study involving 79 patients in 19 centres, were also unable to demonstrate a clinical benefit of plasma therapy. However, they advocated plasma therapy because renal cortical necrosis was seen only in the control group and an elevated serum creatinine level was more prevalent in the control group than in the treatment group at 3 and 6 months' follow-up. After 1 year, though, the differences between the two groups were no longer evident.

Interestingly, those two studies presented opposing views on whether plasma therapy should be used even though the results were similar. Neither study described any measure to standardize therapy between participating centres. Changes in the standards of all aspects of pediatric supportive care, including nutrition, fluid and electrolyte management, antihypertensive therapy and the widespread availability of short-term peritoneal dialysis with the use of minimally invasive appliances, have contributed so much to the improvement in outcome of children with severe HUS that Trompeter and colleagues[12] have estimated that much larger series are necessary to establish a clinical effect of plasma therapy. The price of such a large study is often limitations in the control of the complex care that children with severe HUS require. In addition, differences in care standards make the interpretation of apparent regional differences in HUS morbidity and mortality rates a difficult task. Exploration of such a hypothesis to explain our fortunate results is beyond the scope of this study.

The risks of plasma therapy are considerable. Injudicious use may result in fluid overload and hyperproteinemia, which may prolong the period of acute renal failure.[13] The volume of plasma needed may detract from a limited fluid allowance and thus compromise nutrition. The increasing concern about transmission of viral infection through transfusion, however, may prove to be the ultimate argument against this therapy. The prevalence of childhood HUS in Canada is great enough to permit useful studies of treatment and outcome. Although this report is a review of clinical experience rather than a definitive study we believe that the lack of circumstantial evidence to support plasma therapy and the risks of such therapy argue against the use of further resources for controlled trials.

Plasma therapy may have a place in some forms of HUS. However, we believe that its use for classic HUS in children cannot be justified on the available evidence.

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