Plasma exchange therapy for severe gastrointestinal involvement of Henoch Schönlein purpura in children

Ö. Başaran[1], N. Cakar[1], N. Uncu[1], B.A. Çelikel[1], A. Kara[2], F.S. Cayci[1], A. Taktak[1], G. Gür[1]

[1]Department of Paediatric Nephrology and Rheumatology, Ankara Child Health, Haematology, Oncology Education and Research Hospital, Ankara, Turkey; [2]Department of Paediatric Haematology, Ankara Child Health, Haematology, Oncology Education and Research Hospital, Ankara, Turkey.

Özge Başaran, MD
Nilgun Cakar, MD
Nermin Uncu, MD
Banu Acar Çelikel, MD
Abdurrahman Kara, MD
Fatma Semsa Cayci, MD
Aysel Taktak, MD
Gökce Gür, MD

Please address correspondence to:
Özge Başaran, MD,
Department of Paediatric Nephrology and Rheumatology, Ankara Child Health, Haematology, Oncology Education and Research Hospital, 06610 Ankara, Turkey.
E-mail: ozgesalor@yahoo.com

Received on July 8, 2014; accepted in revised form on September 8, 2014.

Clin Exp Rheumatol 2015; 33 (Suppl. 89): S176-S180.

Key words: Henoch-Schönlein purpura, paediatric, gastrointestinal system, plasma exchange

Competing interests: none declared.

ABSTRACT

Objective. *The aim of this report is to evaluate the plasma exchange as a choice for the management of life-threating gastrointestinal system (GIS) involvement in Henoch-Schönlein purpura (HSP) when refractory to conventional therapies.*

Methods. *We retrospectively reviewed the medical records of HSP patients who had plasma exchange therapy due to massive GIS involvement. We reported age, gender, initial HSP presentation, etiological or triggering factors and disease course. Treatment modalities, side effects and their outcomes were noted.*

Results. *We reported 7 cases of childhood HSP with severe gastrointestinal involvement refractory to common immunosuppression with systemic steroid and cytotoxic therapy. All patients gave inadequate response to pulse methyl prednisolone or oral prednisolone therapy with ongoing GIS bleeding and severe abdominal pain. Therefore, pulse cyclophosphamide was added to the treatment. Two patients received additional intravenous immunoglobulin (IVIG) therapy. Gastrointestinal manifestations continued and plasma exchange was performed. All patients improved after plasma exchange treatment.*

Conclusion. *Treatment of GI involvement in HSP with plasma exchange has been mainly based on case reports. According to our data, we propose that, plasma exchange may be a safe and efficient management choice in paediatric HSP patients with massive GIS involvement that are refractory to other therapies.*

Introduction

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis with vascular deposition of immunoglobulin A (IgA) immune complexes. It is characterised by non-thrombocytopenic palpable purpura, arthritis/arthralgia, abdominal pain, gastrointestinal system (GIS) bleeding and glomerulonephritis. Children are affected more than adults. Typically, it occurs mostly between the ages of three and 15, and is more common in boys than girls. Prognosis and treatment opportunities may show differences due to clinical severity (1). Some case series, although without controls, have been reported suggesting the plasma exchange's effects and benefits in improving the prognosis of rapidly progressive HSP nephritis (2, 3). However, plasma exchange has been reported for massive GIS involvement of HSP in only anecdotal cases (4, 5). We present here a small group of children having GIS involvement of HSP who were treated successfully with plasma exchange. The aim of this report is to evaluate plasma exchange as a choice for the treatment of life-threating GIS involvement in HSP, especially when refractory to routine therapies.

Material and method

We retrospectively reviewed the medical records of HSP patients who had plasma exchange therapy due to massive GIS bleeding between the years 2007–2013. We reported those patients' ages, gender, initial HSP presentation, etiological or triggering factors and disease course. Haemogram, urinalysis, stool analysis for blood, blood chemistry and other laboratory investigations, including viral markers, anti-nuclear antibody (ANA), anti-ds DNA, C3 and C4 levels and throat culture were performed to examine the underlying infection agents and other rheumatologic disorders. Treatment modalities, side effects and their outcomes were noted. Disease severity was defined as massive GIS bleeding with decreasing haemoglobin value 2 gr/dl or more and/

or refractory ongoing abdominal pain despite receiving immunosuppressive treatment. According to the guidelines on transfusion procedures in critically ill children (6), Red blood cell (RBC) transfusion should be given if haemoglobin levels are below 7g/dl. Refractory GIS disease was defined as when patients continue to have GIS symptoms despite receiving immunosuppressive therapies. Remission in GIS involvement was defined as when patients had no further GI symptoms or GI haemorrhage. And response indicators were considered as improvement of GI bleeding or refractory abdominal pain. Plasma volume to change in each plasma exchange session was calculated with the formula of 50 cc per kilograms. Before the procedure, premedication was given using intravenous 1mg/kg prednisolone and intravenous 2mg/kg pheniramine maleat.

Statistical analysis was carried out. For continuous variables, the data were presented as mean ± standard deviation.

Results

Seven patients who had plasma exchange therapy due to GIS involvement were identified. The mean age of the patients was 10.16 years (range 5–16). Two patients were female and five were male. On physical examination, they had palpable purpuric lesions on the lower extremities. Skin biopsy was performed in three patients (patient no. 3, 5 and 6). The results were compatible with leukocytoclastic vasculitis; two also had perivascular deposits of Ig A with direct immunofluorescence staining. All patients suffered from severe abdominal pain, and five patients also had massive GI bleeding (no. 1, 2, 4, 5 and 7). The other two patients (no. 3 and 6) had severe abdominal pain. All patients had haemoglobin decrease over 2 g/dl. Patients 2 and 3 received RBC transfusion as their haemoglobin values were below 7gr/dl. Five patients had one episode of HSP. One of them (patient no. 6) had a prolonged course (over six months) of abdominal pain and haemorrhage and purpuric rash. Patient no. 3 had several intussusception attacks that were confirmed by ultrasonography besides massive GIS bleeding. Patient no. 5 had a previous HSP attack without GIS involvement. This patient has also been previously reported by Acar *et al*. (4), and had two HSP episodes within a five-year period, after receiving hepatitis B vaccine that might be a triggering factor for HSP. Patients 2 and 3 were already under control with the diagnosis of Familial Mediterranean Fever (FMF) and had been receiving colchicine therapy. FMF DNA investigation was performed in patient 4 due to his history of recurrent abdominal pain and arthralgia attacks, revealing M694V homozygousity and was started with colchicine therapy. Patients nos. 6 and 7 had endoscopic investigation and stomach ulcerations were shown. *Helicobacter pylori* (*H. pylori*) was obtained on the mucosal tissue. Both patients received eradication therapy. All patients had high-dose methyl prednisolone (MPZ) treatment (30mg/kg/day for three subsequent days) for the first-line therapy and then conti nued with oral prednisolone (2 mg/kg/day). Despite corticosteroid therapy, all patients' complaints continued, and GI bleeding did not improve. Therefore, we decided to add pulse cyclophosphamide (650 mg/m^2, *i.v.* infusion). In addition to this, two patients received intravenous immunoglobulin (IVIG) therapy. Although having immunosuppressive treatments and IVIG, GI manifestations did not improve, so we started the plasma exchange procedure. The exhanges were made using fresh frozen plasma (FFP), and the patients' number of cycle ranges were two-six (mean four). Each cycle was performed daily or every other day, which was decided according to the clinical severity. Despite premedication before the plasma exchange process, three patients (no. 3, 6 and 7) developed urticarial rashes. Two of them had no more allergic reactions during the other sessions but in patient no. 3 the rashes reappeared during the exchange. Therefore, her other cycles were performed with 4% albumin as a replacement fluid, and she had no further side effects. Patient no. 1 had generalised seizure after MPZ and cyclophosphamide therapy. Concurrently, he had high blood pressure. His cranial magnetic resonance (MR) and MR angiography revealed normal findings. Urinalysis, urea, creatinin levels and renal ultrasonography were normal. Because of only one episode of hypertension and sustaining normality after one dose of anti-hypertensive drug, nifedipine, hypertension was attributed to the pulse methyl prednisolone therapy. Anti-epileptic treatment was initiated and was ceased six months later. He has had no seizures and no neurological manifestations since then. One patient (no. 4) had renal involvement. He had proteinuria with 198 mg/m^2/hour. Renal function tests were normal. Kidney biopsy showed focal segmental glomerulosclerosis (Class II b) (7) with deposition of Ig A. This patient also had a laparotomy with the suspicion of severe GIS perforation. His bowels were haemorrhagic and oedematous with no signs of perforation. Two months after plasma exchange therapy his proteinuria decreased to 1 gr/day and he had normal plasma urea and creatinine levels. All the patients improved after plasma exchange management. None of them have had any GIS complaints since then with normal laboratory parameters and physical examination findings. Only the patient with HSP nephritis continued therapy with oral steroids and antiplatelet agent (acetylsalicylic acid 5 mg/kg/day).

Discussion

The present report confirmed the safety and efficacy of plasma exchange therapy as a management choice in a small group of paediatric HSP patients with massive GIS involvement. HSP is a systemic vasculitis presenting with a classical tetrad of rash, arthralgia/arthritis, abdominal pain and renal disease (1). Gastrointestinal signs and symptoms, including abdominal pain, associated with nausea, vomiting, diarrhoea or constipation develop in more than half of the patients (1, 8, 9). However, more serious complications like intussusception, perforation, and massive life-threatening GIS bleeding may occur rarely (8, 10). The active phase of HSP improves in 94% of children with only supporting therapy (1). Although overall prognosis is excellent, clinicians should make the parents aware of

Table I. Demographic and clinical features of the patients who underwent plasma exchange.

Patient no.	Age (year)	Gender	Clinical findings					number of plasma exchange cycles	Other clinical diagnosis	Treatment
			Purpura	Arthritis	Arthralgia	GIS	Renal			
1	9	M	+	-	-	+	-	3	Seizure	Pulse methyl prednisolone Cyclophosphamide pulse Plasma exchange
2	8	M	+	-	+	+	-	3	*MEFV* (M694V/M680I)	Pulse methyl prednisolone Cyclophosphamide pulse Colchicine Plasma exchange
3	10	M	+	-	+	+	-	2 plasma exchanges 1 albumino-pheresis	*MEFV* (M694V/V726A)	Pulse methyl prednisolone Cyclophosphamide pulse Colchicine Plasma exchange
4	5	F	+	-	+	+	+	6	*MEFV* (M694V/M694V) Class IIb HSP Nephritis	Pulse methyl prednisolone Cyclophosphamide pulse Colchicine Plasma exchange
5	13	M	+	-	-	+	-	4	-	Pulse methyl prednisolone Cyclophosphamide pulse IVIG Plasma exchange
6	16	F	+	+	+	+	-	6	*H. pylor*i gastritis *MEFV* Mutation negative	Pulse methyl prednisolone Cyclophosphamide pulse IVIG Plasma exchange
7	9	M	+	-	+	+	-	4	*H. pylori* gastritis *MEFV* Mutation negative	Pulse methyl prednisolone Cyclophosphamide pulse Plasma exchange

FMF: Familial Mediterranean Fever; F: Female; M: Male; IVIG: Intravenous immunoglobulin.

the possible severe and life-threatening complications of the disease (11). In serious and complicated conditions immunosuppressive therapies, including steroids, azathioprine, cyclophosphamide and cyclosporine might be used. These agents are effective by inhibiting inflammation. There has been no placebo-controlled prospective trial for usage of corticosteroids in treating the GIS involvement of HSP. However, some case reports suggest that corticosteroids were effective in the first-line therapy of abdominal pain in HSP (1). On the other hand, when patients are refractory to immunomodulatory treatment and continue to have life-threating GIS involvement like excessive bleeding, there has been an immediate need for another treatment method. So more treatment modalities have been reported for HSP patients with GIS involvement. One of the choices is IVIG. Some cases have been published previously, which described a complete response to IVIG therapy (8, 10, 12). Fagbemi *et al*. reported a nine-year-old girl who presented with massive GIS bleeding due to HSP and improved after IVIG. They attributed the mechanism of the action of IVIG to sialylation of Ig Fc regions, blockade of FC receptors and down regulation of T-B cell functions (8). Currently, there is evidence supporting the benefits and efficacy of using IVIG in the treatment of Kawasaki disease, especially in prevention of coronary artery dilatations. Moreover, although there is less experience for usage of IVIG in ANCA associated vasculitis, some studies suggest a beneficial effect. However, in other vasculitis syndromes like HSP and polyarteritis nodosa (PAN), only case reports have described a good effect of IVIG to control the disease activity. As a result, the efficacy of IVIG has not yet been proven in HSP and PAN (13). Two of our patients received IVIG therapy after corticosteroid and cyclophosphamide; however, they did not have any benefits and did not improve. That being said, IVIG can still be a choice for the treatment of HSP patients with severe GIS involvement before plasma exchange therapy.

Some publications have discussed the possible role of decreased factor XIII levels in GIS bleeding of HSP patients. Fukui *et al*. and Prenzel *et al*. reported that after receiving Factor XIII concentrate, patients with abdominal symptoms of HSP improved remarkably (15-16). We did not treat our patients with factor XIII concentrates, as currently this drug is not readily available in Turkey and has to be obtained from abroad. Therefore, we can speculate that FFP given to our patients might

have helped to increase their factor XIII levels and might have helped their improvement during the plasma exchange period (5).

Plasma exchange is a procedure that withdraws blood, separates plasma from the cellular components and returns it to the patient. FFP and human 5% serum albumin are the choices for replacement fluid (2). Furthermore, plasma exchange is a relatively well tolerated procedure. The reported adverse event rate is five – 11%. Most adverse-events are hypocalcaemia, hypotension and allergic reactions. They are mild and also preventable. Although thousands of plasma exchanges are performed each year, there are only a few reports of complications. 0.12% of plasma exchange procedures were associated with severe complications such as anaphylactic reactions and bleeding. And the incidence of death with plasma exchange has been estimated to be 0.05% (2, 17, 18) There have been some cases with HSP GIS involvement, which were refractory to immunosuppressive therapy and have been successfully treated with plasma exchange (4, 5, 11, 19). Moreover, plasma exchange has been used as an effective therapy choice for HSP patients having severe cerebral involvement (20, 21). Also, in ANCA-associated vasculitis plasma exchange may be a good choice for both renal and pulmoner involvement (22). Plasma exchange may show its effect by the removal of immunoglobulin, immune complexes, autoantibodies and pro-inflammatory cytokines. In this way, elimination of circulating Ig A complexes may cause a rapid and long-standing improvement (2). Similarly, leukocyapheresis has been used for refractory HSP patients with GIS involvement as a treatment option recently. Leukocyapheresis is effective by removing the lymphocytes and also prevents the production of new proinflammatory cytokines. The authors have thought that removing proinflammatory cytokines produced by lymphocytes and macrophages might be attributed to the improvement mechanism (9, 23). There are no known differences in efficacy, adverse reactions and risk of mortality between leukocyapheresis and plasma exchange. Since both are invasive and also expensive procedures (24), the type of procedure could be chosen according to the patient and technical availability of the centre.

Immune suppressive therapy may also be needed to sustain the immediate effect of plasma exchange and to stop the active disease course. We did not previously use plasma exchange as a first-line therapy and in addition started immunosuppressive agents. Similar to the literature, we thought that using immune modulator therapy before or concurrently with plasma exchange may be necessary to suppress the inflammation more effectively and to inhibit the production of new cytokines (5, 11).

Among our small case series with severe GIS involvement, three had the diagnosis of FMF. One had homozygous mutation, and two had compound heterozygous mutations. As in our country *MEFV* mutations and FMF diagnosis are very frequent, our patients' results could be a statistical possibility. But the relationship of vasculitis and FMF has been discussed many times before in the literature (25-30). Ozcakar *et al*. assessed the clinical and laboratory characteristics of paediatric HSP patients with and without *MEFV* mutations. They concluded that *MEFV* gene alterations are important susceptibility factors for the development of HSP and also affect the clinical presentation of the disease (34% of paediatric HSP patients were found to carry *MEFV* mutations). In this study, HSP patients having *MEFV* mutations were reported to be younger, to have more oedema and higher elevated acute phase responses than those without mutations (25). Ozdoğan *et al*. reviewed 207 FMF patients and found 15 patients with HSP. They also investigated 36 FMF patients for the presence of occult blood in the first stool specimens after an attack and found 47% positive results. They speculated that this result might be due to increased vascular permeability, exudation and haemorrhage in the intestinal wall or intestinal vasculitis (26). Aksu and Keser thought that the association of FMF and vasculitis did not show a coincidence; rather it seems that FMF patients might be at an increased risk of vasculitis. In addition to this, authors have suggested that vasculitis might be an essential feature of FMF. Although the exact pathogenesis of FMF-associated vasculitis is not known, increased proinflammatory cytokines seem to be important in the development of vasculitis in FMF patients (27).

Conclusion

Treatment of GI involvement in HSP with plasma exchange has mainly been based on case reports. As a result of our experience, we propose that plasma exchange might be an effective treatment choice for the patients who are refractory to conventional drugs. A detailed history of FMF should be obtained from the patients with severe GIS ınvolvement of HSP. Moreover, *MEFV* mutations can also be performed in those children. Our limitation is the small sample size. Therefore, we need further research and studies in a large number of patients to determine the indications and effectiveness of plasma exchange in HSP with severe intestinal symptoms.

References

1. ROBERTS PF, WALLER TA, BRINKER TM, RIFFE IZ, SAYRE JW, BRATTON RL: Henoch-Schönlein purpura: a review article. *South Med J* 2007; 100: 821-4.
2. MAHR A, CHAIGNE-DELALANDE S, DE MENTHON M: Therapeutic plasma exchange in systemic vasculitis: an update on indications and results. *Curr Opin Rheumatol* 2012; 24: 261-6.
3. KAWASAKI Y, ONO A, OHARA S *et al*.: Henoch-Schönlein purpura nephritis in childhood: pathogenesis, prognostic factors and treatment. *Fukushima J Med Sci* 2013; 59: 15-26.
4. ACAR B, ARIKAN FI, ALIOGLU B, ONER N, DALLAR Y: Successful treatment of gastrointestinal involvement in Henoch-Schönlein purpura with plasmapheresis. *Pediatr Nephrol* 2008; 23: 2103.
5. WORTMANN SB, FISELIER TJ, VAN DE KAR NC, AARTS RA, WARRIS A, DRAAISMA JM: Refractory severe intestinal vasculitis due to Henoch-Schönlein purpura: successful treatment with plasmapheresis. *Acta Paediatr* 2006; 95: 622-3.
6. PARKER RI: Transfusion in critically ill children: indications, risks, and challenges. *Crit Care Med* 2014; 42: 675-90
7. EMANCIPATOR SN: Ig A nephropaty and Henoch-Schönlein purpura. *In Heptinstall's Pathology of the Kidney*, JENNETTE JC, OLSON JL, SCHWARTZ MM, SILVA FG (Eds.). Phila-

delphia, Lippincott-Raven Publishers, 1998.
8. FAGBEMI AA, TORRENTE F, HILSON AJ, THOMSON MA, HEUSCHKEL RB, MURCH SH: Massive gastrointestinal haemorrhage in isolated intestinal Henoch-Schönlein purpura with response to intravenous immunoglobulin infusion. *Eur J Pediatr* 2007; 166: 915-9.
9. NAKAHATA T, TANAKA H, SUZUKI K, ITO E. Successful treatment with leukocytapheresis in refractory Henoch-Schönlein purpura: case report. *Clin Rheumatol* 2003; 22: 248-50.
10. LAMIREAU T, REBOUISSOUX L, HEHUNSTRE JP: Intravenous immunoglobulin therapy for severe digestive manifestations of Henoch-Schönlein purpura. *Acta Paediatr* 2001; 90: 1081-2.
11. DONGHI D, SCHANZ U, SAHRBACHER U *et al*.: Life-threatening or organ-impairing Henoch-Schönlein purpura: plasmapheresis may save lives and limit organ damage. *Dermatology* 2009; 219: 167-70.
12. HELDRICH FJ, MINKIN S, GATDULA CL: Intravenous immunoglobulin in Henoch-Schönlein purpura: a case study. *Md Med J* 1993; 42: 577-9.
13. ARIES PM, HELLMICH B, GROSS WL: Intravenous immunoglobulin therapy in vasculitis: speculation or evidence? *Clin Rev Allergy Immunol* 2005; 29: 237-45.
14. SHIN JI, LEE JS: Severe gastrointestinal vasculitis in Henoch-Schönlein purpura: pathophysiologic mechanisms, the diagnostic value of factor XIII, and therapeutic options. *Eur J Pediatr* 2007; 166: 1199-200.
15. FUKUI H, KAMITSUJI H, NAGAO T *et al*.: Clinical evaluation of a pasteurized factor XIII concentrate administration in Henoch-Schönlein purpura. Japanese Pediatric Group. *Thromb Res* 1989; 56: 667-75.
16. PRENZEL F, PFAFFLE R, THIELE F, SCHUSTER V: Decreased factor XIII activity during severe Henoch-Schönlein purpura -- does it play a role? *Klin Padiatr* 2006; 218: 174-6.
17. WRIGHT E, DILLON MJ, TULLUS K: Childhood vasculitis and plasma exchange. *Eur J Pediatr* 2007; 166: 145-51.
18. BASIC-JUKIC N, KES P, GLAVAS-BORAS S, BRUNETTA B, BUBIC-FILIPI L, PURETIC Z: Complications of therapeutic plasma exchange: experience with 4857 treatments. *Ther Apher Dial* 2005; 9: 391-5
19. GASKELL H, SEARLE M, DATHAN JR: Henoch-Schönlein purpura with severe ileal involvement responding to plasmapheresis. *Int J Artif Organs* 1985; 8: 163-4.
20. CHEN CL, CHIOU YH, WU CY, LAI PH, CHUNG HM: Cerebral vasculitis in Henoch-Schönlein purpura: a case report with sequential magnetic resonance imaging changes and treated with plasmapheresis alone. *Pediatr Nephrol* 2000; 15: 276-8.
21. WEN YK, YANG Y, CHANG CC: Cerebral vasculitis and intracerebral hemorrhage in Henoch-Schönlein purpura treated with plasmapheresis. *Pediatr Nephrol* 2005; 20: 223-5.
22. ALBA MA, FLORES-SUÁREZ LF: Seven clinical conundrums in the treatment of ANCA-associated vasculitis. *Clin Exp Rheumatol* 2013; 31 (Suppl. 75): 74-83.
23. OKI E, TSUGAWA K, SUZUKI K, ITO E, TANAKA H: Leukocytapheresis for the treatment of refractory Henoch-Schönlein purpura resistant to both prednisolone and intravenous immunoglobulin therapy. *Rheumatol Int* 2008; 28: 1181-2.
24. MILLER FW, LEITMAN SF, CRONIN ME *et al*.: Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. *N Engl J Med* 1992: 326: 1380-4.
25. OZÇAKAR ZB, YALÇINKAYA F, CAKAR N *et al*.: MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. *J Rheumatol* 2008; 35: 2427-9.
26. OZDOGAN H, ARISOY N, KASAPÇAPUR O *et al*.: Vasculitis in familial Mediterranean fever. *J Rheumatol* 1997; 24: 323-7.
27. AKSU K, KESER G: Coexistence of vasculitides with familial Mediterranean fever. *Rheumatol Int* 2011; 31: 1263-74
28. TEKIN M, YALÇINKAYA F, TÜMER N, AKAR N, MISIRLIOĞLU M, CAKAR N: Clinical, laboratory and molecular characteristics of children with Familial Mediterranean Fever-associated vasculitis. *Acta Paediatr* 2000; 89: 177-82.
29. GERSHONI-BARUCH R, BROZA Y, BRIK R: Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schönlein purpura. *J Pediatr* 2003; 143: 658-61.
30. BAYRAM C, DEMIRCIN G, ERDOĞAN O, BÜLBÜL M, CALTIK A, AKYÜZ SG: Prevalence of MEFV gene mutations and their clinical correlations in Turkish children with Henoch-Schönlein purpura. *Acta Paediatr* 2011; 100: 745-9.