Int J Clin Exp Med 2020;13(1):293-299
www.ijcem.com /ISSN:1940-5901/IJCEM0099907

Original Article

Efficacy of Yupingfeng San for assisting in treatment of children with Henoch-Schonlein purpura and its effects on oxidative stress and the immune system

Yu Cui[1*], Junhua Li[3*], Jing Zhang[4], Tingting Han[5], Lei Gao[1], Hongmin Wang[1], Yingjie Hua[2], Xiuqing Jia[6]

Departments of [1]Pediatrics, [2]Emergency Pediatrics, Zibo City Linzi District People's Hospital, Zibo, Shandong Province, China; [3]Second Department of Pediatrics, The Second People's Hospital of Dongying, Dongying, Shandong Province, China; [4]Department of Pediatrics, Dezhou Traditional Chinese Medicine Hospital, Dezhou, Shandong Province, China; [5]Children's Respiratory and Severe Disease Area, Binzhou Medical University Hospital, Binzhou, Shandong Province, China; [6]Central Dispensing Room, Ji'ning First People's Hospital, Ji'ning, Shandong Province, China. [*]Equal contributors and co-first authors.

Received July 21, 2019; Accepted November 6, 2019; Epub January 15, 2020; Published January 30, 2020

Abstract: Objective: To explore the efficacy of Yupingfeng San (YPFS) for assisting in the treatment of children with Henoch-Schonlein purpura (HSP) and its effects on the children's oxidative stress and immune system. Methods: A total of 120 children with HSP were enrolled and divided into an observation group and a control group (n=60) according to prospective randomized control method. Children in the control group were conventionally treated, while those in the observation group were additionally treated with YPFS. The improvement time of clinical symptoms and recurrence rate, the changes of oxidative stress responses, immune states, and other blood parameters before and after treatment were detected and compared between the two groups. Results: Compared with the control group, children in the observation group had significantly shorter disappearance time of purpura, time of relief in abdominal pain, and time of relief in arthralgia (P<0.01), and significantly lower recurrence rate (P<0.05). After treatment, the serum concentration of MDA, IgE, IgA, IL-10, IL-33, and S-100 protein in the two groups were significantly decreased (P<0.001), and the levels in the observation group were significantly lower than those in the control group (P<0.01). After treatment, the levels of SOD, GSH-PX, and IL-21 in the two groups were significantly increased (P<0.05), and the levels in the observation group were significantly higher than those in the control group (P<0.01). There was no significant difference in IgG level before and after treatment within groups, or between the groups (P>0.05). Conclusion: For children with HSP, conventional treatment combined with YPFS can significantly relieve the clinical symptoms, reduce the oxidative stress and inflammatory responses, and improve the immune system function, so it is worthy of clinical application.

Keywords: Henoch-Schonlein purpura, Yupingfeng San, oxidative stress, immune system, efficacy

Introduction

Henoch-Schonlein purpura (HSP) is a common clinical allergic vasculitis caused by the invasion of small arteries or capillaries in the skin or other organs of the body, but the mechanism of the disease at this stage is still unclear [1-3]. At present, the common clinical use of dexamethasone as a hormonal drug, however the long-term use can disrupt the body's normal immune function, making the disease prolonged and difficult to heal, so that it is an effective drug for relieving clinical symptoms, but cannot reach complete remission [4, 5]. At present, relevant studies have shown that oxidative stress and micro-inflammation are closely related to HSP, while long-term western medicine treatment can not eliminate free radicals but further inhibits the chain reaction in lipid oxidation [4, 5]. According to the theory of traditional Chinese medicine [6, 7], HSP is caused by external evils, which leads to heat invasion and blood stasis or not important to spleen, or spleen yin deficiency, which makes the blood line outside the pulse, and then the disease turns from virtual to virtual. The lung qi deficiency is not solid outside the body, and eventually the blood does not follow the normal path, and the skin mucous

membrane forms a purple spot [6, 7]. Therefore, the treatment should be based on the principle of supporting the positive solid state.

According to Chinese medicine, the clinical features of HSP in children belong to "purpura" and "emia", mostly caused by the insufficiency of vital energy and blood, and spleen and stomach disorders [6]. Some scholars of traditional Chinese medicine believe that Yupingfeng San (YPFS), as a Chinese medicine, can be used as an auxiliary drug through affecting the immune function of children [7]. According to the ancient book, derived from Jiu Yuan Fang (Formulary of Exploring Cause), YPFS is a classic prescription for invigorating qi for consolidating superficies, mainly consisting of Astragalus membranaceus, Atractylodes macrocephala koidz, and Saposhnikovia divaricata. Astragalus membranaceus, sweet and warm, is the sovereign drug, which invigorates qi for consolidating superficies and nourishes spleen and stomach. Atractylodes macrocephala koidz is the minister drug, which invigorates qi and strengthens spleen, eliminates dampness and reinforces qi, and consolidates superficies for arresting sweating. Saposhnikovia divaricata is the assistant drug, which expels wind to relieve superficies, and overcomes dampness and alleviates pain. The three drugs nourish spleen and defensive qi, and invigorate qi for consolidating superficies together. As the saying goes, Astragalus membranaceus combined with Atractylodes macrocephala koidz can invigorate qi for consolidating superficies, and the combination assisted by Saposhnikovia divaricata can eliminate pathogens and strengthen vital qi [8]. Some scholars have reported that the combination of YPFS and conventional treatment (including anti-allergy and hormone anti-inflammatory therapy) for children with chronic urticaria can significantly relieve the clinical and itching symptoms, reduce the recurrence rate of the disease, and significantly improve the immune function [9]. In another study, 90 children with HSP were randomized into the observation and control groups (n=45). Children in the observation group were treated with YPFS on the basis of the control group. The results showed that 8 cases in the observation group experienced recurrence, with a recurrence rate of 18.60%, while 17 cases in the control group experienced recurrence, with a recurrence rate of 47.22%, which was significantly higher than that in the observation group [10]. In this study, the effects of YPFS on interleukin-33 (IL-33), S-100 protein, and other cytokines in children with HSP were discussed. The reports are as follows.

Materials and methods

General information

According to the prospective randomized control method, 120 children with HSP treated in Ji'ning First People's Hospital from January 2017 to November 2018 were divided into the observation and control groups (n=60) based on a random number table. Inclusion criteria were as follows: (1) children met the diagnostic criteria formulated by the American College of Rheumatology in 2001 [11]; (2) children had no contraindications to drugs used in this study; (3) children were treated in Ji'ning First People's Hospital within 5 days after the onset of the disease; (4) children had complete clinical data; (5) children with initial cases; (6) children who had no history of allergy or eczema; (7) and children who had normal renal function.

Exclusion criteria were as follows: (1) children with poor compliance; (2) children treated with antibiotics and glucocorticoids within 2 weeks; (3) children accompanied by other serious organ diseases; (4) children with coagulation disorders; (5) or children with severe infection. The study was approved by the Medical Ethics Committee of Ji'ning First People's Hospital. The participants and their families signed an informed consent form.

Therapeutic methods

Children in the two groups were conventionally treated with western medicine. Specific steps were as follows: rutin tablets (Shanghai Shangyao Xinyi Pharmaceutical Factory Co., Ltd., 20 mg) were orally administrated, 3 times/day and 20 mg/time. Dipyridamole tablets (Hefei Lifeon Pharmaceutical Co., Ltd., 25 mg) were orally administrated, 3 times/day and 25 mg/time. Chlorphenamine maleate injection (Guangzhou Baiyunshan Tianxin Pharmaceutical Co., Ltd., 1 mL/10 mg) was intravenously dripped, once/day and 10 mg/time. Vitamin C tablets were orally administrated, 2 times/day and 0.1 g/time. On this basis, children in the observation group were additionally and orally adminis-

Table 1. Baseline data

Group	Observation group (n=60)	Control group (n=60)	t/χ^2	P
Gender (n)			0.133	0.715
Male	32	30		
Female	28	30		
Age (year)	6.70 ± 2.90	6.80 ± 2.80	0.192	0.848
Average duration (d)	3.53 ± 0.91	3.56 ± 0.92	0.180	0.858
Disease type (n)			0.292	0.962
Henoch	15	13		
Schonlein	15	17		
Hybrid	16	15		
Pure skin type	14	15		
BMI (kg/m^2)	17.44 ± 0.22	17.38 ± 0.24	1.427	0.156

Note: BMI: body mass index.

trated with Yupingfeng particles (Guangdong Global Pharmaceutical Co., Ltd., 5 g), 3 times/day and 5 g/time. A total of 14 days was 1 course of treatment. Children in both groups were treated for 1 course of treatment and then followed up for 3 months.

Outcome measures and efficacy evaluation

The disappearance time of purpura, time of relief in abdominal pain, time of relief in arthralgia, and recurrence rate in the two groups were counted. Recurrence rate refers to the recurrence of HSP symptoms after it disappeared for at least 1 month. The children's fasting venous blood (5 mL) was collected in the morning before and after treatment, and centrifuged at 3,500 r/min to separate the serum, which was then stored at -20°C for testing. Indices of oxidative stress were detected by enzyme-linked immunosorbent assay (ELISA) and compared between the two groups, including superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione peroxidase (GSH-PX). The ELISA kits were purchased from Nanjing Jiancheng Biological Products Company, with steps carried out in strict accordance with the instructions. The immune states of children were detected by a fully automatic biochemistry analyzer (SIEMENS ADVIA-2400, Germany) and compared between the two groups, including immunoglobulin (Ig) E, IgA, and IgG. The levels of interleukin (IL)-10, IL-21, and IL-33 in the two groups were detected by ELISA. The ELISA kits were purchased from Beijing Zhongshan Biotechnology Company, with steps carried out in strict accordance with the instructions. The changes of S-100 protein level were measured by double antibody sandwich method and compared between the two groups.

Statistical methods

In this study, SPSS 20.0 was used for statistical analysis. Measurement data, which conformed to normal distribution after analysis with D-test and normal distribution test, were expressed by mean ± standard deviation ($\bar{x}$ ± sd). Comparison before and after treatment within groups was analyzed by paired t test, and comparison between two groups was analyzed by independent t test. Count data were expressed by the number of cases/percentage (n/%), and analyzed by χ^2 test. When $P<0.05$, the difference was statistically significant.

Results

No significant difference of baseline data shown in the two groups

There were no statistically significant differences between the observation and control groups in terms of gender, age, average course of disease, disease types, and body mass index (BMI) ($P>0.05$). See **Table 1**.

Shortened improvement time of clinical symptoms and lower recurrence rate after additional supplementation of YPFS

The disappearance time of purpura, time of relief in abdominal pain, and time of relief in arthralgia in the observation group were significantly shorter than those in the control group ($P<0.01$). After 3-months of follow-up, 5 cases in the observation group experienced recurrence, with a recurrence rate of 8.33%, while 13 cases in the control group experienced recurrence, with a recurrence rate of 21.67%, which was significantly higher than that in the observation group ($P<0.05$). See **Table 2**.

Weakened oxidative stress responses after additional supplementation of YPFS

Before treatment, there were no statistically significant differences between the observa-

Table 2. Comparison of improvement time of clinical symptoms and recurrence rate

Group	Disappearance time of purpura (d)	Time of relief in abdominal pain (d)	Time of relief in arthralgia (d)	Recurrence rate (%)
Observation group (n=60)	4.88 ± 0.50	3.37 ± 0.41	4.81 ± 0.37	8.33
Control group (n=60)	6.37 ± 0.59	5.19 ± 0.52	6.11 ± 0.51	21.67
t/χ^2	14.924	21.289	15.982	4.183
P	0.000	0.000	0.000	0.041

Table 3. Comparison of oxidative stress responses ($\bar{x}$ ± sd)

Group	SOD (μmol/L)	MDA (nmol/L)	GSH-PX (μmol/L)
Observation group (n=60)			
Before treatment	70.84 ± 7.71	6.75 ± 1.37	75.89 ± 15.44
After treatment	90.03 ± 8.35$^{**,\#\#\#}$	3.97 ± 0.59$^{**,\#\#\#}$	92.04 ± 12.88$^{**,\#\#\#}$
Control group (n=60)			
Before treatment	70.77 ± 7.79	6.78 ± 1.34	75.90 ± 15.43
After treatment	85.13 ± 6.27$^{\#\#\#}$	4.88 ± 0.63$^{\#\#\#}$	83.11 ± 13.29$^{\#\#\#}$

Note: compared with control group, **P<0.01; compared with the same group before treatment, $^{\#\#\#}$P<0.001. SOD, superoxide dismutase; MDA, malondialdehyde; GSH-PX, glutathione peroxidase.

Table 4. Comparison of immune states ($\bar{x}$ ± sd, g/L)

Group	IgE	IgA	IgG
Observation group (n=60)			
Before treatment	0.91 ± 0.35	3.69 ± 0.51	10.69 ± 1.30
After treatment	0.54 ± 0.28$^{**,\#\#\#}$	1.75 ± 0.28$^{**,\#\#\#}$	10.70 ± 1.28
Control group (n=60)			
Before treatment	0.93 ± 0.39	3.71 ± 0.48	10.71 ± 1.29
After treatment	0.70 ± 0.21$^{\#\#\#}$	2.24 ± 0.37$^{\#\#\#}$	10.72 ± 1.28

Note: compared with control group, **P<0.01; compared with the same group before treatment, $^{\#\#\#}$P<0.001. IgE, immunoglobulin E; IgA, immunoglobulin A; IgG, immunoglobulin G.

tion and control groups in oxidative stress responses (P>0.05). After treatment, MDA level in the two groups significantly decreased (P<0.001), and the level in the observation group was significantly lower than that in the control group (P<0.01). After treatment, SOD and GSH-PX levels in the two groups were significantly increased, and the levels in the observation group were significantly higher than those in the control group (P<0.01). See **Table 3**.

More quick recovery of immune states after additional supplementation of YPFS

Before treatment, there were no statistically significant differences between the observation and control groups in the levels of immune parameters (P>0.05). After treatment, serum IgE and IgA levels in the two groups were significantly decreased (P<0.001), and the levels in the observation group were significantly lower than those in the control group (P<0.01). There was no significant difference in serum IgG level before and after treatment within groups, or between groups (P>0.05). See **Table 4**.

Significantly decreased inflammatory factor level expression after additional supplementation of YPFS

Before treatment, there were no statistically significant differences between the observation and control groups in the levels of IL-10, IL-21, and IL-33 (P>0.05). After treatment, IL-21 level in the two groups was significantly increased (P<0.001), and the level in the observation group was significantly higher than that in the control group (P<0.01). After treatment, IL-10 and IL-33 levels in the two groups were significantly decreased (P<0.001), and the levels in the observation group were significantly lower than those in the control group (P<0.01). See **Table 5**.

Lower expression of S-100 protein level after additional supplementation of YPFS

Before treatment, there was no statistically significant difference between the observation and control groups in S-100 protein level (P>0.05). After treatment, the level in the two groups was significantly decreased (P<0.001),

Table 5. Comparison of serum levels of IL-10, IL-21, and IL-33 ($\bar{x}$ ± sd)

Group	IL-10 (pg/mL)	IL-21 (pg/L)	IL-33 (ng/L)
Observation group (n=60)			
Before treatment	45.01 ± 6.21	149.01 ± 58.77	401.33 ± 29.44
After treatment	20.89 ± 3.58$^{**,\#\#\#}$	215.97 ± 60.22$^{**,\#\#\#}$	290.87 ± 30.17$^{**,\#\#\#}$
Control group (n=60)			
Before treatment	45.03 ± 6.18	149.03 ± 58.79	400.37 ± 29.45
After treatment	31.22 ± 3.02$^{\#\#\#}$	181.44 ± 61.35$^{\#\#\#}$	342.65 ± 28.07$^{\#\#\#}$

Note: compared with control group, **P<0.01; compared with the same group before treatment, $^{\#\#\#}$P<0.001. IL-10, interleukin-10; IL-21, interleukin-21; IL-33, interleukin-33.

Table 6. Comparison of serum S-100 protein level ($\bar{x}$ ± sd, μg/mL)

Group	S-100 protein
Observation group (n=60)	
Before treatment	0.23 ± 0.10
After treatment	0.09 ± 0.02$^{**,\#\#\#}$
Control group (n=60)	
Before treatment	0.22 ± 0.12
After treatment	0.18 ± 0.04$^{\#\#\#}$

Note: compared with control group, **P<0.01; compared with the same group before treatment, $^{\#\#\#}$P<0.001.

and the level in the observation group was significantly lower than that in the control group (P<0.01). See **Table 6**.

Discussion

Currently, Western medicine treats HSP mainly through anti-allergic, hormone anti-inflammatory drugs, but some children show side effects such as lethargy and gastrointestinal reactions, resulting in ineffective results [12-14]. From the view of traditional Chinese Medicine, HSP in children with its clinical characteristics were explained including “purple spots”, “Hematic disease”, mostly due to lack of qi and blood, spleen and stomach disorders [15]. Some Chinese medicine practitioners have proposed that Yupingfeng powder, as a proprietary Chinese medicine, can be used as an auxiliary medicine by affecting the immune function of children [16].

In this study, compared with the control group, children in the observation group had significantly shorter disappearance time of purpura, time of relief in abdominal pain and arthralgia, and significantly lower recurrence rate. This shows that YPFS combined with conventional treatment can significantly relieve the clinical symptoms of children and reduce the recurrence rate of the disease. A study has shown that the development and progression of HSP are closely related toe oxidative stress in the body, which may be because the occurrence of allergic reactions leads to inflammatory responses in capillaries and arterioles [17, 18]. The concentration of reduced coenzyme oxidase in infiltrating inflammatory cells abnormally increases, which promotes the body to release a large amount of free radicals, and eventually leads to lipid peroxidation and a chain reaction of free radicals. MDA is an important indicator for evaluating the levels of oxygen free radicals, which could characterize the severity of lipid peroxidation damage. SOD is an active enzyme of anti-oxidative stress, which could inhibit the occurrence of lipid peroxidation. In this study, after treatment, MDA level in the two groups was significantly decreased, and the level in the observation group was significantly lower than that in the control group; SOD and GSH-PX levels in the two groups were significantly increased, and the increase in the observation group was significantly greater. These findings indicate that YPFS can better inhibit the progression of stress reactions, which is possibly because this prescription exerts anti-inflammatory and anti-allergic effects. Therefore, YPFS removes free radicals in the body, improves SOD activity, and then facilitates the improvement of capillary fragility and permeability.

According to studies at home and abroad, immunologic abnormalities during the progression of HSP are mainly the polyclonal activation of B cells, which results in the abnormally high expression of IgA. Eventually, immune complexes dominated by IgA deposit in the walls of small blood vessels, which damages vascular endothelium. Moreover, allergic reactions dominated by IgE also play a role during the progression of HSP [19]. Clinical reports have

shown that the development of HSP is closely correlated with inflammatory responses, and abnormal IL-33 level aggravates the responses, significantly improves the activity of lymphocytes and eosinophils, and then leads to immune dysfunction [20]. In this study, after treatment, serum IgE and IgA levels in the two groups were significantly decreased, and the levels in the observation group were significantly lower than those in the control group. After treatment, serum IL-21 level in the two groups was significantly increased but serum IL-10 and IL-33 levels were significantly decreased. This is possible because the drugs in YPFS play a significantly two-way immuno-regulatory effect, to maintain the normal immune function of the body, and further inhibit allergic allergy, thereby reducing IgE and IgA levels. According to previous studies, children with HSP may have abnormal electroencephalogram; their S-100 protein, whose main metabolic pathway is the kidney, is sensitively expressed in neuroglial cells and belongs to brain-specific protein [21, 22]. In this study, after treatment, serum S-100 protein level in the two groups was significantly decreased, and the level in the observation group was significantly lower than that in the control group, which suggests that adjuvant therapy with YPFS can inhibit the increase of S-100 protein level in children with HSP. However, the sample size in this study was small, so the exact mechanism of YPFS on HSP needs to be fully explored in large-scale multicenter studies.

In summary, for children with HSP, conventional treatment combined with YPFS can significantly relieve the clinical symptoms, reduce the oxidative stress responses and S-100 protein level, and inhibit the inflammatory responses, as well as improve the immune system function, so it is worthy of clinical application.

Disclosure of conflict of interest

None.

Address correspondence to: Xiuqing Jia, Central Dispensing Room, Ji'ning First People's Hospital, No. 6 Jiankang Road, Ji'ning 272000, Shandong Province, China. Tel: +86-0537-2102747; Fax: +86-0537-2102747; E-mail: jiaxiuqing6ac2@163.com

References

[1] Van Der Helm-Van Mil AH, Smith AC, Pouria S, Tarelli E, Brunskill NJ and Eikenboom HC. Immunoglobulin a multiple myeloma presenting with henoch-schonlein purpura associated with reduced sialylation of IgA1. Br J Haematol 2003; 122: 915-917.

[2] Prathiba Rajalakshmi P and Srinivasan K. Gastrointestinal manifestations of Henoch-Schonlein purpura: a report of two cases. World J Radiol 2015; 7: 66-69.

[3] Feng D, Huang WY, Hao S, Niu XL, Wang P, Wu Y and Zhu GH. A single-center analysis of Henoch-Schonlein purpura nephritis with nephrotic proteinuria in children. Pediatr Rheumatol Online J 2017; 15: 15.

[4] Saito-Sasaki N, Sawada Y, Ohmori S, Omoto D, Haruyama S, Yoshioka M, Nishio D and Nakamura M. Anaphylactoid purpura triggered by cellulitis as a favorable prognosis: case report and literature review. Springerplus 2016; 5: 1112.

[5] Lu S, Liu D, Xiao J, Yuan W, Wang X, Zhang X, Zhang J, Liu Z and Zhao Z. Comparison between adults and children with Henoch-Schönlein purpura nephritis. Pediatr Nephrol 2015; 30: 791-796.

[6] Lee YH, Kim YB, Koo JW and Chung JY. Henoch-schonlein purpura in children hospitalized at a tertiary hospital during 2004-2015 in Korea: epidemiology and clinical management. Pediatr Gastroenterol Hepatol Nutr 2016; 19: 175-185.

[7] Saito Y, Ookawara S, Uchima H, Ishida T, Kakei M and Sugawara H. Anaphylactoid purpura associated with streptococcal cellulitis: a case report and literature review. Case Rep Med 2017; 2017: 5960898.

[8] Li Y, Zhou Y, Zhu D and Wang Y. The role of T cells in the development of Henoch-Schonlein purpura. Front Biosci (Landmark Ed) 2018; 23: 837-851.

[9] Zhang J, Zeng H, Wang N, Tian X, Dou W and Shi P. Beneficial effects of creatine phosphate sodium for the treatment of Henoch-Schonlein purpura in patients with early renal damage detected using urinary kidney injury molecule-1 levels. Eur J Pediat 2016; 175: 49-55.

[10] Xu H, Pan Y, Li W, Fu H, Zhang J, Shen H and Han X. Association between IL17A and IL17F polymorphisms and risk of Henoch-Schonlein purpura in Chinese children. Rheumatol Int 2016; 36: 829-835.

[11] Yuan L, Wang Q, Zhang S and Zhang L. Correlation between serum inflammatory factors TNF-α, IL-8, IL-10 and Henoch-Schonlein purpura with renal function impairment. Exp Ther Med 2018; 15: 3924-3928.

[12] Fidan K, Kandur Y, Ucar M, Gucuyener K and Soylemezoglu O. Posterior reversible encephalopathy syndrome in Henoch-Schonlein purpura and hemolytic uremic syndrome. J Clin Med Res 2016; 8: 544-547.

[13] Chen AC, Lin CL, Shen TC, Li TC, Sung FC and Wei CC. Association between allergic diseases and risks of Henoch-Schonlein purpura (HSP) and HSP nephritis: a population-based study. Pediatr Res 2016; 79: 559-564.
[14] Mao SJ and Huang XM. Tripterygium wilfordii Hook F is efficacious in the treatment of Henoch-Schonlein purpura nephritis in children. World J Pediatr 2016; 12: 375-376.
[15] Patheja RS and Chidgey A. A rare case of bilateral cystoid macular oedema associated with decompensated Henoch-Schonlein purpura-related nephropathy. Clin Exp Ophthalmol 2016; 44: 209-212.
[16] Elmas AT and Tabel Y. Platelet counts in children with Henoch-Schonlein purpura-relationship to renal involvement. J Clin Lab Anal 2016; 30: 71-74.
[17] Helbling R, Lava SA, Simonetti GD, Camozzi P, Bianchetti MG and Milani GP. Gallbladder and pancreas in Henoch-Schonlein purpura-review of the literature. J Pediatr Gastroenterol Nutr 2016; 62: 457-461.
[18] Paydary K, Emamzadeh Fard S, Mahboubi AH, Ziaee V, Moradinejad MH and Kajbafzadeh AM. Penile skin involvement as the first presentation of Henoch-Schonlein purpura report of nine cases and review of literature. Iran J Pediatr 2015; 25: e2177.
[19] Ben-Chetrit E and Yazici H. Non-thrombocytopenic purpura in familial Mediterranean fever-comorbidity with Henoch-Schönlein purpura or an additional rare manifestation of familial Mediterranean fever? Rheumatology (Oxford) 2016; 55: 1153-1158.
[20] Kato-Okada S, Suzuki H, Inoue T, Kikuta T and Okada H. Successful prednisolone therapy in elderly patients with severe forms of henoch-schonlein purpura nephritis. Jpn Clin Med 2015; 6: 5-7.
[21] Iorio N, Bernstein GR, Malik Z and Schey R. Acute esophageal necrosis presenting with henoch-schonlein purpura. ACG Case Rep J 2015; 3: 17-19.
[22] Su Z, Lv X, Liu Y, Zhang J, Guan J and Gai Z. Circulating midkine in children with Henoch-Schönlein purpura: clinical implications. Int Immunopharmacol 2016; 39: 246-250.