



Comparison of conventional and low dose steroid in the treatment of PFAPA syndrome: Preliminary study

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ABSTRACT

Background: Steroids have been widely used to relief symptoms in the patients with PFAPA syndrome. **Objectives:** This study was constructed to show the effectiveness of low-dose steroid therapy in patients diagnosed with PFAPA syndrome.

Methods: 41 patients (86 febrile attacks) who were diagnosed using the criteria suggested by Thomas et al. were involved in the study. The cases were classified into two groups and the selection of patients in groups was made randomly. Twenty patients received prednisolone at a dose of 2 mg/kg/day (first group: 40 attacks) and 21 patients received a dose of 0.5 mg/kg/day (second group: 46 attacks). The effectiveness of the treatment was especially determined by the time needed to reduce the fever and the effect on the duration between the two attacks. The patients were re-examined 24 hours later, after a steroid treatment.

Results: The patients who were in the first group received 2 mg/kg/day dose of prednisolone and their fever was dramatically decreased in 6–8 hours (7.6 ± 0.9 hours). The second group received 0.5 mg/kg/day dose and 19 of these patients' fever was decreased in 8–12 hours. Two patients whose temperature did not decrease, received another dose of prednisolone 24 hours after the first dose and their fever was reduced 12 hours after the second dose (11.3 ± 6.4 hours). A comparison of the rate of fever reduction and the interval between the attacks (Group I: 5.11 ± 1.01 week and Group II: 5.2 ± 1.13 week) in the two groups did not show any statistical significance ($p = 0.104$).

Conclusion: Low-dose steroid treatment is as effective as normal dose in PFAPA syndrome but there is need to study with a larger group.

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1. Introduction

PFAPA syndrome is the clinical entity of unknown etiology characterized by periodic episodes of high fever which is accompanied by aphthous stomatitis, pharyngitis/tonsillitis, and cervical adenitis. It is characterized by regularly recurrent episodes of high fever which occurs in every 3–8 weeks and lasts for 3–6 days. The other symptoms may include nausea, vomiting, headache and abdominal pain [1–8]. Diagnosis of PFAPA is based on suggested clinical criteria with the exclusion of other periodic

fever syndromes [1]. In treatment, tonsillectomy and steroid are used successfully [8]. In the literature, the low-dose steroid therapy (0.6–2 mg/kg/day [9]) was studied in PFAPA but comparative studies have not been performed. We studied the effectiveness of 0.5 mg/kg/day and 2 mg/kg/day prednisolone therapy, particularly on the fever attack and febrile intervals.

2. Material and methods

41 patients admitted to the Children's outpatient clinic at Sema Hospital between June 2008 and May 2012 were involved in this study. All patients were diagnosed according to PFAPA criteria established by Thomas and colleagues (Table 1). This study was approved by Local Ethics Committee of our institution. The cases were classified into two groups and the selection of patients in groups was made randomly. The age and gender of the patients, age of diagnosis, duration of attack, frequency of attacks, symptoms and signs, response to steroid treatment (fever) and

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Table 1
Diagnostic criteria for PFAPA syndrome [1].

Regularly recurring fevers with an early age of onset (<5 years of age)
Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
(a) Aphthous stomatitis
(b) Cervical lymphadenitis
(c) Pharyngitis
Exclusion of cyclic neutropenia
Completely asymptomatic interval between episodes
Normal growth and development

side effects of steroids were noted. All the patients were followed at least during two or three attacks. In Group I, twenty patients received 2 mg/kg/day dose of prednisolone and in Group II, twenty-one patients received 0.5 mg/kg/day dose. The effectiveness of the therapy was measured by reducing fever times and effecting the duration between two febrile episodes. The patients were clinically observed for 24 hours and then re-examined. The data were compared using the Mann–Whitney *U* test with statistical significance set at $p < 0.05$.

3. Results

Group I: There were 11 males and 9 females and the average age was 3.2 ± 1.3 and the age of diagnosis was 2.30 ± 1.00 . Duration of attack was 5.11 ± 1.26 days. Frequency of attacks was 5.55 ± 1.01 per week (Table 2). After steroid treatment (2 mg/kg/dose), the fever of the patients was decreased dramatically in 6–8 hours (7.6 ± 0.9 hours). Side-effects of steroids were observed as restlessness and sleep disruption (3/20 patients). There was no significant effect on interval between the attacks of steroid therapy ($0.05 < p$). Fifteen of the twenty-one patients, in Group II, were males and six were females. The average age was 3.70 ± 1.56 year and the age of diagnosis was 2.10 ± 0.99 . The duration of the attacks was 5.40 ± 1.07 a day and their frequency was 5.40 ± 1.01 per week (Table 2). 8–12 hours after administering 0.5 mg/kg/day dose of prednisolone, the fever of 19 out of 21 patients went down. Two patients whose fever was not reduced were given a second dose of prednisolone 24 hours after the first dose. Twelve hours after the second dose, the fever went down. The side-effect of the treatment was detected as sleep disruption (1/21 patients). As a result of the prednisolone treatment, the interval between attacks got shorter in about one patient. A comparison of the rate of fever reduction and duration between two febrile episodes in the two groups did not show any statistical significance ($p = 0.104$). The clinical findings had tendency to improve in both groups 24 hours after prednisolone administration.

Table 2
Demographics and clinical characteristics of PFAPA patients.

Group 1	Group 2
Male/female 6/3	Male/female 4/6
Average age 3.2 ± 1.3 year	Average age 3.70 ± 1.56 year
Age of diagnosis 2.3 ± 1 year	Age of diagnosis 2.10 ± 0.99 year
Mean duration per febrile episode 5.11 ± 1.26 day	Mean duration per febrile episode 5.70 ± 1.07 year
Mean interval between episodes 5.55 ± 1.01 week	Mean interval between episodes 5.40 ± 1.01 year

4. Discussion

Optimal treatment for patients with PFAPA is uncertain. Administration of antibiotics, nonsteroidal anti-inflammatory drugs, acetaminophen and acyclovir are ineffective in controlling the symptoms [6]. Glucocorticoids, cimetidine, colchicine, anakinra and tonsillectomy with or without adenoidectomy have been proven effective in the literature [6,8]. Tonsillectomy and adenotonsillectomy are reported very effective in preventing episode in children but it is not successful in all cases [8–12]. The use of steroids is effective in the resolution of symptoms but they do not prevent future febrile episodes. Using 1–2 mg/kg/day of prednisolone (corticosteroid) at any point during the febrile episode leads to dramatic improvement of symptoms [13–15]. A smaller single dose of prednisone (mean 0.6–2 mg/kg per day) was found to abolish fever within an average of 10 hours in 51 of 54 patients in one uncontrolled series [16]. In our study, the patients who were in the first group received 2 mg/kg/day dose of prednisolone and their fever was dramatically decreased in 6–8 hours. The second group that received 0.5 mg/kg/day dose and 19 of these patients' fever was decreased in 8–12 hours. Two patients whose temperature did not decrease, received another dose of prednisolone 24 hours after the first dose and their fever was reduced 12 hours after the second dose. A comparison of the rate of fever reduction in the two groups did not show any statistical significance ($p > 0.05$). Steroids treatment results in shortening the interval between attacks in about 25–30 percent of cases [6,7]. In our study, there was no significant effect on the intervals between the attacks of steroid therapy ($0.05 < p$). The most common reported side-effect of treatment was restlessness and sleep disruption. However, toxicity related to the low doses of glucocorticoids used in PFAPA, aside from possible restlessness and changes in mood on the day of administration of the drug, have not been reported in either the United States or Israeli cohort [8]. In our study, the sideeffects of the steroids were observed as restlessness and sleep disruption (3/19, 15.7%). These side-effects may be minimized by giving the glucocorticoids at least 4–6 hours before bedtime. In this study, the physical exam performed at the 24th hour after prednisolone administration, other symptoms and signs were found to have improved.

5. Conclusions

We observed that low-dose (prednisolone 0.5 mg/kg/day) steroid treatment is effective in PFAPA, but there is need to study with a larger group.

Financial disclosure

None.

Conflict of interest

The authors confirm that there is no conflict of interest in relation to this paper.

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