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Original Article

PULSE CYCLOPHOSPHAMIDE IN OCULAR MANIFESTATIONS OF BEHCET'S DISEASE: A DOUBLE BLIND CONTROLLED CROSSOVER STUDY

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Background –The ocular lesions of Behcet's disease (BD) naturally progress toward severe loss of vision or blindness. Cytotoxic drugs are the main treatment. To the best of our knowledge, no controlled study has ever been performed to show their efficacy. This study was designed to evaluate the short-term efficacy of intravenous pulse cyclophosphamide (PCP).

Methods – In a randomized double blind controlled crossover study, 35 consecutive patients meeting both the International and Classification Tree criteria for BD and suffering from active posterior uveitis and/or retinal vasculitis were randomly assigned to either PCP or placebo group. Both groups received prednisolone (0.5 mg/kg/day). PCP was administered as 1 g per square meter of the body surface once monthly to the PCP group and normal saline to the placebo group. After 3 months, the two groups were interchanged. Disease activity index (DAI) and visual acuity (VA) were calculated. The study was done at Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences after approval of the Ethics Committee and patients' consent

Results – The mean VA improved from 3.7 to 4.9 (t = 3.309, p < 0.002) in the PCP group and from 4.4 to 4.5 (t = 0.317, p = 0.75) in the placebo group. The difference was significant (t = 2.402, p < 0.02). Other parameters improved more remarkably in the PCP group than in the placebo group, but differences were not statistically significant

Conclusion – This study shows the efficacy of the combination of PCP and prednisolone over prednisolone alone.

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Keywords: Behcet's disease • ocular lesions • pulse cyclophosphamide

Introduction

Ocular lesions are the most important cause of morbidity in Behcet's disease (BD). They are frequently seen in patients with BD. Around 58% of BD cases in Iran[1] and 28% to 69% of those in other countries (Japan, Turkey, Korea, Morocco, and England) are known to suffer from ocular lesions.[2] Like most other lesions of BD, ocular lesions progress by successive attacks, but on the contrary of mucocutaneous lesions the healing process is slow and usually incomplete. In ocular lesions, the inflammatory attack recedes slowly and a new attack may occur before the healing process is complete. Lesions will therefore gradually accumulate from one attack to another, progressing toward severe loss of vision or blindness.

Despite the advent of the new biological agents, cytotoxic drugs (cyclophosphamide, methotrexate, chlorambucil, azathioprine, and cyclosporin) are still the main therapeutic agents for the prevention of this disastrous outcome.[3, 4] They are thought to be effective[5 – 17] in single or in combination therapy,[14, 15, 17] but their efficacy has not yet been demonstrated in a double blind controlled study. One of the main reasons for the lack of a double blind controlled study is the ethical concern for the placebo group. Any delay in the treatment may aggravate the outcome of their ocular

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manifestations.[18] A double blind controlled study on azathioprine, designed to study its efficacy on different manifestations of the disease, showed a poorer outcome in the eyes of the placebo group several years after the termination of the study.[19]

To overcome the ethical concerns of the placebo group, a short-term double blind crossover study was designed, where both the pulse cyclophosphamide (PCP) and the placebo group, received a medium dose of daily prednisolone. Classically, prednisolone alone was one the treatments used for ocular manifestations of BD. Therefore, the placebo group was also under some coverage. After 3 months, the patients were switched from one group to the other, minimizing the placebo effect on the ocular outcome. Again, to minimize the adverse effects of the study on the ocular outcome, no washout period was applied.

The study was therefore designed to evaluate the short-term efficacy of pulse PCP plus prednisolone over prednisolone alone in a randomized double blind controlled crossover study.

Patients and Methods

Drug administration methods

PCP was used as 1 gram cyclophosphamide per square meter of body surface (intravenous infusion in 1 liter of normal saline). Normal saline alone was administered for the placebo group. The procedure was repeated once monthly for both groups. Daily prednisolone 0.5 mg/kg was given to all patients. After 3 months, the two groups were swapped; the PCP group became the placebo group and vice versa.

Inclusion criteria

The patients had to fulfill the *Classification Tree* criteria for BD.[20] They also met International Criteria for BD.[21] Moreover, they had to have active posterior uveitis (PU) and/or retinal vasculitis (RV) to enter the study.

Disease activity index

A disease activity index (DAI) was calculated for each patient and for each section of each eye (anterior chamber, uvea, and retina) upon its inflammatory state. DAI was graded from zero (no inflammation) to 4 (maximum inflammation). Visual acuity (VA) was calculated for each eye by Snellen chart.

Patients

Thirty-five consecutive patients meeting the above criteria were enrolled in the study. They were randomly assigned to either the PCP or the placebo group. At the beginning of the study, 17 started with PCP and 18 with placebo. They were crossed over after 3 pulses. No washout period was applied for the reasons explained above. All patients took 3 months of PCP and 3 months of placebo.

Statistical analysis

Student's paired *t*-test was used for comparison of means before and after the treatment. Since the data obtained from visual acuity and inflammatory indexes were semicontinuous (incremental), two different statistical methods were used in order to compare the results between PCP and the placebo groups: 1) Student's *t*-test by comparing the contrast between the 2 sequences by their means (within sequence) within individual contrasts,[22] and 2) Mainland-Gart test[22] for crossover design study after transformation of semicontinuous incremental data into binary data. The results, expressed in percentage, were calculated by a confidence interval (CI) of 95%.

The study was designed and performed in the Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences after the approval of the Ethics Committee of the center and patients' consent. All patients completed their 6-month period of the trial.

Results

All parameters were analyzed before and after the treatments in each group and then were compared between the placebo group and the treatment group (PCP group).

Visual acuity

The mean VA improved from 3.7 ± 3.2 to 4.9 ± 3.9 ($t = 3.309$, $p < 0.002$) in the PCP group and from 4.4 ± 3.6 to 4.5 ± 3.5 ($t = 0.317$, $p = 0.75$) in the placebo group.

In the PCP group, VA improved in 57% of the eyes (95% CI: 44 – 60), remained stable in 22% (95% CI: 11 – 33), and deteriorated in 21% (95% CI: 10 – 32). In the placebo group, 45% of the eyes improved (95% CI: 32 – 58), 14% remained stable (95% CI: 5 – 23), and 41% deteriorated (95% CI: 28 – 54).

Table 1. Visual acuity. Testing the null hypothesis by Mainland-Gart test.

Sequence	Prefer first period	No preferences	Prefer second period	Total for all preferences
Pulse-placebo	22	9	3	34
Placebo-pulse	12	12	12	36
Total for both sequences	34	21	15	70

Mainland-Gart test; $\chi^2 = 6.631$; $p = 0.01$.

Using Mainland-Gart test, the difference between PCP and placebo groups was statistically significant in terms of the proportion of improvement in each group ($\chi^2 = 6.631$, $p = 0.01$).

Anterior uveitis

The mean DAI for AU improved from 1.2 ± 0.8 to 0.4 ± 0.7 ($t = 3.273$, $p < 0.003$) for the PCP group and from 1.2 ± 1.2 to 0.7 ± 0.8 ($t = 1.972$, $p = 0.57$) for the placebo group. AU improved significantly in the PCP but not in the placebo group.

In the PCP group, AU improved in 70% of the eyes (95% CI: 64 – 86), remained stable in 11% (95% CI: 1 – 22), and deteriorated in 19% (95% CI: 6 – 32). In the placebo group, 63% of the eyes improved (95% CI: 46 – 80), 3% remained stable (95% CI: 0 – 9), and 34% deteriorated (95% CI: 18 – 50). The comparison of PCP and placebo groups by Mainland-Gart test resulted in $\chi^2 = 0.183$ and $p = 0.67$. There was no statistically significant difference between the PCP and the placebo groups.

Posterior uveitis

The mean DAI for PU improved from 2.2 ± 1.6 to 1.8 ± 1.5 ($t = 1.898$, $p = 0.063$) in the PCP group and from 2.1 ± 1.6 to 1.8 ± 1.5 ($t = 1.27$, $p = 0.21$) in the placebo group.

In the PCP group, PU improved in 53% of the eyes (95% CI: 40 – 66), remained stable in 19% (95% CI: 9 – 29), and deteriorated in 28% (95% CI: 16 – 40). In the placebo group, PU improved in 55% of the eyes (95% CI: 42 – 68), remained stable in 18% (95% CI: 8 – 28), and deteriorated in 27% (95% CI: 15 – 39).

The comparison of the PCP and placebo groups by Mainland-Gart test resulted in a χ^2 of 0.021 and $p = 0.89$. There was no statistically significant difference between the PCP and the placebo groups.

Retinal vasculitis

The mean DAI for RV didn't change (DAI = 1.2 ± 1, $t = 0.127$, $p = 0.9$) in the PCP group while it declined from 0.9 ± 1.1 to 1.1 ± 1.2 ($t = 1.27$, $p = 0.21$) in the placebo group.

In the PCP group, RV improved in 43% of the eyes (95% CI: 26 – 60), remained stable in 18% (95% CI: 4 – 32), and deteriorated in 39% (95% CI: 22 – 56). In the placebo group, RV improved in 40% of the eyes (95% CI: 23 – 57), remained stable in 17% (95% CI: 4 – 30), and worsened in 43% (95% CI: 26 – 60).

In the comparison of PCP and placebo groups by Mainland-Gart test, $\chi 2$ was 0.046 with $p = 0.83$. There was no statistically significant difference between the PCP and the placebo groups.

Table 2. Anterior uveitis. Testing the null hypothesis by Mainland-Gart test.

Sequence	Prefer first period	No preferences	Prefer second period	Total for all preferences
Pulse-placebo	5	24	5	34
Placebo-pulse	6	24	6	36
Total for both sequences	11	48	11	70

Mainland-Gart test; $\chi^2 = 0.183$; $p = 0.67$.

Discussion

The mean VA improved in the PCP group (PCP + prednisolone), but not in the placebo group (prednisolone alone). The difference was statistically significant. This shows the efficacy of pulse cyclophosphamide and the superiority of their combination over prednisolone alone. The results also indicate that although prednisolone can

Table 3. Posterior uveitis. Testing the null hypothesis by Mainland-Gart test.

Sequence	Prefer first period	No preferences	Prefer second period	Total for all preferences
Pulse-placebo	16	8	10	34
Placebo-pulse	11	14	9	34
Total for both sequences	27	22	19	68

Mainland-Gart test; $\chi^2 = 0.021$; $p = 0.89$.

Table 4. Retinal vasculitis. Testing the null hypothesis by Mainland-Gart test.

Sequence	Prefer first period	No preferences	Prefer second period	Total for all preferences
Pulse-placebo	6	18	3	27
Placebo-pulse	8	18	7	33
Total for both sequences	14	36	10	60

Mainland-Gart test; $\chi^2 = 0.046$; $p = 0.83$.

improve inflammation, it is not able to improve the mean visual acuity of all patients when used in combination. The improvement of VA with prednisolone alone was seen in less than half of the patients, which is much lower than what is believed classically.[3] The mean DAI for AU improved in the PCP but not in the placebo group. However, the difference between the two groups was not statistically significant. Neither groups showed any improvement in the mean DAI for PU and RV. This may be explained by the short period of the study. In open studies with longer periods of observation, both PU and RV improved with PCP.[5, 14] However, considering individual eyes, in the PCP group, PU, and RV improved or remained stable in 72% and 61%, respectively while in the placebo group, the same figures were 73% and 57%, respectively.

The similarity of the results observed in PU and RV may be explained by the design of the study. The major disadvantage of the crossover study with short-term treatments in each arm, no washout periods, and with prednisolone for both groups was the minimization of cyclophosphamide effect in favor of prednisolone (the placebo group). Patients who stared their treatment in the placebo group received sufficient doses of prednisolone to efficiently suppress the inflammatory attack in the short-term period of that arm. When they were switched to PCP, little gain remained to achieve (Table 3). Those patients in the PCP group gained the maximum benefit of their treatment. All of the above factors had a minimizing impact on the beneficial effect of PCP. Longer periods of treatment, observation of an adequate washout period, and setting a real placebo group (without any treatment) could have best shown the real efficacy of PCP in the ocular manifestations of BD.

Conclusion

The combination of PCP and prednisolone was superior to the combination of placebo and prednisolone (0.5 mg/kg/day). The result demonstrates the superior efficacy of PCP to placebo. In this short-term study, the efficacy was shown only for the visual acuity. Longer periods of observation are needed to look for efficacy of this therapy for different inflammatory indexes.

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