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CLINICAL STUDY

Intravenous dexamethasone *vs* methylprednisolone pulse therapy in the treatment of acute endothelial graft rejection

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Abstract

Purpose **To study the outcome of therapy for acute endothelial graft rejection with an intravenous (i.v.) pulse of dexamethasone *vs* methylprednisolone, in addition to topical corticosteroids.**

Methods **Records of 98 eyes of 99 patients treated for endothelial graft rejection with a single i.v. pulse of dexamethasone or methylprednisolone in addition to topical steroids, between January 1999 and June 2004, were retrospectively reviewed. Baseline characteristics such as surgery-rejection interval, time taken to consult after onset of symptoms, history of failed grafts, extent of stromal vascularization, best-corrected visual acuity (BCVA) and corneal thickness at the time of presentation were noted. Main outcome measures following treatment for rejection included improvement in BCVA, change in corneal thickness, and reversal of graft rejection.**

Results **Fifty-one patients were treated with i.v. methylprednisolone and 47 with i.v. dexamethasone, in addition to topical steroids. Both groups were found to be comparable with respect to baseline parameters, that is, time taken to present, history of failed grafts, extent of stromal vascularization, BCVA, and graft thickness. Graft rejection could be successfully reversed in 72.3% cases in the dexamethasone group and 49% in the methylprednisolone group ($P = 0.018$). A significant improvement in visual acuity was recorded following treatment in both groups, with a better outcome in the dexamethasone group ($P = 0.012$). Post-treatment pachymetry values were lower than pretreatment values in both groups, with significantly lower final pachymetry in the dexamethasone group ($P = 0.017$). No adverse effects were observed.**

Conclusion **I.v. pulse therapy with dexamethasone may be used as an effective alternative to methylprednisolone in reversing acute endothelial graft rejection.**

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Keywords: endothelial graft rejection; intravenous pulse therapy; methylprednisolone; dexamethasone; topical steroids

Introduction

Corneal graft rejection remains an important cause of graft failure all over the world.[1] Corticosteroids are the mainstay of treatment for successful reversal of graft rejection, but there are wide variations in the choice of steroid, route of administration, and dosage.[2–5] Evidence available so far suggests a beneficial role of intravenous (i.v.) methylprednisolone when combined with topical steroids over frequent topical steroids alone,[6] and also over oral steroids in combination with topical steroids,[7] in selected cases. In addition, pulse therapy also carries the advantage of avoiding the potential side-effects of prolonged oral medication.[7] In our clinical experience, frequent topical steroids alone have been inadequate in successfully reversing corneal endothelial rejection, necessitating the use of pulse therapy. Since i.v. methylprednisolone is an expensive drug, it is not within the reach of many patients in this part of the world. In clinical situations,

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where therapy with i.v. methylprednisolone is not possible, i.v. dexamethasone has been successfully used as a substitute.[8–10] The purpose of this study is to report our experience on the outcome of therapy with a single i.v. pulse of dexamethasone as compared to i.v. methylprednisolone, in addition to topical steroids, in reversing corneal endothelial graft rejection.

Materials and methods

The study was a retrospective, non-randomized, interventional case series. The medical records of patients treated for acute endothelial graft rejection with i.v. pulse therapy between January 1999 and June 2004 at the Cornea and Refractive Surgery Services of our centre were retrospectively reviewed. Ninety-eight eyes of 98 consecutive patients were identified.

Data were collected by chart review. Demographic data such as age, sex, and primary diagnosis of the patients were noted. Baseline characteristics recorded at the time of presentation including the surgery-rejection interval, time taken by the patient to reach the hospital after the onset of symptoms, extent of stromal vascularization, history of failed grafts, best-corrected visual acuity (BCVA), corneal thickness determined by ultrasonic pachymetry (Sonomed Inc., NY, USA), and intraocular pressure measured by Goldman applanation tonometry were noted.

Endothelial graft rejection was defined as an eye with a previously clear graft that developed stromal oedema and aqueous cells associated with an endothelial rejection line and/or presence of keratic precipitates on the corneal endothelium. Treatment of corneal endothelial graft rejection consisted of administering either 100 mg dexamethasone or 500 mg of methylprednisolone in 150 ml of 5% dextrose solution as a slow i.v. infusion over 1–2 h as a single-pulse therapy. The choice of pulse therapy was determined by affordability of the drug by each patient. Patients were monitored for haemodynamic stability during i.v. infusion. Topical prednisolone acetate 1% eyedrops were administered in addition to i.v. pulse therapy in all the cases. Initially, the eyedrops were recommended at hourly intervals during the day for 1 week, two hourly for the next week, and tapered off thereafter depending on the clinical response and signs of graft rejection reversal. Supportive therapy in the form of topical chloramphenicol (0.3%) four times a day, homatropine hydrobromide (2%) three times a day, timolol maleate (0.5%) twice a day, and lubricating eyedrops was prescribed. No follow-up oral corticosteroids were administered in either group.

Patients were followed-up at regular intervals as was considered necessary depending on their clinical response. At every follow-up visit, a complete ophthalmological examination was carried out including recording of visual acuity, slit-lamp examination, tonometry, and ultrasonic pachymetry.

Primary outcome measures included improvement in BCVA, change in corneal thickness as evident by serial ultrasonic pachymetry measurement and reversal of graft rejection following treatment as evident by slit-lamp biomicroscopy. Reversal of graft rejection was defined as a point where there were no cells in the anterior chamber and graft oedema had completely resolved.

BCVA and pachymetry values at the end of first month following treatment were noted from the records and were used for the purpose of statistical analysis.

Before commencing treatment, an informed consent had been obtained from the subjects and they were made aware of the various treatment options available to them. We certify that all institutional regulations concerning the ethical use of human volunteers were followed during this research.

Statistical analysis

Statistical analysis was performed using STATA 9.0. (College Station, TX, USA). Data were presented as either number (%) or mean ± SD as appropriate. Continuous baseline characteristics (such as age, BCVA, and corneal thickness) and post-treatment BCVA and pachymetry values were compared between two treatment groups using an independent *t*-test, whereas categorical baseline characteristics (such as failed graft, surgery-rejection interval, time taken to present after onset of symptoms, stromal vascularization and the outcome variable of graft rejection) were compared using χ^2-test. Wilcoxon rank test was used to compare the difference in the medians of surgery-rejection interval between the two treatment groups since the data was non-normal. Unadjusted and adjusted odds ratio (adjusted for surgery-rejection interval) for treatment were calculated for the outcome variable of graft rejection. A P-value less than 0.05 was considered statistically significant.

Results

Out of 98 patients who were identified as having been treated with pulse therapy for acute endothelial rejection during the study period, 51 were treated with i.v. methylprednisolone and 47 with i.v. dexamethasone, along with topical steroids. There were 78 males and 20 females with a mean age of 45.2 ± 19.7 years. Both groups were comparable with respect to baseline parameters, that is, mean age ($P = 0.417$), time taken to present after the onset of symptoms ($P = 0.553$), failed grafts

($P=0.306$), stromal vascularization ($P=0.726$), visual acuity ($P=0.615$), and corneal thickness ($P=0.55$). The time interval between corneal transplant surgery and the onset of graft rejection (surgery-rejection interval) was significantly greater in the dexamethasone group ($P=0.036$). Table 1 summarizes the demographic data, primary diagnosis and baseline characteristics.

As far as the overall outcome following treatment was concerned, graft rejection was successfully reversed in 59 out of 98 eyes (60.2%) and graft failure was observed in 39 (39.8%) eyes. The time taken by the patient to present to the hospital after onset of symptoms was directly related to the outcome. We found that an early presentation (within 5 days of onset) was associated with a better outcome ($P=0.013$).

Patients treated with methylprednisolone had a 2.72 times higher odds of failure as compared to those treated with dexamethasone (Table 2, $P=0.018$, OR = 2.72 (1.17, 6.31)). Since the surgery-rejection interval was significantly greater in the dexamethasone group and a shorter interval between surgery and onset of graft rejection may be associated with a poorer outcome, we adjusted for the imbalance in the surgery-rejection interval and found that there was no significant difference between the two groups in reversal of graft rejection ($P=0.115$).

The dexamethasone group was associated with a significantly better post-treatment BCVA ($P=0.012$) and lower pachymetry values ($P=0.017$) than the methylprednisolone group (Table 3). No adverse effects of i.v. pulse therapy with methylprednisolone or dexamethasone were observed in any of the patients.

Discussion

Both methylprednisolone and dexamethasone are synthetic corticosteroids, which have more potent glucocorticoid activity and minimal mineralocorticoid activity as compared to natural steroids. Similar pharmacokinetics of both drugs indicate that they can both be used as pulse therapy in cases of graft rejection. The drug most frequently used worldwide as i.v. pulse therapy is methylprednisolone. However, due to its easy availability and lower cost, i.v. dexamethasone is sometimes preferred for pulse therapy in India for various indications.[8–10] Although pulse therapy with

Table 1 Demographic profile, primary diagnosis, and baseline parameters

Characteristics	*Treatment*		P-*value*
	Methylprednisolone (n = *51*)	*Dexamethasone* (n = *47*)	
Demographic profile			
Mean age (years) (SD)	43.6 (21.7)	46.9 (17.2)	0.417
Sex distribution			
Male	44	34	
Female	7	13	
Primary diagnosis			
Healed keratitis	18	15	
Failed graft	9	14	
Corneal dystrophy	9	6	
Pseudophakic bullous keratopathy	9	7	
Aphakic bullous keratopathy	4	3	
Keratoconus	2	1	
Chemical burns	0	1	
Baseline parameters			
Failed grafts (no.)	9	14	0.306
Surgery-rejection interval (months)	8 (1–120)	12 (1–108)	0.036
Time taken to present after onset of symptoms (days)			
$\leqslant 5$	17	18	
6–10	22	22	0.553
$\geqslant 11$	12	7	
BCVA	0.09 ± 0.13	0.07 ± 0.13	0.615
Corneal thickness (μ)	810 ± 97	798 ± 99	0.55
Stromal vascularization (no.)			
$\geqslant 2$ quadrants	21	21	0.726
< 2 quadrants	30	26	

BCVA, best-corrected visual acuity.

Table 2 Outcome of graft rejection following treatment

Treatment	*Outcome of graft rejection*		*OR (95% CI)*	
	Reversal	*Failure*	*Unadjusted*	*Adjusted*[a]
Dexamethasone ($n=47$)	34 (72.3%)	13	1	1
Methylprednisolone ($n=51$)	25 (49.0%)	26 (51.0%)	2.72 (1.17, 6.31)	2.07 (0.83, 5.15)
P-value			0.018	0.115

[a]Adjusted for surgery-rejection interval.

Table 3 Pachymetry values and BCVA before and after treatment

Outcome	*Treatment*		P-*value*
	Methylprednisolone (n = *51*)	*Dexamethasone* (n = *47*)	
Pachymetry[a]			
Pretreatment	798.4 ± 99.9	810.5 ± 97.1	0.55
Post-treatment	710.7 ± 152.8	627.5 ± 148.0	0.017
BCVA[b]			
Pretreatment	0.07 ± 0.14	0.09 ± 0.14	0.615
Post-treatment	0.22 ± 0.25	0.35 ± 0.29	0.012

BCVA, best-corrected visual acuity.
[a]Pretreatment *vs* post-treatment in methylprednisolone, $P=0.0005$ and in dexamethasone, $P=0.0001$, significant.
[b]Pretreatment *vs* post-treatment in methylprednisolone, $P=0.0001$ and in dexamethasone, $P=0.0001$, significant.

methylprednisolone has been used worldwide to treat graft rejection, there are no published studies reporting the use of dexamethasone pulse therapy for this condition. Also, the comparative efficacy of these two drugs in the management of acute graft rejection has not been reported so far.

Dexamethasone has a greater glucocorticoid activity and a comparatively longer biological half life (24–72 h) as compared to methylprednisolone (12–36 h).[11] Therefore, dexamethasone can be expected to have a greater anti-inflammatory and immunosuppressive effect as compared to methylprednisolone. In our series, we found that graft rejection was successfully reversed in 72.3% eyes treated with dexamethasone as compared to 49% with methylprednisolone ($P=0.018$), when they were used in combination with topical steroids.

An overall rejection reversal rate of 60.2% was observed in our study. Other studies have reported a reversal rate between 50 and 92%.[7,12–16] We found that an earlier presentation was directly related to a favourable outcome. Lower success rates due to delay in initiating treatment has also been reported by previous studies.[7,13]

Although the choice of treatment was determined by affordability of the drug by individual patients in this case series, there were no significant differences in baseline variables between both groups, which could be of prognostic value in affecting the outcome of treatment. These variables included age of the patient, time taken to consult after the onset of symptoms, presence of stromal vascularization, surgery for failed grafts, and parameters such as visual acuity, and corneal thickness at the time of presentation. An exception was the mean time interval between corneal graft surgery and the onset of graft rejection, which was lower in the methylprednisolone group. Since we cannot exclude the possibility that endothelial rejection occurring earlier following surgery may be more resistant to treatment,[16] we adjusted for the imbalance between the surgery-rejection interval between the two groups. It was found that the adjusted values showed no significant difference between the two groups ($P=0.115$). Hence, we can infer that i.v. pulse therapy with dexamethasone can be used as an alternative to methylprednisolone in reversing acute endothelial graft rejection, in addition to topical steroids.

The adverse effects of pulse steroids include a sudden rise in blood pressure, cardiac arrhythmias, hypokalemia, raised intracranial pressure, seizures, psychosis, superimposed infections, hyperglycaemia, gastrointestinal bleeding, and hypersensitivity reaction including anaphylaxis. All patients were closely monitored for the development of any adverse effects but no complications that could be attributed to pulse therapy were observed in either group.

It must be pointed out that the present study was not designed to compare the two drugs prospectively, but is a retrospective review of our experience in managing these patients, where the choice of pulse therapy was only based on economic factors related to the patient. Hence, it has an inherent weakness common to all such retrospective studies. Undoubtedly, a double-masked,

randomized controlled clinical trial would be the best method to compare the two drugs, but falling short of that, since the two groups were similar with respect to various baseline characteristics that could influence the outcome, the results can be interpreted with reasonable reliability.

In conclusion, this study provides some evidence that dexamethasone pulse therapy may be used as an effective alternative to methylprednisolone in reversing acute endothelial graft rejections when used in combination with topical steroids.

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