

# Do topical ophthalmic corticosteroids suppress the hypothalamic-pituitary-adrenal axis in post-penetrating keratoplasty patients?

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CLINICAL STUDY

## Abstract

**Purpose** To establish whether hypothalamic-pituitary-adrenal axis suppression is possible secondary to long-term topical ophthalmic corticosteroid use in patients who have undergone penetrating keratoplasty (PKP).

**Methods** Patients who had undergone a PKP and had been using corticosteroid-based eye drops continuously for more than 6 months, with no history of concomitant steroid (oral, inhaled, or cutaneous) use, were included within the study. A low-dose short Synacthen (LDSST) test was performed in each patient followed later by a short Synacthen test (SST). The mean SST and LDSST after 30 min were calculated along with their corresponding 95% confidence intervals (CIs). Correlation between both baseline SST and baseline LDSST with duration of treatment was determined using Spearman's correlation.

**Results** In all, 20 patients were included within the study. The mean duration treatment was 28.2 months (range 11–96 months). All patients had normal baseline cortisol levels in both SST and LDSST tests. The mean 30 min SST was 753.8 nmol/l (95% CI: 696.6 nmol/l, 811.0 nmol/l) and no patients displayed inadequate adrenal response. The mean 30 min LDSST was 709.8 nmol/l (95% CI: 665.1 nmol/l, 754.5 nmol/l) and only one patient had an inadequate adrenal response. There was no correlation between baseline SST or LDSST and duration of treatment.

**Conclusions** This study found no evidence that patients using continuous long-term corticosteroid eye drops after PKP experienced inadequate adrenal response. We did not find any evidence of a negative correlation between length of treatment and SST or LDSST measurements at baseline.

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## Introduction

Topical corticosteroid treatments have been widely used within the management of many conditions over the past 50 years, they provide therapeutic local effects whilst reducing the systemic bioavailability when compared with oral and parenteral administration.<sup>1</sup> Despite this, recent reports suggest that the topical and inhaled use of corticosteroids can lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis<sup>2–5</sup> that is, exogenous, supraphysiological corticosteroid levels suppress both corticotrophin-releasing factor production in the hypothalamus and adrenocorticotrophic hormone production in the pituitary gland. This suppression, depending on its severity, may significantly reduce cortisol production by the adrenal glands (leading to adrenal atrophy), causing

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systemic effects that can lead to confusion, hyponatremia, and life-threatening hypotension in the event of a trauma, surgery, or illness, known as an 'adrenal crisis'.<sup>2</sup>

In addition, suppression of the HPA axis secondary to topical corticosteroid use is also well documented in children,<sup>6</sup> including the use of ophthalmic preparations.<sup>7</sup> Animal studies have also shown that ophthalmic topical corticosteroid therapy has the potential to cause adrenocortical suppression.<sup>8</sup>

Several studies have sought to identify whether topical steroids used for ocular pathologies cause suppression of the HPA axis.<sup>9,10</sup> In 1968, Burch *et al*<sup>9</sup> found reduced adrenal corticosteroid production in four patients receiving 0.1% dexamethasone drops on a short-term basis. Krupin *et al*<sup>10</sup> demonstrated partial adrenal suppression (reduced serum cortisol levels with normal HPA response on testing) in patients treated with 0.1% dexamethasone drops over 6 weeks.

The long-term use of topical corticosteroids is often necessary in patients who have undergone penetrating keratoplasty (PKP) to prevent rejection. The purpose of this study is to identify whether there is a link between the prolonged continuous use of topical ophthalmic corticosteroid preparations and adrenal suppression or insufficiency after corneal transplantation.

## Materials and methods

Patients were recruited prospectively from the corneal transplantation service in a tertiary referral eye department in the United Kingdom between January and November 2001. Patients who had been using prednisolone 1%, rimexolone 1%, prednisolone 0.5% or fluorometholone (FML) 0.1% eye drops continuously for >6 months, with no history of concomitant steroid (oral, inhaled, or cutaneous) use were included within the study. After consent was obtained for investigation of adrenal suppression, all patients had measurements of serum cortisol (09:00 hours) followed by a low-dose short Synacthen test (LDSST), and then a short Synacthen test (SST) over 1 week after the initial test.<sup>11</sup>

- (1) Low-dose short synacthen test—At 09:00 hours, a blood sample LDSST 0 was taken at 0 min (baseline cortisol level), followed by an intravenous injection of tetracosactrin (1 µg). A further blood sample, LDSST 30 was taken at 30 min after the injection.
- (2) SST—At 09:00 hours, a blood sample SST 0 was taken at 0 min (baseline cortisol level), followed by an intravenous injection of tetracosactrin (250 µg). A further blood sample, SST 30 was taken at 30 min after the injection.

Normal baseline cortisol values were taken as  $\geq 190$  nmol/l. Adrenal suppression or insufficiency was defined as a response of  $\leq 550$  nmol/l at SST 30 or LDSST 30.<sup>11</sup>

Plasma cortisol measurements were carried out by a technician, using a commercially available immunoassay (Bayer ADVIA Centaur, Siemens Medical Solutions Diagnostics, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

Informed consent was obtained from all subjects after the nature of the procedure had been fully explained. The tenets of the Declaration of Helsinki were followed and registration was obtained with the Royal Victoria Infirmary for a prospective audit of all corneal transplantation surgery outcomes. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

The mean SST and LDSST after 30 min were calculated. The corresponding 95% confidence intervals (CIs) were calculated to determine the range that the mean was likely to fall in and whether this included 550. Correlation between both baseline SST and LDSST with duration of treatment was determined using Spearman's correlation.

Statistical analyses were performed using Stata 11 (StataCorp LP, College Station, TX, USA), and  $P < 0.05$  was considered statistically significant.

## Results

In all, 20 patients were included within the study. There was a similar frequency of males and females in the data set, but age and treatment type varied considerably from patient to patient (Table 1). The mean duration of

**Table 1** Patient baseline characteristics

| Characteristic                   | Number (%) |
|----------------------------------|------------|
| <i>Treatment type</i>            |            |
| Prednisolone 1%                  | 13 (65%)   |
| Rimexolone 1%                    | 5 (25%)    |
| Fluorometholone 0.1%             | 2 (10%)    |
| <i>Sex</i>                       |            |
| Male                             | 9 (45.0)   |
| Female                           | 11 (55.0)  |
| <i>Original pathology</i>        |            |
| Fuchs dystrophy                  | 4 (20.0)   |
| Pseudophakic bullous keratopathy | 8 (40.0)   |
| Keratoconus                      | 4 (20.0)   |
| Interstitial keratitis           | 1 (5.0)    |
| Acanthamoeba keratitis           | 1 (5.0)    |
| Herpes simplex keratitis         | 1 (5.0)    |
| Macular dystrophy                | 1 (5.0)    |

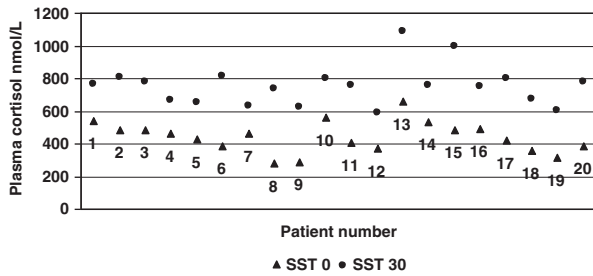


Figure 1 Short synacthen test results.

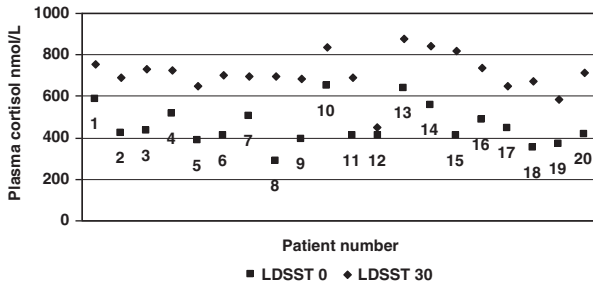


Figure 2 Low dose short synacthen test results.

treatment was 28.2 months (range 11–96 months). The mean baseline SST and LDSST were 451.0 nmol/l and 458.9 nmol/l, respectively, with corresponding 95% CIs that indicated the ranges the means were likely to fall in were both >190 nmol/l (95%CI: 403.1–495.1 and 95%CI: 415.0–502.7, respectively). All patients had normal baseline cortisol levels ( $\geq 190$  nmol/l).

The mean 30-min SST was 753.8 nmol/l, with a 95% CI that suggests the range the mean is likely to fall in is >550 nmol/l (696.6 nmol/l, 811.0 nmol/l). On the basis of these 30-minute SST cortisol levels, all patients had adequate adrenal function, >550 nmol/l (Figure 1).

Similarly, the mean 30-min LDSST was 709.8 nmol/l with a 95% CI indicative that the range the mean is likely to fall in is >550 nmol/l (665.1 nmol/l, 754.5 nmol/l). However, one patient did show an inadequate adrenal response with a 30-min LDSST of only 449 nmol/l (Figure 2).

There was no significant correlation (Spearman's rank ( $\rho$ ,  $\rho$ )) between baseline SST or LDSST and the duration of treatment ( $\rho = 0.04$ ,  $P = 0.87$  and  $\rho = 0.14$ ,  $P = 0.56$ , respectively).

## Discussion

An intact HPA axis is essential for the appropriate production of cortisol in response to stress.<sup>1</sup> The insulin tolerance test (ITT) is an established method for assessment of the integrity of the HPA axis but is potentially dangerous, resource intensive, and contraindicated in the elderly, epilepsy, and ischaemic heart disease.<sup>12</sup> In light of this, SST grew in popularity and studies have consistently demonstrated a high

correlation between results obtained from both ITT and SST.<sup>13</sup>

SST was originally designed as a test for primary adrenal failure and delivers a supraphysiological dose (250  $\mu$ g) of tetracosactrin, which may lead to some falsely high results in cases of insidious adrenal insufficiency.<sup>14</sup> In light of this, we choose to include a LDSST, which delivers a more physiological dose of tetracosactrin (1  $\mu$ g) and may identify more subtle forms of adrenal insufficiency. The results of the LDSST have been shown to correlate highly with both ITT and SST, whilst producing less false-positive results.<sup>15</sup>

One patient was identified as having adrenal insufficiency by the LDSST. This patient had been using prednisolone 1% drops once per day to prevent corneal graft rejection, for >6 months. The patient had been otherwise well with no signs or symptoms to suggest clinically apparent adrenal insufficiency, and has developed no subsequent problems since testing. All remaining patients had a normal adrenal response, and in addition we did not find any evidence of a negative correlation between the length of treatment and SST or LDSST measurements at baseline.

The results suggest that prolonged continuous use of low-dose topical ophthalmic steroid preparations as prophylaxis against graft rejection in patients after PKP, does not cause adrenal insufficiency in adults. However, many ophthalmic conditions require the long-term use of topical steroids at higher doses than the patients within this case series have received, often in combination with systemic steroids. Such patients are at a higher risk of adrenal insufficiency, especially when reducing the dosage of long-term systemic steroids. Therefore, the contribution of the topical ophthalmic steroids to any adrenal insufficiency should be considered.

We recognise that the results of this small case series are limited and that the association between long-term ocular topical steroid use and normal adrenal function may not be representative of the general population. Larger studies are needed to help confirm the findings.

## Summary

### What was known before

- It is known that steroids given by inhalation, applied topically to skin or given endonasally can cause adrenal suppression. Ophthalmic studies on topical steroid use and adrenal suppression performed in the 1960s and 1970s suggested that adrenal suppression may be possible. There have been recent studies looking at this subject.

### What this study adds

- This study suggests that long-term low dose ophthalmic topical steroids do not cause adrenal suppression in adults. Consideration should be given to the contribution of topical steroids to adrenal suppression in patients who are on both topical and systemic steroid.

### Conflict of interest

The authors declare no conflict of interest.

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