Corticosteroids do not prevent optic nerve atrophy following optic neuritis

S J Hickman, R Kapoor, S J Jones, D R Altmann, G T Plant, D H Miller

Methods

The design, conduct and clinical results of the trial have been reported previously. Briefly, 66 patients with a first episode of acute unilateral optic neuritis within 30 days of onset were enrolled into the study. The median duration of symptoms before randomisation was eight days (range 1–30). Six of the patients had clinically definite MS, another 14 had clinically probable MS, and the rest had clinically isolated optic neuritis. Their optic nerves were imaged with a short tau inversion recovery (STIR) sequence (TR 2500 ms, TE 40 ms, TI 175 ms, matrix 256×128, field of view 16 cm×16 cm, 2 excitations, 5 mm contiguous slices) and were then randomised to receive either 1 g/day IVMP for three days or intravenous saline. Reimaging was performed six months later. In addition, at six months, a detailed clinical assessment was performed including Snellen visual acuity, contrast sensitivity using the Pelli-Robson chart, 30-2 Humphrey visual field examination, and colour vision using the Farnsworth-Munsell 100 (FM 100) Hue test. Normal values were taken to be a visual acuity of 6/6 or better, contrast sensitivity of 1.65 or better, Humphrey mean deviation of −3 dB or higher, and the total error score of the FM 100 of less than 11.0.4 a field and central field pattern evoked visual evoked potentials (VEP) were also recorded.

Only images that were acquired on a Signa 1.5 T imager (General Electric, Milwaukee, WI) were available. Some early patients in the study were imaged on a Picker 0.5 T imager (General Electric, Milwaukee, WI) before randomisation was eight days (range 1–30). Six of the patients had clinically definite MS, another 14 had clinically probable MS, and the rest had clinically isolated optic neuritis. Their optic nerves were imaged with a short tau inversion recovery (STIR) sequence (TR 2500 ms, TE 40 ms, TI 175 ms, matrix 256×128, field of view 16 cm×16 cm, 2 excitations, 5 mm contiguous slices) and were then randomised to receive either 1 g/day IVMP for three days or intravenous saline. Reimaging was performed six months later. In addition, at six months, a detailed clinical assessment was performed including Snellen visual acuity, contrast sensitivity using the Pelli-Robson chart, 30-2 Humphrey visual field examination, and colour vision using the Farnsworth-Munsell 100 (FM 100) Hue test. Normal values were taken to be a visual acuity of 6/6 or better, contrast sensitivity of 1.65 or better, Humphrey mean deviation of −3 dB or higher, and the total error score of the FM 100 of less than 11.0.4 a field and central field pattern evoked visual evoked potentials (VEP) were also recorded.

Only images that were acquired on a Signa 1.5 T imager (General Electric, Milwaukee, WI) were available. Some early patients in the study were imaged on a Picker 0.5 T imager and these images were not available for study. In total, images from 45 patients at baseline and 59 patients after six months (30 given IVMP and 29 given placebo) were examined. The images were transferred onto workstations (Sun Microsystems, Mountain View, CA). Mean optic nerve area was measured by an observer blinded to image identity, treatment group, and acquisition order from two consecutive 5 mm orbital slices from the orbital apex forwards using a semiautomated contouring technique as described previously. Each measurement was carried out three times independently of each other. In a previously reported study of a different patient cohort, five consecutive 3 mm orbital slices from a short echo fast fluid attenuated inversion recovery (sTE fFLAIR) sequence were measured. It was not possible to measure a 15 mm segment in all subjects from the STIR images as in some patients the most anterior slice occurred at the point that the nerve sheath dilated as it attached on the back of the globe leading to an artificially increased area; hence a 10 mm segment was measured. This was less of a problem with the previous study because the sTE fFLAIR sequence suppresses the signal from cerebrospinal fluid. The presence of high signal lesions in the measurement area was noted and lesion lengths at baseline and six months were recorded from the data of the original study, measured by an experienced neuroradiologist.

Results

Table 1 gives measurement reproducibility results. At baseline optic nerve mean area was 18.4 (SD 3.8) mm² in diseased optic nerves and 17.8 (SD 3.6) mm² in healthy optic nerves (n = 45). The estimated geometric mean ratio (diseased nerve area:healthy nerve area) was 1.035 (95% CI 0.96 to 1.11; p = 0.33). At baseline, high signal was present in the measurement area in 36/45 patients. The presence of a lesion did not affect the ratio; however, the degree of swelling increased by 7.5% (95% CI 3.3% to 11.7%; p = 0.001) for each slice that a high signal lesion was visible on.

Abbreviations: IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; NO, nitric oxide; STIR, short tau inversion recovery; VEP, visual evoked potentials
After six months optic nerve mean area was 16.4 (SD 3.8) mm² in diseased optic nerves and 17.4 (SD 3.5) mm² in healthy optic nerves (n = 59) (fig 1). The estimated geometric mean ratio (diseased nerve area:healthy nerve area) was 0.93 (95% CI 0.87 to 0.99; p = 0.02). A lesion was present in 56/59 patients in the orbital portion measured at this time point. Neither the lesion length at baseline or six months correlated with the degree of atrophy. There was no evidence of association between any of the clinical and VEP variables and six month diseased nerve area.

The mean area of affected optic nerves at six months in the IVMP group was 15.9 (SD 3.9) mm² (n = 30) compared with 16.9 (SD 3.8) mm² in the placebo group (n = 29). The ratio of six month diseased:six month healthy optic nerve area was 6.8% lower in the IVMP group than in the placebo group (95% CI, 16.1% lower, 3.6% higher, p = 0.19). The ratio of six month diseased nerve area:baseline diseased nerve area was 0.8% lower in the IVMP group than in the placebo group (95% CI, 14.8% lower, 15.5% higher, p = 0.92). Neither the MS status nor the duration of symptoms before treatment was instigated affected these ratios.

DISCUSSION
This technique was able to show optic nerve atrophy following optic neuritis with good reproducibility as witnessed by the high reliability coefficients. The area measurements are greater than those produced from ste fFLAIR images as the measurements from the STIR images include the nerve sheath. Even though the measurements were of the optic nerve–sheath complex, atrophy was still detected after six months. At the time that the images were acquired during the trial, the ste fFLAIR sequence had not been developed and STIR was the preferred sequence for optic nerve lesion identification.

A study using ste fFLAIR in a more chronic cohort of optic neuritis patients showed that increasing optic nerve atrophy was associated with worse vision and decreased VEP amplitudes.9 Qualitative assessment of the ste fFLAIR images from that study suggests that atrophy of the optic nerve sheath occurred as well (SJ Hickman, unpublished observations). The lack of correlation between the clinical outcome measures and optic nerve mean area in the present study may be caused by functional reorganisation in the visual system in the early recovery process,10 potentially achieved by utilising redundant optic nerve capacity.11 This plasticity may fail over time and this may be one explanation for the development of late clinical progression in MS.

There is no evidence from these data that a course of IVMP prevents the short term development of optic nerve atrophy following acute optic neuritis. This is consistent with the lack of long term functional benefit seen as a result of IVMP in both this and other studies.

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Table 1 Measurement reproducibility for the different subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (mm²)</th>
<th>Within subject SD</th>
<th>95% reference range*</th>
<th>CV (%)</th>
<th>Reliability coefficient (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute diseased nerve area</td>
<td>18.4</td>
<td>1.13</td>
<td>± 2.21</td>
<td>6.4</td>
<td>0.92 (0.88 to 0.96)</td>
</tr>
<tr>
<td>Acute healthy nerve area</td>
<td>17.8</td>
<td>1.21</td>
<td>± 2.37</td>
<td>6.8</td>
<td>0.89 (0.84 to 0.94)</td>
</tr>
<tr>
<td>Six month diseased nerve area</td>
<td>16.4</td>
<td>0.76</td>
<td>± 1.49</td>
<td>4.6</td>
<td>0.96 (0.95 to 0.98)</td>
</tr>
<tr>
<td>Six month healthy nerve area</td>
<td>17.4</td>
<td>1.11</td>
<td>± 2.18</td>
<td>6.4</td>
<td>0.91 (0.87 to 0.95)</td>
</tr>
</tbody>
</table>

*1.96 × within subject SD; 95% of measurements are expected to lie within this departure from the true value.
†The proportion of total variance caused by between subject variation. Under assumptions which are plausible here, one minus this value is the proportion of variation caused by measurement error.
CV, coefficient of variation.

REFERENCES
The West Riding Lunatic Asylum

“Few subjects in medicine are so intimately connected with the history and philosophy of the human mind as insanity. They are the subject of so many errors and prejudices, and so many prejudices to remove. Derangement of the understanding is generally considered as an effect of an organic lesion of the brain, consequently as incurable; a supposition that is, in a great number of instances, contrary to anatomical fact.” Philippe Pinel, Treatise on Insanity, 1801

Until the second half of the 19th century, the study of the brain and its interplay with the mind was beset by mysticism and confusion. Speculation was rife and constituted little better than a repository for the guesswork of ignorance. In varying degree, both neurology and psychology were culpable. In his book, *The metaphysical foundations of modern physical science*, EA Burtt described the concept of mind as “a convenient fiction for the use of the mathematician.”

The asylum had enjoyed highest repute founded on care and compassion, but it was subjected to criticism by Robert Ferrier in 1858. It was reported that the asylum had become overcrowded, and the patients were not provided with adequate care. The asylum was moved to Fieldhead Hospital in 1995, after which the museum was closed.

Samuel Tuke gave advice about its workings and plans. It opened on 23 November, 1818. William and Mrs Ellis were the superintendent and matron from 1818 to 1831. It was a large establishment, and it was repeatedly expanded. It was under the control of the West Riding Magistrates; and the initial land, buildings, and furniture cost about £100,000. CC Corsellis, MD, was an early resident physician and director and had under his care about 450 lunatics. Henry Audsley, born in Settle, in the Yorkshire dales, was briefly the director; he was the most esteemed psychiatrist of the day, and founded the Audsley Hospital. Slater in 1864 noted its expansion: “The asylum is situated about a mile north east of the town. Another building was erected in 1849, which far surpasses the old one, both in size and architecture; the whole combined are calculated to give accommodation to upwards of 1000 patients.”

The hospital had many clinical clerks, clinical assistants, and physicians who attended the sick. By 1 January 1844, there were 433 patients—all paupers. The Stephen Beaumont Museum of Mental Health was in the hospital until it closed in 1995; it was moved to Fieldhead Hospital. It relates the history of the asylum and contains many exhibits. In 1948 a report on Wakefield was made by a medical officer to the new Leeds Regional Hospital Board. It described: “The old gaol-like buildings at Wakefield are gloomy and depressing and the galleries where many patients aimlessly spend so much of their time are deficient in natural lighting. The accommodation can best be described as austere and Dickensian, falling short of usually acceptable standards…”

A major salmonella outbreak at Stanley Royal Hospital in 1984 led to the deaths of 14 psychogeriatric patients and the infection of nearly 400 others. The hospital closed in 1995. The asylum had enjoyed highest repute founded on care and its renowned researchers. The most eminent were Sir David Ferrier* and Sir James Crichton-Browne.*

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3. Ashley AL. Stanley Royal Hospital, Wakefield. One hundred and fifty years: A history. Wakefield Area Health Authority, 1975.
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