Clinical review

Evidence based case report

Corticosteroids for HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome

Timothy L Clenney, Anthony J Viera

Uniformed Services
University of Health
Sciences, F Edward
Hébert School of
Medicine, Bethesda,
MD, USA
Timothy L Clenney
assistant professor of
family medicine
Anthony J Viera
assistant professor
Correspondence to:
T L Clenney
t_l_clenney@sar.
med.navy.mil

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Patient

At our monthly meeting on maternal morbidity we discussed a 31 year old woman at 35 weeks' gestation. She was admitted to the labour and delivery ward because of elevated blood pressure (155/90 mm Hg). Laboratory tests showed increased levels of aspartate aminotransferase and alanine aminotransferase in addition to proteinuria. Her platelet count was 68 000. She received no corticosteroids antepartum or post partum for HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, and both she and her infant did well.

In recent months we had cared for other women with HELLP syndrome who were given corticosteroids on the recommendation of our obstetrical consultants (none were present at the meeting). This experience raised the issue of whether such patients benefit from corticosteroids. The family physicians, obstetricians, and nurse midwives at the meeting were unable to reach consensus on this topic, and those with opinions were unaware of supporting evidence. As our question remained unanswered, we decided to assess current evidence. In doing so we framed the question: "Among patients with HELLP syndrome, does the administration of corticosteroids improve maternal morbidity in terms of both laboratory and clinical parameters?"

Search

We searched Medline from 1966 to February 2004 using the key words "HELLP syndrome" (all subheadings) AND "corticosteroids" (which mapped to "adrenal cortex hormones"). Our search produced 36 citations. We reviewed the titles to determine which articles might answer our question. When the study objective was not clear from the title, we read the abstract. Although we found no systematic reviews of randomised controlled trials in the Cochrane Library, there is a protocol for a systematic review.¹

Intervention

Observational studies

We found six observational studies (one case report and five retrospective reviews) that assessed corticosteroids in women with HELLP syndrome (table 1).²⁻⁷ These studies showed improvement in laboratory variables such as platelet counts and aminotransferase levels and in some clinical measures such as urine output, mean arterial pressure, and length of hospital stay. Caution is needed in drawing conclusions based solely on retrospective studies, given their propensity for bias. Having considered the hierarchy of evidence (figure), we focused on prospective studies with the highest available evidence we could find.

Table 1 Observational studies of corticosteroids in patients with HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome

Study	Design	Population	Intervention	Results
Schlembach et al 2000 ²	Case report	26 year old primigravida woman with HELLP syndrome at 25 weeks' gestation	40 mg intravenous methylprednisolone daily	Delayed delivery for 33 days
Crane et al 2003 ³	Retrospective	30 women antepartum with HELLP syndrome	Two antepartum doses of dexamethasone 12 mg intramuscular either 12 or 24 hours apart (given for maturation of fetal lung)	Temporary improvement in laboratory variables
O'Brien et al 2000 ⁴	Retrospective	37 women antepartum with HELLP syndrome in four year period	One group received standard dose of corticosteroid for maturation of fetal lung; one group received high dose corticosteroid; one group received no corticosteroid	Improved laboratory variables and lengthened time to delivery in corticosteroid groups
Martin et al 2003 ⁵	Retrospective	Comparison of high dose corticosteroid during two time periods	6% use during 1985 to 1991; 90% use during 1994 to 2001	Improved laboratory and clinical variables in period of higher use of corticosteroids
Vigil-De Gracia et al 1997 ⁶	Retrospective	34 women post partum with HELLP syndrome	17 women given total of 30 mg intravenous dexamethasone within 36 hours of delivery; 17 served as controls	Improved platelet count in dexamethasone group
Martin et al 1997 ⁷	Retrospective	280 women post partum with HELLP syndrome	43 women received dexamethasone; 237 received no dexamethasone	More rapid improvement of platelet counts and lactate dehydrogenase levels in steroid group. Clinically significant reduction in need for transfusion and respiratory therapy, invasive monitoring, bleeding or infectious morbidity, and length of postpartum hospital stay

Hierarchy of evidence⁹

Prospective studies

We assessed the three prospective studies on the basis of the method described by the Evidence Based Medicine Working Group.^{9 10} Table 2 details our assessment.

We identified one prospective randomised controlled trial of corticosteroids in women with HELLP syndrome antepartum. In this small study (25 participants) women given 10 mg dexamethasone every 12 hours had clinically and statistically significant increases in platelet counts and decreased levels of lactate dehydrogenase and alanine aminotransferase.¹¹ Maternal oriented outcomes included improved urinary output. Investigators failed to note whether controls at 34 weeks' or less gestation received steroids for maturation of fetal lung. Any effect from this should have been minimised by the patients being randomised equally. However, because baseline platelet counts were significantly lower in the steroid group than in the control group (69.3 v 106.8, $P=0.034$), the effectiveness of randomisation and allocation is uncertain.

Our search also identified two prospective randomised controlled studies that evaluated corticosteroids among women with HELLP syndrome post partum.^{12 13} In one of these studies 40 women were randomised to receive either two doses of dexamethasone 10 mg 12 hours apart followed by 5 mg at 24 and 36 hours (total 30 mg) or no corticosteroids.¹² Women in the dexamethasone group had clinically and statistically significant increases in urine output and platelet counts. Likewise, lactate dehydrogenase and aspartate

aminotransferase levels decreased significantly in this group. No mention is made of whether women at less than 34 weeks' gestation received dexamethasone for fetal indications. Randomisation should have minimised any effects.

In a more recent prospective randomised trial, 30 women with HELLP syndrome post partum also received two doses of dexamethasone 10 mg 12 hours apart followed by 5 mg at 24 and 36 hours or no corticosteroids.¹³ The dexamethasone group had meaningful improvements in several variables. At 48 hours post partum, women receiving dexamethasone had a significantly decreased mean arterial pressure (115 mm Hg v 94 mm Hg; $P<0.05$) and mean aspartate aminotransferase level (100 IU/l v 50 IU/l; $P<0.05$). During this time they also showed improvements in urine output (60 ml/h v 40 ml/h; $P<0.05$) and mean platelet count (115 000 v 70 000; $P<0.05$). The authors concluded that their findings supported high dose corticosteroid treatment of women with HELLP syndrome for 36 hours after delivery. They also noted that although three patients (one control) had infectious complications, there were no statistically significant differences in morbidity.

Outcome

To determine whether these results would help us in caring for our patients, we addressed three questions to ask when reviewing articles on treatment.

Can the results be applied to my patients' care?—Yes. We often give dexamethasone to women between 24 and 34 weeks' gestation at risk of preterm delivery to accelerate maturation of fetal lung. Although HELLP syndrome is not a common disorder, it occurs frequently enough that we should be prepared to start appropriate management before transfer of patients to our tertiary referral centre.

Were all clinically important outcomes considered?—Yes. Clinically important outcomes addressed by these studies included relevant laboratory variables (liver transaminase levels and platelet counts) and meaningful patient oriented outcomes (mean arterial pressure and urine output).

Are the benefits worth the harms and costs?—Yes. Dexamethasone is cheap and almost universally available. Although the sample sizes used in these studies were comparatively small, the outcome data show a clear benefit from starting corticosteroids early. Although animal studies have shown fetal complications such as growth retardation and low birth weight with repeated doses of corticosteroids in the antepartum period, these findings have not been shown in observational studies in humans.^{14–16} Randomised trials are needed to evaluate the safety of multiple courses of corticosteroids antepartum. In the treatment of

Table 2 Validity assessment of prospective studies

Study	Randomisation	Concealment of allocation	All participants accounted for	Intention to treat analysis	Blinding*	Study and control groups similar	Groups treated equally†
Magann et al 1994 ¹¹	Yes	Uncertain	Yes	Yes	No	No†	Yes
Magann et al 1994 ¹²	Yes	Uncertain	Yes	Yes	No	Yes	Yes
Yalcin et al 1998 ¹³	Yes	Uncertain	Yes	Yes	No	Yes	Yes

*Participants, health professionals, and study staff.

†Maternal platelet count was significantly lower in steroid group (69.3 v 106.8; $P=0.034$).

‡Intervention varied.

HELLP syndrome post partum, there are no concerns about harm to the fetus. In treatment antepartum, the duration of corticosteroid treatment is relatively brief, and the time to delivery should be rapid. The complications from repeated corticosteroid use should therefore not be an issue.

Given the preponderance of current evidence, we recommend that women with HELLP syndrome both antepartum and post partum should be given two doses of dexamethasone 10 mg 12 hours apart followed by 5 mg at 24 and 36 hours. The results of the Cochrane systematic review should further clarify this issue.

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Give a disease a bad name

Diseases may be known by the localities where they were first described or were common. Thus undulant fever, a particularly debilitating illness that often led to rheumatism, became known as Malta fever—to which many Maltese objected. There were many other names for it: Rock or Gibraltar fever, as well as Cyprus, Neapolitan, Italian, and Crimean fever. But Malta fever was the favoured name. Mediterranean fever was recommended by an international congress but was really unsuitable as the fever was found in many other localities.

Sir David Bruce discovered the causative organism in the spleen of a soldier who had died in Malta and in 1886 named it *Micrococcus melitensis*—melita being the old name for Malta. The Colonial Office in 1903 wrote to the Royal Society "with regard to Malta Fever." Bruce replied that "when a name . . . has got fixed in medical literature it is difficult to change it. The word Mediterranean, however, is too long and people cling to the older and shorter word Malta." When he succeeded the next year in his ambition to investigate the transmission of the bacteria, he used the name Mediterranean Fever Commission. Nevertheless, he used Malta fever in the titles and text of papers published in 1906 and 1907, as well as the Research Defence Society booklet in 1908 *The Extinction of Malta Fever (A lesson in the use of animal experimentation)*.

Maltese doctors continued to be displeased with the continued use of Malta fever. In 1927 the members of the Camera Medica di Malta and the Malta Branch of the British Medical Association pleaded for the discontinuance of the geographical designations of

undulant fever in a three page pamphlet in English, Italian, French, Spanish, and German versions.

Four years later, Major General Sir David Bruce FRS died and the *Malta Chronicle and Imperial Services Gazette* reprinted part of the obituary from the *Times*, which incorrectly attributed to Bruce the discovery of the transmission of Malta fever by the milk of goats.

Dr J E Debono promptly replied, giving the credit for this important discovery to Sir Themistocles Zammit, the great Maltese doctor, chemist, archaeologist, author, and politician—and once again pleaded for the term undulant fever. Debono suggested that "the last vestige of association with Malta would disappear. Whether such a change is desirable I do not know, but it would satisfy many who are perhaps unduly sensitive."

Sir David Bruce would be pleased that the disease is now known as brucellosis and that in our more sensitive age no one uses the objectionable geographical term.

H V Wyatt *retired medical scientist, Hollyshaw Terrace, Leeds*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com>. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.