Are steroids really ineffective for severely head injured patients?

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The “Guidelines for the Management of Severe Head Injury” states that the use of glucocorticoids is not recommended for improving morbidity outcome. Conversely, the “National Acute Spinal Cord Injury Study” (NASCIS) in the United States concluded that treatment with very high doses of methylprednisolone (30 mg/kg) is indicated for acute spinal cord trauma. In this paper, the author will discuss the reasons for this great discrepancy between head injuries and spinal cord traumas. A 30-mg dose of methylprednisolone was used as a bolus dose in the spinal cord study to inhibit oxygen free radical-induced lipid peroxidation. In most of the papers cited containing Class I data on severe head injury studies the investigators used smaller doses of glucocorticoids as compared with those in the spinal cord study. Moreover, some of the papers included cases in which the time from insult to the initiation of treatment had been poorly controlled. Therefore, based on previous papers, it is appropriate to relinquish megadose steroid therapy for head injury patients. A good prospective multicenter trial of high-dose methylprednisolone for traumatic brain injury should be considered in which dosage and timing parameters similar to those enacted for the NASCIS studies are used.

KEY WORDS • head injury • glucocorticoid • methylprednisolone • brain contusion

The “Guidelines for the Management of Severe Head Injury” (GMSHI) states that the use of glucocorticoids is not recommended for improving morbidity outcome. Conversely, in the “National Acute Spinal Cord Injury Study” (NASCIS) it was concluded that treatment with very high doses of methylprednisolone is indicated for acute spinal cord trauma. There exists a great discrepancy between research previously completed on head injuries and on spinal cord traumas. In this paper, I will describe those randomized controlled studies on the effects of glucocorticoid therapy in severe head injury that are not compatible with currently published SCI studies.

In the second NASCIS, a 30-mg dose of methylprednisolone was used as a bolus dose to inhibit oxygen free radical–induced lipid peroxidation.4–6 In most of the previously reviewed studies that are cited as Class I data in the GMSHI, the investigators used smaller doses of glucocorticoids as compared with the SCI cases.3,7,8,12,27 Moreover, some of the studies also included cases in which treatment has been poorly controlled from the time of insult to initiation of medical care.8,12 The GMSHI states that use of glucocorticoids are not recommended for improving outcome or reducing intracranial pressure in patients with severe head injury.2 Recently, Alderson and Roberts1 conducted a systemic review of randomized controlled trials, forming conclusions that demonstrated considerable uncertainty concerning the validity of the aforementioned statement. In this study, dose amounts of steroids were not considered. However, in the second and third NASCIS, it was concluded that treatment with very high doses of methylprednisolone, followed by one continuous dose of the same medication for 24 to 48 hours, were indicated for acute spinal cord–injured patients presenting within 8 hours after injury.4–6

THEORETICAL BACKGROUND FOR MEGADOSING METHYLPREDNISOLONE

In basic studies the complex function of methylprednisolone has been demonstrated in spinal cord traumas, and it is well documented in the review by Hall.17 In these studies the authors determined that the major neuroprotective mechanisms of high-dose methylprednisolone (30

Abreviations used in this paper: GCS = Glasgow Coma Scale; GMSHI = Guidelines for the Management of Severe Head Injury; NASCIS = National Acute Spinal Cord Injury Study; SCI = spinal cord injury.
mg/kg) led to an inhibition of oxygen free radical–induced lipid peroxidation. This mechanism is quite appropriately independent and separable from the glucocorticoid steroid activities. Hall insisted the dose-response curve for this “antioxidant” effect was biphasic. In other words, by increasing the doses up to 60 mg/kg in each experimental animal, a loss of effect is demonstrated. Inherently, another dose increase of up to 90 mg/kg would actually triple the methylprednisolone dose given in the trial, and the reverse effects by promoting oxygen free radical–induced lipid peroxidation would occur.

Hall\(^1\) has also conducted an acute experiment on head-injured mice by using various doses of glucocorticoid. In the study he concluded that doses of 30 mg/kg of methylprednisolone and 60 mg/kg of prednisolone were optimum, whereas lower and higher doses showed less or no effect. Ildam, et al.,\(^19\) have completed an acute experiment in the brains of head-injured rats. They demonstrated decreases of lipid peroxidation and attenuation of ultrastructural alteration by using methylprednisolone after inducing head trauma. In addition, Park\(^25\) has also conducted an acute experiment in rats with moderate blunt injury, and he derived evidence that revealed 30-mg/kg doses of methylprednisolone administered within 4 hours after injury had reduced cerebral edema in the brains of the rats.

Hall\(^17\) has additionally stated that early initiation of treatment is imperative for achieving a therapeutic effect in the injured spinal cord. A more important factor in predicting limited therapeutic time is the extent of progressive decrease in blood flow to the injured site. As secondary tissue degeneration rapidly occurs after an injury, due to the aforementioned lipid peroxidation, the resulting effect may be irreversible. A loss of the patented microcirculation after 2 to 3 hours of increasing free radical damage may also explain the irreversibility of regional cerebral ischemia.\(^9\) An attempt to inhibit spreading free radical damage requires large doses of antioxidants administered over the entire course of reactions.\(^21,28\) Demopoulos, et al.,\(^10\) have suggested that high antioxidant doses of the steroids will curtail the development of free radicals and prevent tissue degeneration, thus permitting functional restoration. In the studies reported by Hall\(^16-18\), the ability of the steroid to reverse ischemia once it had developed was limited to a few hours of onset. It has previously been reported in my past studies on steroid use that the result of the experiment in head-injured rats was confirmed to be effective 1 hour after injury when 20 mg/kg of prednisolone was given within 1 week of observation.\(^20,25\)

**SPINAL CORD INJURY TRIAL**

After the success of the second trial of NASCIS in 1990 in which 30 mg/kg of methylprednisolone was used to treat SCIs, the third randomized trial of NASCIS 3 was conducted in 1997 to estimate the duration of successive treatments, and several conclusions were drawn.\(^4,6\) They demonstrated that patients with an SCI who received methylprednisolone (30 mg/kg) within 3 hours of injury should be maintained on a treatment regimen of a methylprednisolone infusion of 5.4 mg/kg/hour for 24 hours. Additionally, when methylprednisolone is initiated 3 to 8 hours after injury, patients should be maintained on the steroid therapy for 48 hours. Detailed observations and assessments were also recorded for an established study of doses of methylprednisolone administered to spine-injured patients; the findings seemed to contribute to the efficacy of the glucocorticoids. Statistically significant differences were obtained for motor function, and significant differences were also observed in patients with total sensory and motor losses in the emergency room, as well as in those with some preservation of sensory and motor function. These observations were based on six classifications in which motor function scores were recorded in 14 muscle segments. Additionally, three-step evaluations by using pinprick and light touch assessments in 29 segments from C-2 to S-5 were performed in this study. It might be noted that NASCIS 2 was replicated in Japan, and yielded similar results.\(^24\)

**PROBLEMS OF THE PREVIOUSLY PERFORMED DOUBLE BLIND TEST**

Most of the papers that are cited as Class I data in the GMSHII have included patients in whom smaller doses of the glucocorticoid were administered than were found effective in NASCIS 2 and 3. Braakman, et al.,\(^1\) and Faupel, et al.,\(^12\) have used 100 mg of dexamethasone as an initial dose, and this dose was then tapered off after 8 and 10 days, respectively, in their tests. The 100-mg dose of dexamethasone might have been equivalent to 500 to 550 mg (approximately 10 mg/kg) of methylprednisolone.\(^31\) This dose was derived from the usual antiinflammatory potency without considering its function to inhibit oxygen free radical–induced lipid peroxidation. According to the standard of Hall,\(^18\) at least a 300-mg dose (6 mg/kg) of dexamethasone is necessary. When a loading dose was taken into account the findings in the study by Giannotta and collaborators\(^14\) were solely compatible with the NASCIS series.

Faupel, et al.,\(^12\) included patients in whom dexamethasone administration (the intravenous loading dose was 100 mg for the high-dose group and 12 mg for the low-dose group) was initiated approximately 6 hours or more after injury. They included patients whose treatment was initiated more than 24 hours postinjury. When the drug was first injected within 6 hours, a marked improvement in the mortality rate was demonstrated within the dexamethasone-pooled groups particularly.

Although Cooper, et al.,\(^7\) excluded patients who arrived in the emergency room more than 6 hours postinjury, dexamethasone and placebos were administered to three groups within the 1st hour postadmission. Their high-dose group received only 60 mg of dexamethasone as a loading dose, which was followed by a 24-mg dose every 6 hours for 6 days. In a study by Dearden, et al.,\(^8\) 40 of 68 patients in a steroid group received a 50-mg bolus dose of dexamethasone within 6 hours of injury. This dose can be seen as almost equal to the 5-mg/kg dose of methylprednisolone. Additionally, 10 of the 68 patients were thereby medicated within 8 hours after injury. The remaining 18 patients received the same dose of steroid more than 8 hours after injury. This study included the patients who presented beyond the probable therapeutic time window and demon-
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strated no significant differences with the use of steroid treatment.

Saul, et al.,27 included patients who were admitted within 6 hours postinjury, but they did not describe the phase of their standardized treatment protocol at the time of steroid administration. The patients in the steroid group received 250 mg (approximately 3–5 mg/kg only) of methylprednisolone as a loading dose and a 125-mg dose every 6 hours. The authors found no statistically significant differences in their prospective randomized study.

Among the studies cited as Class I data, in that by Braakman, et al.,3 they initiated treatment within 6 hours of injury. Cooper, et al.,7 and Saul, et al.,12 excluded the patients who had presented after 6 hours, and in other studies patients were included beyond the probable therapeutic window.8,12,14

**Favorable Points in Randomized Studies**

Giannotta, et al.,14 performed a prospective random study in 88 patients with severe head injuries, in which they compared patients receiving a placebo, low-dose methylprednisolone (initial dose of 1.5 mg/kg), and patients receiving high-dose methylprednisolone (initial dose of 30 mg/kg) concurrently. A mortality rate of 39% was demonstrated in the high-dose group as compared with a 52% mortality rate in the low-dose and placebo groups combined, because the low-dose group received only 1/20 of the dose received by the high-dose group (see End Note). Mortality rates were most different in patients less than 40 years of age as compared with those under 50 years of age. In patients in the high-dose group there was a 6% mortality rate in 16 patients compared with a 43% mortality rate in 35 patients in the low-dose and placebo groups combined. In patients under 50 years of age, the incidence of recovery of speech in the high-dose group was 62% compared with 36% in the low-dose and placebo groups combined. They concluded that the increased survival rate resulted from treatments with high doses of corticosteroid medication. However, a low mortality rate was associated with an increased incidence in the poor outcome, which included vegetative or severely disabled patients.

In their prospective randomized study Faupel, et al.,12 reported significant improvements of patients in whom therapy was initiated within 6 hours postinjury, despite their lower doses. Analysis of the findings revealed a 21% mortality rate in steroid-treated groups compared with a 71% mortality rate in placebo groups. However, overall outcome was not improved. If the authors had classified unconscious, stabilized patients as a bad outcome, then their results would have worsened. It seems that in a limited number of patients, this form of treatment leads to a prolongation of life with an inability to regain consciousness. Even in the light of such results, we should stay mindful that glucocorticoids may improve mortality rates, and this fact may lead to improvement of quality of life in less severely injured patients.

Although Saul, et al.,27 found no statistically significant differences in their prospective randomized study, some interesting findings were described. Their patients were classified as early “responders” or “nonresponders” to the overall treatment protocol without regard to steroid ad-

ministration. On the basis of a change in GCS score during the first 3 days after admission, the “responders” in the steroid group had a better outcome. Approximately 26% of patients in the steroid group were dead or vegetative compared with 44% in the nonsteroid “responder” group.

In the study by Grumme, et al.,13 which was not included in the GMHRI, the authors concluded that their controlled multicenter trial revealed the efficacy of the steroid triamcinolone (200 mg) when given intravenously within 4 hours postinjury. In patients with focal cerebral lesions and admission GCS scores lower than 8, a much more favorable outcome had been recorded. Apparently the investigators suggested that administration of steroids at the scene of an accident would prove to be more beneficial. Although the investigators in other German multicenter trials used ultrahigh doses of dexamethasone (500 mg as a loading dose), the statistical difference failed to provide a reasonable variance between the dexamethasone and the placebo group when observed within the therapeutic milieu. In the end, it was reported that results in both groups were surprisingly favorable.13

**RECOMMENDATIONS FOR FUTURE STUDIES**

Compared with spinal cord–injured patients changes in mental status and thus physiological condition may occur very rapidly in head-injured patients. Even the GCS score obtained in a patient may fluctuate, depending on timing of estimation and development of brain edema or hematoma. The plan or design of a double-blind test on a head injury patient is very difficult. Consequently, if an estimation of the effect of the glucocorticoid depends simply on a 6-month outcome in which mortality alone is evaluated, a majority of the positive or favorable effects of less severely injured patients would be underestimated. In the NASCIS series, the life-threatening morbidity of a patient is one of the reasons to exclude him from the studies. Therefore, the perspective of studies on spinal cord traumas and those on head injuries are quite different. To evaluate effectiveness of the glucocorticoid treatment from the standpoint of precise observation, the report by Giannotta, et al.,14 which noted recovery of speech, becomes very important.

Cooper, et al.,7 performed postmortem examinations in up to 82% of their severely head injured patients who died. These patients were treated with steroids, and no significant differences were determined. The authors stated that 90% of all death in this series were caused by parenchymal hemorrhage and tissue disruption. These findings imply that the injuries were too severe for the investigator to expect a change in outcome when corticosteroid therapy had been administered. Marion, et al.,22 have conducted a double-blind study of severely head injured patients and treated them by inducing moderate hypothermia. They found that hypothermia did not improve the outcome in patients with admission GCS scores of 3 or 4. Conversely, hypothermia was associated with significantly improved outcomes in the patients with GCS scores of 5 to 7. Analysis of their results suggests the need to determine the severity of the head-injured patients if possible and to exclude those patients whose recovery is definitely not expected.
In the studies described in this paper the effects of therapy on prolongation of life have been limited. In addition, when administering the type of treatment discussed by Faupel, et al., an increased proportion of patients failed to regain consciousness in contrast to a decrease in the mortality rate. Even if the dying patients had survived due to steroid treatment and recovered in a vegetative or severely disabled state, these facts are not socially welcomed. Medically and scientifically, however, these facts should be evaluated and seen as improvements. Therefore, as in the spinal cord trauma and the hypothermia study conducted by Marion, et al., some improvement in the status the less severely injured patients (GCS scores of 5 to 7) should not be underestimated. The mechanisms of brain injury are not solely dependent on propagation of lipid peroxidation and therefore should not be denied as possible contributors to an extending research effort when considering the result of the NASCIS series.

Further double-blind studies to examine the efficacy of methylprednisolone are appropriate as was determined by Alderson and Roberts in their responses to the comments made by Newell and colleagues on their paper. These trials were designed to detect reductions of 10% or more in bad outcome and will inevitably lead to more clinically important effects that have not been discovered. Alderson and Roberts speculated that if corticosteroids could reduce the risk of death by 2% and the risk of disability by a similar amount, then theoretically the treatment of 100,000 patients with corticosteroids could avoid 2,000 deaths and prevent 2,000 disabilities. It should be concluded that new study designs are needed and would include patients who are treated within the therapeutic windows and on sufficient doses of corticosteroids. However, these studies leave considerable uncertainty as to whether megadose steroid therapy should be relinquished for the treatment of head injury patients. To evaluate these patients for even more efficacious patient medications used and thus lead to more efficacious patient treatment.

Because the therapeutic time window of glucocorticoids is narrow, the effect of glucocorticoids depends on the interval between injury and initiation of its administration. The time to initiation of the treatment should be strictly controlled, and sufficient optimum doses of glucocorticoids should be applied.

END NOTE

The table that appeared in the GMSHI erroneously described Giannotta’s low-dose methylprednisolone (30 mg/kg/day) and their high-dose methylprednisolone (100 mg/kg/day). The low/high dose ratio in Giannotta’s paper is 1/20 (1.5 mg/kg:30 mg/kg) for the first two doses and 1/10 (25 mg:250 mg) for the successive doses. Therefore, the doses were approximately .4 mg/kg/day and approximately .70 mg/kg/day for the 1st day, for the low- and high-dose groups respectively.

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