Sex-related differences in patients with severe head injury: greater susceptibility to brain swelling in female patients 50 years of age and younger

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Object. The goal of this study was to study the influence of sex and age on factors affecting patient outcome in severe head injury.

Methods. Data from the prospectively conducted international trial of tirilazad mesylate in patients with head injury were analyzed retrospectively. Included were 957 patients, 23% of whom were female and all of whom were between the ages of 15 and 79 years. All patients presented with a Glasgow Coma Scale (GCS) score between 3 and 8 and evidence of structural brain damage and/or subarachnoid hemorrhage (SAH) on the initial CT scan. Frequencies of recognized risk factors, including brain swelling, intracranial hypertension, systemic hypotension, advanced age, SAH, and injury severity (based on GCS scores), as well as dichotomized Glasgow Outcome Scale (GOS) scores (good recovery or moderate disability compared with severe disability, persistent vegetative state, or death) obtained 6 months postinjury were compared between male and female patients.

Conclusions. Overall significantly greater frequencies of brain swelling and intracranial hypertension were found in female compared with male patients (35% compared with 24% [p < 0.0008] and 39 compared with 31% [p < 0.03], respectively). The highest rates were found in female patients younger than 51 years old (38% compared with 24% [p < 0.002] and 40% compared with 30% [p < 0.02], respectively, in male patients younger than 51 years of age). This effect was independent of injury severity (GCS) scores, which were not different in male and female patients. Female patients younger than 50 years tended to have worse outcomes, but the difference was not statistically significant. Thus, female patients who sustain severe head injury, especially (presumably) premenopausal ones aged 50 years and younger, are significantly more likely to experience brain swelling and intracranial hypertension than male patients with a comparable injury severity, suggesting that younger women may benefit from more aggressive monitoring and treatment of intracranial hypertension.

KEY WORDS • brain edema • intracranial hypertension • brain injury • sex-related difference

Sexevere head injury is a major cause of mortality and morbidity among young people in the Western world. The majority (70–80%) of severe head trauma victims are male patients. Evidence for sex-related differences and gonadal hormone effects on the incidence, outcome, and treatment response of neurological disorders has been reported for Alzheimer disease, multiple sclerosis, epilepsy, and stroke. The influence of sex on the outcome of TBI has been the subject of several recent analyses with somewhat contradictory results, possibly due to the relatively small number of women and girls in clinical studies of severe head injury. Probably for the same reason, the recognition of various risk factors and the treatment guidelines for severe head injury are heavily influenced by findings in male patients. Thus, several variables have been identified in TBI research over the last few decades as significant risk factors for poor prognosis. These include injury severity, advanced age, SAH, intracranial hypertension and systemic hypotension. Differences between the sexes in the frequencies of these risk factors have not been systematically investigated to date.

The recent completion of the largest controlled clinical trial in brain injury to date offered the opportunity to address these issues in a study population large enough to enable statistically robust comparisons between male and female patients suffering from head injury. The well-documented effects of female gonadal hormones on fluid balance and the high frequency of idiopathic intracranial hypertension in premenopausal female patients led us to focus on possible differences between the sexes in frequencies of brain swelling and intracranial hypertension, with an additional emphasis on presumably premenopausal women (≤ 50 years of age). This age cutoff is commonly used to separate mostly pre- and mostly postmenopausal female patients because the majority of women reach menopause during the decade between 45 and 55 years of age, whereas in men a continuous decline in testosterone levels is associated with ages greater than 50 years. Other factors such as advanced age, presence of SAH, and injury severity (based on GCS scores) were also compared according to the sex of the patient. The influence of these risk factors on outcomes in male and female patients was compared as well.

Abbreviations used in this paper: CT = computerized tomography; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.
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**Clinical Material and Methods**

Data from the prospective, double-blind, placebo-controlled international trial of the effect of tirilazad mesylate in patients with severe or moderate head injury were analyzed retrospectively. The trial, which failed to show efficacy in these populations, was conducted from 1992 to 1994 at 50 centers in more than 15 countries. Central coordination for the trial was performed by the Clinical Trials Center of the Division of Neurological Surgery at the University of California at San Diego. Organizational support for the trial was provided by Upjohn Co. in Kalamazoo, Michigan. Statistical support for the analyses that we report in this paper was provided by the General Clinical Research Center at the University of California at San Diego.

**Patient Selection**

Patients were eligible for the trial if the following criteria were met. 1) The patient’s GCS score had to be between 3 and 8 with one reactive pupil (severe stratum) or between 9 and 12 (moderate stratum). The present analysis includes only the cohort with severe head injury. 2) The age of the patient had to be between 15 and 79 years inclusive. 3) Structural brain damage and/or SAH had to be evident on the initial CT scan. 4) Last, treatment had to be initiated within 4 hours after the time of injury. Patients were also excluded if they were pregnant, had received another investigational medication within 30 days of enrollment into the study, or were considered to have a concomitant disease that was either systemic or related to the nervous system and would make outcome analysis difficult at 6 months post-trauma.

**Study Design**

Patients in the trial were randomized to receive either 10 mg/kg tirilazad mesylate or placebo every 6 hours for 5 days. The determination of sample size was predicated on a 10% improvement with 80% power in patients in the severe stratum and was made to ensure a power of 90% in the overall stratum. Of 1132 enrolled patients, 957 (85%) had received a severe head injury.

Blood pressure measurements were collected hourly during the treatment phase. The GCS score was determined daily when possible. Intracranial pressure was monitored in all patients with a GCS score of 6 or less and in those patients with evidence of raised ICP on the initial CT scan. The protocol required measurement of ICP and treatment of the ICP when it was higher than 20 to 25 mm Hg. The patients’ CT scans were coded according to the Traumatic Coma Data Bank classification.

**Statistical Analysis**

The analyses of risk factor distribution by sex were performed on data obtained in all patients, regardless of whether they were randomized to receive drug or placebo. The patient’s age, GCS, CT classification, and the presence of hypotension were all assessed as part of the screening procedure prior to randomization and, therefore, could not be influenced by the drug. In addition, the per-protocol analysis of the study revealed no significant effects of the drug treatment on intracranial hypertension or neurological outcome, justifying the combination of data from the two treatment groups for the latter variables as well.

All variables were coded dichotomously as high as opposed to low risk, as described later in this paper. Patient outcomes were categorized as favorable (a 6-month GOS score of good recovery or moderate disability) compared with unfavorable (a 6-month GOS score of severe disability, persistent vegetative state, or death). Tests for independence of pairs of variables were performed using the Pearson chi-square or the Fisher exact test. Logistic regression models were developed to assess the independent effect of risk factors on outcome status as well as to assess interactions between variables. Unreported probability values were not significant at the 0.05 level.

**Brain Swelling**

The relationship between brain swelling (defined as CT Classifications 3 [diffuse injury with swelling] and 4 [diffuse injury with midline shift]), age, and sex is shown in Fig. 1. Overall, female patients had a significantly greater frequency of brain swelling than male patients—35% compared with 24% (p < 0.0008). This increased frequency was mostly characteristic of premenopausal women and girls (< 51 years of age), who had a 38% rate of swelling compared with 24% among their male counterparts (p < 0.002). The frequency in postmenopausal female patients (> 50 years of age) was comparable to the frequency in men.

Figure 2 shows that the increased frequency of brain swelling in female patients was not due to increased injury severity. In fact, the difference in the frequency of brain swelling between male and female patients was more pronounced among less severely injured patients (GCS Scores 7–8 [37% in female and 22% in male patients; p < 0.007]) compared with those patients with more severe injuries (GCS Scores 4–6 [34% in female and 25% in male patients; p = 0.03]). Although hypotension has been shown to be associated with brain swelling, female patients were predisposed to...
brain edema even in the absence of hypotension; in Fig. 3, one can see that 34% of normotensive female patients had brain edema compared with 23% of nonhypotensive male patients (p < 0.002).

**Intracranial Hypertension**

The relationship between intracranial hypertension (defined as an ICP > 20 mm Hg during > 25% of the time it was monitored) and sex is shown in Fig. 4. There was a significantly greater frequency of intracranial hypertension among female compared with male patients (39% compared with 31%; p < 0.03). The sex-related difference in frequency was even more dramatic in the population of patients aged 50 years and younger (40% compared with 30%; p < 0.02).

The increased frequency of intracranial hypertension in women and girls was not due to increased injury severity. As was the case with brain edema, the difference in rates of intracranial hypertension between the sexes was most significant among the less severely injured patients (GCS scores of 7 or 8 [33% compared with 20%; p < 0.02]) (Fig. 4). Among the nonhypotensive population, the greater frequency of intracranial hypertension in female patients approached statistical significance (38% compared with 30%; p = 0.07).

**Systemic Hypotension**

The frequency of hypotension in female patients appeared to exceed that in their male counterparts; however, this difference was not statistically significant (18% in female and 14% in male patients; p < 0.08). The trend appeared to originate from the postmenopausal subgroup, in which it was more pronounced (24% in women and 11% in men, p < 0.06).

The sex-related difference in the frequency of systemic hypotension was even more pronounced among patients in the more severely injured cohort (22% in female and 14% in male patients; p < 0.03), the opposite of what was observed with brain swelling.

**Clinical Outcome**

Brain swelling, intracranial hypertension, and systemic hypotension were associated with a significantly higher rate of unfavorable outcomes in both male and female patients. Female patients showed an overall trend toward a high-

![Fig. 2. Bar graph demonstrating the influence of sex and injury severity on the frequency of brain swelling in patients with severe head injury. The difference between the sexes was significant among patients with more severe injuries (GCS Scores 4-6; p = 0.03) and was even more pronounced among patients who were less severely injured (GCS Scores 7 and 8; p < 0.007; two-tailed Fisher exact test).](image1)

![Fig. 3. Bar graph depicting the influence of sex on the frequency of brain swelling in normotensive patients with severe head injury. The difference was significant (p < 0.002; two-tailed Fisher exact test).](image2)

er rate of unfavorable outcomes (6-month GOS categories of severe disability, persistent vegetative state, and death) when compared with male patients (51% compared with 44%), but this difference did not reach statistical significance (p = 0.08).

**Other Variables**

Age distribution was similar between the sexes, with more than 80% of patients younger than 50 years of age and 30 years being the mean age for both sexes. The frequency of SAH was also similar in male and female patients in general, but the frequency of SAH was greater in men older than 50 years compared with women in that age group (70% in men and 58% in women). Injury severity, as expressed by the distribution of GCS scores, was similar in male and female patients, both in patients younger than 51 years old and in those older than 50 years.

**Discussion**

The influence of sex on the outcome of TBI has been the subject of several analyses with somewhat contradictory results. The studies differed widely in size, injury severity (ranging from mild concussion to severe head injury), and outcome measures (for example, GOS score, Barthel index, language ability, and the presence of headaches or depression), suggesting that the issue of sexually dimorphic patterns of recovery from head injury requires further elucidation. Nevertheless, differences between the sexes in the frequencies of negative prognostic markers have not been systematically investigated in the past. We have shown that female patients with severe head injury have significantly higher rates of brain swelling and intracranial hypertension compared with male patients. This difference rests entirely on the population of women and girls 50 years old or younger, because the frequency of brain swelling and intracranial hypertension was similar in men and women older than 50 years of age. Conversely, systemic hypotension tended to be more common among older women. The mean age and distribution of injury severity (GCS score) were similar in male and female patients. The frequency of favorable outcome on the dichotomized GOS at 6 months postinjury was lower (by 7%) in younger female patients compared with male patients in the same age group, but the difference did not reach statistical significance (p = 0.08). To achieve statistical power, this kind of difference would require a study population of approximately 2000 patients, or twice the number enrolled in this trial. The lack of a significant difference in outcome, despite a highly significant differ-

![Image](image1)

![Image](image2)
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ence in the frequency of a major risk factor (brain swelling) in female patients, might result from the fact that other risk factors are more common in male patients. These factors may include a higher rate of SAH (the present study), progressive hemorrhage (recently reported by Oertel, et al.21), or progressive atrophy.2 Another possible explanation is that the negative effects of the hormonal environment on fluid balance, which make female patients more susceptible to acute brain swelling, is at least partially offset, in the long term, by the neuroprotective and neurorestorative action of female gonadal hormones on neurons, which repeatedly has been suggested by the effects of estrogen and progesterone on recovery from TBI and ischemic brain injury in animal models.27

The possibility of a subgroup-specific effect of the drug treatment cannot be completely ruled out in the context of the present study. Nevertheless, subgroup analyses that were performed in the tirilazad study indicated that male patients were more likely to benefit from the drug than female patients,16 a trend that, if substantiated, would have increased the expected sex-related difference in outcomes of young women rather than decreased it.

Because the frequency of posttraumatic brain edema appears to be higher during childbearing years and decreases afterward, it is likely that the edema is related to gonadal hormone status. During the premenopausal phase, women and girls have elevated levels of estrogen and progesterone,25,32 both thought to play a role in fluid retention and tissue swelling.26,30 Two physical manifestations of premenstrual syndrome are headache and fluid retention, which are often relieved by diuretics.18,32 The success of this therapy suggests mild brain edema as a possible cause of headaches that are associated with premenstrual syndrome. Both estrogen and progesterone levels decline drastically and remain low after menopause.3,20 The linkage among gonadal hormone status, fluid regulation, brain swelling, and intracranial hypertension is also supported by the observation that hyponatremia1 and idiopathic intracranial hypertension12,29 are both significantly more common in premenopausal women and girls than in men or in postmenopausal women. Although hormone samples were not collected during the tirilazad study, it is highly likely that the female patients younger than 50 years (with the exception of those who had undergone surgical removal of the ovaries) had intact ovaries that produced estrogen and progesterone, predisposing them to posttraumatic brain edema and increasing the likelihood of intracranial hypertension and unfavorable outcome. Similarly, the women older than 50 years were likely to have been postmenopausal, with low levels of estrogen and progesterone, unless they were receiving hormone replacement therapy. The ultimate resolution of this issue awaits a prospective study in which hormone levels in individual blood samples can be related to posttraumatic brain swelling and patient outcome.

As expected,4,9 the different patterns of brain swelling in female and male patients with respect to patient age and GCS score was echoed by differences in the rates of intracranial hypertension between the sexes. Women tended to have systemic hypotension at a higher frequency than men, a trend that was almost significant (p < 0.06) among patients older than 50 years. Women may be predisposed to hypotension because, for a given injury, they may lose a greater percentage of their total blood volume than do men.

Certain compensatory mechanisms may be more likely to fail with increased age in women, resulting in a relatively high rate of hypotension in older women. The increased frequency of brain swelling in women and girls does not appear to be secondary to other risk factors such as hypotension or a low GCS score. Thus, although it has been demonstrated that hypotension can be predictive of brain swelling,4,9 we have shown that, even among nonhypotensive patients, there is still a greater frequency of brain swelling in female patients than in male patients. In addition, the population most likely to be hypotensive (women > 50 years of age) is different from the population most likely to have brain swelling (girls and women < 51 years of age). Women’s relative predisposition to brain swelling is most pronounced among patients with a GCS score of 7 or 8, whereas among patients presenting with a GCS score between 4 and 6, women are more likely to be hypotensive compared with men. The fact that differences between the sexes in brain swelling and hypotension peak at different age ranges and at different levels of injury severity suggests that that women’s increased rate of brain swelling cannot be attributed purely to an increased rate of hypotension.

Similarly, the increased frequency of brain swelling does not appear to be a reflection of increased injury severity in women and girls because the injury severity was similar in male and female patients. Furthermore, unlike differences observed in males, the rate of brain swelling in females with less severe injuries (GCS Score 7 or 8) was not different from that in females with more severe injuries (GCS Scores 4–6), underscoring the increased susceptibility of female patients to brain swelling across the range of GCS scores commonly grouped under severe brain injury.

These findings have several important clinical implications. The increased susceptibility of younger women and girls to brain swelling and intracranial hypertension warrants more aggressive monitoring and treatment of intracranial pressure in this population and conservative use of fluids and pressors to improve outcome. The reverse may be true in elderly women, in whom aggressive treatment of hypotension is likely to improve outcome.

The exact mechanisms underlying the sex-related differences reported here have not been elucidated to date, al-
though it is highly likely that gonadal hormones play an important role, as has been indicated by findings of numerous studies in animal models. A planned prospective study of gonadal hormone levels at the time of injury in relation to the frequency of brain swelling and patient outcome may provide relevant mechanistic and therapeutic insights into the possible role these hormones play in human brain injury.

Conclusions

There may be factors contributing to a unique response to severe head injury that predisposes female patients to increased frequencies of brain swelling and systemic hypotension compared with male patients.

Identification of the causes of high rates of brain edema in young women and girls may lead to interventions that modify sex- and age-specific response mechanisms, resulting in better outcomes from TBI in this population. Presently, it seems reasonable to assume that younger female patients may benefit from more aggressive treatment of intracranial hypertension and brain edema, whereas older female patients might have better outcomes with earlier and more vigorous treatment of hypotension.

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