PAPER

Mortality in Adolescent Girls vs Boys Following Traumatic Shock

An Analysis of the National Pediatric Trauma Registry

Adil H. Haider, MD, MPH; David T. Efron, MD; Elliott R. Haut, MD; David C. Chang, MPH, MBA, PhD; Charles N. Paidas, MD, MBA; Edward E. Cornwell III, MD

Hypothesis: Female sex imparts a survival benefit after traumatic injury in children.

Design, Setting, and Patients: Review of patients (aged 0-17 years) included in the National Pediatric Trauma Registry between April 1994 and September 2001. Multiple logistic regression was used to analyze the effect of sex on mortality, adjusting for age, severity of injury (New Injury Severity Score and Pediatric Trauma Score), severity of head or extremity injury, injury mechanism, intent, and comorbidities. Subset analysis focused on severely injured children (New Injury Severity Score ≥ 16) with shock (systolic blood pressure ≤ 90 mm Hg, adjusted for age).

Main Outcome Measure: Adjusted odds of mortality between sexes.

Results: Of 46 859 children, 67% were boys. Girls had a higher crude mortality rate than boys (3.1% vs 2.7%, respectively; $P < .05$), but after adjustment, no significant difference was found in the odds of mortality between sexes (odds ratio, 1.16; 95% confidence interval, 0.89-1.37). Among children meeting the definition of severe injury with shock (n = 697), mortality was 39%. On regression analysis, sex did not predict outcomes in prepubescent children (aged ≤ 11 years; n = 532; 95% confidence interval, 0.56-1.22). However, among adolescents (aged 12-17 years), girls demonstrated significantly decreased odds of death when compared with equivalently injured boys (odds ratio, 0.38; 95% confidence interval, 0.14-0.90; n = 165).

Conclusions: Adolescent girls exhibit lower mortality than boys following traumatic shock. This effect is not seen in prepubescent children. These findings suggest that hormonal differences may play a role in the sex-based outcome disparities following traumatic shock in children.

Arch Surg. 2007;142(9):875-880

Multiple basic science research studies suggest that sex influences survival following traumatic shock. In various animal models of experimentally induced hemorrhagic shock, exposure to female sex hormones (and/or lack of exposure to male sex hormones) has been shown to improve humoral and cell-mediated immunity, leading to improved survival.[1-3]

The relationship between sex and recovery from posttraumatic shock in the clinical arena is unclear. A multicenter review by Wohltmann et al[4] suggests that women have superior survival after trauma. On the other hand, 2 large clinical database reviews by Napolitano et al[5] and Gannon et al[6] failed to show any disparate outcomes between sexes. Other studies assert that premenopausal females[7] and women with trauma-associated shock and sepsis may have improved survival outcomes after severe injury.[8]

The independent effect of sex on pediatric trauma is largely unknown and offers a potential area of productive study. If indeed there is a hormone-dependent survival benefit, then girls who have attained menarche might be expected to exhibit lower mortality compared with similarly aged adolescent boys. Conversely, there should be no survival difference between premenarche girls and similarly aged preadolescent boys.

METHODS

We undertook a retrograde analysis of the prospectively collected data in the National Pediatric Trauma Registry (NPTR). The NPTR is designed to study the epidemiology, management, and outcomes of the acutely injured pediatric trauma patient. Ninety-three pediatric trauma centers or adult trauma centers with pediatric commitment contributed to this database, which includes trauma patients younger than 20 years admitted with a primary diag-

Author Affiliations: Division of Trauma and Critical Care, Department of Surgery, Johns Hopkins School of Medicine, Baltimore, Maryland (Drs Haider, Efron, Haut, Chang, and Cornwell); and Department of Surgery, University of South Florida, Tampa (Dr Paidas).

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013

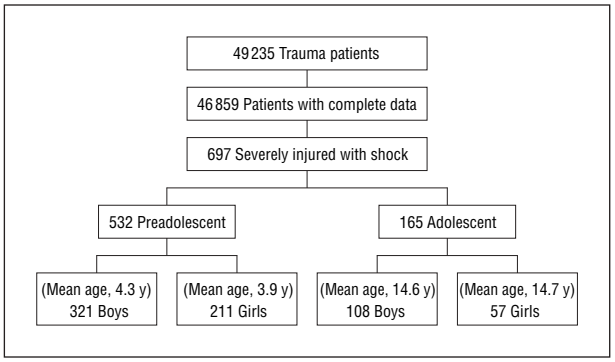

Figure 1. Patient selection and categorization into sex and age or adolescence groups. No significant age difference was noted between sexes within the age groups.

nosis of injury. Burns, drowning, near drowning, and poisoning are excluded from the data set. Patients enrolled in the database between April 1994 and September 2001 were selected for analysis and the main outcome measure was mortality.

The *t* test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables during univariate analysis. Following this, multiple logistic regression was used to analyze the independent effect of sex on mortality, adjusting for differences in demographics, injury severity, injury mechanism, type of injury, intent of injury, and any preexisting comorbid conditions.

To adequately adjust for injury severity, we used measures that would reflect the extent of each patient's anatomic injury and its physiologic sequelae. We also incorporated measures that controlled for head injury and extremity injury if present. For each patient, the New Injury Severity Score (NISS)[9] was calculated and used to adjust for severity of anatomic injury. The NISS was chosen in place of the more commonly known Injury Severity Score.[10] This was done because the NISS accounts for the 3 most severe injuries in patients irrespective of body part, whereas the Injury Severity Score is based on the most severe injury in 3 different body parts and may underestimate the injuries of patients with multiple severe injuries in the same cavity or body part. This may explain why the NISS has been shown to be a better predictor of outcomes in the pediatric age group.[11] To control for the physiologic sequelae of injury, we used the pediatric population–specific Pediatric Trauma Score.[12] To accurately control for interpatient variation, we also adjusted for the presence of severe head injury using the Relative Head Injury Severity Scale[13] and severe extremity injury using the Abbreviated Injury Scale (Abbreviated Injury Scale scores >3 in the extremity body part were regarded as severe extremity injury). We further controlled for type of injury (penetrating vs blunt), intent of injury (intentional vs unintentional), and mechanism of injury (motor vehicle crashes, falls, bicycle crashes, etc), with mechanism groups determined by *International Classification of Diseases, Ninth Revision* external cause of injury codes. The age of each patient (in years) was also included in the regression analysis to control for any interyear age differences. Similarly, the presence of any documented preexisting medical condition (eg, asthma, sickle cell anemia, or attention-deficit/hyperactivity disorder) was also controlled for (for this purpose, a categorical variable that signified the presence or absence of any comorbidity was used).

These numerous variables were included in the logistic regression models to adequately control for the multiple factors that affect outcomes after trauma. In previous work,[14,15] we have shown these variables to independently predict outcomes in pediatric trauma and we believe that adjusting for these sources of variance allowed us to accurately compare equivalently injured children on the basis of sex.

After initially analyzing all of the patients collectively, we then focused on severely injured children with trauma-associated shock, defined as a patient with an NISS of 16 or higher and hypotension (severe injury with shock [SIS] group). Hypotension was determined by documented systolic blood pressure (SBP) in the emergency department, adjusted for age. Hypotension was defined as SBP less than 74 mm Hg for patients aged 0 to 2 years; SBP less than 78 mm Hg for patients aged 2 to 4 years; SBP less than 82 mm Hg for patients aged 4 to 6 years; SBP less than 86 mm Hg for patients aged 6 to 8 years; and SBP of 90 mm Hg or less for patients older than 8 years. To analyze the effect of puberty and the natural emergence of sex hormones, we further stratified the patients into 2 groups by age: a preadolescent group (aged 0 to <12 years) and an adolescent group (aged ≥ 12 years). Age 12 years was chosen because the median age of menarche for girls in the United States is currently estimated to be 11.4 years.[16]

RESULTS

During the years studied, 49 235 records of children and their injuries were added to the NPTR. Complete data were available on 46 859 patients (95% of records), and these were selected for analysis. Boys accounted for 67% of the patients, and the mean age of patients in the registry was 8.2 years. Girls had a higher crude mortality rate than boys (3.1% vs 2.7%, respectively; $P<.05$), but after adjustment, no significant difference was found in the odds of mortality between sexes (odds ratio, 1.16; 95% confidence interval, 0.89-1.37). Stratification by adolescence or by the age group also did not yield any significant differences.

Approximately 1.5% of patients included in the NPTR met our strict definition of SIS (NISS ≥ 16 and hypotension). There was a preponderance of boys in both the preadolescent group and the adolescent group (60% and 65%, respectively, were boys). **Figure 1** shows patient selection, stratification, and demographics for our study.

Among children who met the criteria for SIS, patients in the adolescent group had a significantly higher proportion of penetrating trauma compared with those in the preadolescent group (20% vs 6%, respectively; $P<.05$). Adolescents in the SIS group also had a significantly higher proportion of severe extremity injury than preadolescents in the SIS group (31% vs 9%, respectively; $P<.05$), whereas preadolescent children had a higher proportion of severe head injury than adolescent children (83% vs 46%, respectively; $P<.05$) (**Table 1**).

Crude mortality among children with SIS (all ages) was similar for boys and girls (42% vs 41%, respectively; $P\leq .99$). Similar crude mortality was also seen when children with SIS were compared by age and adolescence group. The preadolescent group (both sexes combined) had a crude mortality of 46%, whereas the adolescent group had a mortality of 40% (no significant difference, $P=.2$). As depicted in **Figure 2**, the unadjusted mortality of adolescent girls was 11% lower than that of adolescent boys, but this trend difference was not statistically significant ($P=.2$). Among these patients with SIS, there was no significant difference in the unadjusted odds of death when girls were compared with boys. The odds of a girl dying as compared with a boy dying among all of the patients with SIS (n=697) was 0.92 (95%

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013

Table 1. Injury Type and Severity for Each Sex by Adolescence Group

Injury Type and Severity	Preadolescent Group: Boys (n=321)	Preadolescent Group: Girls (n=211)	Adolescent Group: Boys (n=108)	Adolescent Group: Girls (n=57)
NISS, mean	33	33	34	33
Patients with blunt trauma, %[a]	95	93	75	85
Patients with moderate or severe head injury, %[a]	81	85	49	44
Pediatric Trauma Score, mean	5.04	4.6	3.9	5.1
Patients with severe extremity injury, %	11[b]	6[b]	28	31
SBP, mean, mm Hg[c]	79	74	71	76

Abbreviations: NISS, New Injury Severity Score; SBP, systolic blood pressure.
[a] Significantly different between age groups ($P<.05$) but not between sexes.
[b] Significantly different between sexes within the age group ($P<.05$).
[c] Restricted to children older than 8 years.

confidence interval, 0.68-1.26). Stratifying by age, we found that for preadolescents (n=532), the odds of a girl dying compared with a boy dying was 1.02 (95% confidence interval, 0.72-1.45); for adolescents (n=165), it was 0.62 (95% confidence interval, 0.31-1.22). The latter shows a strong, albeit statistically insignificant, survival benefit for adolescent girls.

Table 2 presents the adjusted odds of death for girls compared with boys for the different age groups among patients with SIS. After adjusting for severity, mechanism, type and intent of injury, and comorbidities, we found no difference in survival between sexes in the preadolescent age group. However, adolescent girls demonstrated significantly decreased odds of death when compared with equivalently injured adolescent boys. After adjustment for all of the factors described earlier, we found that female sex reduced the risk of death by 62% among adolescent patients with trauma-associated shock.

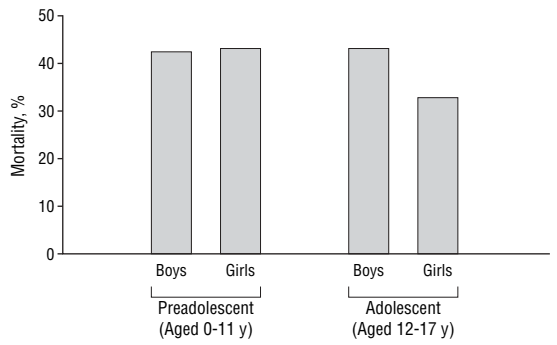

Figure 2. Unadjusted mortality for each sex by age or adolescence group. No significant mortality difference was noted between sexes within the age groups.

Table 2. Adjusted Odds of Deaths for Girls Compared With Boys for the Different Age Groups[a]

	All Children	Preadolescent Children	Adolescent Children
Patients, No.	697	532	165
Odds ratio (95% confidence interval)	0.76 (0.53-1.18)	0.82 (0.56-1.22)	0.38 (0.14-0.90)

[a] Includes severely injured children with trauma-associated shock only.

COMMENT

Although improved outcomes in trauma care have been demonstrated following the development of trauma systems, advanced resuscitation paradigms, and evidence-based practices such as appropriate use of antibiotics,[17-19] the more persistent challenge exists in improving the substantial mortality and morbidity that occur following posttraumatic shock.

Given the substantial experimental research that suggests a hormone-dependent difference in outcomes between males and females, we took advantage of the natural hormonal divergence that occurs at puberty and attempted to compare sexes based on the presence or absence of sex hormones. After stratifying patients by adolescence and controlling for injury characteristics with multivariate logistic regression, we observed that preadolescent children with SIS had no difference in survival between sexes. However, among adolescent children with trauma-associated shock, girls exhibited an improved survival compared with boys, with female sex conferring a 2.5-fold survival advantage.

This sex dimorphism may be explained by emerging research suggesting that female traits, from either sex-linked genes or the presence of sex hormones, are associated with improved survival.[20] Chaudry and colleagues have made substantive contributions to this field, suggesting that female sex hormones (estrogens) have an immunoenhancing effect that helps protect patients after hemorrhagic shock. In one study, they showed estradiol to enhance the function of both cell-mediated and humoral immunity.[21] In a subsequent study using the murine model, they demonstrated proestrus female mice to have improved macrophage and lymphocyte responses after trauma-hemorrhagic shock, leading to improved survival.[22] Conversely, male mice have been found to have depressed immune responses and worse survival in simi-

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013

lar models.[23] Male sex hormones, or androgens, are believed to have an immunomodulating effect that suppresses the immune system. This may explain why castration of male mice has been shown to improve survival after the induction of trauma-hemorrhagic shock.[24]

Further indication that sex hormones play a role in improving outcomes after trauma comes from 2 clinical studies that demonstrate improved outcomes after trauma among younger, premenopausal women only,[25,26] suggesting that female sex hormones have a protective effect after traumatic injury, similar to the known protective effect of estrogens against coronary heart disease.

These results may have significant application in advancing novel and currently experimental sex-based therapies for patients with the sequelae of severe trauma and sepsis. Immunomodulating agents including flutamide, an androgen antagonist,[27] and dehydroepiandrosterone, an estrogen precursor, hold promise in this regard.[28]

This study is limited by the fact that the NPTR is now 6 years old and data collection has been stopped. The study also has limitations common to most trauma registry analyses, as it does not have sequential clinical data on patients that would allow us to determine how individual patients responded to resuscitation efforts. We were also not able to determine the location of the deaths of patients (intensive care unit, emergency department, floor, etc), nor could we adjust for the amount of fluids or blood products the patients may have received. The absence of these data prevented us from investigating the interaction between posttraumatic sepsis and sex-based outcomes, which would have been of great interest.

On the other hand, one of the strengths of our study is the use of the NPTR, which is recognized as a nationally representative sample of injured children. Many severely injured pediatric patients are brought directly to or transferred to large academic trauma centers that have submitted data to the NPTR, allowing it to capture a large number of severely injured children—a feature unique to this national database. We found our results to exhibit considerable construct validity, as results of our baseline data analysis were in the directions expected. For example, an increased proportion of teenagers was found to have severe extremity injuries, whereas the main cause for severe trauma in younger children was head injury. These findings are in line with previously published literature and are expected.[29]

CONCLUSIONS

Among children with trauma-associated shock, adolescent girls exhibit lower mortality than equivalently injured boys. This effect is not seen in similarly injured prepubescent children. These findings suggest that hormonal differences may play a role in the sex-based outcome disparities following traumatic shock in children.

Accepted for Publication: May 25, 2007.
Correspondence: Adil H. Haider, MD, MPH, Division of Trauma and Critical Care, Department of Surgery, Johns Hopkins School of Medicine, 600 N Wolfe St, Blalock 688, Baltimore, MD 21287 (ahaider1@jhmi.edu).

Author Contributions: *Study concept and design:* Haider, Efron, Haut, Paidas, and Cornwell. *Acquisition of data:* Haider, Chang, and Paidas. *Analysis and interpretation of data:* Haider, Efron, Haut, Chang, Paidas, and Cornwell. *Drafting of the manuscript:* Haider, Efron, Paidas, and Cornwell. *Critical revision of the manuscript for important intellectual content:* Haider, Efron, Haut, Chang, Paidas, and Cornwell. *Statistical analysis:* Haider, Chang, and Paidas. *Administrative, technical, and material support:* Haider, Chang, Paidas, and Cornwell. *Study supervision:* Efron and Cornwell.
Financial Disclosure: None reported.
Previous Presentation: This paper was presented at the 78th Annual Meeting of the Pacific Coast Surgical Association; February 19, 2007; Kohala Coast, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.

REFERENCES

1. Angele MK, Ayala A, Monfils BA, Cioffi WG, Bland KI, Chaudry IH. Testosterone and/or low estradiol: normally required but harmful immunologically for males after trauma-hemorrhage. *J Trauma*. 1998;44(1):78-85.
2. Angele MK, Ayala A, Schwacha MG, Chaudhry IH. Effect of gender and sex on immune responses following shock. *Shock*. 2000;14(2):81-90.
3. Samy TS, Knoferl MW, Zheng R, Schwacha MG, Bland KI, Chaudry IH. Divergent immune responses in male and female mice after trauma-hemorrhage: dimorphic alterations in T lymphocyte steroidogenic enzyme activities. *Endocrinology*. 2001;142(8):3519-3529.
4. Wohltmann CD, Franklin GA, Boaz PW. A multicenter evaluation of whether gender dimorphism affects survival after trauma. *Am J Surg*. 2001;181(4):297-300.
5. Napolitano LM, Greco ME, Rodriguez A, Kufera JA, West RS, Scalea TM. Gender difference in adverse outcomes after blunt trauma. *J Trauma*. 2001;50(2):274-280.
6. Gannon CJ, Napolitano LM, Pasquale M, Tracy JK, McCarter RJ. A statewide population-based study of gender differences in trauma: validation of a prior single-institution study. *J Am Coll Surg*. 2002;195(1):11-18.
7. Mostafa G, Huynh T, Sing R, William SM, Norton HJ, Thomason HJ. Gender-related outcomes in trauma. *J Trauma*. 2002;53(3):430-435.
8. Oberholzer A, Keel M, Zellweger R, Steckholzer U, Trentz O, Ertel W. Incidence of septic complications and multiple organ failure in severely injured patients is sex specific. *J Trauma*. 2000;48(5):932-937.
9. Osler T, Baker SP, Long W. A modification of the injury severity score that both improves accuracy and simplifies scoring. *J Trauma*. 1997;43(6):922-925.
10. Baker SP, O'Neill B. The injury severity score: an update. *J Trauma*. 1976;16(11):882-885.
11. Sullivan T, Haider A, DiRusso SM, Nealon P, Shaukat A, Slim M. Prediction of mortality in pediatric trauma patients: new injury severity score outperforms injury severity score in the severely injured. *J Trauma*. 2003;55(6):1083-1088.
12. Tepas JJ, Mollitt DL, Talbert JL, Bryant M. The pediatric trauma score as a predictor of injury severity in the injured child. *J Pediatr Surg*. 1987;22(1):14-18.
13. Susman M, DiRusso S, Sullivan T, et al. Traumatic brain injury in the elderly: increased mortality and worse functional outcome at discharge despite lower injury severity. *J Trauma*. 2002;53(2):219-224.
14. Haider AH, Risucci DA, DiRusso SM, Sullivan T, Slim M, Paidas CN. Mechanism of injury predicts clinical and functional outcomes in pediatric trauma patients. *J Am Coll Surg*. 2003;197(3):s67.
15. Haider AH, Efron DT, Haut ER, DiRusso SM, Sullivan T, Cornwell EE. Black children experience worse clinical and functional outcomes after traumatic brain injury: an analysis of the national pediatric trauma registry. *J Trauma*. 2007;62(5):1259-1263.
16. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. *Pediatrics*. 2003;111(1):110-113.
17. Cornwell EE III, Chang DC, Phillips J, Campbell KA. Enhanced trauma program commitment at a level I trauma center: effect on the process and outcome of care. *Arch Surg*. 2003;138(8):838-843.
18. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*. 2006;354(4):366-378.
19. Cornwell EE III, Dougherty WR, Berne TV, et al. Duration of antibiotic prophy-

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013

laxis in high-risk patients with penetrating abdominal trauma: a prospective randomized trial. *J Gastrointest Surg*. 1999;3(6):648-653.
20. Angele MK, Chaudry IH. Surgical trauma and immunosuppression: pathophysiology and potential immunomodulatory approaches. *Langenbecks Arch Surg*. 2005;390(4):333-341.
21. Wichmann MW, Zellweger R, DeMaso CM, Ayala A, Chaudry IH. Enhanced immune responses in females as opposed to decreased responses in males following hemorrhagic shock. *Cytokine*. 1996;8(11):853-863.
22. Diodato MD, Knöferl MW, Schwacha MG, Bland KI, Chaudry IH. Gender differences in the inflammatory response and survival following hemorrhage and subsequent sepsis. *Cytokine*. 2001;14(3):162-168.
23. Angele MK, Ayala A, Cioffi WG, Bland KI, Chaudry IH. Testosterone: the culprit for producing splenocyte depression following trauma-hemorrhage. *Am J Physiol*. 1998;274(6, pt 1):C1530-C1536.
24. Angele MK, Ayala A, Monfils BA, Cioffi WG, Bland KI, Chaudry IH. Testosterone and/or low estradiol: normally required but harmful immunologically for males after trauma-hemorrhage. *J Trauma*. 1998;44(1):78-85.
25. George RL, McGwin G Jr, Metzger J, Chaudry IH, Rue LW III. The association between gender and mortality among trauma patients as modified by age. *J Trauma*. 2003;54(3):464-471.
26. George RL, McGwin G Jr, Windham ST, et al. Age-related gender differential in outcome after blunt or penetrating trauma. *Shock*. 2003;19(1):28-32.
27. Wichmann MW, Angele MK, Ayala A, Cioffi WG, Chaudry I. Flutamide: a novel agent for restoring the depressed cell-mediated immunity following soft-tissue trauma and hemorrhagic shock. *Shock*. 1997;8(4):242-248.
28. Angele MK, Frantz MC, Chaudry IH. Gender and sex hormones influence the response to trauma and sepsis: potential therapeutic approaches. *Clinics*. 2006; 61(5):479-488.
29. Haider AH, Risucci DA, DiRusso SM, et al. Determination of national pediatric injury prevention priorities using the Injury Prevention Priority Score. *J Pediatr Surg*. 2004;39(6):976-978.

DISCUSSION

Gail Tominaga, MD, Honolulu, Hawaii: Although laboratory studies indicate that female rodents better tolerate the deleterious consequences of trauma and have higher survival rates than male rodents, it remains unclear whether a similar gender dimorphic pattern is evident in humans. Teleologically it makes sense that premenopausal women would have a survival advantage. However, the adult literature has been mixed.

There have been reports of improved survival in women following trauma, others that show no association, and still others that show a subset of female patients with survival advantage. Interestingly, gender differences following blunt vs penetrating trauma have also been divergent. Chaudry's group reviewed their experience at the University of Birmingham in Alabama and found that male blunt trauma patients less than 50 years old had a 2.5-times higher risk of death than females. However, male penetrating-trauma patients greater than or equal to 50 years old had a survival advantage.

Pediatric data on gender differences and outcome are sparse. The current study is a review of the National Pediatric Trauma Registry. After controlling for various factors, they found no difference in survival between genders as a whole. However, on review of trauma patients with severe injuries (NISS $\geq$ 16) and traumatic shock (based on age-determined BP [blood pressure]), they found adolescent females to have significantly lower odds of death compared with adolescent males. They found no gender difference in preadolescent children. This supports laboratory work that has demonstrated the benefits of estradiol on the inflammatory response and survival following hemorrhage and the detrimental effects of androgens on survival following trauma and hemorrhage.

I have 4 questions for the authors. Can you postulate on how the mechanism of injury (ie, blunt or penetrating trauma) might affect gender-based hormones and outcome? Do you think the relationship of female gender and survival benefit is a causal one? Can you give your thoughts on why the results have been mixed in the adult trauma literature on this topic? And finally, how do you think we should use the data demonstrated in your study? Should we be considering orchiectomy or estrogen supplementation in our severely injured male blunt trauma patients?

Dr Cornwell: Dr Haider's work points out several things, we believe, in terms of what will be an emerging and important question in outcomes as it relates to trauma patients. Over the last few decades, I have seen us kind of hitting the ceiling in terms of improving outcomes from things such as the appropriate use of antibiotics, endpoints of transfusion, trauma systems, and prehospital transport. We have been more frustrated, though, in trying to understand and address the question of host issues—a cytokine response gone awry or, in this case, the hormonal milieu of some of our patients. Therefore, it's still not clear to us why some patients with identical injuries have different outcomes.

The basic science research, as Dr Tominaga touched on, is fairly compelling. A castrated male rat does better than a noncastrated rat. Estradiol-blocked rats do worse than non–estradiol-blocked rats following trauma hemorrhage. The issue of how this relates to clinical studies is why we addressed this. At the extremes of age where males and females have a less disparate hormonal milieu is where we would expect there not to be a gender-based outcome difference, and then after adolescence on through adult life, if there is something to this, we would expect differences to become apparent. But in pursuing this, several things have become clear. It has to be a well-done multivariate analysis so that we can control for all of the interrelated variables. This is going to be the responsibility of both program committees and journal editors because this sort of outcomes research is going to be more prevalent.

We have to be very careful that we don't send the wrong messages. Our univariate analysis suggested that the girls had worse outcomes across the board, but then when we looked on multivariate analysis at the subset, and we are only talking about 700 some odd patients out of 46 000, the subset with high injury severity and blood pressures less than 90, it was in that group and that group alone where postadolescent girls actually had a survival benefit.

To get to Dr Tominaga's questions, why do we see a differential effect? We think blunt and penetrating trauma not only are different diseases in terms of response and likelihood of shock and requirement for surgical intervention and the associated neuroendocrine response associated with that, but also some of these papers rely on just anatomic injuries, and it's fairly well established, I think, that certain injury severity scores don't work well or underestimate the severity of injury with penetrating injuries. The Injury Severity Score that most of us grew up with can be no higher than 25 if a patient has a gunshot wound isolated to the abdominal compartment, and yet the New Injury Severity Score that Dr Haider described takes that into account.

Another question along those lines is why there would be mixed results, and I think that also gets to the issue of the appropriate multivariate analyses to identify just the group at risk for morbidity and mortality.

In terms of clinical application, Dr Chaudry himself has suggested that, and we are on the verge of a new era where the androgen receptor blockade flutamine may have some applications. I will say that I think that it is quite possible within the next decade or so we may be embarking on a trial for appropriate patients. I would emphasize that in a database of 46 000 patients, the appropriate subset of patients would have been on the order of 700 patients in this series.

So, I think that we are coming closer to identifying those factors in the hormonal milieu and the appropriate patients, and therefore, the next step will be transient blocking agents.

David Hoyt, MD, San Diego, California: This is a very nice study. Wonderful analysis. I personally carry estrogen in my glove compartment because I do believe the animal data. Why

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013

do you think we have trouble teasing this out of databases? Is it not in fact because we don't have the salient data point and that is what point in the estrous cycle females are? How can we get around that? If we design a clinical trial, how would we pick the right patients?

Dr Cornwell: Thanks for your comments, David. I think that is exactly right. We have to identify just the right patients. The National Study of Cost and Outcomes of Trauma (NSCOT) database that Dr MacKenzie described last year actively reviewing patients who went to a trauma center vs patients who did not go to a trauma center with similar injuries ended up showing a benefit in patients under the age of 55 who went to a trauma center. This work was a landmark, not only for the fact that we have the best study of patients not going to a trauma center, but for the statistical method of imputation that is a statistician's way of filling in gaps of missing information.

In that database, there was a survival benefit in older females vs older males. So, I think we do have to identify the right group. This probably needs to be between the ages of 15 or so and 55 and the most severely injured patients who have some significant likelihood of developing mortality.

Very quickly, let me just describe, if I could, a case. This is just a case that we had at our institution 3 years ago. I had a patient 25 years old; multiple gunshot wounds, right chest, left chest, thigh, abdomen, with bleeding; in and out of the ED [emergency department] in 15 minutes, into the OR [operating room], chest tube on the right, 1100 cc's out initially, left chest with 500 cc's; a right thoracotomy, tractotomy, beautifully documented resuscitation and blood gases by the anesthesiologist showing pH's for a period of an hour and 15 minutes of 7.03, 7.11; a prolonged period of shock. His scrotal gunshot wound destroyed his left testicle and took out seven-eighths of his right testicle, so he is left with about 6% of his testicular mass from a gunshot injury at the same time as the one that produced his prolonged period of hemorrhagic shock. He had 18 units of blood, he had a prolonged period of shock, his physiologic and anatomic Injury Severity Scores would have predicted a high likelihood of ARDS [adult respiratory distress syndrome], SIRS [systemic inflammatory response syndrome], organ failure, and even mortality. He was out of the ICU [intensive care unit] in a day. He was extubated 1 day later. There is something to this. All of the women in the audience, shame on you for what you are thinking. But, perhaps transient blockade with androgen receptor blocker in the appropriate setting would achieve the same thing without the near total castration that this patient experienced concomitant with his hemorrhagic shock.

James E. Goodnight Jr, MD, PhD, Sacramento, California: Dr Cornwell, Dr Haider, a very nice study. I presume the survivors in this database will not have a normal survival curve, that it will be worse over a long period of time, and it would raise some interesting questions with the neuroendocrine changes relative to cancer risk and so forth. But, I presume that the survival curves overall are worse than an uninjured population. Is there any difference in gender in those long-term survivals?

Dr Cornwell: We don't know because this is a pediatric trauma database that doesn't have that longitudinal follow-up, but that will be an important question to follow both in the updated studies and longitudinally. I think that is important to look at.

James W. Holcroft, MD, Sacramento: I, too, am a believer. It seems that there are at least 2 approaches in applying this analysis to future studies. One, you can block androgens, or two, you can give estrogens. If you were to block androgens, would you do so for all men, even those in the later stages of life when the levels are on the low side anyway? If you were to give estrogens, when would you give them and how long would you give them? What sort of experimental studies would you do to try to tease that out? Maybe you want to enhance immunity part of the time but suppress immunity at other times. If you were to give supplements to women, would you give estrogens to women who are in a stage of their cycle or stage of life when their estrogen levels are low or would you give them to everyone? The list of questions could go on and on. Thanks, I think this is an extremely clever study and one that could have an enormous clinical impact.

Dr Cornwell: That's a great question. I would end up yielding to basic research as much as anything. But, since there is a disproportionate representation of males among the group with severe enough injury and shock who are at risk for dying, then it would probably be an easier application to transiently block the testosterone than to promote the estrogens, and therefore, we would have that available to the majority of our patients who come to us. I think we are talking short term. I think we are talking in the first couple of days because what happens in that first day or so seems to have, at least on multivariate studies looking at surrogates for organ failure and death, a lot to do with long-term outcome even among survivors. So, I think we are looking at short-term blockage and probably androgen blockage rather than estrogen promotion.

Financial Disclosure: None reported.

©2007 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/18/2013