Alternative end points for trauma studies: A survey of academic trauma surgeons

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Introduction. *Changing the epidemiology of trauma makes traditional end points like 30-day mortality less than ideal. Many alternative end points have been suggested; however, they are not yet accepted by the trauma community or regulatory bodies. This study characterizes opinions about the adequacy of accepted end points of studies of trauma and the appropriateness of several novel end points.*
Methods. *An electronic survey was administered to all members of the American Association for the Surgery of Trauma. Questions involved demographics, research experience, appropriateness of proposed study end points, and the role of nontraditional, surrogate, and composite end points.*
Results. *Response rate was 16% (141 of 873) with 74% of respondents practicing at Level 1 Trauma Centers. The respondents were very experienced, with 81% reporting >10 years of practice at the attending level and 87% actively involved in research. The majority of respondents rated the following end points favorably: 24-hour survival, 30-day survival, and time to control of acute hemorrhage with approval rates of 82%, 78%, and 76%, respectively. Six-hour survival, intensive care unit-free survival, and days free of multiorgan failure were rated as appropriate or very appropriate less than 66% of the time. Only 45% of respondents judged the currently used end points of trauma to be appropriate. More than 80% respondents disagreed or strongly disagreed that there was no role for of surrogate or composite endpoints in research of trauma resuscitation.*
Conclusion. *There is strong interest in finding efficient end points in trauma research that are both specific and reflect the changing epidemiology of trauma death. The alternative end points of 24-hour survival and time to control of acute hemorrhage had similar approval rates to 30-day mortality.*
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Trauma remains the third most common cause of death across the entire age range, and specifically for individuals between the ages of 1 and 44 years, it is the most common cause of death.[1] During the last 30 years, improvements in trauma care have decreased the incidence of late trauma deaths, especially those occurring several or more days after injury.[2-4] Yet, many deaths still occur soon after trauma, especially from exsanguination. The unexpected and time-sensitive nature of trauma introduces difficulties unique to trauma research. In 2008 and 2009, leaders in trauma met to characterize and develop solutions to challenges to clinical trials in trauma. Cornerstone to this discussion was the necessity and difficulty of selecting good end points for research in trauma resuscitation and the desirability of efficient end points that are both specific and reflect the changing the epidemiology of trauma death.[5]

Although traditional primary measures of study outcomes like 30-day mortality performed well in

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identifying interventions that decrease late mortality, these same end points might fail to detect incremental improvements in the care of the acutely bleeding patient, adding more cost to enroll more patients and have greater follow-up, which might be challenging in trauma patients.[6-10] Suggestions included developing composite and surrogate outcome measures, a technique that has been applied to great effect in other fields of biomedical research.[5,10-12] There was also interest in the use of a shorter-term measure of traditional outcome, eg, 7-day mortality instead of 30-day mortality. These novel end points, if validated, have the potential to decrease cost, increase statistical power to detect improvements in morbidity, and to more clearly depict the effects of early treatments.

Before undertaking any efforts directed at trauma research that use nontraditional end points, it is important to define clearly the proposed outcome measures and to ensure that the results will be considered valid by the trauma community and by regulatory agencies. Providers who do not accept studies as methodologically sound will not change their clinical practice based on the results. Using the discussion of our working group as a starting point, we reviewed the relevant literature and developed definitions and brief rationales for 8 proposed end points for studies in trauma resuscitation. We then undertook this cross-sectional survey of physician-level trauma providers to better characterize the understanding, familiarity, and acceptance by the surveyed group of several proposed surrogate and composite end points of research in trauma resuscitation.

METHODS

The study was designed as a web-based census survey of members the American Association for the Surgery of Trauma (AAST). Stringent requirements for membership ensure that members are both active in caring for and/or conducting research to benefit trauma patients and have substantial training in trauma.

The survey instrument was developed based on existing recommendations.[13,14] Three key categories for inquiry were posited: background/practice environment of the provider, adequacy of traditional end points, and appropriateness of composite or surrogate end points for research. For the first and second domains, a substantial list of potential questions was generated. Each investigator then reviewed the potential questions in each category. Group discussions identified the questions perceived to be most relevant. For the third category, we undertook an extensive review of previous end points of trauma studies and of the use of surrogate and composite end point in biomedical research. A list of candidate end points was created. Each candidate end point was then given an explicit definition and a description of its rationale. Again, extensive literature search and repeated group discussions were used to select the candidate end points that were judged to be most acceptable or promising.[15-19] Finally, high-ranking items from all 3 categories were assembled into a survey designed to be completed easily in approximately 10 minutes.

Subsequently, we pilot tested the survey with the trauma faculty and fellows at our local institution. Pilot-test responses are not included in final study analysis. The results of the pilot-tests were used in an iterative process until the survey had strong face validity and acceptable completion time. The final survey is available as Appendix A (online version only).

After we obtained approval from the local institutional review board and AAST Multi-Institutional Trials Committee, we sent subjects an e-mail with an invitation to participate and a URL address to a online survey hosted by SurveyMonkey (Portland, OR), where they could indicate their consent and complete the questionnaire. Data were logged anonymously, and only one response was allowed per uniquely identified computer. Data collection began on June 3, 2011, with an invitation to participate distributed in the monthly AAST newsletter. Additional reminders were sent as isolated e-mail messages to all subjects inviting them to participate if they had not already done so 2.5, 7, and 13 weeks after the survey opened. Data collection ceased on November 5, 2011.

At the time of completion of data collection, a de-identified data set was downloaded, and responses were searched for patterns, such as all questions answered with the same number, indicating deliberate misrepresentation; such surveys were excluded from analysis.

Response rate was calculated as the number of complete surveys divided by the number of deliverable e-mail addresses reported by the AAST. General demographics of the surveyed population are reported as counts and proportions. Responses on a Likert scale to the items were grouped into favorable (response levels 5 and 4), indifferent (response level 3), and unfavorable (response levels 2 and 1) and are reported as counts as well as proportions. By consensus, a priori decision was made by the authors that well-accepted end points with approval rates of 75% or greater would take priority in our recommendations. Sensitivity analyses had been planned,