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RAUMATIC brain injury remains a leading cause of death and disability among young people worldwide. In the US it is estimated that ~ 1.4 million closed TBIs occur annually. Of these, more than 235,000 require hospitalization and 50,000 die. Since the 1970s, a number of measures have been introduced in an effort to improve survival and recovery of brain-injured patients. These include prehospital, emergency room, and intensive care measures. Despite the widespread adoption of many procedures, such as ICP monitoring, their value has been questioned repeatedly.

In 1995 an expert panel, under the sponsorship of the Brain Trauma Foundation, reviewed the world literature and made recommendations for the care of severe closed TBI. Their recommendations were updated in 2000 and again in 2007. However, despite the search for an evidentiary basis to support intensive treatment of these patients, there is as yet no universal agreement that any of the commonly used procedures is effective in preserving life or improving functional outcome. A recent critique of ICP monitoring has emphasized the lack of expert consensus.

Intracranial pressure monitoring, the basis for much of our aggressive treatment in severe TBI, has been widely used since the 1960s. However, even its use is of unproven benefit, and there are many neurosurgical units worldwide in which monitoring is not routine. Studies comparing aggressive management techniques with less intensive care have been inconclusive. The use of historical controls, the lack of randomization, and the small numbers of cases have all limited the value of such studies. There have even been suggestions that ICP monitoring, for example, is associated with poorer patient survival. Despite calls for well-controlled, randomized, multicenter trials of ICP monitoring and other elements of aggressive TBI management, none have been performed.

Analysis of previously published results is complicated by variations in practices among trauma centers, geographical differences in injury mechanisms, changes in
outcome over time, and so on. The purpose of this report is to explore the possibility that meta-analytical pooling of existing literature may help overcome these shortcomings and address the question of whether aggressive care of severe TBI improves clinical outcome. Our hypothesis is that more intensive (or “aggressive”) treatment of severe TBI improves patient outcome, as measured by rates of mortality and of favorable outcomes.

Methods

We surveyed Medline in January 2009 for English-language publications on the outcome of severe TBI. The definition of “severe” followed historical usage; it was equated with coma before Glasgow Coma Scale scores were in common use, and equaled a score of ≤ 8 thereafter. We included articles summarizing outcomes in case series containing at least 90 patients with severe closed TBIs. Data collected from each series included country(s) of origin, number of hospitals in the series, years of patient entry, total numbers of patients, and length of follow-up. Outcome variables used were deaths and “favorable” outcomes (6-month Glasgow Outcome Scale scores of 4 or 5). We included case series in which deaths, but not other outcomes, were reported at hospital discharge or before 6 months.

We separated series by years of patient enrollment and by intensity of treatment rendered. The enrollment dates were used to judge the time of each case series, rather than publication date. This was done to judge more accurately the years during which the study was actually conducted. A so-called high-intensity center was one in which relatively aggressive means of managing TBI were used for the time. Before 1996, this involved ICP monitoring of at least 50% of patients whose Glasgow Coma Scale scores were ≤ 8. Since 1996, treatment intensity was judged on whether the Brain Trauma Foundation Guidelines16 were followed. Two of us reviewed each case series to determine treatment intensity at the centers involved, and only series in which agreement could be reached were included. For some reports in which the specifics of ICP monitoring were not explicitly reported, we relied on secondary analyses, such as those of Murray98 and Ruff et al.116

The first report of a series in which patient care that might be termed “high intensity” was used was that of Becker and colleagues,10 reporting on cases enrolled between 1972 and 1976. Accordingly, we evaluated case series in which the mean time of subject enrollment was 1970 and later. For case series reporting high- and low-intensity therapy groups separately, data were treated as separate studies for analysis.

Combining data from multiple sources presents several potential obstacles. Because few series involve the same numbers of cases, there is the question of how to pool their results. If no weighting of individual series is used, smaller series will be overrepresented in the pooled result. Weighting by study size (“n-weighting”) may give too much emphasis to large case series. We used inverse variance weighting, which is a compromise14 between the two. There is also the heterogeneity of the populations studied. Different mechanisms of injury, different patient ages, definitions, and entry criteria and treatment options are among the types of heterogeneity encountered in a study of this sort. Data from multiple case series were tested for heterogeneity18 and pooled meta-analytically, by using inverse variance weighting and random effects models.41 This model corrects, within limits, for both within-study and between-study variance.

Another potential confounder is the possibility that variables other than treatment intensity affect outcome. We considered that time was likely to be such a variable, especially since there has likely been progress in TBI care over the period studied. Therefore, a case series conducted in 1975 would probably have more deaths and fewer favorable outcomes than one conducted in 2005. For independent assessment of the contributions of temporal and intensity variables to outcomes, we used meta-regression,143 a technique that combines meta-analysis with regression. An analysis of this sort can tell us whether the pooled means of the 2 treatment-intensity groups are significantly different. It can also assess whether there are temporal trends in the outcomes of the 2 intensity groups and whether the differences between the groups changes over time. We considered differences for which the probability was < 0.05 to be significant. All statistical comparisons used Stata version software 9 (StataCorp).

Results

We found data on mortality rates in a total of 127 case series, involving > 125,000 patients with severe TBI,2–7,9–15,17–30,32,34,36–40,42–49,51–58,61–71,73–75,77–79,85,87,90–102,104–116,118–122,124,126,127,129–144,149 Many reports used possibly duplicated and overlapping data, reporting more than once on some of the same patients. The use of years of patient enrollment allowed us to identify and exclude duplicates, although we elected to include overlapping series. This presented, in those series, a form of “rolling” average.

Figure 1 is a scattergram, plotting the mortality rates of case series against their mean years of case enrollment. As is evident from visual inspection, there is a downward trend over time. Patients undergoing more intensive treatment (black diamonds) appear to have somewhat lower mortality rates than do those with less aggressive care (gray diamonds). Meta-regression (Fig. 2) reveals the rate of decrease to be ~ 4% per decade (r² = 0.039, p < 0.001). This means any comparison of series by level of treatment intensity must be on a time-matched basis. In a multivariate regression analysis, treatment intensity can be shown to contribute more to the fall in mortality rate than does date of study (r² = 0.116, p < 0.001). The difference is evident in Fig. 3, where the mortality rate is plotted against the mean year of study, and the high- and low-intensity groups are plotted separately. The mortality level in the low-intensity group was almost 12% higher than in patients undergoing high-intensity treatment who were studied concurrently.

Six-month favorable outcome data were reported in 98 of the 127 series, encompassing > 41,000 patients with severe TBI. As shown in Fig. 4, meta-regression showed a modest upward trend in favorable outcomes over time, but
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no significant change ($r^2 = 0.0011$, $p = 0.376$). This allows us to pool the means of different studies without resorting to meta-regression. Patients with high-intensity treatment had a pooled mean rate of favorable outcomes of 46% (95% CI 43–49%), whereas the rate in the low-intensity group was 39.8% (95% CI 38–42%). This difference is significant ($p < 0.001$, 2-tailed t-test).

Discussion

Since the widespread introduction of ICP monitoring and intensive treatment of severe TBI, patients receiving rigorous therapy have done significantly better than their less aggressively treated counterparts. On average, their mortality rate has been 12% lower and favorable outcomes 6% higher, and these differences have been consistent over time.

Although the belief that monitoring patients with severe TBI and aggressively treating them is widely accepted, evidence supporting the practice is weak. No prospective RCTs have been reported. Comparative studies are inconclusive; not all report better outcomes in the intensively treated patients. Some recent reports have concluded that measures such as routine ICP monitoring are associated with poorer outcomes and may not be necessary in all cases. However, it is difficult to conclude cause-and-effect relationships from any of the case series reported. All used historical controls or data for which it is unclear how the level of care was chosen. Most reports involve too few subjects for adequate statistical power. The 2 large case series reported have been criticized for selection bias, because patients dying within 1 or 2 days were excluded from analysis. If aggressive care had extended the lives of the most seriously injured patients only a few days, the mortality figures would be skewed in favor of the less intensively treated group. There are other indicators that the level of care at trauma centers affects outcome after severe TBI. There is a strong association between a trauma center’s case volume and its results. Hesdorffer and Ghajar documented that larger centers were more likely to adhere to the Brain Trauma Foundation’s TBI guidelines.

Clear progress has been made in reducing deaths among patients with severe TBI. We speculate that this is the result of small, incremental changes in therapy and the diffusion of these newer treatment modalities. New monitoring techniques and therapies are being investigated continuously in the expectation that they will improve outcomes even further.

Fig. 1. Scattergram of case series of severe TBI included in the analysis. The mortality rate in each series is plotted against the mean year of patient enrollment. Data points for patients who underwent high-intensity treatment are in black, and for low-intensity treatment the data points are in gray.

Fig. 2. Graph showing meta-regression of mortality rates against time. The line represents the pooled mean rate, the gray area is the 95% CI. The x-axis represents the average year of the study, the y-axis the average mortality rate.

Fig. 3. Graph showing mortality rates of patients who underwent low-intensity treatment compared with those who received high-intensity treatment. Pooled means and 95% CI of the 2 meta-regressions are superimposed. The difference in the mean mortality rate falls from 12.5% in the 1970s to 11.5% in the 2000s. The difference between the 2 groups is significant ($p < 0.001$).
There are a number of potential limitations in our study. The use of overlapping data reported by individual trauma centers and large data repositories gives them undue representation and may bias our results. On the other hand, our data exhibit great heterogeneity in both place and time, having been gathered from widespread sites and over more than 35 years. However, we would contend that the data’s very heterogeneity makes our conclusions more generalizable. The lack of a uniform definition of “intensive” or “aggressive” treatment is unfortunate but unavoidable, in view of the evolution of TBI therapy during the period studied. Even among centers claiming to follow Brain Trauma Foundation guidelines, it is unclear how many instances of lapses in care occurred. The fact that intensive treatment lowered the mortality rate 12% but raised favorable outcomes only 6% suggests many of the patients saved by intensive treatment may have been severely disabled or vegetative at 6 months. We leave it to others to judge whether these results justify aggressive intervention. We pooled all mortality data, despite varying follow-up periods (from hospital discharge to 6 months). Recent reviews suggest, however, that patient death in the months following hospital discharge is not common enough to invalidate our conclusions. Finally, we did not stratify cases by patient age, severity, trauma center status, or other demographic variables known to affect outcome. Unfortunately, this is impossible without access to the original study databases.

We concede that this study cannot replace a well-designed and -powered prospective RCT, one that has been recommended by proponents of both sides of the intensity debate. However, it is not likely that a randomized trial will ever be performed. As recently summarized by Ghogawala et al., a neurosurgical RCT requires clinical equipoise, “genuine uncertainty within the expert medical community” about the best approach to a problem. The strong support of intensive TBI treatment by most advanced trauma centers clearly lacks equipoise. Refusal of these centers to participate in such an RCT would limit case enrollment, but participating in this type of trial raises ethical concerns. Even were an RCT to be performed, results might be inconclusive. Even small differences among study centers in details of therapy may obscure potential treatment effects, as apparently occurred in the recent hypothermia trial. Crossovers in treatment, families deciding to switch from one arm to the other, may also interfere with the intent-to-treat strategy that is integral to most RCTs.

Conclusions

We conducted a meta-analysis of clinical series of treatment for severe TBI performed after 1970, and divided patient groups into those with and without ICP monitoring and intensive therapy. Aggressive treatment is associated with a mean 12% decrease in the mortality rate and a 6% increase in favorable outcomes. This suggests that ICP monitoring and intensive treatment have a significant impact on the outcome of severe TBI.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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