Evaluation of the Impact of Implementing the Emergency Medical Services Traumatic Brain Injury Guidelines in Arizona: The Excellence in Prehospital Injury Care (EPIC) Study Methodology

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Abstract

Traumatic brain injury (TBI) exacts a great toll on society. Fortunately, there is growing evidence that the management of TBI in the early minutes after injury may significantly reduce morbidity and mortality. In response, evidence-based prehospital and in-hospital TBI treatment guidelines have been established by authoritative bodies. However, no large studies have yet evaluated the effectiveness of implementing these guidelines in the prehospital setting. This article describes the background, design, implementation, emergency medical services (EMS) treatment protocols, and statistical analysis of a prospective, controlled (before/after), statewide study designed to evaluate the effect of implementing the EMS TBI guidelines—the Excellence in Prehospital Injury Care (EPIC) study (NIH/NINDS R01NS071049, "EPIC"; and 3R01NS071049-S1, "EPIC4Kids").

The specific aim of the study is to test the hypothesis that statewide implementation of the international adult and pediatric EMS TBI guidelines will significantly reduce mortality and improve nonmortality outcomes in patients with moderate or severe TBI. Furthermore, it will specifically evaluate the effect of guideline implementation on outcomes in the subgroup of patients who are intubated in the field. Over the course of the entire study (~9 years), it is estimated that approximately 25,000 patients will be enrolled.

It is difficult to overstate the societal impact of traumatic brain injury (TBI). Annually in the United States, nearly 1.7 million victims of TBI are seen in emergency department (EDs),

275,000 are hospitalized, and over 50,000 die.[1–3] The Centers for Disease Control and Prevention (CDC) estimates that at least 5.3 million Americans (about 2% of the population) have TBI-related long-term requirements for help performing activities of daily living.[4] The direct and indirect costs of TBI totaled an estimated $60 billion in 2000.[2] While the burden of injury is enormous across all age groups, children are disproportionately affected.[5] In fact, TBI is the leading cause of death and disability in children.[6]

In major TBI (the term being used here for both moderate and severe injury), after the initial trauma ("primary brain injury"), additional secondary injury often occurs soon after the event.[1,7–11] There is growing evidence that the care provided in the first few minutes may have a significant effect on outcome. Failure to immediately optimize treatment and limit secondary injury may lead to neurologic damage that is indelible, despite subsequent heroic in-hospital efforts.[6–18] Based on these findings, evidence-based guidelines have been promulgated for in-hospital[6,7,19] and prehospital[10,19] TBI treatment.

The emergency medical services (EMS) TBI guidelines focus on the prevention and rapid correction of hypotension, hypoxia, and hyperventilation (in patients receiving positive-pressure ventilation). This is because of a large and growing literature showing the disastrous effect of these factors on outcomes.

Hypotension is common during both EMS and in-hospital TBI care[8,20,21] and significantly decreases survival.[6,8,9,20–38] A single episode is associated with a doubling of mortality, and this risk increases dramatically with repeated episodes (odds ratio = 8.1 in one study).[27] Conversely, the aggressive correction of hypotension early in the course of TBI is associated with improved outcomes.[6,7,10,22,39]

Hypoxia (O_2 saturation < 90%) occurs frequently during the prehospital care of TBI patients[13,16,31,40,41] and is associated with a major increase in mortality,[8,20,22,24,28–31,42–44] with some studies reporting as much as a sevenfold increase.[28] Even a single hypoxic measurement in the field is associated with increased risk of death.[8,42,43]

Until the early 1990s, "therapeutic hyperventilation" for TBI was commonly used because of studies suggesting it might improve outcome.[45–49] However, there is now overwhelming evidence that even mild to moderate hyperventilation is detrimental to the brain due to vasoconstriction-induced ischemia and other factors.[3,8,10,14,23,50–76] Unfortunately, inadvertent hyperventilation is extremely common in EMS when intubated patients are manually ventilated.[3,14,51,52,77–84] The resulting hypocapnea is often severe, with end-tidal carbon dioxide ($ETCO_2$) levels of <25 mm Hg in as many as one-third of cases and <30 mm Hg in two-thirds of cases.[78] Denninghoff et al.[85] identified that, in the acute setting, failure to properly control postintubation ventilation is associated with a sixfold increase in severity-adjusted mortality.

The foregoing discussion highlights why the proper management of oxygenation, ventilation, and hemodynamics are at the core of the TBI guidelines. This robust literature, along with studies showing the effect of implementing the in-hospital guidelines,[2,86–89] make it likely that implementing the guidelines in the field will significantly improve outcomes. However, the guideline development process acknowledged that the evidence

supporting the EMS TBI treatment recommendations is weak,[6,7,10,19] and no large studies have yet evaluated their effectiveness. Here we describe a large prospective, before–after, statewide study evaluating the effect of implementing the EMS TBI guidelines—the Excellence in Prehospital Injury Care (EPIC) study. EPIC is funded by the National Institutes of Health (NIH/NINDS R01NS071049, "EPIC"; and 3R01NS071049-S1, "EPIC4Kids"; ClinicalTrials.gov NCT01339702).

It is important to note from the outset that EPIC is an effectiveness study. It is not designed to identify the efficacy of specific, individual interventions. Rather, it is evaluating the effectiveness of the entire guideline "bundle" in a "real-world" setting across a vast demography and geography. This type of outcomes research goes hand-in-hand with classical randomized clinical trials aimed at identifying the efficacy of highly defined, carefully constructed, specific interventional questions.[90,91]

The objectives of the study are to evaluate the following hypotheses:

- *Overall Study Hypothesis*—statewide implementation of the adult and pediatric EMS TBI guidelines will significantly reduce mortality and improve nonmortality outcomes in patients with moderate and severe TBI.

- *Specific Hypotheses*—implementation of the guidelines will: 1) significantly reduce overall mortality, 2) significantly reduce mortality among patients who are intubated in the field, and 3) significantly improve nonmortality outcomes (e.g., hospital length-of-stay, patient disposition).

Preimplementation TBI Care in Arizona

A prestudy survey evaluating 51 agencies (covering about 75% of the population) demonstrated highly variable TBI treatment across the state of Arizona. Only half had protocols specifying target ranges for O_2 saturation or blood pressure (BP), and only one-third had specific treatment protocols. While nearly 70% of agencies had $ETCO_2$ monitoring capabilities, only one-third of these had protocols specifying postintubation $ETCO_2$ targets. No agency had implemented the guidelines, thus creating the opportunity to prospectively evaluate the effect of implementation.

METHODS

Study Design

The EPIC study is a prospective, statewide, before–after, system study[91–99] evaluating implementation of the EMS TBI guidelines throughout Arizona. EPIC has three phases (Figure 1). Phase 1 was the preimplementation ("before") phase during which baseline risk adjustment and outcome measures were collected, from 2007 until implementation (most agencies implemented in 2012). Phase 2 was a "run-in" period. For each agency, Phase 2 began at the initiation of training and continued until implementation is complete. Data from Phase 2 are excluded from the analysis. Phase 3 is the postimplementation ("after") phase. A study timeline is given in Figure 2.

Ethical Considerations

The necessary regulatory approvals for the EPIC project have been obtained from the Arizona Department of Health Services (ADHS) and the State Attorney General. The University of Arizona Institutional Review Board and the ADHS Human Subjects Review Board have approved the project and have determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitute human subjects research.

Study Setting and Population

In Arizona, a statewide EMS evaluation partnership has been developed that includes the ADHS, scientists from the University of Arizona, and over 100 EMS agencies (caring for approximately 80% of the population). This partnership implemented statewide EMS treatment changes for out-of-hospital cardiac arrest[92,93,100–102] that tripled survival.[92,100] This created the setting for conducting the EPIC project.

Inclusion criteria were as follows: patients with physical trauma (all ages) who 1) are transported directly or transferred to a Level I or II trauma center by participating EMS agencies; 2) have hospital diagnosis(es) of TBI (isolated or multisystem trauma that includes TBI); and 3) meet at least one of the following criteria: Abbreviated Injury Scale score for the head of 3, CDC Barell Matrix-Type 1 classification, or prehospital positive-pressure ventilation via bag-valve-mask, endotracheal intubation (ETI), supraglottic airway, nasal intubation, or cricothyrotomy.[6,7,10,17,19,85,95,103–107]

Exclusion criteria included injuries of the following types: 1) nonmechanical mechanisms (e.g., drowning); 2) choking/strangulation; 3) environmental injury (e.g., hyperthermia); 4) poisoning (e.g., drug overdose, carbon monoxide); 5) nontraumatic intracranial hemorrhage; and 6) other nontraumatic, acute neurologic emergencies (e.g., bacterial meningitis).

Study Protocol

Management Guidelines for EMS TBI Care—Each of the guideline recommendations[6,7,10,19] that are directly related to EMS was integrated into specific protocols and algorithms by the investigator team. Because the EMS guidelines were written to emphasize specific, actionable interventions in the field, the "translation" was direct and followed the guidelines themselves.

<u>**Overall Approach to Monitoring:**</u> Continuous oxygen saturation via pulse oximetry, continuous quantitative $ETCO_2$ monitoring in intubated patients (when available), and systolic BP (sBP) measured every 5 minutes. We performed a prestudy survey to evaluate agency monitoring capabilities across the state. All agencies have pulse oximetry, 83% have BP monitors, 70% have $ETCO_2$ monitors, and 36% have ventilators.

<u>**Overall Approach to Treatment:**</u> The essence of the EMS guidelines are the prevention and rapid correction of hypoxia, hypotension, and hyperventilation (in patients receiving positive-pressure ventilation).[6,7,10,19] Thus, the main thrust of EPIC training is focused on these issues. The details of the treatment protocols are given in Table 1.

EMS Training—Training occurs through a local and regional train-the-trainer model that has been very successful in our statewide cardiac arrest project.[92,100,101] This occurs via regional training of "master trainers" who receive a full written description of the program, explanation and scientific rationale for the protocols, and training materials. The investigators and/or lead EPIC educators then provide on-site education to teach the agency-based master trainers. This includes a detailed didactic presentation and hands-on laboratory experiences that are used by the trainers when doing the provider courses. At the agency training sites, the didactic and hands-on training is interactive and focuses on scenario-based education. The master trainer program is 3 hours and provider training is a minimum of 1 hour with optional additional modules available. A pretest/posttest evaluation is used to verify content knowledge. Each agency submits training rosters to the study coordinator to verify provider training. Recurrent training occurs via a combination of methods including the training materials on the EPIC website (www.EPIC.Arizona.edu); video training; case reviews at EMS base hospitals; e-newsletters; and multiple different "packages" of refresher training, both didactic and online. In addition, a free application for personal communication devices is available and helps reinforce learning of treatment protocols. Ongoing feedback to the agencies occurs through updates on progress of the study via multiple means and venues to providers, agency leaders, and medical directors.

Outcome and Severity/Risk Adjustment Measures—Using the Arizona State Trauma Registry (ASTR) and the EMS patient care records, EPIC has access to an extensive array of risk adjustment and outcome measures (Table 2; Data Supplements S1 and S2, available as supporting information in the online version of this paper).[91,94,108,109] The risk adjustment measures are used for inclusion or exclusion from the study and for risk stratification and analysis. The primary outcome measure is survival to hospital discharge.[7,8,10,11,17,18,23,85,86,89,95,96] The secondary outcomes are prehospital mortality, hospital days, intensive care unit (ICU) days, ventilator days, hospital complications, discharge disposition (e.g., home, long-term care facility), and trauma center costs (charges).[86–89,91]

Data Collection—Because EPIC is an ADHS-sponsored public health initiative, the State Attorney General has determined that it is exempt from HIPAA policy. The ADHS has maintained the ASTR since 2005 (with complete data since 2007). There is a detailed and explicit set of inclusion and exclusion criteria that are used by all trauma centers to determine which cases are submitted to the ASTR. Cases meeting specific EPIC study inclusion criteria are identified through the ASTR. This allows development of agency-specific lists of EPIC cases for linking the EMS patient care records to the ASTR data.

Prehospital/Trauma Center Case Linkage: Approximately 65% of EMS cases in Arizona are cared for by agencies that use paper-based systems, and the remainder use electronic patient care records. In agencies with paper-based records or with electronic patient care records where study staff do not have direct, online electronic access, the agency-specific case list is used to identify the matching patient care records by hand, and then study staff verify the linkage. Because of the high quality of the ASTR demographic data, in over 95% of cases the patient care record is easily matched by using the five "base" identifiers to

establish patient identity (first name, last name, date of birth, sex, and incident date). If an unequivocal match is not made using the base identifiers, study staff review other fields based on incident street location, incident type or mechanism (e.g., motor vehicle crash), incident time, and specific EMS and trauma center case descriptions (e.g. specific descriptions of external injuries). Such detailed searching for linkage occurs in fewer than 5% of cases. We have direct, online access to electronic patient care records for approximately 35% of study cases. The same matching process is followed for these as for paper-based agencies. Upon confirmation of a matched record, a unique identifier is established to merge the prehospital and hospital record for all future reference queries.

To demonstrate our ability to link the data, we performed a pilot study. Using the ASTR, we identified 75 consecutive severe TBI patients being brought to a trauma center by EMS and were able to match 100% of the cases and to verify that the EMS and trauma center data were available for all 75.

The EPIC electronic data warehouse is the repository for all cases meeting inclusion criteria. The trauma center data are stored on MS SQL 2008 servers, and the EMS data are stored on MY SQL 5.5 servers. Both data sets are stored on encrypted disk drives and transmitted only via encrypted file transfer or encrypted e-mail. A secure, encrypted key is used for linkage between the two data sets (Data Supplements S1 and S2).

Recent studies have identified that, in some systems, seriously injured trauma patients may be taken to nontrauma hospitals.[110–112] However, we believe that the statewide trauma system in Arizona creates a very high case capture rate for EPIC, since nearly all major TBI patients go to trauma centers (either directly or by transfer). To verify this, we used the comprehensive data from the ADHS Statewide Hospital Discharge and ED database. Because the primary outcome in the EPIC study is hospital mortality, we assessed the TBI deaths occurring in 2008. There were only 32 TBI deaths in the entire state that stayed at nontrauma centers (and, thus, were not in the ASTR). Essentially all of these were elderly patients with nonsurvivable injuries who were kept in local hospitals for supportive care. Because we have ongoing access to the discharge database, we will be able to identify TBI deaths occurring at nontrauma centers throughout the course of the study to help assess the effect of this factor on the case capture rate.

Evaluation of Guideline Compliance—The EPIC data elements deal specifically with guideline-related issues. The data extraction process from the patient care records identifies guideline-relevant information (e.g., O_2 saturation, treating with high-flow O_2, sBP, IV fluids infused). These will be used to evaluate guideline compliance.

Sample Size

The study was powered based upon the EMS-intubated TBI subgroup because sufficient literature exists to make a reasonable estimate of treatment effect size in this cohort. First, using ASTR data (2007 through 2009), we are able to estimate the number of intubated cases that will be enrolled in Phase 1 (about 4¾ years in length, including 1,391 adults and 318 children [age < 18 years]).

Because no human studies have directly evaluated the effect of the EMS guidelines, the best data available for estimating the potential benefit (and, therefore, the number of cases needed in Phase 3) come from Wang et al.,[104] Davis et al.,[17] and Denninghoff et al.[85] In these studies, intubated TBI patients transported with controlled $ETCO_2$ levels were compared to patients who had manual ventilation. These studies showed a remarkable 42% to 66% relative decrease in mortality in the properly ventilated cohorts. Based on these studies, a reasonable "best-case" estimate of treatment effect is a 42% relative reduction in mortality in intubated patients.

The study is powered based on an a priori plan of performing two sequential analyses. To calculate the power of the first interim analysis to detect a significant difference in mortality, the statistical "best-case" scenario was used (i.e., 42% relative decrease in mortality, an absolute decrease from 42.6% to 24.7% in adults, an absolute reduction from 36.9% to 21.4% in children, and a cluster effect of zero). Given these estimates for the interim analysis, in adults we will have a power of 0.99 and in children 0.77 ($\alpha = 0.01$, two-tailed) to detect a significant reduction in mortality (Fisher's exact test).[113–119]

The final analysis was powered based on a conservative treatment effect (21% relative decrease in mortality for adults and 34% decrease in children) and the assumption that there will be a significant clustering effect. The adult final analysis assumptions are as follows: Phase 1 intubated cases 1,391; Phase 3 intubated cases 987; $\alpha = 0.04$; intraclass correlation $= 0.01$; design effect $= 2.184$. Given these assumptions, the power of the study to detect a 21% relative reduction in mortality is 0.79.

Given the above calculations, we are able to estimate the number of moderate and severe, nonintubated TBI cases that will be enrolled. This is an important cohort to evaluate because previous inpatient studies make it likely that this group will benefit from guideline treatment as well.[86–89] In adults, we estimate about 10,305 cases in Phase 1 and about 8,015 in Phase 3 (about 18,320 combined). Thus, in total, we expect to enroll over 20,000 adults in the EPIC study (2,416 intubated cases + 18,320 severe, nonintubated cases, totaling 20,736). In children, we anticipate enrolling 2,389 cases in Phase 1 and 1,760 in Phase 3 for a total of 4,149 cases of intubated and nonintubated TBI. Thus, the entire EPIC study is expected to enroll approximately 25,000 cases. Data Supplements S3 and S4 (available as supporting information in the online version of this paper) contain detailed descriptions of the analysis and sample size estimations.

Data Analysis

Descriptive statistics will be reported as means and standard deviations when data are normally distributed and median and interquartile ranges or 95% confidence intervals as appropriate for nonnormal data. Generalized linear mixed models (GLMM) will be used for multivariate analyses.[120,121] The GLMM allow assessment of differences in Phase 1 versus Phase 3 for outcome variables that are binary, categorical, or continuous. Compared to logistic, multinomial, and multiple regression models, GLMM have the added advantage of simultaneously adjusting for the within-agency cluster correlation and the resulting increased variance.[120,122] Continuous covariates will be tested for linearity and, if not linear,

they will be transformed for linear fit using fractional polynomials or converted into categorical variables as appropriate.

The primary outcome variable (mortality), which is binary, will be modeled specifying a binomial distribution and logistic link function. Continuous outcome variables will use the GLMM with a Gaussian distribution and identity link function. The α-level is 0.05 for all statistical tests except the sequential analyses of the effect of implementation on mortality (interim, α = 0.01; final, α = 0.04). This gives an overall α = 0.05 for the mortality analysis (0.01 + 0.04 = 0.05). All tests are two-tailed unless specified otherwise.

Analysis of Mortality—Because controlling for injury severity is essential when assessing the effect of an intervention on trauma survival,[96,123–127] multiple complementary methodologies will be incorporated into the GLMM for this purpose. First, both the initial EMS and the initial trauma center Revised Trauma Scores (RTS) will be used in separate calculations. This is critical because guideline-based interventions may improve physiologic parameters that affect RTS (e.g., sBP). If this happens, then using only the trauma center RTS could be incorrectly interpreted as meaning that injury severity is lower in Phase 3 when, in fact, it was the EMS care that actually caused improved trauma center RTS values (and led to concomitant decreased mortality). Second, Injury Severity Score (ISS), a purely anatomic risk adjustment measure not influenced by treatment, will be used in the GLMM. In addition, a propensity score will be used to adjust for multiple severity-related parameters that are not included in the RTS or ISS (e.g., serum alcohol level).[85,104,115,128–132] The propensity score will be included as a covariate in the GLMM. Given the data available in the ASTR (Data Supplement S2), multiple demographic (e.g., insurance status, race), medical (e.g., surgical interventions), and trauma center–associated variables (e.g., length of ICU stay) will be incorporated into the propensity score.[104,130] A final propensity score will be generated by first incorporating all potentially relevant components and then reducing the list of components to optimally satisfy the balancing property.[132] This will then be assessed for optimal fit in the models by using both continuous and categorical versions.[104] A detailed statistical analysis plan is given in Data Supplements S3 and S4.

TRISS Methodology—The Trauma and Injury Severity Score (TRISS) methodology will be used to determine if the case severity has changed over time (Phase 1 vs. Phase 3). It is based on logistic regression coefficients derived from the Major Trauma Outcome Study (MTOS).[123,124] TRISS has been validated in both adults and children and is used widely for risk adjustment in trauma.[96,123–125,132–135] This will be used for stratification of survival across categories of survival probabilities and to assess for any differences in severity between study cohorts, comparing them to the reference group of the MTOS (details in Data Supplement S5, available as supporting information in the online version of this paper).

Analysis of Nonmortality (Secondary) Outcomes—Previous in-hospital reports have shown improvement in nonmortality outcomes from guideline therapy.[86–89] The effect of EMS implementation on hospital/ICU length-of-stay, ventilator days, disposition (e.g., home, skilled nursing facility), and hospital cost (charges) will be compared in Phase 1 versus Phase 3 using the appropriate GLMM.

Analysis of Variations in Implementation—In a study of this size and diversity, variations in guideline utilization are inevitable.[92,95,96,100–102,136] To test the effect of these variations, we will include interaction terms in the GLMM between variables related to guideline compliance. The fact that there will be "granularity" (e.g., variation in compliance of treating hypotension) will allow stratification of patients for subgroup analysis.

Analysis of ETCO₂ in Intubated Patients—Many animal and clinical studies have shown a profound negative effect of hyperventilation on cerebral blood flow and survival in TBI.[8,10,14,17,50–53,55–76,85,104] Because of the large number of intubated cases, EPIC will allow specific analysis of the association between outcomes and 1) various $ETCO_2$ ranges and 2) the *presence* of $ETCO_2$ monitoring (~30% of agencies do not have monitors). Since the availability of $ETCO_2$ data will vary, several approaches will be considered, including $ETCO_2$ in the GLMMs as a predictor variable. The first approach will create categorical variables: none (no $ETCO_2$ data), normocapnea, single hypocapneic, multiple hypocapneic, single hypercapneic, and multiple hypercapneic episodes. Another approach will be to analyze the subgroups that have multiple or continuous measurements by regressing each individual's $ETCO_2$ values versus time. This will allow us to determine if temporal trends in $ETCO_2$ are significant predictors of outcomes.

Analysis of Missing or Incomplete Data—Inevitably, some cases will have missing data for important covariates (although preliminary evaluation of the EMS data abstraction process reveals a very low missing data rate). Rather than removing these cases from analysis, multiple imputation will be used for missing covariates.[93,115,135,137] Imputation of missing data is generally preferable to alternatives, which are more likely to lead to biased and misleading results.[93,115,137]

LIMITATIONS

Use of Diagnostic Criteria for Study Inclusion

No studies have evaluated which patient populations should receive guideline treatment. Thus, EPIC training emphasizes implementing the protocols in patients who have mechanisms consistent with significant TBI and who had loss of consciousness. The rationale for this broadly applied protocol was that we felt it was better to have some patients who received guideline treatment, but do not end up having major TBI, than to have patients who end up having major TBI, but did not receive guideline-based treatment. This approach is consistent with EPIC being a public health initiative. However, for the purpose of inclusion in the analysis, the patients must meet diagnostic and anatomic criteria for major TBI. This is important in a before–after study because it will prevent introduction of ascertainment bias by EMS personnel being more (or less) likely to "diagnose" TBI since the EMS impression will not determine inclusion in the analysis.

We believe that one of the strengths of EPIC is that it will allow, for the first time on such a large scale, the matching of data about EMS presentation and distal risk adjustment and outcome measures in true TBI. Hopefully this will help identify the patients who will most likely benefit from guideline-based treatment, based on their clinical presentations.

Nonrandomization

While no studies have evaluated the prehospital TBI guidelines, the supporting evidence is sufficient to have led to officially vetted guidelines.[6,7,10,19,86,87,89] Thus, randomization (to guideline vs. nonguideline therapy) is probably not feasible since few, if any, systems would approve of randomization after full disclosure of the evidence. Because of this, we believe that the best available methodology to answer the critical questions proposed in this study is a large, prospective, before–after, observational trial.[90,91,95–97,102,138,139]

Variations in Hospital Care

Interpretation of observational EMS trials can be complicated by changes in trauma center care. These may affect outcomes and can be inappropriately attributed to EMS interventions. To mitigate this potential we will conduct appropriate risk adjustment using factors such as diagnoses, ICD codes, probability of survival (TRISS),[124,125,132–135] injury severity (e.g., ISS),[124,125] and trauma center care.

Secular Trends in Severity

Coincidental changes in severity can affect outcomes. To evaluate this potential, we will perform concomitant analysis of patients transported by nonparticipating agencies to trauma centers. While we will not have detailed EMS data for these patients, we will have ASTR data. This will allow analysis for secular trends in demographics, injury diagnosis/severity, treatment, and outcomes, thus serving as a concurrent "control."

Hawthorne Effect

During Phase 1 (before implementation), any potential differences between the retrospective and prospective groups will be assessed. This will yield useful information about the potential for an observer/Hawthorne effect that might occur simply because it is known that data are being collected.

CONCLUSIONS

The societal burden of traumatic brain injury is immense. While the potential for reducing morbidity and mortality by early treatment appears to be great, the effectiveness of the emergency medical services guidelines remains unproven. The Excellence in Prehospital Injury Care study will evaluate the effect of implementing the traumatic brain injury guidelines across a vast network of emergency medical services systems with an estimated enrollment of approximately 25,000 patients over the course of the study. Demonstrating the effect of guideline therapy would potentially lead to widespread implementation of the effective interventions. This could dramatically reduce morbidity and mortality from this major public health problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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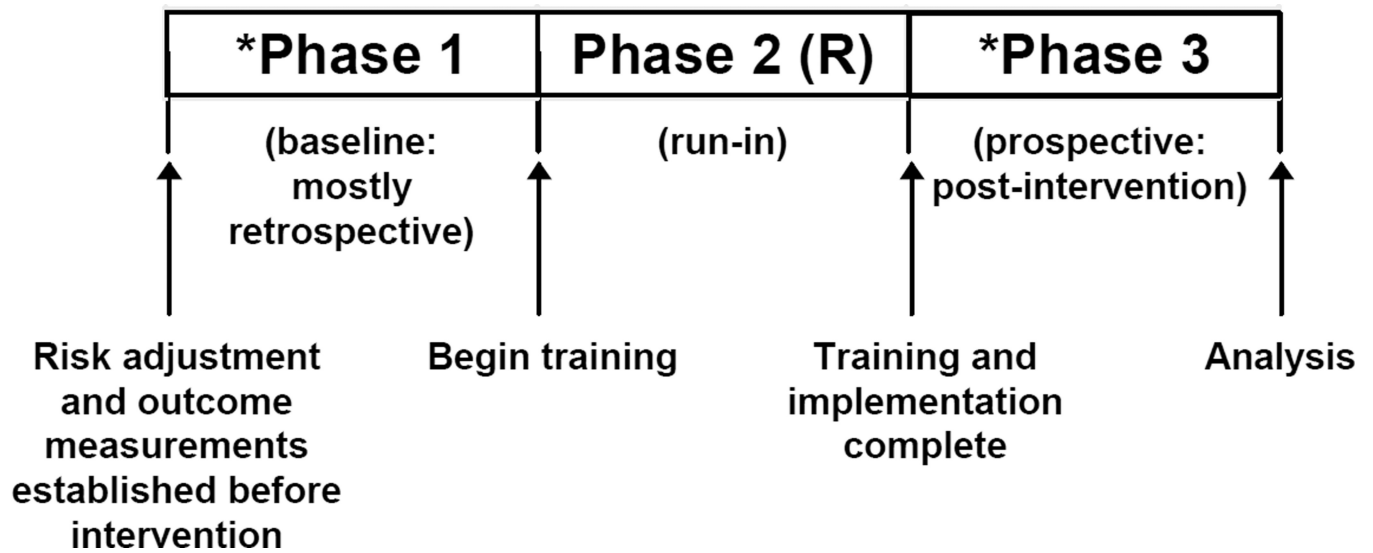**Figure 1.**
EPIC study design before-after system evaluation. *Note: Start and end dates for phases are different for each agency. EPIC = Excellence in Prehospital Injury Care; "R" = "Run-in" (training/implementation) phase during which cases are removed from the analysis
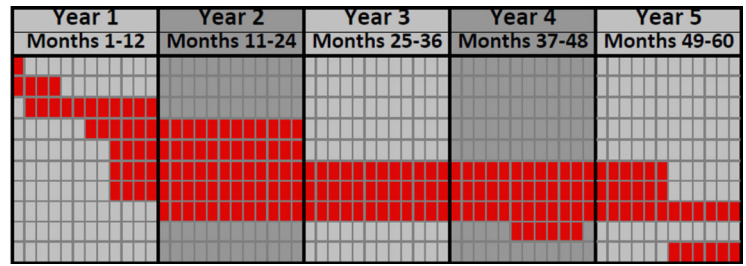
Figure 2.
EPIC study timeline, tasks, and milestones. EPIC = Excellence in Prehospital Injury Care.

Table 1

Specific, Guideline-based Management EMS Protocols

Age definitions* for monitoring and management[6,19]

Infant: 0 to 24 months

Child: 2 to 14 years

Adolescent: 15 to 17 years

Adult: 18 years and older

Management of airway/oxygenation

Prevention, identification, and treatment of hypoxia (O_2 saturation < 90% and/or cyanosis) is a major emphasis.[6–8,10,19,20,22,44] Care is initiated by continuous high-flow O_2 for all *potential* TBI cases. If high-flow O_2 fails to correct hypoxia, airway repositioning maneuvers are performed. If this does not restore eupoxia, or if there is inadequate ventilatory effort, bag-valve-mask (BVM) ventilation is performed using appropriate airway adjuncts (e.g., oropharyngeal airway). If airway compromise or hypoxia persists, ETI is performed if an experienced ALS provider is available.[6–8,10,11,19,40,140] Following ETI, tube placement is confirmed via multiple means including $ETCO_2$ detection/capnography.

Management of ventilation

Special emphasis is placed on identifying and treating hypoventilation as well as preventing hyperventilation when assisting ventilation.

Hypoventilation (ineffective respiratory rate for age, shallow or irregular respirations, periods of apnea, or measured hypercarbia): if there is evidence of hypoventilation despite high-flow O_2 therapy, assisted ventilation is initiated via BVM and, if ineffective, ETI is performed.[6,7,10,19,51,52,140]

Intubated patients: $ETCO_2$ target is 40 mm Hg with careful attempts to maintain $ETCO_2$ between 35 and 45 mm Hg when monitoring is available.[6,7,10,14,15,52] All agencies are encouraged to use ventilation rate timers and flow-controlled ventilation bags to assist in maintaining age-appropriate ventilatory rates and decrease the risk of inadvertent hyperventilation.[6,7,10,51,52,77,78,80–84] Target initial ventilatory rates are from the pediatric and prehospital TBI guidelines:[6,10,19] *infants, 25 breaths/min; children, 20 breaths/min; adolescents/adults, 10 breaths/min.

Mechanical ventilation: When available, ventilators will be used postintubation to optimize ventilatory parameters and O_2 therapy.[6,17,51,52,141,142] Target tidal volume will be 6 to 7 mL/kg with rates adjusted to keep the $ETCO_2$ within target range. This is consistent with the TBI guidelines and the recent literature showing that intrathoracic pressure, lung mechanics, hemodynamics, and intracranial pressure are optimized by this tidal volume compared to the "classic" 10 to 12 mL/kg that remains common in EMS and other settings.[51,77,142–147]

Nonintubated patients: All relevant monitoring/treatment will be applied except $ETCO_2$ monitoring.

Ventilation for impending cerebral herniation: During *early* TBI management (prehospital/ED), the guidelines recommend strongly against any "prophylactic hyperventilation" even with severe brain injury, because there is strong evidence that this is detrimental. The guidelines recommend hyperventilation *only* for *obvious* signs of herniation. In such cases, only *mild* hyperventilation is recommended:[6,7,10,19] *infants, 30 breaths/min; children, 25 breaths/min; adolescents and adults, 20 breaths/min. The $ETCO_2$ target range during "mild therapeutic hyperventilation" is 30 to 35 mm Hg.

Management of blood pressure

Hypotension: Most TBI studies have used sBP < 90 mm Hg to identify hypotension in adults and older children.[8,20–23,25–27,30–38] In the pediatric guidelines, hypotension is defined as sBP below the fifth percentile for age. This is estimated using the formula [70 mm Hg + (age × 2)][6,10,19,148]

Age-appropriate definitions for hypotension

Adults: < 90 mm Hg

Adolescents: < 90 mm Hg

Children age   10 years: < 90 mm Hg

Infants and children ages younger than 10 years: 70 mm Hg + (age × 2)

Adults and children age 10 years and older

Treatment of hypotension: The TBI guidelines recommend keeping the sBP   90 mm Hg.[6,7,10,19] A single sBP measurement < 90 mm Hg will initiate intravenous (IV) fluid resuscitation with an initial bolus of 1 L of normal saline or Ringer's lactate in adults and adolescents and 20 mL/kg in older children. This will be followed by IV fluid administration at sufficient rate and volume to keep sBP   90 mm Hg.[6,7,10,19]

Treatment of hypertension: In TBI, treatment of acute hypertension is not recommended.[6,7,10,19,149] However, IV fluids will be restricted to a minimal "keep open" rate in patients with sBP 140 mm Hg.

Infants and children age younger than 10 years

Treatment of hypotension: For hypotension or other signs of shock, isotonic fluids will be given. Sufficient volume (via 20 mL/kg boluses every 5 minutes) will be given to return sBP to at least [70 mm Hg + (age × 2)].[6,10,19] Intraosseous access should be attempted if there is hypotension or other signs of shock and peripheral venous access cannot be quickly established.

Treatment of hypertension: As with adults and older children, treatment of acute hypertension is not recommended in TBI.[6,7,10,19,149] IV fluids will be restricted to a minimal keep open rate in infants/ young children with sBP 100 mm Hg.

$ETCO_2$ = end-tidal carbon dioxide; ETI = endotracheal intubation; TBI = traumatic brain injury.

Table 2

Severity/Risk Adjustment and Outcome Measures

Risk adjustment/severity measures[91,108,109] (from EMS [CE1]patient care records and the ASTR)

> *Demographics/history/EMS system response:* Age, sex, mechanism of injury (ICD-9/10-CM E-code Injury Descriptors), preexisting medical conditions, EMS time intervals[150] (e.g., interval from 9-1-1 call to trauma center arrival).

> *Prehospital data:* Initial and additional respiratory rate; heart rate; sBP; Glasgow Coma Scale (GCS) score; O_2 saturation and $ETCO_2$; prehospital procedures including IV fluids given (mL), ETI, rapid sequence intubation, supraglottic airway use, RTS, prehospital impression (conditions/"diagnoses") by EMS.

> *Trauma center data:* The ASTR data set contains nearly 200 data elements related to demography, severity, risk adjustment, treatment, procedures, and outcomes. Examples (detailed data set in Data Supplement S3)—initial and additional vital signs, GCS, RTS, probability of survival (TRISS), procedures (ICD-9/10-CM procedure codes), need for emergent surgery, need for emergent neurosurgery, intracranial pressure monitoring (yes/no), Abbreviated Injury Scale score, ISS, injury diagnoses (ICD-9/10-CM N-codes), preexisting comorbidities, hospital complications, hospital/ICU length of stay.

Outcome measures[7,8,10,11,17,18,23,85,86,95,96]

> *Primary outcome measure:* Survival to hospital discharge.

> *Secondary outcomes:* Prehospital mortality (patients with spontaneous circulation on EMS arrival who then require cardiopulmonary resuscitation by EMS and have no signs of life on arrival at the trauma center), hospital days, ICU days, total ventilator days, hospital complications, discharge disposition (e.g., home, long-term care facility, inpatient rehabilitation), and trauma center costs (charges).

ASTR = Arizona State Trauma Registry; $ETCO_2$ = end-tidal carbon dioxide; ETI = endotracheal intubation; ICU = intensive care unit; ISS = Injury Severity Score; RTS = Revised Trauma Score; TRISS = Trauma and Injury Severity Score.