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The Pediatric Guideline Adherence and Outcomes Program in Severe Traumatic Brain Injury: A Single Center Hybrid Implementation-Effectiveness Study

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Abstract

Background—There are no tested in-hospital traumatic brain injury (TBI) care programs. We examined the implementation and effectiveness of the Pediatric Guideline Adherence and Outcomes (PEGASUS) program in severe pediatric TBI.

Methods—In this prospective hybrid implementation-effectiveness study, we examined service provision, achieving key performance indicator (KPI) adherence, and discharge outcomes in children (age < 18 years) with severe (GCS ≤ 8) TBI (trauma mechanism and imaging findings)

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associated with the PEGASUS program. Implementation outcomes and achieving KPI adherence are described. Poisson regression with robust standard errors estimate the association between achieving KPI adherence and discharge outcomes.

Findings—Among the 199 participants 11.9 (12.7) years who received the PEGASUS program between 2011-2017, 193 (97%) program recipients had severe TBI. Adherence to at least one KPI was achieved in 101 (96.2%), and 44 (41.9%) achieved adherence to all three KPIs. Program participants achieved KPI adherence to hypocarbia KPI (72.4%), nutrition KPI (81.4%), and cerebral perfusion pressure KPI (64.3%). Adherence to KPI-nutrition was associated with 2.70-fold (95% CI 1.54-4.73) higher discharge survival and 3.05-fold (95% CI 1.52-6.11) more favorable discharge disposition. Adherence to KPI-CPP was also associated with higher discharge survival (RR 1.33; 95% CI 1.12-1.59) and favorable disposition (RR 1.53; 95% CI 1.19-1.96). Adherence to each additional KPI was significantly associated with 1.27 (95% CI, 1.12-1.44) times higher survival rate and 1.46 (95% CI, 1.23-1.72) times higher favorable discharge disposition in a dose-response fashion.

Interpretation—The new multilevel hospital-wide high fidelity and comprehensive PEGASUS program achieved favorable levels of service provision, KPI adherence and was associated with favorable discharge outcomes across the full spectrum of pediatric patients with severe TBI. Adherence to CPP, nutrition and hypocarbia KPI targets are essential program components and associated with favorable discharge outcomes. The PEGASUS program may benefit children and adolescents hospitalized with severe TBI.

INTRODUCTION

Worldwide, traumatic brain injury (TBI) is a leading cause of pediatric morbidity and mortality.¹ The Brain Trauma Foundation publishes evidence-based guideline recommendations to improve severe TBI outcomes,² which clinicians can use to design TBI care programs. However, there are no TBI care programs and TBI guideline adherence is variable.^{3,4}

A 2014 retrospective multicenter observational study of 236 pediatric patients from 5 U.S. centers showed that higher adherence to indicators in the TBI guidelines is associated with improvement in discharge survival, and that adherence is cost effective.^{3,5} Achieving adherence to three acute care key performance indicators (KPIs) of adherence (avoidance of any hypocarbia [$\text{PaCO}_2 < 30\text{mmHg}$] in absence of cerebral herniation, maintenance of all cerebral perfusion pressure [$\text{CPP} > 40\text{mmHg}$], and early nutrition start) during the first 72 hours are the main drivers of the relationship between TBI guideline adherence and outcomes.³ Yet, there are barriers to achieving KPI adherence: 1) lack of guideline credibility/applicability, 2) lack of implementation, dissemination, and enforcement, and 3) suboptimal provider culture, communication styles, and attitudes towards protocols.⁶ However, clinicians and families want consensus, interdisciplinary cooperation, and facilitated adherence to evidence based care.⁷

Two pediatric TBI studies suggest that implementation science approaches facilitate TBI guideline adherence in children with severe TBI.^{8,9} In 2012, Pineda and colleagues reported that compared to the six year pre-implementation period (N=63), the six year post- pediatric

neurocritical care unit implementation programme (N=60) was associated with more favorable discharge disposition from 48% to 67%.⁸ However, this study only examined intracranial pressure (ICP) monitoring, and patient level adherence was not evaluated. While O’Lynn et al. reported an increase in discharge to home from 36% to 69% after implementation of a standard care pathway,^{8,9} patient level adherence was not studied and the sample size was small (N=29).

Implementation science frameworks and optimization of systems of care are considered essential to achieve guideline adherence but there are no prospective studies testing implementation strategies to improve outcomes in either adult or pediatric TBI.^{10,11} We tested the implementation and effectiveness of a new hospital wide program in severe pediatric TBI. We hypothesized that high-fidelity implementation of the hospital-based PEGASUS program would achieve acute care KPI adherence, and that achieving KPI adherence would be associated with better discharge outcomes.

METHODS

In this hybrid implementation-effectiveness study, we prospectively examined the effect of the PEGASUS program (implementation strategy) on program service provision (implementation outcomes), achieving KPI adherence (evidence based practice), and discharge outcomes (health outcomes) in children with severe TBI. The University of Washington IRB approved this study.

Setting

Harborview Medical Center is a 450-bed mixed Level-1 adult and pediatric trauma hospital and serves the 5-state (Washington, Wyoming, Alaska, Montana, Idaho) Pacific Northwest region. The 18 bed PICU admits approximately 120 pediatric trauma patients with TBI annually. Operating rooms (OR) are staffed 24 hours per day and 7 days per week, the PICU is staffed by 10 pediatric intensivists and six neurosurgeons, and rehabilitation physicians are consulted early. Pediatric, general surgical and neurosurgical residents provide 24-hour in-hospital coverage. Patients with moderate-severe TBI are routinely admitted to the PICU and patients with mild TBI are admitted to the PICU as deemed necessary. Patients are discharged from HMC to either home, Seattle Children’s Hospital in-patient rehabilitation unit, skilled nursing facility, or long term acute care facilities.

PEGASUS Program (Implementation strategy)

There was no formal TBI program or pathway before May 2011 when PEGASUS program development began. The PEGASUS program was implemented over a three-year period hospital wide (emergency department [ED], PICU, OR, and hospital ward); the program was fully implemented in May 2014.³ We evaluated the PEGASUS program from May 2011 - June 2017. Data from first 14 program participants were examined for program adoption in early interim analysis.¹²

Pre-program patients refers to patients examined between December 2006-April 2011,¹³ and the program period refers to the cohort of 199 participants with expanded inclusion criteria between May 2011 to July 2017. Data was gathered on pre-program patients who were

expected to survive beyond 72 hours and receive mechanical ventilation for at-least 48 hours from previously used strict inclusion criteria (age <18 years, admission GCS < 8, head abbreviated injury scale (AIS) > 3, TBI diagnosis by head CT, mechanical ventilation for 48 hours, and alive for 72 hours). Starting with program implementation in May 2011, data was gathered on patients under age 18 years with severe TBI (GCS < 8 and TBI diagnosis by head CT) at any point during hospitalization (expanded inclusion criteria). We also allowed for the clinical pathway to be initiated and terminated when children are diagnosed and recover from severe TBI, respectively; irrespective of diagnosis of abusive head trauma or duration of anticipated need for pathway use.

PEGASUS program development was informed by prior work,^{3,6,7} by Damschroeder's Consolidated Framework for Implementation Research, and by the Comprehensive Unit-Based Safety Program.^{13–17} The interdisciplinary multi-level PEGASUS program considers stakeholder perspectives, value-added processes of care, and a flexible clinical care pathway (Appendix Supplementary Table 1). The clinical care pathway contains recommendations specific to BTF guideline based severe TBI care (general critical care per usual protocol), specifies desired timing and ordered processes of TBI care, and is responsive to scope of clinical practice.^{2,18}

Thus, although the PEGASUS program involves other indicators, this study focused on CPP, nutrition, and hypocarbia KPI as targets for the PICU, and adopted CPP and hypocarbia targets for the OR and ED because of the prior work suggesting their importance. The hospital ward pathway contains general pediatric care recommendations and plans for discharge home and follow up. Children with polytrauma and abusive head trauma are included.⁷ The program allowed PICU nurses to initiate clinical pathway use at any point patients were diagnosed with severe TBI and leveraged OR use of activated decision support routinely used to support pediatric TBI anesthesia care. The PEGASUS program includes strategies known to work in acute care and intentionally addressed potential moderators such as comprehensiveness of hospital policies, strategies to facilitate implementation, and quality of delivery that facilitate implementation of clinical innovation.¹²

Program Service Provision (Implementation outcomes)

Program service provision was assessed in terms of implementation fidelity and program penetration. Fidelity measures were organizational frequency of hospital meeting occurrence, time [hours] to adoption of pathway, timely tasks completion (i.e., organizational presentations, and activation of clinical decision support for eligible participants in the OR, ED length of stay [LOS]) and provider (ED nurse signature on ED pathway, start of PICU clinical care pathway within 24 hours of severe TBI diagnosis, daily PICU nursing documentation in pathway, use of PICU pathway through PICU discharge and physician documentation of participant as a “PEGASUS” patient in medical record) level. We examined program penetration as percent participants with severe TBI receiving the clinical care pathway.

Achieving KPI Adherence (Evidence based practice)

The three KPIs were: early start of enteral (oral or tube feeds) or parenteral nutrition (KPI-nutrition), avoidance of any unwanted hypocarbia (KPI-hypocarbia; $\text{PaCO}_2 < 30\text{mmHg}$ in absence of brain herniation), and maintenance of all CPP $> 40\text{mmHg}$ (KPI-CPP) for 72 hours after severe TBI diagnosis since we have previously demonstrated that they are the main KPI drivers of the association between acute care indicators of guideline adherence and outcomes in pediatric TBI.^{3,12} The hypocarbia variable was conditional on the presence/absence of cerebral herniation. When hourly ICP data were not available (i.e. no ICP monitor placed), mean arterial pressure (MAP) data substituted for CPP data by subtracting 10mmHg from each measured MAP value and because many participants received severe TBI care guided by MAP.¹⁹ The hypocarbia analysis was restricted to those participants with PaCO_2 data since most participants had a PaCO_2 value, care was guided by PaCO_2 and because strong correlation between end-tidal CO_2 and PaCO_2 cannot be assumed in trauma.^{20,21} PaCO_2 and CPP data were examined hourly; the lowest value was used to increase the sensitivity of non-adherent event. All three KPIs were coded as yes/no only when all measured values fell into biologically plausible ranges, and only when 100% of KPI target values were achieved for each participant. Adherence rates for each KPI were determined for each participant.

Discharge Outcomes (Effectiveness/Participant outcomes)

Exposures were achieving KPI adherence (yes/no, number of KPIs, and combination of KPIs). Outcomes were discharge survival and discharge disposition. In-hospital death was examined. Disposition was categorized as favorable (discharged home or inpatient/outpatient rehabilitation service) or unfavorable (in-hospital death or discharge to skilled nursing facility or discharge to long term facility). Discharge GCS and TBI severity category were abstracted from the medical record verbatim as recorded at discharge, regardless of whether participants had a diagnosis of severe TBI care at some point during hospitalization.

Data Abstraction

Hospital admission logs captured the number of PEGASUS program eligible participants. Demographic, injury severity, and discharge outcomes were obtained from the Harborview Trauma Registry. Implementation fidelity measures were abstracted from the clinical care pathway packets (TBI care) and from meeting minutes (organizational). Key performance indicator data were abstracted from review of completed pathway packets, anesthesia information management systems, and the electronic medical record.²² The severity of TBI at ED admission, PICU admission and discharge were abstracted as recorded.

Statistical Analyses

We used descriptive statistics to examine clinical characteristics, injury characteristics, implementation fidelity, time to nutrition start, and achieving KPI adherence. For KPI-nutrition and KPI-CPP, we used the entire cohort of eligible program participants. For KPI-hypocarbia, analyses were limited to the subset of severe TBI patients to whom it applied; participants without brain herniation.

When comparing pre-program to program participants, we restricted analyses to patients who met strict inclusion criteria at any point between 2011 and 2017; these participants are labeled as the “strict comparison group.”

Boxplots were used to examine the distribution of adherence to KPIs among those in whom complete adherence was not achieved. The distribution of PaCO₂ and CPP data over the first 72 hours by pre- and post-program participation were examined using Loess plots fitted with hour-by-hour standard deviations.²² We also examined discharge outcomes for participants by combinations of achieved KPI adherence. As some program participants did not contribute data on all three KPIs, description and analyses of KPI dose effects and combinations of adherence to all three measures were conducted only on the subset of participants with data on all three KPIs. Median and interquartile range (IQR) were used to describe variables not normally distributed. To represent program application to all children with severe TBI, we used unadjusted Poisson regression with robust standard errors to estimate: 1) the dose-response effect of number of achieved KPI adherence on discharge outcomes (Model a), 2) the association between achieving adherence to each KPI and discharge outcomes (Models b,c,d for KPI-hypocarbica, KPI-CPP, and KPI-nutrition, respectively), and 3) the relative contribution (relative risk) of each KPI to discharge outcomes when all three KPIs were included in a single model (Model e)²³ As some of the most critically ill participants might not survive before any nutrition start, we restricted Model d to those who survived over 24 hours after admission to avoid immortal time bias. We conducted a sub-analysis to understand how results are influenced by covariates. For models a-e, we selected covariates from an a priori list of potentially outcome-associated variables. These included age, sex, abusive TBI, polytrauma, AIS-head, AIS-abdomen (only for KPI-nutrition related models), highest non-head AIS and GCS at ED admit. By using the best subsets leaps-and-bounds algorithm, covariates were selected when the corresponding model generated the largest adjusted R-squared value among all possible combination of possible subsets from the aforementioned list.²⁴ Covariate list, selected covariates and adjusted R-squared values for corresponding models are summarized in Appendix Supplementary Table 2.

Since not all participants received ICP monitoring, and the clinical course may differ between participants with and without ICP monitors, we conducted a post hoc sensitivity analysis to examine discharge outcomes of participants who achieved and did not achieve KPI-CPP adherence by ICP monitoring status. Since nutrition start may be deferred in the most critically ill but may be relevant to evaluating program effects on achieving KPI adherence, we examined the relationship between program implementation and KPI adherence for nutrition in two ways: 1) excluding deaths within 72 hours, and 2) for all participants.

To examine the effect of early sedation and paralysis on GCS and TBI severity categorization, McNemar’s test was used to assess agreement of severe TBI categorization (GCS < 9) between ED admission and PICU admission, and also between ED admission and hospital discharge.

To provide more granularity across the age spectrum, age was categorized into 0-4, 5-9, 10-14, and >14 years. Sex, abusive head trauma and polytrauma were coded as binary variables, whereas AIS-head, AIS-abdomen and total GCS at ED admit were coded as continuous variables.

All statistical analyses were performed using STATA version 14.2 and R software package version 3.4.3.^{25, 26}

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RESULTS

Program Service Provision

Quarterly hospital reporting occurred at 100% of pre-specified meetings. Mean ED length of stay was $3 \cdot 6 \pm 1 \cdot 2$ hours, and ED pathway use occurred in 88% of eligible participants. In the OR, activated decision support was deployed in 98% of eligible cases. In the PICU, clinical care pathway was adopted (used) within 24 hours of severe TBI diagnosis in 98% of eligible cases. Daily nursing documentation of attempted/completed PICU pathway tasks occurred in 98% of eligible cases; 2% were missing during initial months 0-3. Critical care physicians documented clinical care pathway use in 91% of medical record admission notes.

Two hundred and thirty nine patients were diagnosed with severe TBI at some point during hospitalization during the study period; 18 (7.5%) patients did not receive the program (missed cases). Figure 1 shows that among the final 199 program participants, 193 (97%) participants had severe TBI and six participants had moderate TBI (Figure 1). Of the 24 participants diagnosed with mild-moderate TBI at ED admission, 18 (75%) deteriorated in hospital to severe TBI, with median (IQR) time to GCS deterioration after ED admission of $3 \cdot 9$ (6.3) hours; 20% deteriorated after the first 24 hours. Appendix Supplementary Table 3 describes pre-program patients, the subgroup of program participants meeting strict inclusion criteria, and the overall cohort of 199 program participants.

Program participants were 11.9 (12.7) years, mostly (70.9%) male, and sustained motor vehicle crash (33.2%; Table 1). Fifteen (7.5%) patients were diagnosed with abusive head trauma and 86 (43.2%) patients had polytrauma. Median admit GCS motor score was 1(0), head AIS score was 5(1), and injury severity score was 29 (16), respectively. Sixty-one (30.7%) patients were treated in the OR prior to PICU admission. Median admission ED and PICU GCS scores were 3(3) and 8(5), respectively. There was no relationship between ED and PICU GCS ($r=0.04$) but PICU admission GCS correlated with median PICU GCS during the first 12 hours ($r=0.85$).

Appendix Supplementary Table 4 shows that 88 (44.2%) participants had a change in recorded TBI severity classification at least once between ED admission, PICU admission and at discharge but severe TBI at ED admission was associated with severe TBI at PICU admission ($p < 0.001$) and at hospital discharge ($p < 0.001$). Fifteen participants had abusive

head trauma; 12 (80%) had severe TBI at some point during hospitalization. One hundred and ninety three program participants had severe TBI at some point during hospitalization and 61 program participants had severe TBI diagnosis at discharge. Overall, 72 (36.1%) participants from the whole cohort, 63 (36%) participants with severe TBI at ED admission, and 53 (46.5%) participants with severe TBI at PICU admission received ICP monitoring. Of those with ICP monitoring, 71 (98.6%) had one or more GCS < 9, and one participant had one or more GCS < 13. Of the 15 participants with abusive head trauma, three (20%) participants had ICP monitoring.

Of 199 members of the cohort, 160 (80.4%) participants survived to hospital discharge, and 135 (67.8%) had favorable discharge disposition. Appendix Supplementary Table 3 shows that compared to 55.4% of pre-program participants, 63% of program participants with similar inclusion criteria had favorable disposition.

Program Implementation and Achieving KPI Adherence.

Among the 199 program participants, adherence to at least one KPI was achieved in 101 (96.2%) participants, and 44 (41.9% of 105 who contributed all three KPI data) participants achieved adherence to all three KPIs (Supplemental Figure 1).

Among all 199 program participants, adherence to KPI-CPP, KPI-nutrition, and KPI-hypocarbia was achieved in 64.3%, 72.4%, 81.4%, respectively. Adherence to KPP-nutrition was 94.6% when analysis was restricted to those who survived beyond 72 hours (Figure 2). Among strict criteria program participants, adherence to KPI-CPP, KPI-nutrition, and KPI-hypocarbia was achieved in 60.0%, 97.0%, 60.0%, respectively. Median (IQR) time to nutrition start was 28 (23) hours (modal 12 hours) for pre-program participants and 24 (26) hours (modal 16 hours) among similar program participants (strict comparison). Among the 15 infants with abusive head trauma, adherence to KPI-CPP, KPI-nutrition, and KPI-hypocarbia were achieved in 26.7%, 66.7%, and 57.1%, respectively. There was no difference in achieving adherence to KPI-CPP, KPI-nutrition, or KPI-hypocarbia between preprogram patients and the subgroup of program participants who met strict inclusion criteria.

Although not statistically significant, supplemental Figures 2a and 2b suggest a reduced spread of outliers and shorter time to KPI-nutrition start, among participants who did not meet 100% KPI adherence goals. Similarly, Figures 3a and 3b suggest reduced variation KPI-CPP and KPP-hypocarbia over the first 72 hours after severe TBI diagnosis.

Achieving KPI Adherence and Discharge Outcomes.

Appendix Supplementary Table 5 shows a beneficial dose-response effect between achieved KPI adherence and discharge outcomes. Unadjusted, adherence to each additional KPI was significantly associated with 1.27 (95% CI, 1.12-1.44) times higher survival rate and 1.46 (95% CI, 1.23-1.72) times higher favorable discharge disposition, respectively. This association remained after adjusting for abusive TBI, head AIS, highest non-head AIS (only for model with disposition as outcome) and ED GCS. Appendix Supplementary Table 6 shows discharge outcomes of program participants in relation to the combination of KPIs where adherence was achieved.

Figure 4a shows that higher discharge survival was associated with achieving adherence to KPI-CPP (RR 1.33; 95% CI 1.12-1.59) and KPI-nutrition (RR 2.70; 95% CI 1.54-4.73) targets; the point estimate suggests that adherence to the hypocarbia target may be important for discharge survival (RR 1.11; 95% CI 0.93-1.33) but did not achieve statistical significance. Figure 4b shows that adherence to KPI-CPP and KPI-nutrition were also associated with favorable discharge disposition (RR 1.53; 95% CI 1.19-1.96 and RR 3.05; 95% CI 1.52-6.11); the point estimate suggests that adherence to the hypocarbia target may be important for better discharge disposition (RR 1.25; 95% CI 0.94-1.66) but this did not reach statistical significance. There were no changes after adjusting for corresponding covariates. Sensitivity analysis supported the robustness of the findings, despite the limitations introduced by assumptions on ICP and CPP values in non-monitored and monitored patients. In other words, there were no changes when KPI-CPP effects were examined only among those with ICP monitoring. Appendix Supplementary Table 7 describes outcomes by ICP monitoring status and KPI-CPP adherence for the smaller number of patients with ICP monitoring.

When all three KPIs were entered in the same model, the association between adherence to the KPI-nutrition and discharge outcomes and the association between adherence to the KPI-CPP and favorable disposition remained significant (Appendix Supplementary Figure 3a and 3b). The point estimate for the relationship between the KPI-CPP and discharge survival (RR 1.10; 95% CI 0.97-1.26) as well as for the association between the KPI-hypocarbia and discharge survival (RR 1.09; 95% CI 0.98-1.20) and favorable discharge disposition (RR 1.21; 95% CI 0.97-1.52) suggests that these targets may be important.

DISCUSSION

The two main findings of this hybrid implementation-effectiveness study in children representing the full spectrum of severe pediatric TBI are that: 1) PEGASUS program implementation achieved favorable levels of service provision and KPI adherence, and 2) achieving KPI adherence early after severe TBI diagnosis was associated with favorable discharge outcomes. This study confirms the important role of CPP, nutrition and hypocarbia as beneficial KPI targets in the context of program implementation. The flexibility of the PEGASUS program allows for children with mild-moderate TBI who deteriorate in-hospital to benefit.²⁷ This is the first study to examine both implementation and effectiveness of a hospital wide program to improve TBI care and outcomes.

Traumatic brain injury knowledge generation cannot improve care and outcomes unless organizations and providers know how to translate evidence into practice.^{5, 28-30} The TBI guidelines do not specify “how” to achieve TBI care goals.² Hence, clinicians have no roadmap for implementing evidence-based TBI treatments. The PEGASUS program, which includes a number of components, uses implementation science frameworks, a multilevel approach, and tailored clinical pathways, appears to be an effective organizational tool to increase evidence-based practice and improve outcomes in children with severe TBI. While successful implementation and favorable discharge disposition may be driven by a complex set of factors such as organizational support, reducing variation in provider behavior and by facilitating patient level adherence, achieving KPI adherence served as an indicator of

program service provision and emerged as important to outcomes. Present data confirm prior findings that achieving adherence to KPI targets during the first 72 hours after severe TBI benefits discharge outcomes, and may benchmark organizational performance.³

Most PEGASUS participants achieved adherence to one or more KPI targets, and achieving KPI adherence for all three indicators was high when considering the clinical context. For example, maintenance of all CPP (all patients), and avoidance of any unwanted hypocarbia in patients without brain herniation are considered critical therapeutic strategies to prevent cerebral ischemia and may be actively pursued, whereas nutrition start may be intentionally delayed in the most critically injured. Since the relationship between KPI-nutrition and outcomes remained after excluding early deaths, we think provision of timely nutrition is important to improving outcomes. We intentionally examined the distribution of KPI adherence among participants who did not achieve 100% adherence because of the potential for continued improvement in this group and to examine spread. The temporal trends in KPI adherence over 72 hours allow us to convey information about reality of bedside practice and attempts to achieve these goals. The rate of pathway implementation was high across the ED, OR and ICU, and the gap between pathway implementation and KPI adherence likely reflects the real world bedside challenges in achieving 100% KPI adherence in all severe TBI patients.

Our consideration of ICP monitoring in this program is worth discussing. At our early adopter level 1 trauma center, ICP monitoring is considered in the care of every patient with severe TBI and used in the care of children with severe TBI who are suspected of having high ICP, but ICP monitoring was not specifically selected as a KPI target since not all children with severe TBI receive ICP monitoring. We used KPI-CPP because provision of adequate CPP is a physiological consideration for clinicians even in the absence of ICP monitoring, and since prior work shows that CPP maintenance (avoidance of cerebral hypotension), which considers ICP in its determination, is associated with favorable outcomes. We reasoned that while there is clinical and research equipoise regarding the role and necessity for ICP monitoring as a must for all patients with severe TBI, there is no debate that all children with severe TBI require adequate cerebral perfusion. What that level of CPP is, however, can be debated since host factors such as age and autoregulation status may affect optimal CPP. We recognize that since patients without ICP monitoring could be systematically worse or better, it is unknown how their inclusion may affect findings. While we did not evaluate the decision making around or the value of ICP monitoring, ICP monitoring rates may have been lower than expected with program implementation, reflecting the broader inclusion of patients with severe TBI who received the pathway for brief periods of time or futile cases where ICP monitors were not placed. At our institution, MAP is clinically used as a blood pressure target when ICP monitoring is not available or ICP monitors are not placed, and we recognize that the assumption of an ICP of 10mmHg in the absence of ICP monitoring may not be valid in all patients with severe TBI (within the framework of our assumption that ICP was 10mmHg). Results of this study show that outcome findings did not change in sensitivity analyses when CPP analyses were restricted to those with ICP monitoring. The novelty of the comprehensive multilevel PEGASUS program is that while it suggests (consistent with guideline recommendations) ICP

monitoring, it provides care support for all patient with severe TBI, irrespective of ICP monitoring status, and for those patients with GCS above 8 but who deteriorate.²⁹

Typically, deterioration in GCS results in use of a new order set and delivery of more intensive treatments. Yet, orders are static, often require revising, and do not consider task order. While the program was not intended specifically for patients with mild or moderate TBI, providers were able to activate pathways in any patient with TBI when GCS decreased into the severe TBI category.²⁷ We intentionally retained discharge diagnoses of mild-moderate TBI to severe TBI even if participants received the clinical pathway for severe TBI because our primary purpose was to examine use of the program for intended recipients even if the “treatment” occurred for a limited period of time. Findings that discharge diagnoses underestimated the number of children with severe TBI at some point during hospitalization and description of deterioration of those initially admitted with less than severe TBI adds to our understanding of how to optimize the care of children with or at risk of severe TBI.

This study has strengths and limitations. Limitations include lack of randomization to program (not possible within single trauma center), limited number of program KPIs, small number of participants within age groups, inconsistent recording of pre-hospital data on rescue factors from referral regions, and lack of long term outcomes.³⁰ We cannot definitely exclude effects of confounding by indication, residual confounding, hidden bias, and missing data. The gap between pathway implementation and KPI adherence may reflect the fact that the pathway contains many elements and adherence to the various components may vary. Observed KPI adherence and outcomes may be due to secular trends but this is unlikely given the comprehensive and multilevel nature of the implementation strategy. We show pre-program data but are not able to predict outcomes for patients had they not received the program. Our experience might not be generalizable, a contributing factor related to adherence might be the Hawthorne effect and unmeasured benefits of the program, and discharge diagnoses may not always reflect the maximal TBI severity in hospital. We did not collect reasons for use of or lack of use of ICP monitoring, and ICP monitors were not placed in all patients with severe TBI. Our post hoc sensitivity analysis showed no meaningful change in effect size between CPP and outcomes when only the ICP monitored group was examined but our assumptions that ICP is 10mmHg in the un-monitored group may be inaccurate and could not be addressed. We used the definitional threshold of crossing the critical CPP limit of 40mmHg and CPP requirements likely increase with age. We did not use age based thresholds because these are not well studied or defined. Therefore, the impact of age related CPP in monitored patients cannot be practically addressed. The results of the posthoc sensitivity analysis should be interpreted in that context to avoid underestimating the importance of ICP monitoring when managing CPP or overgeneralizing the 40mmHg CPP threshold. Therefore, and to take a conservative approach, we defined the KPI-CPP as any episode of CPP < 40mmHg (prevention of any cerebral hypotension). There may be misclassification in GCS categories due to sedation and neuromuscular blockade; patients with GCS higher than 8 may have been included due to influence from sedatives and analgesics, particularly since many patients ended not undergoing ICP monitoring once in the PICU. Finally, we cannot determine ICP monitoring benefits, CPP thresholds by age and sex, role of sedatives/analgesics on changes in GCS or outcomes, nor the role of cerebral autoregulation on outcomes due to scope and focus of the project. Much of the evidence in

the BTF guidelines is Class II or III and there has not been a prospective evaluation of the all guideline indicators. These gaps should be examined in future larger studies. This study was conducted at a Level 1 trauma center with expertise in TBI management and hence, the external validity of results to other trauma centers with variable resources and levels of expertise should be confirmed. Strengths are strong conceptual frameworks, biological plausibility, analyses that contextualize clinical practice, high program fidelity, tailored clinical care pathways, hospital-wide use, study of achieving KPI adherence rather than aiming for KPI adherence, confirmation of the essential role of three acute care KPIs, concurrent examination of program fidelity and patient level outcomes, inclusion of contextualized interpretation on KPI adherence, such as time to nutrition versus CPP and PaCO₂ over time, and consideration for immortal time bias. As determining the “correct” GCS was not the goal of this study, we intentionally used hospital admission (ED) GCS to describe participants in this prospective “real world” study given that severe TBI care (clinical pathways) is often needed and started prior to knowing whether confounders such as sedatives would re-classify patients in non-severe TBI categories. While guidelines endorse use of GCS to define severe TBI, the range of GCS 3-8 is broad, and some patients with GCS 9-10 deteriorate and have severe TBI. Moreover, biomarkers are not clinically used with regularity, and early use of MRI scans to refine TBI severity definitions is not common in a real world setting. For these reasons, we triangulated data sources to confirm that we captured those patients who clinicians considered to have severe TBI and actually received care for severe TBI. The clinical pathways are flexible and were started for patients with deterioration to severe TBI and terminated upon recovery. Finally, this study provides Class II evidence recommendations regarding CPP, hypocarbia and nutrition benefits, thereby informing the guidelines themselves.

CONCLUSION

We examined a hospital-wide multilevel and comprehensive high fidelity program in acute severe pediatric TBI. Program implementation achieved favorable levels of service provision and was associated with favorable discharge outcomes across the full spectrum of pediatric patients with severe TBI. Adherence to CPP, nutrition and hypocarbia KPI targets is an essential program component. The PEGASUS program may be an effective in-hospital intervention to achieve favorable outcomes in pediatric TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research into Context

Evidence before the study

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and Science Citation Index from January 1, 1966 to May 29, 2018 without language restrictions. We searched for studies addressing programs in acute severe TBI, if acute care TBI studies included implementation science methods, if TBI guideline adherence was part of a hospital based programs, if TBI pathways were tested, and if known key performance indicators were examined. Specific search terms were “pediatric TBI,” “implementation science,” “traumatic brain injury,” “pediatric trauma,” “guidelines and trauma,” and “guideline adherence.” One retrospective multicenter study of 236 patients identified that adherence to cerebral perfusion pressure, hypocarbia and nutrition KPI targets during the first 72 hours after severe TBI benefits discharge survival and disposition, and that higher KPI adherence is associated better discharge outcomes. A second retrospective study of 63 patients reported higher rates of intracranial pressure monitoring before and after implementation of a pediatric neurocritical care program. Another small study of 29 patients reported on use of hyperosmolar therapy and discharge disposition after pathway implementation.

Added value of this study

This is the first implementation-effectiveness study in TBI. The PEGASUS program is a new implementation strategy and a clinical innovation in the care of children with severe TBI. This study is the first to report on the relationship between a multilevel implementation science-based hospital wide program and discharge outcomes in either adult or pediatric TBI. This prospective study demonstrates high implementation fidelity and favorable levels of service provisions that confirm the importance of previously recommended key performance indicators to discharge outcomes in severe pediatric TBI. Results of the current analysis show that 1) adherence to cerebral perfusion pressure, hypocarbia and nutrition KPI targets during the first 72 hours after severe TBI benefits discharge survival and disposition, and 2) higher KPI adherence is associated better discharge outcomes. The clinical care pathways which are a part of the PEGASUS program are flexible; they can be started and terminated when eligibility criteria no longer apply. Pathways can be started not just at admission but at any point when severe TBI is diagnosed and treated in the emergency department, operating room or pediatric intensive care unit. Further evidence is needed to assess the usefulness of the PEGASUS program in other settings where children with severe TBI get care and on long term outcomes.

Implications of all available evidence

The PEGASUS program may be a promising tool to improve adherence to acute care indicators of TBI guideline adherence and outcomes for hospitals that care for children with severe TBI. Children with mild-moderate TBI who deteriorate to severe TBI may also benefit. This study provides Class II evidence on the importance of maintaining

cerebral perfusion pressure, starting nutrition early, and avoiding unwanted hypocarbia early after severe pediatric TBI.

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Figure 1: 199 Patients Who Received the PEGASUS Program for Severe Traumatic Brain Injury (TBI) Care between May 2011 and June 2017.

*Pathway started and stopped upon definitive non-TBI diagnosis. During the study period, 239 children had a severe TBI diagnosis at some point during hospitalization. Total number of mild and moderate TBI who did not participate in the PEGASUS program are not shown. Dashed box shows study participants. 105 program participants did not have brain herniation.

Figure 2: Key Performance Indicator (KPI) Adherence with PEGASUS Program Implementation.

KPI adherence is measured for the first 72 hours after severe TBI diagnosis. Pre-program (N=56; Vavilala Crit Care Med, 2014) patients (age <18 years, admission GCS = 8, head abbreviated injury scale = 3, TBI diagnosis by head CT, mechanical ventilation for ≥ 48 hours, and alive for ≥ 72 hours) are compared to similar program participants (N= 71) for strict comparison, as well as to the whole cohort of 199 program participants for generalizability. KPIs are maintenance of all cerebral perfusion pressure (CPP) > 40mmHg, avoidance of any unwanted hypocarbia (all PaCO₂ > 30mmHg for 72 hours from severe TBI diagnosis in those without brain herniation, and early nutrition start (initiation of enteral or parenteral nutrition) within 72 hours of severe TBI diagnosis. *Nursing staff documented being unable to increase CPP despite effort (refractory cases). ** Dashed bar shows percent adherence to early nutrition start for group with expanded inclusion criteria when 31 patients who died within 72 hours of hospital admission are excluded from analysis. Logistic regression found no significant difference in percent of patients who achieved adherence to

CPP ($p = 0.62$), early nutrition start ($p = 0.27$), or avoidance of any unwanted hypocarbia in absence of brain herniation ($p = 0.34$) between pre-program patients and the subgroup of program participants who met strict inclusion criteria.

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Figures 3a and 3b: Temporal Trends in Cerebral Perfusion Pressure (3a) and PaCO₂ (3b) Values. Data compare pre-program with program participants meeting criteria for strict comparison. Values were aggregated hourly since severe TBI diagnosis for 72 hours for each subject. When multiple values were present in an interval minimum value was used. Lines indicate the loess fit mean value for all subjects per hour with bands representing spread of values with a 95% confidence interval. Figure 3b describes patients without brain herniation.

4a

4b

Figure 4a and 4b. Association between Adherence to Key Performance Indicators (KPI) and (4a) Survival and (4b) Favorable Discharge Disposition among 199 PEGASUS Program Participants.

Favorable discharge disposition defined as discharged home and inpatient/outpatient rehabilitation. Avoid any unwanted hypocarbia defined as maintenance of all $\text{PaCO}_2 > 30\text{mmHg}$ for 72 hours from severe TBI diagnosis in those without brain herniation (covariate selected by best subsets leaps-and-bounds algorithm for adjusted model: age, abusive TBI, head AIS, highest non-head AIS and ED GCS.). Patients who experienced brain herniation ($n = 94$) were excluded from analysis from any unwanted hypocarbia. Maintain all cerebral perfusion pressure defined as all $\text{CPP} > 40\text{mmHg}$ for 72 hours from severe TBI diagnosis (covariates: abusive TBI, polytrauma (only for survival model), head AIS, highest non-head AIS and ED GCS). Early nutrition start defined as initiation of enteral or parenteral nutrition within 72 hours of severe TBI diagnosis (covariates: age (only for disposition model), abusive TBI, polytrauma (only for survival model), head AIS, highest non-head AIS and ED GCS). Abbreviation: RR=Risk ratio, CPP=cerebral perfusion

pressure, AIS= Abbreviated Injury Score. * Describes program participants without brain herniation.

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Table 1:

Clinical Characteristics of 199 PEGASUS Program Participants between 05/2011 – 07/2017 · Inclusion criteria = any GCS $\geq$ 8 and confirmed TBI diagnosis. · Data as n (%)

	Cohort n=199	0 – 4 y n=64 (28.1)	5 – 9 y n=31 (18.1)	10 – 14 y n=30 (16.6)	15 – 18 y n=74 (37.2)
Age (yr), median (IQR)	11·9 (12·7)	2·1 (2·5)	7·3 (2·2)	13·9 (2·2)	16·50 (1·6)
Male sex, n (%)	141 (70·9)	39 (60·9)	19 (61·3)	22 (73·3)	61 (82·4)
Mechanism, n (%)					
<i>Motor vehicle crash</i>	66 (33·2)	9 (14·1)	16 (51·6)	8 (26·7)	33 (44·6)
<i>Fall</i>	49 (24·6)	24 (37·5)	9 (29·0)	6 (20·0)	10 (13·5)
<i>Struck by vehicle</i>	41 (20·6)	11 (17·2)	6 (19·4)	9 (30·0)	15 (20·3)
<i>Abusive TBI</i>	15 (7·5)	15 (23·4)	0 (0)	0 (0)	0 (0)
<i>Sport/recreation</i>	15 (7·5)	1 (1·6)	0 (0)	6 (20·0)	8 (10·8)
<i>Gunshot</i>	12 (6·0)	3 (4·6)	0 (0)	1 (3·3)	8 (10·8)
<i>Other</i>	1 (0·5)	1 (1·6)	0 (0)	0 (0)	0 (0)
EMS GCS, median (IQR)	3 (4·5)	3 (5·5)	3 (1·5)	4 (4·5)	3 (3·5)
Pediatric Trauma Score, median (IQR)	3 (3·0)	3 (3·5)	3 (3)	4 (4·0)	1 (0·5)
Transport Type, n (%)					
<i>Ambulance</i>	81 (41·1)	24 (37·5)	13 (43·3)	12 (40·0)	32 (43·8)
<i>Helicopter</i>	58 (29·5)	21 (32·8)	11 (36·7)	9 (30·0)	17 (23·3)
<i>Fixed wing aircraft</i>	57 (28·9)	18 (28·1)	6 (20·0)	9 (30·0)	24 (32·9)
<i>Personal vehicle</i>	1 (0·5)	1 (1·6)	0 (0)	0 (0)	0 (0)
Advanced Life Support Transport, n (%)	181 (91·9)	61 (95·3)	26 (86·7)	29 (96·7)	65 (89·0)
Pre-hospital tracheal intubation, n (%)	186 (93·5)	59 (92·2)	29 (93·5)	27 (90·0)	71 (95·9)
ED admit Glasgow Coma Scale score, median (IQR)	3 (3·0)	3 (3·0)	3 (2·5)	3 (3·8)	3 (4·8)
PICU admit Glasgow Coma Scale score, median (IQR)	8 (5·0)	7 (5·0)	8 (4·0)	9·5 (4·0)	7 (6·0)
ED Glasgow Coma Scale (motor), median (IQR)	1 (0)	1 (0)	1 (2·5)	1 (0·8)	1 (0)
Discharge Glasgow Coma Scale score (motor), median (IQR)	6 (0)	6 (0)	6 (1)	6 (0)	6 (0)
Head Abbreviated Injury Scale (AIS), median (IQR)	5 (1·0)	5 (1)	5 (1·0)	5 (1·0)	5 (1·0)
Non-head highest AIS, median (IQR)	2 (2·0)	2 (2)	3 (2·5)	2 (1·8)	3 (2·0)
Injury severity score (ISS), median (IQR)	29 (16·0)	26 (12·2)	30 (15·5)	28 (14·5)	33 (15·0)
Polytrauma, n (%)	86 (43·2)	20 (31·2)	17 (54·8)	12 (40·0)	37 (50·0)
Any surgery, n (%)	122 (61·3)	37 (57·8)	16 (51·6)	19 (63·3)	50 (67·6)
Craniotomy, n (%)	56 (28·1)	21 (32·8)	8 (25·8)	7 (23·3)	20 (27·0)
Intracranial pressure monitoring, n (%)	72 (36·1)	20 (31·2)	13 (41·9)	8 (26·7)	31 (41·9)
No brain herniation, n (%)	105 (52·8)	30 (46·9)	19 (61·3)	19 (63·3)	37 (50·0)
Avoidance of unwanted hypocarbia*, n (%)	76 (72·4)	24 (80·0)	12 (63·2)	15 (78·9)	25 (67·6)
Maintenance of all CPP, n (%)	127 (64·3)	26 (41·3)	18 (58·1)	25 (89·3)	58 (78·4)
Early nutrition start, n (%)	162 (81·4)	53 (82·8)	23 (74·2)	26 (86·7)	60 (81·1)
Hospital discharge survival, n (%)	160 (80·4)	49 (76·6)	25 (80·6)	27 (90·0)	59 (79·7)
Favorable hospital discharge disposition, n (%)	135 (67·8)	36 (56·2)	22 (71·0)	24 (80·0)	53 (71·6)

Abbreviation SD, standard deviation; IQR, interquartile range. ED = Emergency Department,

EMS = Emergency Medical Services

KPIs are maintenance of all cerebral perfusion pressure (CPP) > 40mmHg, and avoidance of any unwanted hypocarbia (all PaCO₂ > 30mmHg in absence of cerebral herniation for 72 hours from severe TBI diagnosis, and early nutrition start (initiation of enteral or parenteral nutrition) within 72 hours of severe TBI diagnosis.

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