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Behavioral Clinical Trials in Moderate to Severe Pediatric Traumatic Brain Injury: Challenges, Potential Solutions, and Lessons Learned

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Background

Randomized clinical trials (RCTs) of interventions to address child and family behavioral adaptation following pediatric traumatic brain injury (TBI) were virtually nonexistent prior to 2000.[1] Since then, both small and larger RCTs have addressed this topic. This commentary grows from our experience implementing eight RCTs of family-centered interventions to reduce child behavior problems and caregiver/parent distress. These studies, involving nearly 400 participants from eight clinical centers, support the feasibility of conducting RCTs with children following TBI while highlighting challenges and threats to validity. Controversy regarding the merit of RCTs pertains to the, at times, limited information that they yield relative to costs. Studies fail because of insufficient recruitment, inappropriate or insensitive outcome measures, or samples/designs that preclude answering the research question. In this commentary, we outline challenges and share potential solutions for surmounting these issues.

Developmental and Age Considerations

TBI in children occurs when the brain is undergoing rapid development.[2] Outcomes are heterogeneous and vary by injury severity, age at injury, family and individual characteristics, and acute medical treatment.[3] The effects of TBI on brain development also depend on when the injury occurred, e.g., infancy versus adolescence/young adulthood. Even among children of similar ages and injury severity, outcomes vary widely. This intra-individual variability is a source of noise and may not be adequately controlled for through randomization. Conversely, identifying and recruiting a homogeneous cohort (e.g., children ages 10–12 with comparable injury severity and executive dysfunction without comorbidities) may be prohibitively difficult. Moreover, findings from a study with very restrictive enrollment criteria would not generalize beyond the narrowly targeted sample. The investigator must resolve the dilemma of reducing heterogeneity while preserving

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feasibility and generalizability. Awareness of this challenge can guide investigators to consider sources of heterogeneity that may moderate efficacy. For example, we found that both child's age and family SES moderated treatment effects, with older adolescents and families of lower SES benefiting more from the online problem-solving treatments.[4,5] Furthermore, it is sometimes difficult to determine if cognitive and behavioral problems that developed post TBI are directly related to the injury or if the problems would have developed later regardless of the brain injury (e.g., Attention Deficit Hyperactivity Disorder). Developmental and age considerations may significantly impact decisions around trial design, recruitment/enrollment, outcome selection, and interpretation of findings. It is important to be cognizant of developmental factors when planning a pediatric TBI trial and to identify a target population with similar developmental characteristics (e.g., adolescents).

Choosing Sensitive Outcome Measures

Few measures are available to specifically assess outcomes of behavioral interventions for pediatric TBI. The NINDS Common Data Elements workgroup recommended the Child Behavior Checklist and Strengths and Difficulties Questionnaire to evaluate behavioral consequences of pediatric TBI.[6] However, these measures are most appropriate for interventions targeting broad-band behavior problems. Because the phenotype for behavior problems following TBI varies across individuals, with some experiencing internalizing symptoms such as depression and others experiencing secondary attention deficit disorder and behavioral dysregulation, [7,8] improvements in one or more domains may be obscured by looking at problem totals. Some measures are more responsive to intervention effects than others[6] and choosing a non-sensitive measure may preclude finding effects even if the intervention operates as hypothesized. When selecting outcome measures it is critical to consider age/development factors, the target construct of the intervention, and the sensitivity of the measure to change and/or the intervention.

What Constitutes an Appropriate and Ethical Control Group?

The most basic RCT design randomizes participants to active treatment or to standard care or wait-list comparison group. A standard-care comparison provides an estimate of how much better outcomes would be if patients received the treatment relative to what they have been receiving. For pediatric TBI, standard care often constitutes minimal/no services, even among children with moderate to severe TBI. [9,10] Additionally, there is often wide variability in management approaches, as strong evidence of efficacy is lacking. Consequently, a usual-care arm is largely equivalent to a wait-list control group, consists of high variability in treatments received, and fails to equate the groups on treatment time and therapist attention. Additionally, withholding or delaying clinical interventions may be viewed as unethical. Therefore, finding an adequate and appropriate active-control group is often challenging.

In our web-based trials, we have used a control group that receives access to online information and resources about TBI (an internet resource comparison; IRC).[11] The IRC arm equates the groups for access to TBI information and resources, but does not provide problem-solving training. A limitation of this approach is its failure to control for therapist

attention making it impossible to distinguish the effects of problem-solving training from the generic benefits of discussing concerns with an empathic therapist. An active treatment providing equivalent therapist attention is often considered an optimal comparison. However, it is difficult, if not impossible, to completely separate the hypothesized active treatment elements. For example, even a nutrition intervention comparison would likely involve elements of self-monitoring and problem-solving around meal choices. It is worth noting that the IRC intervention was as effective as family problem-solving training for higher SES families, suggesting that IRC is not inert and may in fact constitute an effective treatment for some families.[12]

RCTs can also compare the effectiveness of two or more treatments presumed to be associated with improved outcomes, with hypotheses focusing on comparative effectiveness and identifying characteristics of those who benefit. In this vein, we have compared individual problem-solving training for adolescents with TBI to problem-solving training with the family. This approach is most valuable when one or both of the treatments has documented efficacy and the study can distinguish the contributions of various treatment components (family involvement, mode of delivery). Because evidence-based treatments are largely lacking for pediatric TBI rehabilitation, studies that evaluate for initial efficacy (i.e., comparison to no treatment) are often a necessary first step. When designing a clinical trial for the pediatric TBI population, it is critical to consider how the intervention fits with standard of care practices at the trial sites and the best comparison condition in that context.

Do you only include children with deficits?

For interventions targeting the social and behavioral challenges that accompany TBI, the optimal threshold for pretreatment symptoms is unclear. Additionally, there are often overlapping or comorbid problems that may interact, thus leading to differential intervention effects. If a trial enrolls children without difficulties, it may prevent emerging difficulties; however, floor effects may preclude detection of treatment differences. Participants with few problems may also be less motivated to continue treatment and drop out at higher rates. Conversely, if only children with clinically-elevated problems are enrolled, it is not possible to examine the benefits for the broader population of children with subthreshold difficulties. While there is no right or wrong answer, investigators who choose to include participants with low levels of symptoms at treatment initiation will need to consider this issue and decide whether it is best to account for these issues in the design or analysis phase of the trial.

Timing of Intervention Delivery

Animal studies and nascent studies of human TBI interventions suggest that intervention timing likely influences their effectiveness. [13,14] There are likely windows to maximize neuroplasticity that we are just beginning to understand. Input from parents suggests that behavioral interventions delivered in the initial months following severe TBI may be difficult to adhere to and benefit from due to the considerable medical demands early after injury. Conversely, parents who participated in treatments more than a year post injury indicated that they would have benefited more from information and skills closer to the time of injury

and that many of the challenges addressed in the intervention content had already resolved. Our single study with a narrower time-window post injury (1–7 months) revealed some initial treatment effects but others that emerged over the course of 12 month follow-up.[4,15] Our experiences suggest that the timing of intervention matters, with early versus late intervention having different sets of challenges. Intervention development, delivery, and assessment must account for timing of intervention delivery (early versus late recovery) to maximize the relevance and benefit for families.

Key Challenges-Recruitment-If you build it will they come?

The lack of academic and behavioral services for children recovering from TBI is well-documented and caregivers have consistently expressed a desire for information and resources.[16,17] Nonetheless, TBI intervention studies often struggle with recruitment which results in compromises in enrollment criteria (e.g., enrolling children with any form of acquired brain injury or all ages) and potentially untenable heterogeneity and uninterpretable findings. Many factors influence a family's willingness to engage in intervention studies including the time demands involved and the perceived costs (time, hassle, stigma) versus benefits (reduced stress). We have moved to online assessment and intervention and conducting consent and initial data collection in the home to reduce time demands and hassle. However, this approach puts greater demand on the research team. Soliciting family input regarding how an intervention and associated assessments are implemented may also improve engagement. Researchers also need effective strategies for identifying and contacting potentially eligible patients such as patient registries. Given the declining numbers of children with moderate to severe TBI, future studies will require collaboration across multiple institutions to be successful.

Retention-Ensuring an Adequate Dose

Dose typically reflects the amount consumed (i.e., number of sessions completed). However, with both drug and behavioral studies actual uptake may differ from what was consumed. Factors such as motivation, engagement, homework completion, and skill implementation in everyday life are likely to influence treatment efficacy, but may be difficult to capture in analytic models. Intent to treat models retain participants, regardless of treatment dose. While this approach reduces the possibility of nonrandom attrition influencing outcomes, it also sets an unduly high bar for treatment efficacy. With all designs, but particularly intent to treat, it is essential to maximize the intervention dose (assuming more treatment is better) and minimize attrition. Strategies such as engaging stakeholders in intervention design and implementation, flexible scheduling, incentives for completing sessions, and addressing cultural differences are critical for reducing attrition. However, much of it comes down to establishing a trusting relationship with the participant and their family. Given that minority participants are less likely to be represented in clinical research and more likely be lost to follow-up, it is particularly important to implement strategies, such as demographically similar recruiters, for engaging these patients.[18]

Emerging Improvements and Maintenance of Effects over Time

Most studies limit follow-up to a single assessment immediately post treatment with some studies conducting an additional follow-up months later. In the Counselor Assisted Problem Solving study, we assessed outcomes post treatment and at follow-up assessments six and 12 months later. At the final follow-up, we found emerging improvements in functional outcomes and internalizing symptoms suggesting that some intervention effects that are not apparent at treatment completion may still appear later. [4,11] These findings raise questions regarding follow-up length and what types of long-term data can be collected without burdening families. Additionally, because of the rapid development occurring in children, it is critical to consider the feasibility of extending assessments beyond completion of the intervention.

The Role of New Trial Designs

RCTs remain the gold standard; however, they have a number of limitations. One challenge is developing an intervention protocol that is clearly defined and replicable, yet flexible enough to accommodate patient and family heterogeneity. Therefore, it is critical that high quality preliminary clinical trials focusing on identifying optimal clinical trial parameters and intervention delivery and dosing characteristics are performed.[19] Findings from these trials will inform development of definitive efficacy trials. Adaptive trial designs, such as sequential, multiple assignment, randomized trials (SMART), allow planned treatment tailoring by randomizing participants at multiple time points based on their initial response to treatment (responder versus nonresponder). [20,21] This approach facilitates testing of different combinations of intervention components to identify more effective treatments for nonresponders. Evidence-based practice, pragmatic, and comparative effectiveness have also emerged as an alternative to RCTs, [22] but remain unfeasible for outpatient pediatric TBI given that most children receive minimal psychosocial follow-up care. Alternative statistical methods, such as use of propensity score, may provide further options. A limitation to success of many alternative approaches is the need for larger data bases that contain high quality intervention and outcome related data; however, larger consortiums or models systems collecting standard data do not currently exist for pediatric TBI. Meta-analytic approaches pooling data from multiple smaller trials may also provide an alternative to large, multisite RCT.

Conclusions

The challenges of behavioral trials for pediatric TBI are apparent but not insurmountable. Careful consideration of the issues outlined in this commentary when planning your project can inform design choices and analyses. It is critically important that investigators share their failures as well their successes to move the field forward. Also, alternative study designs and approaches should be considered, keeping in mind their strengths and limitations.

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References

1. Singer GH, Glang A, Nixon C, et al. A comparison of two psychosocial interventions for parents of children with acquired brain injury: An exploratory study. The Journal of head trauma rehabilitation. 1994; 9(4):38–49.
2. Babikian T, Merkley T, Savage RC, Giza CC, Levin H. Chronic Aspects of Pediatric Traumatic Brain Injury: Review of the Literature. J Neurotrauma. 2015; 32(23):1849–1860. [PubMed: 26414654]
3. Mushkudiani NA, Engel DC, Steyerberg EW, et al. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. Journal of neurotrauma. 2007; 24(2):259–269. [PubMed: 17375990]
4. Wade SL, Kurowski BG, Kirkwood MW, et al. Online Problem-Solving Therapy After Traumatic Brain Injury: A Randomized Controlled Trial. Pediatrics. 2015
5. Kurowski BG, Wade SL, Kirkwood MW, Brown TM, Stancin T, Taylor HG. Long-term benefits of an early online problem-solving intervention for executive dysfunction after traumatic brain injury in children: a randomized clinical trial. JAMA Pediatr. 2014; 168(6):523–531. [PubMed: 24781374]
6. McCauley SR, Wilde EA, Anderson VA, et al. Recommendations for the use of common outcome measures in pediatric traumatic brain injury research. J Neurotrauma. 2012; 29(4):678–705. [PubMed: 21644810]
7. Wade SL, Stancin T, Kirkwood M, Brown TM, McMullen KM, Taylor HG. Counselor-assisted problem solving (CAPS) improves behavioral outcomes in older adolescents with complicated mild to severe TBI. The Journal of head trauma rehabilitation. 2014; 29(3):198–207. [PubMed: 23640543]
8. Kurowski BG, Wade SL, Kirkwood MW, Brown TM, Stancin T, Taylor HG. Online problem-solving therapy for executive dysfunction after child traumatic brain injury. Pediatrics. 2013; 132(1):e158–166. [PubMed: 23753094]
9. Karver CL, Kurowski B, Semple EA, et al. Utilization of behavioral therapy services long-term after traumatic brain injury in young children. Arch Phys Med Rehabil. 2014; 95(8):1556–1563. [PubMed: 24755047]
10. Slomine BS, McCarthy ML, Ding R, et al. Health care utilization and needs after pediatric traumatic brain injury. Pediatrics. 2006; 117(4):e663–674. [PubMed: 16533894]
11. Wade SL, Taylor HG, Cassedy A, et al. Long-Term Behavioral Outcomes after a Randomized, Clinical Trial of Counselor-Assisted Problem Solving for Adolescents with Complicated Mild-to-Severe Traumatic Brain Injury. J Neurotrauma. 2015; 32(13):967–975. [PubMed: 25738891]
12. Wade SL, Walz NC, Carey J, McMullen KM. A randomized trial of teen online problem solving: Efficacy in improving caregiver outcomes after brain injury. Health Psychology. 2012; 31(6):767. [PubMed: 22746261]
13. Kurowski BGWS, Kirkwood MW, Brown TM, Stancin T, Taylor HG. Behavioral Predictors of Outpatient Mental Health Service Utilization within 6 Months after Traumatic Brain Injury in Adolescents. PM & R : the journal of injury, function, and rehabilitation. Accepted August 2013.
14. Hovda DA, Lee SM, Smith ML, et al. The neurochemical and metabolic cascade following brain injury: moving from animal models to man. J Neurotrauma. 1995; 12(5):903–906. [PubMed: 8594218]
15. Karver CL, Wade SL, Cassedy A, et al. Cognitive reserve as a moderator of responsiveness to an online problem-solving intervention for adolescents with complicated mild-to-severe traumatic brain injury. Child Neuropsychol. 2013

16. Aitken ME, McCarthy ML, Slomine BS, et al. Family burden after traumatic brain injury in children. Pediatrics. 2009; 123(1):199–206. [PubMed: 19117883]
17. Hawley CA. Reported problems and their resolution following mild, moderate and severe traumatic brain injury amongst children and adolescents in the UK. Brain injury. 2003; 17(2):105–129. [PubMed: 12519639]
18. Blaha RZ, Arnett AB, Kirkwood MW, et al. Factors Influencing Attrition in a Multisite, Randomized, Clinical Trial Following Traumatic Brain Injury in Adolescence. The Journal of head trauma rehabilitation. 2014
19. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. Clin Transl Sci. 2011; 4(5):332–337. [PubMed: 22029804]
20. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy S. A “SMART” design for building individualized treatment sequences. Annual review of clinical psychology. 2012:8.
21. Almirall D, Compton SN, Rynn MA, Walkup JT, Murphy SA. SMARTer Discontinuation Trial Designs for Developing an Adaptive Treatment Strategy. Journal of child and adolescent psychopharmacology. 2012; 22(5):364–374. [PubMed: 23083023]
22. Bogner JA, Whiteneck GG, Corrigan JD, Lai JS, Dijkers MP, Heinemann AW. Comparison of scoring methods for the participation assessment with recombined tools-objective. Arch Phys Med Rehabil. 2011; 92(4):552–563. [PubMed: 21367397]