Published in final edited form as:

Pediatr Crit Care Med. 2013 September ; 14(7): . doi:10.1097/PCC.0b013e31829f6c77.

Treating Cerebral Edema in Diabetic Ketoacidosis: Caveats in Extrapolating from Traumatic Brain Injury

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Keywords

pediatrics; diabetic ketoacidosis; cerebral edema; hypertonic saline

When encountering children with diabetic ketoacidosis (DKA), the possibility of DKA related cerebral edema is usually at the forefront of anticipated worries facing treating clinicians. This is because neither the pathophysiology of cerebral edema is well understood, nor are proven treatments for cerebral edema available. Both these gaps force clinicians to rely on either theoretical conceptual frameworks of other neurological diseases or a given body of general knowledge of pharmacological agents to address this devastating complication in DKA. Evidence suggests that an ischemic (1) and/or vasogenic (2) process play a role in the genesis of DKA related cerebral edema, but details of the time course of these processes are not clear. Thus, clinicians are left with employing treatment strategies in DKA with some level of scientific evidence from other neurological conditions where cerebral edema occurs. In children, the reference disease state is typically traumatic brain injury (TBI).

The issue of how best to prevent or treat DKA related cerebral edema is significant, given that the incidence of Type I diabetes mellitus is increasing worldwide (3) and because DKA is its most common complication, occurring in 25–40% of these children.(4) Published literature suggests that the use of hypertonic saline appears to be increasing in comparison to mannitol for a variety of neurological conditions, including DKA and TBI. (5,6) There may be some common pathways involved in the genesis of DKA related cerebral edema and cerebral edema occurring after TBI, and using either mannitol and/or hypertonic saline to treat DKA related cerebral edema similar to TBI is theoretically beneficial in DKA. There are some significant similarities between DKA (metabolic condition) and TBI (injury). *First*, both disease states can be complicated by critical illness and cerebral edema. (7,8) *Second*, cerebral edema in both disease states contributes to mortality.(8) *Third*, imaging such as computed tomography and magnetic resonance scans are clinically employed to detect cerebral edema in the acute stages of both DKA and TBI. *Fourth*, data suggest that the predominant pathophysiology early after initial cerebral injury (broadly defined) is cerebral ischemia, followed in the subacute stages by a more vasogenic process.(9) *Finally*, impaired cerebral autoregulation is documented in both TBI and DKA, either reflecting the disease

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Conflict of Interest: The author has no conflicts of interest relevant to this article to disclose.

Reprints: None

severity or playing a role in the development of cerebral edema. (10,11) There are some other similarities including but not limited to increased blood brain barrier permeability (2), white matter integrity changes (12,13), cardiac arrhythmias (14,15), and stroke (16,17) which may also affect outcomes after illness in both DKA and TBI.

Based on these similarities, it might then seem appropriate to consider evaluation modalities and treatments in TBI as empirically applicable to DKA. However, there are problems with this assumption. Acid base imbalance (acidosis and ketosis) is not a classic feature in isolated TBI. Tracheal intubation and mechanical ventilation are commonly employed in TBI patients with altered mental status, but not so in DKA.(18) In TBI, the Glasgow Coma Scale (GCS) score is a valid measure of disease severity and has also been used to prognosticate outcomes. Although GCS is used to evaluate mental status in DKA, it is not a validated measure of mental status in DKA. Interestingly, GCS is not used in sepsis, despite the striking phenotypic similarity in mental status and acid base imbalance. It is therefore, unclear whether our diagnosis of neurological injury, including early cerebral edema using the GCS score is valid in DKA. Despite ongoing efforts advocating for early MRI scanning, head CT scans are still the most common imaging modality in TBI whereas, in DKA, the threshold for head CT scanning is less predictable and one reason for this difference may be that TBI can be a surgical condition whereas DKA is not. Therefore, in DKA and in the absence of early imaging, administration of hyperosmolar agents whether it be mannitol or hypertonic saline, may be based on bedside GCS alone. This empiric practice may be associated with inaccuracies in estimates of prevalence of cerebral edema and may cause harm. Finally, current national guidelines recommend considering ICP monitoring in severe TBI (Class III evidence) even in the absence of documented cerebral edema whereas in DKA, clinicians often use ICP monitoring on a case by case basis and typically after cerebral edema has been documented on imaging.

Despite these differences, we are currently left with little choice but to rely on the GCS to assess mental status and on the use of hyperosmolar agents to empirically treat cerebral edema in DKA. The trouble is that we do not have a clear answer as to whether mannitol or hypertonic saline is superior in decreasing ICP or reducing cerebral edema, or what differential effects these agents have on the brain in DKA. The best available evidence comes from the 2012 Pediatric Guidelines for Severe TBI which recommends the use of 3% hypertonic saline with Class II evidence (19). In-fact, the relationship between hyperosmolar agent and outcome may depend on the underlying neurological condition. For example, in one study of adult surgical patients undergoing craniotomy for a variety of conditions who were randomized to receive either 5mL/kg of 20% mannitol or 3% hypertonic saline, where normocapnia and euolemia were maintained, Rozet and colleagues reported no difference in brain relaxation or arteriovenous lactate or increases in cerebrospinal fluid (CSF) lactate whereas 3% hypertonic saline was associated with higher CSF Na concentrations over time. (20) Moreover, mannitol and hypertonic saline differ in their cerebrovascular profiles which may impact changes in DKA differently than in other neurological conditions.

The present study by DeCoursey and colleagues reporting a 4 fold higher use of 3% hypertonic saline over the 11 year study period highlights the problem with empiric extrapolation of treatment from one disease state to another.(6) Contrary to their hypothesis that declining mortality in DKA may be due to the shift away from mannitol, the authors report higher mortality among patients who received 3% hypertonic saline even after adjustment for the propensity to receive this medication. While this study is not definitive in terms of answering the question relating hyperosmolar therapy with DKA related cerebral edema and/or mortality, DeCoursey et al offer food for thought in a number of areas pertaining to the treatment of DKA related cerebral edema. *First*, the study demonstrates a change in clinical practice in favor of hypertonic saline across the US, despite the absence of

supporting evidence or guidelines. This change might not be problematic if hypertonic saline benefits DKA patients. However, this is not the case and the data are significant, especially given the overall decline in DKA related mortality, which may be due to change in other treatment or evaluation practices such as intravenous fluid administration or the use of standardized clinical care pathways.

The importance of DeCoursey's study highlighting harm with the use of 3% hypertonic saline in DKA questions our clinical practice of empiric therapeutic extrapolation and addresses the need for critical evaluation of treatments in DKA from DKA patients, and not patients with other neurological conditions. The authors correctly point out that there continues to be scientific equipoise for efficacy in the use of the two hyperosmolar agents in DKA. Pending further clarification and studies, underlying differences between neurological conditions should be considered before empirically adopting treatments from one disease state (TBI) to another (DKA).

Acknowledgments

Funding: R01 NS072308-03 (Vavilala)

Dr. Vavilala received support for article research from the National Institutes of Health.

References

1. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001; 344(4):264–9. [PubMed: 11172153]
2. Vavilala MS, Richards TL, Roberts JS, et al. Change in blood brain barrier permeability during pediatric diabetic ketoacidosis treatment. *Pediatr Crit Care Med*. 2010; 11(3):332–8. [PubMed: 19838141]
3. Ma RC, Chan JC. Diabetes: incidence of childhood type 1 diabetes: a worrying trend. *Nat Rev Endocrinol*. 2009; 5(10):529–530. [PubMed: 19763122]
4. Pinkey JH, Bingley PJ, Sawtell PA, et al. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. *Diabetologia*. 1994; 37(1):70–74. [PubMed: 8150233]
5. Brenkert TE, Estrada CM, McMorro SP, Abramo TJ. Intravenous hypertonic saline use in the pediatric emergency department. *Pediatr Emerg Care*. 2013; 29(1):71–3. [PubMed: 23283268]
6. DeCoursey DD, Steil GM, Wypij GM, Agus MSD. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric DKA: An 11 year retrospective analysis of mortality. *Pediatr Crit Care Med*. 2013in-press
7. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JL. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med*. 1985; 312(18):1147–51. [PubMed: 3920521]
8. Bennett Colomer C, Solari Vergara F, Tapia Perez F, et al. Delayed Intracranial Hypertension and Cerebral Edema in Severe Pediatric Head Injury: Risk Factor Analysis. *Pediatr Neurosurg*. 2013 Epub ahead of print.
9. Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. *Neurosurg Focus*. 2007; 22(5):E1.
10. Philip S, Udomphorn Y, Kirkham FJ, Vavilala MS. Cerebrovascular pathophysiology in pediatric traumatic brain injury. *J Trauma*. 2009; 67(2 Suppl):S128–34. [PubMed: 19667845]
11. Roberts JS, Vavilala MS, Schenkman KA, et al. Cerebral hyperemia and impaired cerebral autoregulation associated with diabetic ketoacidosis in critically ill children. *Crit Care Med*. 2006; 34(8):2217–23. [PubMed: 16763506]
12. Levin HS, Wilde EA, Chu Z, et al. Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. *J Head Trauma Rehabil*. 2008; 23(4):197–208. [PubMed: 18650764]

13. Dervan L, Poliakov A, Friedman SD, et al. Change in Fractional Anisotropy during Treatment of Diabetic Ketoacidosis in Children. *Pediatr Res.* in press.
14. Kuppermann N, Park J, Glatter K, et al. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children. *Arch Pediatr Adolesc Med.* 2008; 162(6):544–9. [PubMed: 18524745]
15. Keren O, Yupatov S, Radai MM, et al. Heart rate variability (HRV) of patients with traumatic brain injury (TBI) during the post-insult sub-acute period. *Brain Inj.* 2005; 19(8):605–11. [PubMed: 16175814]
16. Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. *Stroke Res Treat.* 2011; 2011:219706. [PubMed: 21423557]
17. Ransom GH, Mann FA, Vavilala MS, et al. Cerebral infarct in head injury: relationship to child abuse. *Child Abuse Negl.* 2003; 27(4):381–92. [PubMed: 12686323]
18. Tasker RC, Lutman D, Peters MJ. Hyperventilation in severe diabetic ketoacidosis. *Pediatr Crit Care Med.* 2005; 6(4):405–11. [PubMed: 15982426]
19. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatr Crit Care Med.* 2012; 13 (Suppl 1):S1–82. [PubMed: 22217782]
20. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. *Anesthesiology.* 2007; 107(5):697–704. [PubMed: 18073543]