Is Intravenous Fluid therapy associated with Cerebral Oedema in Paediatric Diabetic Ketoacidosis? Literature Review and Critical Appraisal of Evidence

Abstract

Objective

The ongoing controversy regarding fluid management in pediatric diabetic ketoacidosis (DKA) has necessitated this review of whether aggressive fluid therapy aggravates the risk of cerebral edema. The amount of fluid administered in pediatric DKA is estimated with a weight-based formula for correction of deficit, dehydration, and fluids maintenance. Cerebral oedema is known to occur with hyperosmolar treatment or controlled hyperventilation treatment for cerebral oedema.

Method

A literature search was conducted using EMBASE, Medline, and Cochrane databases for systematic reviews and original articles published in the last 18 years from the year 2000 to 2018 using search words individually or in combination, Inclusion criteria were studies limited to pediatric patients treated for diabetic ketoacidosis. In addition, a critical appraisal of the most current evidence was performed.

Result

After the literature search, 913 articles were identified from Medline, Embase, and Cochrane databases. Non-relevant studies, non-full text studies and studies that lacked control groups or articles that were duplicated were excluded leaving a final total of five full test articles for literature review and critical appraisal of evidence.

Conclusion

Almost all the studies showed that cerebral edema was associated with severe acidosis and prerenal azotemia in initial DKA presentation and only one case-control study showed a significant correlation with a higher volume of intravenous fluid therapy within the first three hours. The PECARN study put to rest age-long controversy and traditional teaching that aggressive fluid therapy in pediatric DKA may be responsible for cerebral edema with the conclusion that neither rate of fluid administration nor sodium chloride content significantly influenced neurological outcomes in Pediatric DKA

Keywords*: pediatric ketoacidosis, intravenous fluid therapy, cerebral edema*

Introduction

In newly diagnosed children with type 1 diabetes mellitus (DM), the incidence of diabetic ketoacidosis (DKA) has been reported to occur in 25-40 percent (1). Cerebral edema is a devastating and leading cause of death in pediatric DKA which occurs in approximately 1 percent with 40-90 % mortality rate (2, 3) and about 15-35 % of survivors are left with permanent neurological deficit including memory, attention, and cognitive disturbances due to significant alteration of cerebral microstructure (4). DKA is defined based on biochemical criteria as blood glucose greater than 200mg/dl, with venous pH less than 7.3 or bicarbonate less than 15mmol/L and ketosis (5).

There has been a controversy surrounding DKA treatment that rapid fluid administration decreases serum osmolality resulting in cerebral edema (6) consequently, several treatment guidelines advocate slow rehydration with isotonic fluids. Duck et al reported a common feature with children with cerebral edema and identified 4 children of whom 3 died, had all received fluids over 4000ml in the first 24 hours (7). Several retrospective studies that have reported cerebral edema were subject to selection bias and more in dehydrated children (8) leading to aggressive fluid resuscitation. A systematic review conducted by Hom and Sinert in 2008(9) identified only one study suggested the relationship between cerebral edema and volume of fluid administration, but the study did not discuss the tonicity of the specific fluid used. The ongoing controversy necessitating this review is whether aggressive fluid therapy aggravates the risk of cerebral edema in pediatric diabetic ketoacidosis.

Methodology

A literature search was conducted using EMBASE, Medline, and Cochrane databases for systematic reviews. Keywords applied were" pediatric ketoacidosis, intravenous fluid therapy, cerebral edema". Resultant yield limited to 18 years from 2000 to 2018 using search words individually or in combination, Inclusion criteria were studies limited to pediatric patients treated for diabetes ketoacidosis, observational studies, systematic reviews, and randomized controlled trials. Studies were limited to English and those involving humans. Relevant studies were isolated for further critique.

Results

Following a rigorous search of databases over eighteen years, 913 articles were identified from Medline, Embase, and Cochrane register of controlled trials (CENTRAL) on the Cochrane library and it was down to 312 after deduplication(Figure 1). There was only one randomized controlled study and four several case-control studies. Case reports, case series, case reviews, short communication, and commentaries were excluded which further reduced the total number of articles to 160 articles. Furthermore non-relevant studies, non-full text studies, and studies that lacked control groups were excluded leaving a final total of five full test articles for literature review and critical appraisal of evidence (table) (8, 11, 13, 12, and 14)

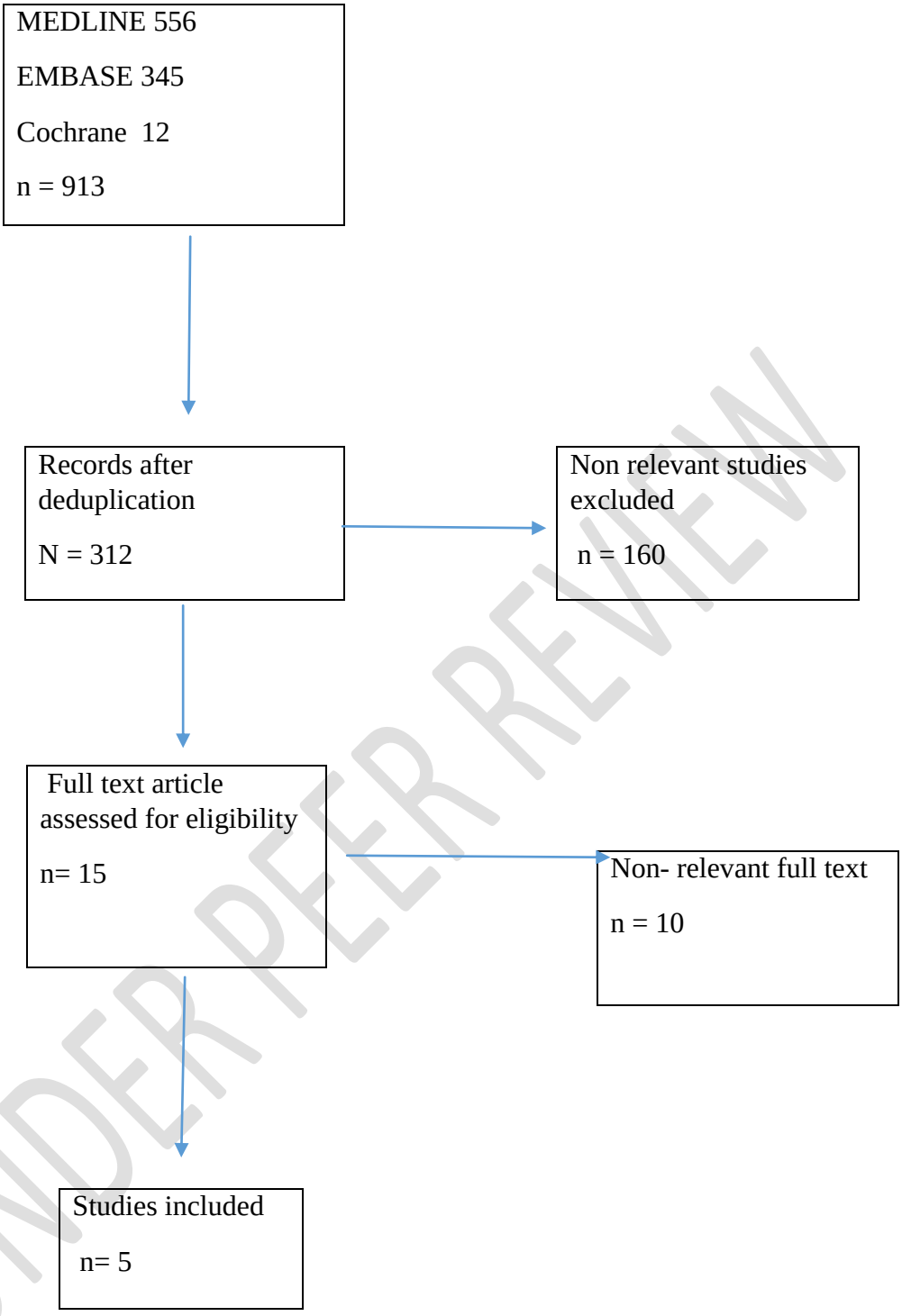

Figure 1: Search flow diagram

Study/year	Design	Patients number	Outcome
Kupperman 2018	A prospective randomized controlled trial	1389	Neither the rate of administration nor sodium chloride content of the intravenous fluid therapy significantly influenced outcomes in pediatric DKA
Hsia 2015	Retrospective Case-control	1868	Decreasing fluid rate and increasing sodium content did not decrease the incidence
Edge 2006	Case-control	43	The results identified significant predictors of risk of developing cerebral edema in DKA including baseline acidosis and abnormalities of sodium, potassium, and urea concentrations, early administration of insulin, and high volume of fluids
Lawrence 2005	Case-control	17	No association was found between the occurrence of DKA and treatment factors
Glaser 2001	Case-control	61	The low partial pressure of carbon dioxide, high serum and nitrogen, and treatment with bicarbonates prone to develop cerebral edema in pediatric DKA

Table 1: Study characteristics

Discussion

Glaser et al(8) conducted a retrospective case-controlled between 1982 and 1997 (15 year period) in ten pediatric centers in USA to identify children less than 18 who developed cerebral edema from DKA. Patients were classified into two groups: the case group of 61 patients who had DKA with cerebral edema as against the age matched controlled control groups of 174 who had similar onset of diabetes mellitus, similar initial glucose concentration, and similar initial venous PH . Both groups were exposed to the intravenous fluid of 5ml/kg/ hour fluid. The result of the comparison between the case and control group showed that cerebral edema was significantly associated with lower initial partial pressures of arterial carbon dioxide (relative risk of cerebral edema for each decrease of 7.8 mm Hg

[representing 1 SD), 3.4; 95 percent confidence interval, 1.9 to 6.3; p<0.001) and higher initial serum urea nitrogen concentrations (relative risk of cerebral edema for each increase of 9 mg per decilitre (3.2 mmol per litre) (representing 1 SD), 1.7; 95 percent confidence interval, 1.2 to 2.5; P=0.003). Only treatment with bicarbonate was associated with cerebral edema. Time to developed cerebral edema in this study was a median of 7 hours. This study is a case-control retrospective record review with small data set of 232 patients over a 15-year period in ten US centers, data abstraction from medical records and the authors did not record if data abstractors were blinded to the primary outcome or hypothesis of the study hence subject to a significant level of selection bias. However, an impressive and standardized data collection protocol was employed with adequate precaution to improve inter-ratter reliability in data gathering. The authors did not give a clear and definite statement on the specific protocol in each center whether they were amended, reviewed, upgraded or changed during the fifteen-year course of this study. This study is grade 2 evidence (10).

Lawrence et al(11) conducted a case-control study to determine incidence, outcomes, and risk factors for pediatric cerebral edema with diabetic ketoacidosis (CEDKA) in Canada from July 1999 to June 2001 in pediatric patients less sixteen years of age presenting with DKA with cerebral edema and. Two unmatched patients per case without cerebral edema. Total numbers of patients were 45 with 13 in the case group and 28 in the control-group over a contiguous 5-yr period identified by record review, intravenous fluids were given as mL/kg/ hour in patients who developed cerebral edema and ml/kg/hour in controls. Out of the 13 patients with cerebral edema, 23% died and 15% survived with neurologic sequelae. In addition, cerebral edema was present in 19% at the initial presentation with DKA and was associated with lower initial bicarbonate (p = .001), higher initial urea (p= .001), and higher glucose at presentation (p = .014). Although there was a trend to association with higher fluid rates and treatment with bicarbonate, these were not independent predictors and no significant association was found. The time to develop cerebral edema in this study was 5.8 hours but did not demonstrate an association between the rate of fluid association and the development of cerebral edema. This is weak grade 2 evidence (10).

Edge et al (12) conducted a UK case-control stony to cerebral edema in children presenting with DKA and through the British Pediatric Surveillance unit 43 cases of cerebral edema were identified. Through a parallel reporting system 2940 episodes of DKA were identified and 169 control subjects were selected based on comparable age, gender, date of admission, and several new or known cases of diabetes. Patients were exposed to cumulative volume and not weight-based intravenous fluid administered during the first four hours of therapy for DKA and stratified by volume cut-off the range. Baseline acidosis, higher sodium, potassium, and urea concentrations at admission, early administration of insulin, and high volume of fluids were associated with a higher risk of cerebral edema. This is a grade 2- evidence [10].

Hsia et al (13) carried out a retrospective cohort study on 1868 patients' admissions with DKA. The cohort was divided into two groups namely group A (1998-2004) and group B (2004-2010) and patients with suspected clinical cerebral edema were identified. The goal of this study was to compare DKA outcomes 6 years prior and 6 years from changing intravenous fluids from half normal saline to ringer lactate and reducing the total intended volume in the first 24 hours from 3500ml/sqm /day to ≤2500ml/sqm/day. The results showed that adverse outcomes were similar in both groups. However the overall incidence of

suspected clinical cerebral edema was more than double for patients who had received initial fluid resuscitation at an outside hospital versus those who received in-house (13.6% vs 5.3%, p<0.001). This is a grade 2- evidence (10).

Kupperman et al (14) conducted a groundbreaking study to finally answer the question of the controversial relationship between intravenous content and rate of fluid administration in the development of cerebral edema in paediatric. Currently this is the only prospective, multicentre randomized controlled trials conducted13 emergency department in the Paediatric Emergency Care Applied Research Network (PECARN). Total 1389 episodes of DKA were noted in 1255 children. Of this 1361 episode of DKA presented with Glasgow Coma Scale (GCS) scores of 14 or 15 and were included in the primary analysis from age less than or equal to 18 years with a diagnosis of DKA with average age of twelve years. After randomization children were placed in four broad groups. Group 1 received fast rehydration with 0.45% sodium chloride for replacement of deficit and included 337 patients. Group 2 received fast rehydration with 0.9% sodium chloride in a similar method of administration as Group 1 and included 345 patients. Group 3 received slow rehydration with 0.45% sodium chloride for replacement deficit. This group included 338 patients. Group 4 received slow administration of 0.9% sodium chloride in a similar method of administration as Group 3. This group had 341 patients. All groups received initial standard bolus of 10ml/kg of 0.9% sodium chloride, Group 1 and 2 received additional bolus. Assumed fluid deficit was 10% in groups 1 and 2 and 5% in ggroups3 and 4. Half of the deficit was replaced in the first 12 hours and then the remaining deficit and maintenance was given in the next 24 hours in grogroupsand 2. In group 3 and 4, the deficit and maintenance was given evenly over 48 hours. The primary outcome was to determine decline in neurological status evidenced by two consecutive GCS scores <14 in the first 24 hours of treatment of DKA. Secondary outcomes were brain injury incidence and short-term memory. The results showed that 3.5% had a GCS score of less than 14 and clinically apparent brain injury was found in 12 episodes (0.9%). The percentages of apparent brain injury episodes among the four broad groups were statistically insignificant, same with level of decline GCS. In addition, short-term memory showed no statistical significance between the four groups. Hence neither the rate of administration nor sodium chloride content of the intravenous fluid therapy significantly influenced outcomes in pediatric DKA. This is an excellent study with appropriate randomisation into four broad groups with similarities in baseline characteristics and demographics. The average age was eleven years in the both fast and slow groups. However, there was no blinding of the treatment group as the clinician needs to know fluid protocol for decision making. Specific outcome analysis was difficult because clinically apparent brain injury occurred in less than 1% episodes of pediatric DKA. The power of this study may be slightly impaired because repeat episodes in the same patients were not excluded but DKA episodes were limited to two patients. Glasgow outcome scale extended (GOSE) could have been a standard to assess their level of discovery but this was absent here (15). This is grade 1- evidence [10].

Conclusion

Almost all the studies showed that cerebral edema was associated with severe acidosis and prerenal azotemia in initial DKA presentation(8, 11, 13)and only one study (observational case-control) showed significant correlation with the highest range of volume of intravenous fluid therapy with first few e hours (12). Differences in the results are due to different study designs (case-control versus randomised controlled study), possible selection bias, and confounding factors which is a major demerit associated with case-control study; all these factors are likely to alter the generalisability and reliability of these studies which are inherent limitations of observational studies. None of the studies mentioned the effect of co-morbidities on the clinical outcomes which may be a confounding factor, children with more co-morbidity will appear sicker (as a result of underlying serious illness) and deteriorate faster than those not.

The well-designed PECARN study is a resounding research breakthrough in putting to rest age-long controversy and traditional teaching that aggressive fluid therapy in pediatric DKA may be responsible for cerebral edema. This is the first and currently only prospective and randomized clinical trial on this subject with the conclusion that neither rate of fluid administration nor sodium chloride content significantly influenced neurological outcomes in Pediatric DKA

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