

Ketogenic Diet Initiation & Management for Refractory Status Epilepticus

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Disclosure

- I have no financial disclosures or conflicts of interest to report

Objectives

- Define Status Epilepticus and discuss current research that supports the use of the ketogenic diet as a viable treatment option
- Analyze ketogenic diet initiation and management protocol
- Review Case Studies
- Discuss challenges and pitfalls of diet initiation and management in the ICU

Defining Status Epilepticus (SE)

- SE is a medical emergency associated with significant morbidity and mortality
- SE is defined as a continuous seizure lasting more than 30 min or two or more seizures without full recovery of consciousness in between
- It has been estimated that up to 150,000 cases of SE occur annually in the US, with 55,000 associated deaths

Refractory Status Epilepticus (RSE)

- Seizure activity is refractory to anti-seizure drug therapy and requires general anesthesia.
- SE that continues or recurs 24 hours or more after the onset of anesthetic therapy
- Prolonged treatment with IV anesthesia can result in hypotension, immunosuppression, gastric paresis, and pneumonia which may contribute to the high mortality rate of up to 30% in RSE

Refractory Status Epilepticus (RSE)

- Limited research on treatment information for RSE
- Ketogenic diet should probably be tried in all severe cases

Shorvan S, Ferlisi M. “The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol.” *Brain* 2011; 134:2802-18.

Best Responders

- Between 2008 and 2013 there were ten publications describing KD therapy for SE
- Best responders:
 - Those with underlying autoimmune or inflammatory conditions leading to SE
 - Encephalitis and Rasmussen syndrome
 - Febrile illness related epilepsy syndrome

Best Responders

- Diet therapy usually worked within 7-10 days of initiation

Kossoff E, Nabbout R. "Use of Dietary Therapy for Status Epilepticus." *Journal of Child Neurology*. 2013; 28(8) 1049-1051.

Ketogenic Diet in RSE Initiated by Fever Induced Refractory Epileptic Encephalopathy

- Nine Patients with FIRES received a 4:1 diet ratio.
- In 7 patients, KD was efficacious within 2-4 days following the onset of ketosis and 4-6 days within starting the diet
- In one responder, early disruption of the diet was followed by a relapse and the patient died

Nabbout R, Mazzuca M. "Efficacy of KD in Severe Refractory Status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES)." *Epilepsia*, 2010. 51(10):2033-2037

Ketogenic Diet for Adults in Refractory Status Epilepticus

- Ten adult patients from 4 medical centers were started on KD for RSE
- Median duration of RSE before initiation of KD was 21.5 days
- Median number and AED's used before initiation was 7
- 90% of patients achieved ketosis and RSE ceased in all patients achieving ketosis in average of 3 days
- 3 had minor complications and 2 died

Thakur, KT, Probasco, J, Hocker, S, et al. "Ketogenic Diet for Adults in super refractory status epilepticus". *Neurology*, 2014;82:665-670

Ketogenic Diet Initiation & Maintenance Protocol

- Drawing Screening Labs
- Orders prior to formula initiation
- Designing Ketogenic Formula
- Formula Initiation and Advancement Protocol
- Diet maintenance protocol
- Goals

Draw Screening Labs

- Plasma Amino Acids
- Urine Organic Acids
- Plasma Acylcarnitine profile
- CMP
- CBC w/diff
- Fasting lipid panel
- Prealbumin
- Free and Total Carnitine
- Ica, phos, mag
- Zinc, selenium
- 25-hydroxy vitamin D
- Urinalysis
 - Results may be pending at the time of initiation

Orders Prior to Formula Initiation

- NPO x 24 hours prior to initiation
- Check accu-check q 4 hours during fast
- Convert all medications to pill/tablet form if possible
- IV fluids without dextrose at least 1x maintenance
 - Use sodium chloride or normal saline solution

Design Ketogenic Tube Feeding

- Choose a Formula
 - Ketocal 4:1 Liquid, Ross Carbohydrate Free Concentrate
 - Various Modular Products: MCT oil, beneprotein powder, duocal, microlipid
- Choose a diet ratio
 - 4:1 diet ratio preferred unless protein need cannot be met at goal calorie level then a lower ratio is chosen (3:1, 2:1 etc)

Design Ketogenic Tube Feeding

- Choose a Calorie Level
 - Take into account growth history if available and current feeding regimen
 - If patient is comatose/sedated calorie needs likely much lower
- Define Feeding Regimen
 - Formula provided continuously via NG or NJ tube x 24 hours

Formula Initiation

- Initiate formula at half calories x 24 hours and advance to goal gradually over 3-5 days

Ketogenic Diet Maintenance Protocol

- Accu-check protocol:
 - Every 3 hours and PRN if blood glucose ≤ 60
 - Every 1 hour and PRN if blood glucose ≤ 50
 - Every 15-30 minutes and PRN if blood glucose ≤ 45 , then administer IV D5 100cc x1.
- Check urine ketones q void
- Check urine specific gravity q void
- Carnitine: Start empirically
 - 50mg/kg/day divided into 3 daily doses

Ketogenic Diet Initiation Protocol

- ◉ Daily beta-hydroxybutyrate (BHB) and CMP until ketosis well-established
- ◉ Recheck free/total carnitine levels in 2 weeks
- ◉ Check Prealbumin weekly

Ketogenic Diet Goals

- ◉ Establish ketosis and stop seizures!
- ◉ Goal blood sugar: 50-80
- ◉ Positive serum and urine ketones
- ◉ $\text{Co}_2 > 17$
- ◉ Try for at least 2 weeks before discontinuing diet therapy

Case Study: L.G 23 y.o Female

- History of epilepsy
- Admitted to outside hospital with altered mental status and went into SE
- Transferred to UCLA in pentobarbital induced coma with outside team unsuccessful at weaning sedation
- On multiple AED's
- Following Modified Atkins Diet PTA

Case Study: L.G 23 y.o Female

- Anthropometrics:

- Weight: 53 kg (116 lbs 13.5 oz)
- Height: 64'' (162.5 cm)
- ~97% IBW

- Estimated Needs

- 25 kcal/kg, 0.8-1.5 g protein/kg

- NG Tube in place. Tolerating Jevity 1.2 @ 50 ml/hr

Case Study: L.G 23 y.o Female

- Ketogenic diet started on day 4 of admission to UCLA
- Goal Ketogenic Formula:
 - 643 g Ketocal 4:1 liquid +
 - 25 g beneprotein powder +
 - 80 g liquigen (equivalent to ~40g MCT oil) +
 - 458 ml water.
 - Total Volume 1260 ml
- Provided 3:1 ratio, 1400 calories, 135.6 g fat, 41.3 g protein, 3.9 g carb

Case Study: L.G 23 y.o Female

- Fasted for 24 hours
- Initiated full strength @25cc/hr (provides half calories) day 1
- High residuals prevented advancement of rate
- GJ tube placed ~7 days later and formula advanced to goal

Case Study: L.G 23 y.o Female

- Negative urine ketones and BHB <1 until day 9 of diet
- Day 9, BHB=2.52 and Urine ketones=moderate
- Glucose ranged from 73-127 mg/dL while receiving diet
- After about 2 weeks on KD, family decided to pursue palliative extubation due to poor prognosis and patient passed away.

Case Study: S.C 6 y.o Male

- Diagnosed with intractable epilepsy 1 year prior to admission
- Transferred from outside hospital in pentobarbital induced coma in SE
- Etiology of SE unknown

Case Study: S.C 6 y.o Male

- Anthropometrics
 - Weight: 19.2 kg (10-25th %ile)
 - Height: NA
- Estimated Needs:
 - 60-70 kcal/kg, 1.3-1.5 g protein/kg
- NG tube in place. Receiving Pediasure with Fiber @50 ml/hr

Case Study: S.C 6 y.o Male

- In pentobarbital induced coma and on multiple AED's including topamax
- Ketogenic diet started on day 36 of admission to UCLA
- Initiated diet full strength and full calories:
 - 2:1 ratio day 1
 - 3:1 ratio day 2
 - 4:1 ratio (goal) day 3

Case Study: S.C 6 y.o Male

- Goal Ketogenic Diet Formula:
 - 167 g ketocal 4:1 liquid +
 - 1030 ml water=
 - Total Volume ~1200 ml
- Provided 4:1 ratio, 120.2 g fat, 25 g protein, 5 g carb

Case Study: S.C 6 y.o Male

- Anesthetics weaned 3-5 days post diet initiation
- Seizures became shorter in duration
- Moderate urine ketones after 2 days at goal diet
- BHB 3.70 mmol/L by day 5
- BHB ranged from 2.9-4.7mmol/L while in PICU
- Blood sugars usually ranged from 80-100 and never dropped below 70

Case Study: S.C 6 y.o Male

- Developed nephrolithiasis shortly after initiating diet
 - Treated with Bicitra which lowered diet ratio and d/c topamax

Case Study: S.C 6 y.o Male

- Discharged from UCLA to rehab facility on ketogenic tube feeds after 3 month stay
- Calories were increased and he started ketogenic purees by mouth 1-2 months post discharge in addition to tube feedings

Case Study: S.C 6 y.o Male

- Progressed textures and continued diet at 4:1
- Became seizure free 4 months after diet initiation
- Weaned diet after 15 months

Managing Pitfalls and Challenges

- Poor Ketosis
- High Blood Sugars and Stress
Hyperglycemia
- Carbohydrate Containing Medications
- Intolerance

Poor Ketosis & High Blood Sugars

- Overfeeding

- Estimating calorie needs often difficult in sedated patients
- Predictive equation suggestions
 - 50% of RDA
 - WHO Equation w/o activity factor

Poor Ketosis & High Blood Sugars

- Obtain Resting Energy Expenditure test prior to diet initiation if possible
- Patients on continuous oxygen excluded
- Consider incorporating MCT oil early on

High Blood Sugars

○ Stress Hyperglycemia

- Peripheral and hepatic insulin resistance, certain drugs, and increased stress hormone release have all been implicated as causes
- Etiology and management requires further study
- May be an unrecognized obstacle to ketogenic diet initiation

Cobo, Sankar, Murata, Sewak, Kezele, Matsumoto. "The Ketogenic Diet as Broad-Spectrum Treatment for Super-Refractory Pediatric Status Epilepticus: Challenges in Implementation in the Pediatric and Neonatal Intensive Care Units". *Journal of Child Neurology* 2015; 30(2):259-66

Carbohydrate Containing Medications

- Work with pharmacy to review carb content of meds and for suggestions on alternatives if available
 - Pentobarbital IV solution contains propylene glycol which can prevent ketosis
 - Propofol is administered in a 10% fat emulsion and contains glycerol (carb) and lecithin (protein)
- Educating nursing staff

Intolerance

⦿ Vomiting/High Residuals

- Consider adding antiemetic
- Jejunal feeding tube placement (NJ tube) recommended to improve tolerance and prevent aspiration of formula into the lungs

⦿ Acidosis

- Bicitra is carb containing

Unanswered Questions

- What is the optimal timing to start KD?
- Best way to design and initiate KD? Fasting?
- Duration of treatment to observe any effect?
 - O'Conner et al suggested trailing KD for 2 weeks
- Duration of treatment after seizure control?
- Could predetermined KD formulas (based on average weights/gender) be designed to allow for quick diet implementation when RD not available?

Unanswered Questions

- Likelihood of improvement with KD?
- Which etiologies best respond?

Kossoff E, Nabbout R. "Use of Dietary Therapy for Status Epilepticus." 2013; 28(8) 1049-1051.

Conclusion

- The ketogenic diet is an exciting and efficacious treatment option for refractory status epilepticus for both adult and pediatric patients.
- Implementation requires an experienced ketogenic diet team.

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