neurocritical care society Neurocrit Care (2009) 11:101–105
DOI 10.1007/s12028-009-9197-9

PRACTICAL PEARL

Continuous Renal Replacement Therapy for Refractory Intracranial Hypertension

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Published online: 7 March 2009

Abstract
Introduction Little is known about the effects of hemodialysis on the injured brain, however; concern exists over the use of intermittent hemodialysis in patients with acute brain injury (ABI) due to its hemodynamic effects and increased intracranial pressure (ICP) associated with therapy. Continuous renal replacement therapy (CRRT) has become the preferred method of renal support in these patients though there is limited data to support its safety. Furthermore, exacerbations of cerebral edema have been reported. CRRT is an option for the treatment of hypervolemia and in theory may improve intracranial compliance. We report the case of a poly-trauma patient with severe traumatic brain injury (TBI) in which CRRT was implemented solely for refractory intracranial hypertension.
Methods A 28-year-old male was involved in a high-speed motor vehicle collision suffering a severe TBI and polytrauma. He required significant volume resuscitation. Intensive care unit course was complicated by shock, acute respiratory distress syndrome, ventilator associated pneumonia, and development of intracranial hypertension (IH). Data were collected by retrospective chart review.
Results Continuous hemofiltration was initiated for IH refractory to medical therapy. Within hours of initiation increase, ICP improved and normalized. Hemofiltration was safely discontinued after 48 h. Modified Rankin Score was 2 at 90 days.
Conclusion Though unproven, CRRT may be beneficial in patients with IH due to gentle removal of fluid, solutes, and inflammatory cytokines. Given the limited data on safety of CRRT in patients with ABI, we encourage further reports.

Keywords Continuous renal replacement therapy · Traumatic brain injury · Hemofiltration · Hypervolemia · Intracranial hypertension

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Introduction

Due to improved cardiovascular and intracranial stability continuous renal replacement therapy (CRRT) has replaced intermittent hemodialysis (IHD) as the preferred method of renal replacement therapy (RRT) in patients with acute brain injury (ABI) [1, 2]. Conventional IHD has been shown to exacerbate cerebral edema, increase intracranial pressure (ICP), and is associated with more hypotensive episodes and arrhythmias than CRRT [3–6]. In theory, CRRT may be beneficial in patients with intracranial hypertension (IH) due to its ability to adjust intravascular volume, remove water, solutes, and inflammatory mediators [7, 8]. Despite the accepted use of CRRT in patients with ABI and co-existing acute renal failure (ARF), there is limited data on safety and no data to support efficacy in controlling IH.

The resuscitation of critically ill patients frequently requires the administration of large volumes of crystalloid fluids. The water and sodium content of these fluids often results in peripheral edema, though a role in cerebral edema and IH are not clearly established. We report the

case of a previously healthy 28-year-old male with polytrauma and severe traumatic brain injury (TBI) in whom CRRT was implemented solely for refractory IH. The patient required a large amount of isotonic fluid during initial resuscitation and was not thought a candidate for decompressive craniectomy due to medical instability. To our knowledge, this is the first reported case of CRRT used solely for the treatment of IH in a patient without ARF.

Case Report

A 28-year-old right-handed male was the restrained driver involved in a high-speed motor vehicle collision. Vital signs on arrival to the emergency department showed a heart rate of 110 beats per minute, blood pressure 74/37 mmHg, temperature of 96.7°F, oxygen saturation of 84% on 100% FiO2, and a Glasgow Coma Score of 3. The patient was in hemorrhagic shock and his catalog of injuries included: severe TBI, left carotid dissection, ascending aortic dissection with hemopericardium, bilateral pneumothoraces and pulmonary contusions, sternal fracture, bilateral pelvic rami fractures, and blunt abdominal trauma.

Due to persistent hypotension, the patient underwent exploratory laparotomy with control of mesenteric bleeding and a grade I liver laceration. Initial computed tomography (CT) scan of the head suggested diffuse cerebral edema and CT angiogram of the neck demonstrated a left carotid dissection in the high cervical internal carotid artery. A fiber optic intraparenchymal ICP monitor was placed. Initial ICP was 11 with a rise to 19 mmHg after 1 h. Over the next 4 h, the ICP continued to increase to a peak of 40 mmHg with sustained ICP in the low 30s. Cerebral perfusion pressure (CPP) decreased to an average of 35 mmHg. The patient's IH was unresponsive to mannitol IV bolus, raising CPP and sedation. Pentobarbital was initiated and titrated to burst-suppression pattern on electroencephalogram resulting in a reduction in ICP. Subsequently an external ventricular drain (EVD) was placed for CSF diversion and pentobarbital was withdrawn. Management was continued according to Brain Trauma Foundation guidelines and vasopressors were used to maintain CPP $>$ 55 mmHg given co-existing aortic dissection and the need for esmolol to control heart rate.

Intensive care unit (ICU) course was complicated by the development of a *Pseudomonas* pneumonia and acute respiratory distress syndrome (ARDS) on hospital day (HD) #5. On HD #6 sedation (midazolam/fentanyl) was increased to achieve a bispectral index (BIS) of 16–26 (Aspect Medical Systems; Norwood MA, USA) and neuromuscular blockade was initiated for progressive hypoxic respiratory failure. On the morning of HD #7, the patient developed re-emergence of IH with ICP ranging from 24 to 38 mmHg (mean 28.6) despite additional increases in sedation, diuresis, induced hypothermia (33°C) and administration of mannitol (serum trough osmolality between 302 and 309; peak serum sodium concentration 150 mEq/l). Pentobarbital was not re-initiated secondary to low BIS score on high dose midazolam infusion and hyperventilation was not employed secondary to the patient requiring inverse ratio ventilation after failing conventional mechanical ventilation. Repeat head CT showed diffuse cerebral edema with multiple focal hypodensities in left occipital, parietal, and right occipital regions. Decompressive surgery was considered but after multi-disciplinary discussion was not performed due to medical instability. Intracranial pressure ranged from 25 to 41 mmHg (mean 30.8) on HD #8 and was not affected by a 30 cc IV bolus of 23.4% saline. A bumetanide drip was initiated early morning on HD # 9 for a large, positive fluid balance in the setting of refractory IH. Although an appropriate rise in urine output (approximately 200–250 cc/h) was seen in the next few hours, ICP was unchanged. Subsequently, CRRT was initiated and the bumetanide drip was discontinued. A summary of clinical interventions during the patient's ICU course is shown in Fig. 1.

The patient underwent continuous venovenous hemofiltration using a Gambro Prisma machine with M100/AN69 hydrogel filter (Gambro America, Lakewood, CO, USA). The circuit was primed with normal saline. A total of three filters' changes were required during the 48 h of CRRT treatment. Blood flow rates and ultrafiltration rates ranged between 80–180 and 500–1200 ml/h, respectively. Replacement fluid consisted of 50 meq sodium bicarbonate, 90 meq sodium chloride, and 500 mg of calcium gluconate per liter of sterile water. A small amount of prefilter heparin was used to prevent filter clogging. Net fluid removal was the greatest in the first 24 h of therapy. No hemodynamic instability occurred while receiving CRRT. Figure 2 shows changes in volume status, ICP, and CPP after initiation of hemofiltration. Intracranial pressure decreased from an average of 35 mmHg in the 12 h prior to initiation of CRRT to an average of 23 mmHg in the following 12 h despite the discontinuation of mannitol and hypothermia. After 12 h of CRRT therapy, ICP remained at or below 20 mmHg. Hemofiltration was discontinued on day HD # 11. Renal function tests were normal and unaffected by CRRT. The patient continued to recover and at 90 days follow-up Modified Rankin Score was 2 and Glasgow Outcome Scale was 4.

Discussion

Sodium and fluid restriction were previously advocated following brain injury when cerebral autoregulation may

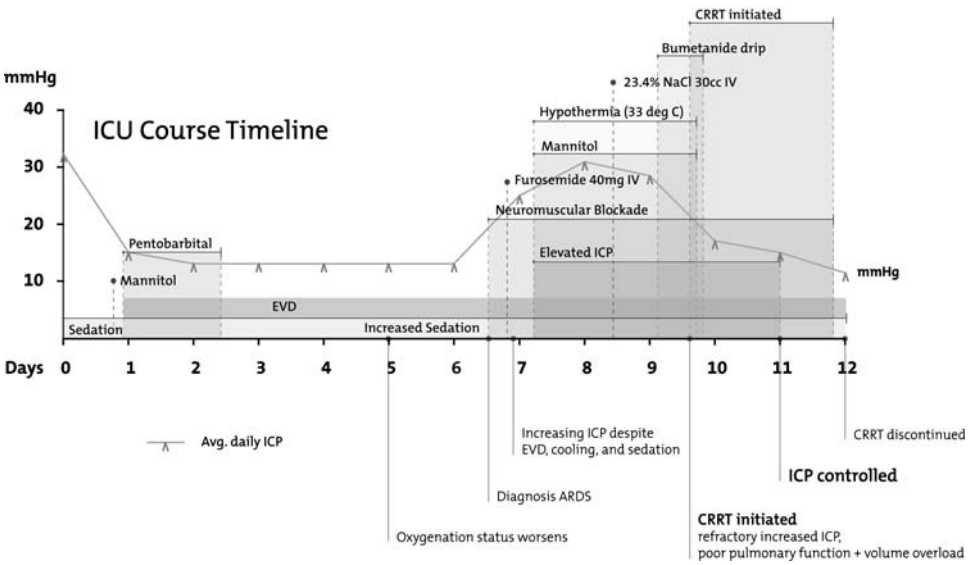

Fig. 1 ICU course timeline

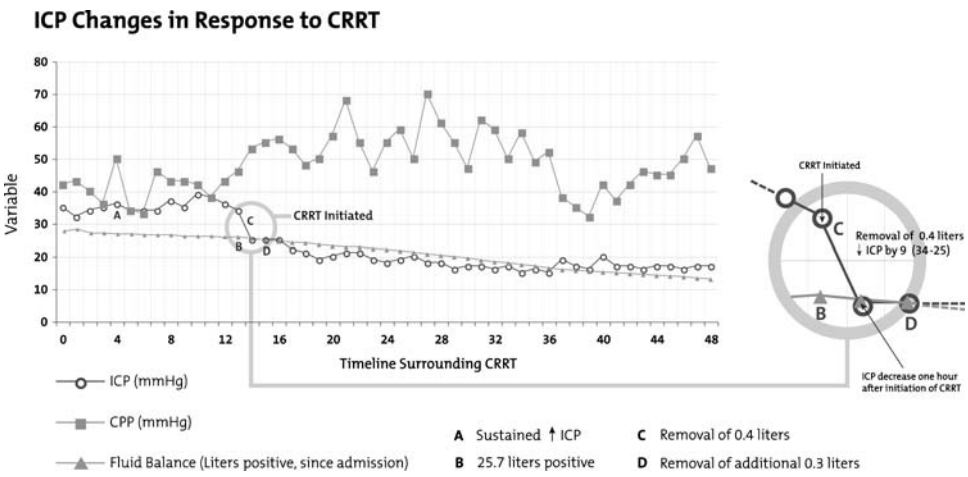

Fig. 2 ICP changes in response to CRRT. Sustained intracranial hypertension (A), 25.7 l positive fluid balance (B), net removal of 0.4 l of fluid (C), and an additional removal of 0.3 l of fluid

be disrupted and blood vessels "leaky." Limited data, mostly from late 1960s through mid 1980s, lend some support to this theory [9, 10] although more recent data suggest the opposite [11–13]. Hypovolemia from under-resuscitation is known to exacerbate secondary brain injury. However, despite overwhelming data to the contrary, the longstanding practice of fluid restriction continues to be practiced in many Neuro/Trauma units. The National Acute Brain Injury Trial on Hypothermia demonstrated a negative fluid balance (more than −594 cc in the first 96 h) was independently associated with worse outcome and the need for more osmotic therapy to treat IH [12]. In patients randomized to the hypothermia arm, a positive fluid balance of more than 5 l in 96 h was associated with a worse outcome but not IH. However, the need for significant volume resuscitation and an association with poor outcome is not unexpected. Though severe hypervolemia may be associated with a worse outcome and at extremes likely affects ICP, a clear fluid threshold has not been established.

The pathophysiology underlying increases in ICP during IHD in patients with ABI is thought to parallel that seen in dialysis disequilibrium syndrome (DDS). Historically, the "idiogenic osmole hypothesis" and "reverse urea effect" have been debated as the cause of increased brain parenchymal water content and central nervous dysfunction following hemodialysis [14–18]. Additionally, some investigators have proposed that the rapid exchange of bicarbonate into the plasma during IHD may be converted to carbon dioxide to enter the brain leading to intracellular acidosis and increased ICP [19]. Recent data support the primary role of the reverse urea effect in CNS dysfunction associated with IHD, although there are still concerns with this theory, specifically in terms of whether the brain to plasma urea concentration is enough to explain cerebral edema.

Though the reverse urea effect, idiogenic osmole hypothesis, and rapid bicarbonate exchange may account for increased cerebral edema and ICP associated with IHD, they may not be the primary mechanisms. Increased ICP is frequently seen shortly after initiation of HD and prior to significant changes in serum osmolality or pH. These early changes are frequently preceded or accompanied by hypotension, decreasing CPP, and cerebral blood flow (CBF) [6]. This may lead to cerebrovascular vasodilatation and increased ICP. Additionally, low CPP may cause cerebral hypoxia and the formation of idiogenic osmoles with increases in cerebral edema [20].

Due to the previously mentioned concerns with IHD in patients with ABI, CRRT has become the preferred mode. It has been widely adopted in critically ill patients with ARF and co-existing systemic inflammatory response syndrome (SIRS) and multi-organ failure due to its improved hemodynamic tolerance. The ability of CRRT to clear cytokines from the human circulation as well as the initial suggestion of improved outcomes with more intense therapy has further promoted the implementation of CRRT in critically ill patients [7, 8, 21, 22]. Despite this initial promising evidence, the recently completed VA/NIH Acute Renal Failure Trial Network failed to show any benefit with intense renal support in critically ill patients with ARF versus standard regimens [23]. The current literature continues to support a better hemodynamic profile with CRRT than IHD but does not support increased survival or a renal protective effect of CRRT over IHD in patients with ARF [24, 25].

Despite the preference of CRRT in patients with ABI and co-existing ARF, there is limited data to support its safety. Davenport et al. demonstrated stability of ICP during continuous arteriovenous hemofiltration (CAVHD) in one patient with fulminant liver failure and oliguric renal failure who had a sustained surge in ICP during previous IHD [26]. In a small series of 10 patients with fulminant liver failure and oliguric renal failure, CAVHD was shown not to affect ICP whereas the six patients undergoing IHD had shown increases in ICP [4]. Continuous venovenous hemodiafiltration has also been used successfully in a patient with a cerebellar hematoma and obstructive hydrocephalous (treated with CSF diversion) who developed ARF and multi-organ dysfunction [27].

Despite the limited data showing intracranial stability with CRRT, it has been reported to exacerbate ICP during rapid exchange and marked rebound surges of ICP resulting in death have been reported [28].

On initiation of CRRT in our patient no concerns existed over the reverse urea effect, as our patient did not have ARF. However, there was concern over the possibility of worsening ICP secondary to the "idogenic osmole hypothesis" given elevated serum osmolality in the past 48 h related to mannitol administration. Despite this concern our patient showed a dramatic decrease in ICP during the first hour of hemofiltration, which was sustained despite discontinuation of mannitol, hypothermia, and de-escalation of sedation. Initial improvement in ICP may have been secondary to removal of brain water content, or improvement in gas exchange secondary to net fluid loss. However, the patient had a positive fluid balance of 26 l at the start of therapy and net fluid removal remained relatively constant at approximately 400 cc/h during the early phase of CRRT. Additionally, in the hours prior to initiation of CRRT, net fluid removal of 250 cc/h with bumetanide infusion did not result in any change in ICP. Hence, the dramatic response during the first hour of filtration brings up the possibility of pro-inflammatory cytokine removal, which is maximal during the first hour of filtration secondary to the negative surface charge of HD filters. Arterial blood gas analysis did improve slowly over time, but no values were available immediately prior to or in the first few hours after initiation of therapy. One concern with using CRRT in our patient, similar to other patients with ABI, is the need for anticoagulation to prevent filter clotting. The use of heparin increases hemorrhagic complications; however, we did not experience any bleeding complications during therapy in our patient. We used low dose heparin despite the history of aortic tear and TBI; however, the patients activated partial thromboplastin time remained normal. This explains the need for three filters over 48 h and also brings up economic concerns over replacing the circuit frequently. Sodium citrate protocols are an alternative and in theory may help maintain a hyperosmolar state in patients with IH. In the future, newer machines may allow higher blood flow and ultrafiltration rates decreasing the need for regional anticoagulation.

Conclusion

Critically ill patients require large volumes of fluid to meet resuscitation end points. After a certain threshold, hypervolemia appears to affect outcome and possibly ICP in patients with ABI. CRRT remains an option for the treatment of hypervolemia, though typically when resistant to diuretics. There is little data on the safety of CRRT in patients with intracranial hypertension and it remains unproven as a therapy to lower ICP. We encourage further reports of CRRT in patients with ABI.

References

1. Davenport A. Renal replacement therapy in the patient with acute brain injury. Am J Kidney Dis. 2001;31(3):457–66.

2. Davenport A. Renal replacement therapy for the patient with acute traumatic brain injury and severe acute kidney injury. Contrib Nephrol. 2007;156:333–9. doi:10.1159/000102124.
3. Silver SM, Sterns RH, Halperin ML. Brain swelling after dialysis: old urea or new osmoles? Am J Kidney Dis. 1996;28(1):1–13. doi:10.1016/S0272-6386(96)90124-9.
4. Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. Nephrol Dial Transplant. 1990;5(3):192–8.
5. Davenport A, Will EJ, Davison AM. Continuous vs. intermittent forms of haemofiltration and/or dialysis in the management of acute renal failure in patients with defective cerebral autoregulation at risk of cerebral oedema. Contrib Nephrol. 1991;93: 225–33.
6. Bertrand YM, Hermant A, Mahieu P, Roeb J. Intracranial pressure changes in patients with head trauma during hemodialysis. Intensive Care Med. 1983;9:321–3. doi:10.1007/BF01692550.
7. Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. Crit Care Med. 1993;21:522–6. doi:10.1097/00003246-199304000-00011.
8. Schetz M. Evidence-based analysis of the use of hemo-filtration in sepsis and MODS. Curr Opin Intens Care. 1997;3:434–41. doi: 10.1097/00075198-199712000-00006.
9. Shenkin HA, Bezier HS, Bouzarth WF. Restricted fluid intake: rational management of the neurosurgical patient. J Neurosurg. 1976;45:432–6.
10. Shenkin HA, Bouzarth WF, Tatsumi T. The analysis of body water compartments in postoperative craniotomy patients: part 1. The effects of major brain surgery alone: part 2. The effects of mannitol administered preoperatively. J Neurosurg. 1967;28:417.
11. Ramming S, Schackford S, Zhuang J. The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. J Trauma. 1994;37(5):705–13. doi:10.1097/00005373-199411000-00003.
12. Clifton GL, Miller ER, Choi SC. Fluid thresholds and outcome from severe brain injury. Crit Care Med. 2002;30(4):739–45. doi: 10.1097/00003246-200204000-00003.
13. Schmoker JD, Schackford SR, Wald SL, et al. An analysis of the relationship between fluid and sodium administration and intracranial pressure after head injury. J Trauma. 1992;33:476–81. doi:10.1097/00005373-199209000-00024.
14. Silver S. Cerebral edema after rapid dialysis is not caused by an increase in brain organic osmolytes. J Am Soc Nephrol. 1995;6: 1600–6.
15. Trachtman H, Futterweit S, Tonidandel W, Gullans S. The role of organic osmolytes in the cerebral cell volume regulatory response to acute and chronic renal failure. J Am Soc Nephrol. 1993;3: 1913–9.
16. Arieff AI, Massry SG, Barrientos A, Kleeman CR. Brain water and electrolyte metabolism in uremia: effects of slow and rapid hemodialysis. Kidney Int. 1973;4:177–87. doi:10.1038/ki.1973.100.
17. Arieff A, Guisade R, Massry S, Lazarowitz V. Central nervous system pH in uremia and the effects of hemodialysis. J Clin Invest. 1976;58:306–11. doi:10.1172/JCI108473.
18. Galons JP, Trouard T, Gmitro AF, Lien YH. Hemodialysis increases apparent diffusion coefficient of brain water in nephrectomized rats measured by isotropic diffusion-weighted magnetic reasonance imaging. J Clin Invest. 1996;98(3):750–5. doi:10.1172/JCI118847.
19. Goldsmith DA, Forni LG, Hilton PJ. Bicarbonate therapy and intracellular acidosis. Clin Sci. 1997;93:593–8.
20. Davenport A. Is there a role for continuous renal replacement therapies in patients with liver and renal failure? Kidney Int. 1999;56:62–6. doi:10.1046/j.1523-1755.56.s.72.3.x.
21. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356: 26–30. doi:10.1016/S0140-6736(00)02430-2.
22. Schiffl H, Lang S, Fischer R. Daily haemodialysis and the outcome of acute renal failure. N Engl J Med. 2002;346:305–10. doi: 10.1056/NEJMoa010877.
23. Palevsky PM, Zhang JH, O'Connor TZ, et al. VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7–20. doi:10.1056/NEJMoa0802639.
24. Ghahramani N, Shadrou S, Hollenbeak C. A systematic review of continuous renal replacement therapy and intermittent haemodialysis in management of patients with acute renal failure. Nephrology. 2008;13:570–8.
25. Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev 2007; Available from: www.cochrane.org.
26. Davenport A, Will EJ, Losowski MS, Swindells S. Continuous arteriovenous hemofiltration in patients with hepatic encephalopathy and renal failure. Br Med J (Clin Res Ed). 1987;295: 1098.
27. Caruso DM, Giancarlo V, Karl AG, et al. Continuous hemodialysis for the management of acute renal failure in the presence of cerebellar hemorrhage. J Neurosurg. 1998;89:649–52.
28. Davenport A, Will EJ, Losowsky MS. Rebound surges of intracranial pressure as a consequence of forced ultrafiltration used to control intracranial pressure in patients with severe hepatorenal failure. Am J Kidney Dis. 1989;14(6):516–9.