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ORIGINAL PAPER

Continuous veno-venous haemodiafiltration in burns patients: a role in hyperpyrexia

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Abstract
Background A burn injury results in the release of pro-inflammatory cytokines and catecholamines, causing a hypermetabolic state which may lead to hyperpyrexia (>40 °C). This risk is increased with concomitant sepsis. Hyperpyrexia is associated with a high mortality. Continous veno-venous haemodiafiltration (CVVHDF) can be used to reduce the circulating cytokines thereby reducing the cause of the hyperpyrexia. CVVHDF use has been well documented in sepsis and SIRS in the ITU population. In our Burns Centre, CVVHDF is routinely used to treat patients with persistent hyperpyrexia. The aim of this study was to evaluate the role of CVVHDF in burns patients with hyperpyrexia.
Methods A retrospective analysis was carried out of all patients admitted to the Burns ITU between 2005 and 2012 who received CVVHDF for hyperpyrexia. The medical notes and electronic database was used to collect data on indication, renal function, duration and outcome.
Results Five hundred seventy patients were admitted over the time period. Sixty-one patients received CVVHDF overall and of these 32 were for hyperpyrexia alone. In these patients, there was a significant reduction in temperature within 3 h of initiating CVVHDF ($p < 0.0001$). The cumulative predicted mortality using Modified Baux score was seven patients. In our group 2 patients died, possibly implying a survival benefit.
Conclusions CVVHDF can be successfully used to regulate the temperature in burns patients with hyperpyrexia.
Level of evidence: Level IV, therapeutic study.

Keywords Haemodiafiltration · Burns · Hyperpyrexia

Introduction

The release of proinflammatory cytokines and catecholamines by tissues damaged by a significant burn injury may induce a hypermetabolic state, raising the patient's basal temperature above the normal level [1]. This, together with episodes of sepsis, may lead to periods of hyperpyrexia during which the patient's temperature may reach 40 °C or above. Sustained hyperpyrexia leads to protein denaturation, disruption of enzyme systems, cellular injury and death.

Elevated temperature has been shown to be independently associated with longer Intensive Care Unit (ICU) and hospital stay and increased ICU mortality [2]. Strategies for temperature regulation include pharmacological agents, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), external cooling by

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ambient temperature regulation, external cooling devices or gel pads and invasive techniques [3]. These include intravascular heat-exchange systems (Coolgard®, Zoll USA) and extracorporeal renal replacement techniques.

Several different extracorporeal techniques exist for renal replacement therapy including haemodialysis, haemofiltration and haemodiafiltration. Haemodialysis relies primarily on the diffusion of molecules from the blood through a semipermeable membrane into the diasylate, which is travelling in a counter current direction. Haemofiltration works by convection of molecules through a highly permeable membrane. In this technique, the waste material is removed as an ultrafiltrate and the fluid can be replaced with a sterile reinfusion if needed. Haemodifiltration combines the techniques of convection and diffusion by using a highly permeable membrane and a counter current diasylate. The renal replacement circuit can run with either an arterial input and venous output (arteriovenous) or a venous input and output (veno-venous) and be intermittent or continuous.

As described above, heamofiltration and haemo diafiltration (HDF) are procedures primarily used as renal replacement therapy [4, 5], but recent research has demonstrated its role in severe sepsis [6, 7] multiorgan failure [8, 9] and hyperpyrexia [10]. These techniques are believed to be effective by removal of the proinflammatory mediators, cytokines and catecholamines [10, 11]. Through the same mechanism, continuous veno-venous heamofiltration has been used successfully for temperature regulation in heat stroke patients with the added benefit of removing circulating myoglobin and preventing rhabdomyolysis related kidney disease [12]. Haemodiafiltration (HDF) combines convection and diffusion and therefore optimises the clearance of molecules of differing molecular weights [13].

The use of HDF in the burns unit is not new and its role in managing fluid overload, hypernatraemia and acute kidney injury is well documented [14–19]. The benefits of HDF include a reduced vasopressor requirement, improved lung function and reduced mortality rate [20].

The process of continuous veno-venous heamo diafiltration (CVVHDF) involves the removal of blood from the patient through a double-lumen central venous line. This blood then passes through the haemodialyser which contains a semipermeable membrane that allows diffusion of small molecules from the blood into the diasylate. The treated blood is then returned to the patient. CVVHDF circuits have a limited lifespan and cease to function when they become clotted or obstructed. On each occasion that this occurs in our practice, the requirement for continued treatment is reassessed. Treatment is discontinued when either renal failure was seen to be resolving, temperature fell below 40 °C or further treatment was considered futile.

CVVHDF protocol for hyperyrexia

We developed a protocol for the use of CVVHDF for hyperpyrexia in patients managed at our burns centre in 2001, when CVVHDF was being used routinely in the General ICU to manage renal failure. We consider using CVVHDF if a patient's temperature is elevated to 40 °C or higher for 6 h consecutively or to more than 41 °C for 2 h consecutively when conventional non-invasive methods of thermoregulation have failed to reduce the temperature (including external cooling, paracetamol and NSAIDs). CVVHDF is also considered when there is refractory acidosis (pH < 7.2) or incipient renal failure, with persistent hyperkalaemia >7 mmol/L or anuria with fluid overload.

The aim of this study was to investigate: (1) the number of patients treated with CVVHDF over a set year period, (2) the indications for treatment in these patients, (3) the impact of CVVHDF on hyperpyrexia and (4) the survival of patients treated with CVVHDF.

Materials and method

A retrospective analysis was carried out of all patients admitted to the burns ICU between 2005 and 2012. Patients were identified using electronic burns and renal databases. Data was retrieved retrospectively from patient's medical records, detailing their demographic information, indication for CVVHDF, observations, temperature changes and eventual outcome. We focused on the temperature change within 3 h as we felt this most closely reflected the impact of CVVHDF. Data from the group who received CVVHDF was compared with that from other patients treated on the burns ICU who did

not receive CVVHDF. Statistical analysis was carried out using Graphpad® software.

Standard burn care

All patients received standard burn care including immediate assessment in theatre including burns assessment, essential surgery if needed (escharotomies) and bronchoscopy for inhalational injury. If inhalational injury is found then treatment including bronchial lavage is implemented. The patients are admitted to a burns intensive care unit (ITU) and once stable (within 24 h) undergo early burns excision and grafting with autograft or allograft. All patients receive early nutritional support with NG or NJ feeding and elemental supplementation (Zinc, selenium etc.). We do not routinely use beta-blockers to control the hypermetabolic response.

Results

Comparing patients who received CVVHDF and those who did not

Five hundred and seventy patients were admitted to the burns ICU during the 7-year period between 2005 and 2012. Of these, 61 were treated with CVVHDF (11%). Demographic data from these two groups are compared in Table 1. The patients treated with CVVHDF had significantly larger burns, were significantly more likely to have had a smoke inhalational injury and had a significantly higher modified Baux score than those who did not receive CVVHDF. They also spent significantly longer receiving ventilator support and spent longer in burns ICU. The groups were compared using either Chi-squared or unpaired *t* tests, and a *p* value of <0.05 was accepted as significant. The mortality among patients who received CVVHDF was higher than those who did not.

Table 1 Comparison of patients who received CVVHDF versus those who did not

	CVVHDF	No CVVHDF	*P* value
Number of patients	61	509	–
♂:♀	1.8:1	3.2:1	0.0975
Av. age (years)	44 (14–85)	41 (18–101)	0.4225
Av. TBSA burn (%)	39 (1–90)	8 (1–95)	<0.0001
Smoke inhalation injury	31 (51%)	95 (19%)	<0.0001
Av. mod. Baux score	92 (42–143)	54 (18–154)	<0.0001
Days ventilated	33 (1–106)	2 (0–52)	<0.0001
Days CVVHDF	7 (1–57)		–
Days in BICU	39 (1–115)	5 (1–52)	<0.0001
Mortality	18 (30%)	21 (4%)	<0.0001

Indication for CVVHDF

The majority of patients received CVVHDF for hyperpyrexia alone (54%), 16% received CVVHDF for renal failure or acidosis and the remaining 30% was for multiple factors (acidosis, renal failure, fluid overload and hyperpyrexia).

Length of CVVHDF

The average length of time CVVHDF was required was 7.5 days for renal failure, acidosis or multiple reasons (range 1–55 days) and 8.5 days (range <24 h–57 days) for hyperpyrexia.

The effect of CVVHDF on temperature in those patients ($n = 32$) who received CVVHDF for hyperpyrexia control alone

Analysis of the mean temperature in the 3 h before and after the initiation of CVVHDF demonstrated a significant reduction in temperature (paired *t* test, $p < 0.0001$, Fig. 1a). Figure 1b shows the individual reduction in temperature in the 3 h following the commencement of CVVHDF. The average (mean) temperature reduction was 0.8 °C as indicated by the horizontal line.

The effect of CVVHDF for hyperpyrexia on survival

The cumulative predicted mortality, using modified Baux score, for the group of patients who received CVVHDF for hyperpyrexia was seven patients,

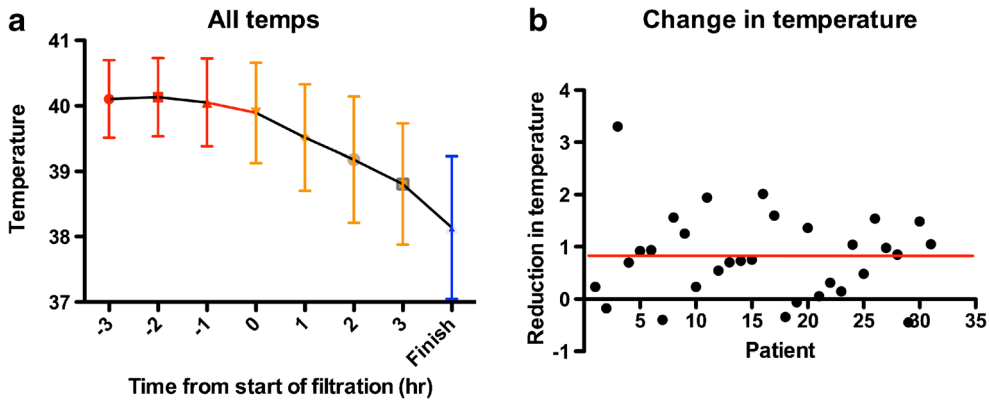

Fig. 1 The effect of CVVHDF on temperature. **a** Temperature changes for the 3 h before and after the initiation of CVVHDF and the temperature at the end of treatment. **b** Average reduction in temperature in the 3 h following the initiation of CVVHDF

however, only two patients died (Fig. 2). This equates to a standardised mortality ratio of 0.29.

Discussion

Continuous veno-venous haemodiafiltration is a technique that has proven to be of value during the treatment of the most severely burn-injured patients in our burns unit. The mortality of this group is understandably high; however, without CVVHDF their mortality is predicted to be higher. In this study, we have focused on the role of CVVHDF for hyperpyrexia (temp >40 °C) alone. We appreciate that ideally we would compare hyperpyrexial patients who received CVVHDF to those who did not however CVVHDF was the standard treatment for all patients with hyperpyrexia.

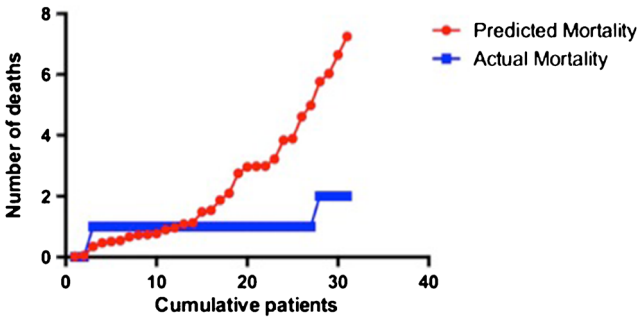

Fig. 2 Predicted and actual mortality for patients who received CVVHDF for hyperpyrexia

CVVHDF is an effective method for controlling temperature even when conventional techniques have failed. We have demonstrated that within 3 h of commencement of CVVHDF temperature is significantly reduced, with all patients experiencing a drop to less than 40 °C. The underlying mechanism for this temperature reduction is probably explained by the extracorporal removal of proinflammatory cytokines and catecholamines [21]. The use of haemofiltration for SIRS and sepsis has increased during the past two decades in the general ITU population. Clinical studies have demonstrated that extracorporeal elimination of circulating cytokines, including tumour necrosis factor alpha, interleukin 1β and interleukin 6, downregulates the excessive inflammatory response that leads to multiorgan failure in sepsis [11]. Our technique of CVVHDF focuses on dialysis and relies more on diffusion than convection. In reality, filtration contributes very little because we do not remove or replace large volumes of fluid. It is probable that a high proportion of the cytokine removal takes place by adherence to the filter membranes rather than passage through them. There is also likely to be a mechanical cooling benefit associated with the blood passing through the diafiltration machine.

We have postulated a survival benefit related to the use of CVVHDF for hyperpyrexia, however in reality the benefit may stem from multiple factors. The

predicted mortality we have used was based on the Baux score and the survival reflects their entire burns care (including early surgery, antibiotics and organ support). Progress in burns care has demonstrated that the Baux score may no longer be the most accurate method of predicting outcome, however, no better methods exist as yet [22].

There are risks associated with using CVVHDF. Patients require central venous access with its associated risks of deep vein thrombosis, line infection, line failure and bleeding; however, there were no significant complications in our group. The patient also requires anticoagulation, which increases their risk of bleeding and can complicate surgical treatment of their burns. The risks of this treatment have to be weighed against its benefits.

To further investigate the potential benefit of CVVHDF on hyperpyrexia, a randomised controlled trial, possibly as a multicentre trial to increase numbers and feasibility, should be undertaken.

Compliance with ethical standards

Conflict of interest Jonathan James Cubitt, Janakan Anandarajah, Meryl Webb, Andrew J. Williams, William A. Dickson and Peter J. Drew declare that they have no conflict of interest.

Patient consent For this kind of article patient consent is not required.

Ethical approval For this type of retrospective study formal consent from a local ethics committee is not required.

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References

1. Atiyeh B, Gunn S, Dibo S (2008) Metabolic implications of severe burn injury and their management: a systematic review of the literature. World J Surg 32:1857–1869
2. Diringer M, Reaven N, Funk S, Uman G (2004) Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 32(7): 1489–1495
3. Hoedemaekers C, Ezzahti M, Gerritsen A, van der Hoeven J (2007) Comparison of cooling methods to induce and maintain normo and hypothermia in intensive care unit patients: a prospective intervention study. Crit Care 11(4):R91
4. Bouman C, Oudermans-van Straaten H, Tijssen J, Zanstra D, Kesecioglu J (2002) Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 30(10):2205–2211
5. Friedrich J, Wald R, Bagshaw S, Burns K, Adhikari N (2012) Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Crit Care 16(4):R146
6. Honore P, Jamez J, Wauthier M et al (2000) Prospective evaluation of short-term, high volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 28(11):3581–3587
7. Honore P, Joannes-Boyau O, Boer W, Collins V (2009) High-volume haemofiltration in sepsis and SIRS: current concepts and future prospects. Blood Purif 28(1):1–11
8. Page B, Vieillard-Baron A, Chergui K et al (2005) Early veno-venous haemodiafiltration for sepsis-related multiple organ failure. Crit Care 9(6):R755
9. Bellamo R, Farmer M, Boyce N (1995) A prospective study of continuous venovenous haemodiafiltration in critically ill patients with acute renal failure. J Intensive Care Med 10(4): 187–192
10. Pestana D, Casanova V, Villagran M et al (2007) Coninuous hemofiltration in hyperthermic septic shock patients. J Trauma-Inj Infect Crit Care 63(4):751–756
11. De Vriese A, Colardyn F, Philippe J, Vanholder R, de Sutter J, Lameire N (1999) Cytokine removal during continuous haemofiltration in septic patients. J Am Soc Nephrol 10: 846–853
12. Zhou F, Song Q, Peng Z et al (2011) Effects of continuous venous-venous hemofiltration on heat stroke patients: a retrospective study. J Trauma Inj Infect and Crit Care 71(6):1562–1568
13. Ledebo I (1998) Principles and practice of hemofiltration and hemodiafiltration. Artif Organs 22(1):20–25
14. Gomez-Cia T, Ortega-Martinez J, Roa L (1996) Dynamic analysis of extracellular fluid exchanges in the burn patient during continuous arteriovenous haemofiltration. Ann Burns Fire Disasters 9:1
15. Chai J, Diao L, Sheng Z, Guo Z, Gao W, Jia X (2000) Heparin-free hemodialysis in the treatment in severely burned patients. Burns 26: 634–637
16. Chung K, Lundy J, Matson J et al (2009) Continuous venovenous hemofiltration in severely burned patietns with acute injury: a cohort study. Crit Care 13(3):R62
17. Tremblay R, Ethier J, Querin S, Beroniade V, Falardeau P, Leblanc M (2000) Veno-venous continuous renal replacement therapy for burned patients with acute renal failure. Burns 26:638–643
18. Chung K, Juncos L, Wolf S et al (2008) Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. J Trauma Inj, Infec Crit Care 64(2): s179–s187

19. Mustonen K, Vuola J (2008) Acute renal failure in intensive care burns patients (ARF in burn patients). J Burn Care Res 29(1):227–237
20. Piccini P, Dan M, Barbacini S et al (2006) Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 32:80–86
21. Peng Y, Yuan Z, Li H (2005) Removal of inflammatory cytokines and endotoxins by veno-venous continuous renal replacement therapy for burned patients with sepsis. Burns 31:623–628
22. Roberts G, Lloyd M, Paker M, Martin R, Philip B, Shelley O, Dziewulski P (2012) The Baux score is dead. Long live the Baux score: a 27-year retrospective cohort study of mortality at a regional burns service. J Trauma Acute Care Surg 72(1):251–256