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BLOOD PURIFICATION IN POISONING

Available Extracorporeal Treatments for Poisoning: Overview and Limitations

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ABSTRACT

Poisoning is a significant public health problem. In severe cases, extracorporeal treatments (ECTRs) may be required to prevent or reverse major toxicity. Available ECTRs include intermittent hemodialysis, sustained low-efficiency dialysis, intermittent hemofiltration and hemodiafiltration, continuous renal replacement therapy, hemoperfusion, therapeutic plasma exchange, exchange transfusion, peritoneal dialysis, albumin dialysis, cerebrospinal fluid exchange, and extracorporeal life support. The aim of this article was to provide an overview of the technical aspects, as well as the potential indications and limitations of the different ECTRs used for poisoned patients.

In 2012, more than 2.2 million human exposures were reported to a poison control center in the United States. Over 600,000 exposures led to a visit in a healthcare facility, 27% of them requiring hospital admission (1). While the vast majority of toxic exposures were treated with supportive care, extracorporeal treatments (ECTRs) were required in 0.1% of intoxications (1).

Extracorporeal treatments represent a heterogeneous group of treatments aimed at promoting removal of endogenous or exogenous poisons, supporting or temporarily replacing a vital organ, or a combination of both. They include intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), intermittent hemofiltration (IHF) and hemodiafiltration (IHDF), continuous renal replacement therapy (CRRT), hemoperfusion (HP), therapeutic plasma exchange (TPE), exchange transfusion, peritoneal dialysis (PD), albumin dialysis, cerebrospinal fluid exchange, extracorporeal membrane oxygenation (ECMO), and emergency cardiopulmonary bypass. These techniques are often used by nephrologists, hematologists, cardiologists, hepatologists, anesthesiologists, and intensivists in clinical settings that are unrelated to intoxications. While few of these techniques were developed with the main intent of enhancing elimination of poisons, they all have potential applications in the field of clinical toxicology. The aim of this article was to review the technical aspects, as well as potential indications and limitations of the different ECTRs that can be used in the treatment of poisoned patients.

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Intermittent Hemodialysis

Dialysis is based on the process of diffusion, during which solutes move across a semipermeable membrane from the side of higher to the side of lower concentration. IHD permits good clearance of small molecular weight toxins and rapid correction of electrolyte and acid–base abnormalities with diffusion, as well as removal of excess fluid with ultrafiltration. Intermittent hemodialysis (IHD) is the most commonly used extracorporeal modality in acute kidney injury (AKI), end-stage renal disease (ESRD), and poisoning (2). IHD is increasingly available even in developing countries and is familiar to healthcare personnel who attend to patients with either AKI or ESRD. Therefore, the time to organize IHD in a poisoned patient would be minimized compared to other ECTRs, which is crucial considering that outcome is likely dependent on how quickly poison can be removed from the body. IHD has a relatively low cost and lower complication rate when compared to hemoperfusion, therapeutic plasma exchange, and albumin dialysis (2–4). These reasons, along with the ability of HD to treat

concomitant metabolic disorders and its significant clearance capacity for a wide spectrum of xenobiotics (5) are probably the main reasons why IHD remains the treatment of choice for most poisonings.

Ideal characteristics of poisons removable by dialysis are a low volume of distribution (V_D), a low percentage of protein-binding and a molecular weight (MW) below the cut-off of the dialysis membrane, as determined by its pores' size (6). Over the last three decades, major improvements in the composition of IHD dialyzers have allowed larger molecules and highly protein-bound poisons like carbamazepine and phenytoin (7–9) to be removed by IHD. Consequently, IHD has largely supplanted other modalities like hemoperfusion. In AKI and ESRD, IHD is usually administered for 4 hours; however, in poisoning, its duration can be prolonged depending on the clinical context and nursing availability.

The dialysate is usually tailored to the patient requiring dialysis. A common error is to forget that a poisoned patient may have a very different metabolic profile than one with renal failure, namely regarding serum potassium, phosphate, and bicarbonate (10). The optimization of dialysis parameters to maximize poison clearance is reviewed separately (11).

Intermittent Hemofiltration and Hemodiafiltration

Intermittent hemofiltration (IHF) is a technique that relies on convection only, while intermittent hemodiafiltration (IHDF) combines convection and diffusion. Convection involves the movement of solvent and solutes according to a pressure gradient (solvent drag). To maintain volume homeostasis, an ultrapure replacement fluid is reinfused to the patient. Dialysate is required for the diffusive component of intermittent hemodiafiltration. The efficacy of convection is mainly dependent on the size of the dialyzer membranes pores. IHF and IHDF can be performed online or with prepared fluid. To perform on-line treatments, a specific water treatment system is needed to produce ultrapure dialysate. Until recently, no on-line IHDF devices were FDA-approved for the United States market (12). Blood flow during convective techniques can be as high as those prescribed during IHD (400 ml/minute).

Convection-based techniques have similar removal properties as IHD regarding the volume of distribution and percentage of protein-binding. However, IHD and IHDF allow a higher molecular cut-off than IHD (13–16), while conserving comparable clearance for small molecules (15,17–20). Although this makes high-efficiency intermittent convective techniques very appealing for poisonings, reports of their use in poisoned patients remain limited because of their greater technical requirements and lesser availability (21).

Continuous Renal Replacement Therapy and Sustained Low-Efficiency Dialysis

Continuous renal replacement therapies (CRRT) comprise continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodiafiltration (CVVHDF). These techniques are performed in the intensive care unit for patients who are too hemodynamically unstable to withstand high-efficiency intermittent treatments. The continuous venovenous techniques have largely replaced continuous arteriovenous hemodialysis (CAVHD), continuous arteriovenous hemofiltration (CAVH), and continuous arteriovenous hemodiafiltration (CAVHDF) because of improved safety and nonreliance on arterial flow. The main advantage of continuous techniques is their capacity to remove fluid and solute over a prolonged period of time.

All principles regarding dialysis and convection mentioned previously for intermittent therapies are applicable to continuous techniques, except that both blood and effluent (which includes dialysate and ultrafiltrate) flows are usually lower than during intermittent treatments like IHD, IHF, and IHDF. Therefore, clearance will be lower over a similar period of time (22). For example, clearances for methanol are usually limited to under 50 ml/minute with CRRT, while they can surpass 200 ml/minute with IHD (5). Similarly, carbamazepine clearances are about three times lower with CRRT than IHD (23).

Sustained low-efficiency dialysis (SLED) is a hybrid technique usually provided as a prolonged treatment using both reduced dialysate (Q_D) and blood (Q_B) flow rate. SLED, also called "Prolonged Intermittent Renal Replacement Therapy", PIRRT, is a modality sometimes reserved for hemodynamically unstable patients who would alternatively be candidates for CRRT (24–27). SLED differs from CRRT in three key areas. First, the typical duration of SLED is shorter than CRRT, ranging from 6 to 12 hours daily, rather than 24 hours. Second, the dialysate flow rate is also higher than in CRRT. For extracorporeal treatments of 8 hours or less, the typical operating parameters are a Q_B of 200–300 ml/minute and a Q_D of 300 ml/minute. For treatments greater than 8 hours, Q_B and Q_D rates of 100–200 ml/minute are used (26). Lastly, SLED can be administered using the same equipment as standard IHD, which has the advantage of easing some of the technical and nursing burdens associated with CRRT.

Though SLED uses a higher Q_D than CRRT, small solute clearance between these two modalities is reportedly similar (28,29). However, in one case report on lithium poisoning, daily clearance was higher with SLED than with CRRT (21). The modeled clearance of middle and large solutes during CRRT is greater than during SLED, likely due to the extended duration and additional convective clearance provided by CRRT (29). There is very

limited literature with the use of sustained low-efficiency dialysis (SLED) in poisoning (21,27,30).

Sustained low-efficiency diafiltration (SLED-f), which provides both diffusive and convective clearances, has been successfully utilized for the treatment of poisonings in a few case reports (25,26,31,32) and can theoretically increase overall clearance compared to SLED with the addition of convection. The limited availability of SLED-f restricts its utilization.

Although both SLED and CRRT can be used for a prolonged duration in a poisoned patient, it remains unclear if they provide any advantage over higher efficiency intermittent techniques. Solute removal is lower per unit of time, as both blood and effluent/dialysate flow rates are lower. Also, intermittent techniques can also be employed for longer than the usual 4–6 hours, if required (33).

Some authors favor the use of CRRT or SLED in poisoned patients because they can prevent the sudden increase in plasma poison concentration following an intermittent treatment. This phenomenon, which happens as the poison transfers from the extravascular space to the vascular compartment, is commonly referred to as "rebound". Except for cases where rebound is caused by ongoing absorption of poison from the gastrointestinal tract, when supplementary treatments may be required, it is uncertain if rebound by itself is concerning: in lithium poisoning, following dialysis, poison may transfer from the site of toxicity (CNS) to a relatively more benign compartment (the vascular space) (34). Theoretically, this has likely positive clinical implications and may further present added opportunity for extracorporeal removal.

Although SLED and CRRT may limit hemodynamic instability in patients requiring fluid removal, it is questionable if this would be the case in poisoned patients when no net ultrafiltration is required. Therefore, the usefulness of SLED compared to IHD in poisoning can be questioned (30). When poison removal is urgent, SLED and CRRT are not the treatments of choice unless no other method is available or ultrafiltration is needed in an unstable patient (22,35).

Hemoperfusion

Hemoperfusion is reviewed separately (36).

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is the process involving the extracorporeal separation of plasma from the cellular components of blood, either by centrifugation or filtration. During centrifugation, blood enters a centrifuge and gravity and density differentiate plasma compounds from erythrocytes, platelets, and leukocytes. During filtration, blood passes through one (single) or two (cascade filtration) large pore filters. The plasma is either discarded or exchanged for a sterile solution (donor plasma, albumin, fresh-frozen plasma, cryoprecipitate-poor plasma, and red blood cells) and returned to the patient together with the blood cells (37,38). The efficacy of both procedures, as indicated by the amount of plasma protein cleared per unit of plasma exchanged, is comparable (39).

Under normal circumstances, the Q_B ranges from 100 to 150 ml/minute to optimize plasma separation in centrifugation (40,41), and from 100 to 200 ml/minute in plasmafiltration (42). The amount of plasma removed during a single exchange is characteristically 30 ml/minute (43,44), although improvement of the technique enables removal of up to 50–60 ml/minute (45). A typical treatment lasts between 2 and 4 hours (46). Although TPE can be successfully performed with a peripheral venous access, using a central catheter will allow for optimization of Q_B and clearance and is therefore recommended in poisoning (40).

The clearance capacity of TPE is dependent on the number of volume exchanged (39,47). For removal of poisons, the benefit appears to plateau beyond two plasma volumes. In poisoning, the American Society for Apheresis (ASFA) guidelines recommend an exchange volume of between one to two total plasma volumes per day until clinical symptoms have decreased and release of toxin from tissues is no longer significant (37).

Because TPE can essentially remove all substances from plasma including proteins, it is particularly suited to eliminate very large (48,49) and highly protein-bound poisons (50–55). However, the clearance capacity of TPE is much lower than IHD, IHF, or HP (39). As most commonly encountered poisons are small or middle-sized, TPE is used infrequently in poisoning (39). In fact, there are no well-established clinical indications for the use of TPE in the treatment of the poisoned patient, although there is some support for it in exposures to the mushroom *Amanita Phalloides* (37,56), thyroxine (55), vincristine (51), and cisplatin (50).

The availability of TPE varies among centers. Although there are case reports of successful TPE in poisoning contexts, with data showing enhancement of poison toxicokinetics in selected situations, TPE should only be considered when alternative ECTRs are useless or unavailable, while taking into account its higher cost and complication rates.

Albumin Dialysis

Albumin dialysis, also named extracorporeal liver assist devices (ELAD), is used to replace liver function in fulminant hepatitis or severe cirrhosis, often as a bridge to liver transplantation. ELADs include the *Molecular Adsorbent Recirculating System* (MARS) (57), the *Prometheus* system (57), and single

pass albumin dialysis (SPAD) (58,59). SPAD is similar to CRRT, but uses a dialysate supplemented with albumin. The albumin is not recycled and needs to be replaced with fresh albumin (60). MARS and Prometheus are similar in that a secondary circuit regenerates the dialysate. In MARS, an albumin-impermeable membrane is used, through which the free fraction of the albumin-bound toxins diffuses to the secondary circuit, where the albumin-enhanced dialysate is recycled after going through a dialysis filter, a resin, and a charcoal cartridge. The Prometheus system uses an albumin-permeable polysulfone filter. Albumin and its bound toxins diffuse to the secondary circuit, where albumin-bound toxins are removed through two adsorbers. The detoxified albumin is then reinfused into the blood circuit, in which a high-flux dialyzer removes water-soluble toxins (57,60,61).

Albumin dialysis has the theoretical advantage of enhancing elimination of protein-bound poisons (62). The principle for their use is that by adding albumin to the dialysate, a protein-binding disequilibrium is created where unbound drug from the blood side could bind to the albumin on the dialysate side. These techniques have been used for treatments of poisoning with varying degrees of success (62–66). Although experimental studies show clearances of endogenous molecules varying from 10 to 75 ml/minute for both MARS and Prometheus (57,58,67–74), the clearance of several drugs rarely exceeds 40 ml/minute, even at a high Q_B (72), which is lower than what can be attainable with other ECTRs. Preliminary data do not show any superiority of albumin dialysis in poisoning to theophylline, valproic acid, or phenytoin (62,64,73,75). Because of its limited availability, high cost (57–59), and unpredictable effectiveness for many xenobiotics (74), the role of albumin dialysis in poisonings is presently unclear.

Peritoneal Dialysis

In peritoneal dialysis (PD), a solution (dialysate) is infused in the peritoneal cavity via a peritoneal catheter. Solutes move from blood to dialysate and vice versa, via a concentration gradient by diffusion through the peritoneal membrane instead of a dialyzer. In PD, the clearance capacity depends on dialysate flow rate (number of exchanges and volume per exchange), the surface area of the peritoneum and the molecular weight of the compound, as well as on the hemodynamic status, as the clearance decreases in hypotensive patients (2,76).

The use of peritoneal dialysis (PD) is infrequent in poisoning, due to its limited clearance capacity (2,77–79). The overall clearances are much lower with PD than other techniques. For example, clearances for theophylline are 10 ml/minute with PD compared to 85 ml/minute with IHD (77).

Continuous flow peritoneal dialysis (CFPD) was developed to offer superior solute clearance from either continuous ambulatory PD or classic automated PD (80). CFPD requires the insertion of a dual lumen PD catheter or two single-lumen catheters at opposite positions. A fixed volume of dialysate is continuously replenished in and out of the peritoneal cavity, either by single pass of sterile dialysate or by regenerated dialysate, using a hemodialysis or sorbent apparatus. Dialysate flows up to 300 mL/min have been reported (81). Higher mass transfer for urea and creatinine has been demonstrated, with reported clearance up to 125 ml/minute for urea (80,81) and up to 63 ml/minute for creatinine (82). While a modelization study showed a gain in clearance for vitamin B_{12}, inulin and, to a lesser extent, ß-2-microglobulin (83), the benefits of this procedure on the clearance of middle molecules have not been substantiated by clinical data, except for a small effect on ß-2-microglobulin (84). Moreover, there is very little data using extremely high dialysate flows during short periods of time for poisons that diffuse well through the peritoneal membrane. In one cohort, patients who received 6 l/hour had a methanol clearance of 70 ml/minute (85). In conclusion, PD has limited benefit in poisoning and is not advocated in this context unless the patient is already receiving PD for ESRD, the poisoning effects are minimal and no other treatment option is available.

Exchange Transfusion

Exchange transfusion is a therapeutic apheresis procedure in which the patient's red blood cells are separated from other blood components and replaced with normal donor red blood cells alone or colloid, or both. Automated procedures allow for precise volumetric exchange and accurate prediction of posttreatment hemoglobin concentration. A single volume exchange will usually remove approximately two-thirds of circulating erythrocytes. The usual indication of exchange transfusion is to reduce a pathogenic factor associated with the red cell (e.g., sickle cells, parasites in severe malaria, or babesiosis, etc.) and in severe hemolysis, resulting for example from arsine gas inhalation (86).

In toxicology, exchange transfusion is seldom used, but has been described in poisoning with xenobiotics highly bound to erythrocytes like cyclosporine (87–89) or tacrolimus (90) and to treat methemoglobinemia induced by a toxic exposure (e.g., propranil (91), aniline (92), dapsone (93), and sodium nitrite (94)). Exchange transfusion has the advantage of being simpler to use in infants, and has been tried in that population for poisonings to salicylates (95), theophylline (96), and barbiturates (97).

Slow Continuous Ultrafiltration

Slow continuous ultrafiltration (SCUF) is an extracorporeal modality that is used to treat

patients with volume overload. Specific indications for SCUF include patients with acute exacerbations of congestive heart failure or hepatic failure who are poorly responsive to diuretics (26). As a modality, SCUF removes the excess fluid by convection. However, the clearances obtained with SCUF are negligible compared to other ECTRs. As a result, SCUF should not be utilized as an extracorporeal modality to remove toxins in poisonings.

Cerebrospinal Fluid Exchange

Cerebrospinal fluid (CSF) exchange is occasionally performed in patients with life-threatening neurological symptoms to certain poisons, especially after therapeutic errors following intrathecal administration. The CSF is drained passively via a ventricular catheter, and replaced by a sterile solution containing albumin and sodium chloride into the lumbar subarachnoid space (98). Most reported cases involve methotrexate poisoning (99,100) and calculated clearance has been promising in certain reports (101,102).

Extracorporeal Life Support

Pulmonary and cardiovascular failure is a potential complication of poisonings and the primary cause of mortality. Technological advances over the past decade have resulted in the emergence of extracorporeal life support (ECLS) as a clinically viable therapy to support patients with cardiac and/or pulmonary failure (103–105). ECLS include Extracorporeal Membrane Oxygenation (ECMO), Emergency Cardiopulmonary Bypass (ECPB), intraaortic balloon pumps (IABP), and left ventricular assist devices (LVAD). In the treatment of poisonings, ECMO is the most frequently used ECLS therapy. There are two major types of ECMO, namely venovenous ECMO (VV-ECMO), which provides pulmonary support only (103,104), and venoarterial ECMO (VA-ECMO) or EPCB, which provides pulmonary and circulatory support (103,104).

Both VV-ECMO and VA-ECMO utilize large bore cannulae and centrifugal or roller pumps to produce an extracorporeal circuit for venous blood oxygenation (103,104). In VV-ECMO, one cannula is placed in the right internal jugular vein or alternatively the femoral vein. The deoxygenated venous blood is then pumped via a centrifugal or roller pump to a membrane oxygenator. The membrane oxygenator acts as the extracorporeal lung for gas exchange where the venous blood is oxygenated and carbon dioxide is removed. In VV-ECMO, the patient's heart serves as the driving force to return the oxygenated blood back to the patient. Blood return occurs via a cannulae placed in the upper or lower vena cava (103,104). For VA-ECMO, the deoxygenated blood is withdrawn by a centrifugal or roller pump and delivered to the membrane oxygenator via a large bore cannula placed in the right internal jugular vein. After the blood is oxygenated, it returns to the patient by a cannula typically placed in the descending aorta. However, unlike VV-ECMO, a centrifugal pump and not the patient's heart is the driving force to return the oxygenated blood to the circulation (103,104).

Though ECMO cannot facilitate poison removal, it is increasingly used as a bridge to recovery in the clinically refractory patient with cardiovascular and/or pulmonary failure not responding to conventional medical therapies. In poisonings, VA-ECMO has been used successfully to support patients with cardiovascular toxicity from calcium channel or beta-blockers (105–113). Conversely, VV-ECMO has provided pulmonary support to patients from inhaled organic hydrocarbons (114–116). ECMO has also been successfully used for a wide variety of other medications such as tricyclic antidepressants, carbamazepine, and chloroquine (117–120). Finally, both types of ECMO support the addition of CRRT to the circuit, which can provide a renal replacement therapy and a modality for toxin removal (121).

Clinical guidelines are currently being developed to direct clinicians in the best use of ECMO. Given its technical complexity and risk for complications, which include bleeding, stroke, and intracranial hemorrhage, ECMO should be reserved for severely ill patients refractory to conventional treatments with a high risk of death (104,105). For example, VA-ECMO can be considered in patients with life-threatening hemodynamic instability despite fluid resuscitation, inotropes and vasopressors, with or without IABP. Some studies have demonstrated that patients have better outcomes if the ECMO is started earlier in a patient's hospital course (104,105).

Conclusion

Although supportive care is the mainstay in the management of poisoned patients, extracorporeal treatments play a crucial, if not essential role in a subset of intoxications. Since the medical literature provides little specific clearance data for most xenobiotics, clinicians must often rely on clinical judgment to determine if and which extracorporeal therapies are susceptible to favorably impact the outcome of a poisoned patient. Besides good knowledge of the poison's toxicokinetic characteristics, a working understanding of extracorporeal therapies, their technical particularities, advantages, and limitations is needed to make a rational use of available modalities. Based on technological advances over the last decades which have increased its clearance capacity, widespread availability, low cost, and limited complications, IHD is the most commonly used therapy for poisoning. IHF and IHDF have

theoretical similar or greater clearance capacities than IHD; however, their clinical use in poisoning is restricted by their limited availability. Hemoperfusion, TPE, SLED, and CRRT may have a role in selected cases, while further studies are required for albumin dialysis.

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