Seminars in Dialysis

BLOOD PURIFICATION IN POISONING

Case Reports of Extracorporeal Treatments in Poisoning: Historical Trends

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ABSTRACT

There are currently limited data on the trends in case reporting of poisoned patients undergoing enhanced elimination with an extracorporeal treatment (ECTR). The present manuscript specifically reviews the longitudinal trends of reports according to technique, poison, and country of publication. To identify case reports of ECTR use in the management of poisoning, multiple databases were searched. There were no limitations on language and year of publication. All case reports describing individual patients undergoing ECTR with the intent of enhancing the elimination of a poison were included in the analysis. Since 1913, 2908 reports were identified. There were an increasing number of published reports with time except for a slight decrease during the 1990s. Hemodialysis was by far the most commonly used ECTR in poisoning, followed by hemoperfusion. The number of reported peritoneal dialyses decreased steadily since 1980s. Methanol, ethylene glycol, lithium, and salicylates remained among the most commonly reported poisons in every decade. The large majority of publications originated from either Europe or North America, and more specifically from the United States, Germany, the United Kingdom, and China. Despite the emerging apparition of new techniques, hemodialysis remains to this day the favoured ECTR in the treatment of poisoned patients.

The first experiment involving extracorporeal removal of a xenobiotic from a living subject was performed by John Abel et al., during their landmark study in 1913 (1). This was followed by various technological improvements of hemodialysis over the years, as well as the invention of peritoneal dialysis (2), hemoperfusion (3), therapeutic plasma exchange (4,5), hemofiltration (6), and more experimental therapies like albumin dialysis (7).

Each of these extracorporeal treatments (ECTRs) has been used to enhance the elimination of a poison. Here, a poison is considered any medicine, xenobiotic, chemical, toxin, metal, or other substance capable of causing poisoning or toxicity to a human. The popularity of ECTR in this context has fluctuated over the years, according to their ability to clear poisons from the blood compartment, regional availability, and safety profile.

Data on the use of ECTR in the management of poisonings, and changes over time, were reported for the United States until 2005 (8); there are no estimate data on their use since or elsewhere in the world. This paper reviews the trends in ECTR reporting in the context of toxic exposures, based on the literature search performed by the EXtracorporeal TReatments In Poisoning workgroup (http://extrip-workgroup.org) during their clinical guidelines initiative.

Methods

The EXTRIP initiative reviewed, when drafting its clinical recommendations, the literature for ECTR use in the management of poisoning from multiple databases. PUBMED and EMBASE were searched using a predetermined search strategy (9). Targeted searches were also conducted in other databases, including Google Scholar, the Literature in the Health Sciences in Latin America and the Caribbean (LILACS), SCOPUS, the Chinese National Knowledge Infrastructure (CNKI) database, the Scientific Electronic Library Online (SciELO), and the Cochrane library (Review and Central). We also reviewed all conference proceedings/meeting abstracts of the EAPCCT and NACCT annual meetings since 2002 and all bibliographies of accepted publications. There were no limitations on language (articles were translated as

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required) and the publications covered every article published from 1913 to today (March 1, 2014) (9).

For the present analysis, all case reports identified from this extensive literature search were included. A case report was defined as an original description of one or more patients. Only manuscripts that describe individual patients who underwent ECTR with the intent of poison removal were included. Manuscripts that only had aggregate or grouped results were excluded. When more than one patient undergoing an ECTR was described in an article, only the first case was kept for the analysis, to avoid overrepresentation of an article on the results.

Case reports were subclassified as follows:

- Per decade of publication.
- Per performed procedure: hemodialysis (HD), hemoperfusion (HP), continuous renal replacement therapy (CRRT), therapeutic plasma exchange (TPE), exchange transfusion (ET), sustained low efficiency dialysis (SLED), cerebrospinal fluid exchange, peritoneal dialysis (PD), intermittent hemodiafiltration (IHDF), and albumin dialysis.
- Per poison, according to generic names (e.g., phenytoin) or drug class (e.g., tricyclic antidepressants).
- Per country of publication, referring to the current world map.

Descriptive statistics were reported as absolute numbers and percentages.

Results

Since 1913, we identified a total of 2908 reports of patients undergoing an ECTR for poisoning.

Trends in reported ECTR

There were 18 ECTR reports in the 1950s, 104 ECTR reports in the 1960s, 306 in the 1970s, 696 in the 1980s, 550 in the 1990s, 974 in the 2000s, and 482 between 2010 and 2014 (Fig. 1); the total of reported ECTRs exceeds the number of publications because some patients in a single publication underwent more than one type of ECTR (in series or one following the other).

Since the 1950s, HD was by far the most commonly used ECTR in poisoning and this continued in every decade, although it was followed closely by ET in the 1950s, PD in the 1960s, and HP in the 1980s (Table 1). A total of 1615 HD reports were published during the study period, compared to 803 for HP, 233 for CRRT, and 218 for PD; other ECTRs were more infrequently reported. Of all ECTR reports, 51.7% involved HD, 25.7% involved HP, 7.3% CRRT, 7.0% PD, 4.1% TPE, 2.4% ET, 0.7% albumin dialysis, 0.6% IHDF, 0.3% CSF exchange, and 0.2% SLED. The proportion of publications on HD compared to all other techniques increased every decade since 1970, to reach 61% in 2010-2014. The number of reported PDs decreased steadily since the 1980s. Reported ETs peaked during the period from 1970 to 1990.

When looking at individual years, HD surpassed HP every year except for the time period from 1978 to 1988. After 1990, the number of HP publications decreased progressively, especially from the Western literature; the last report of HP performed outside of Asia was in 2011 (10), while the last report of HP reported from the United States was in 2010 (11). The large majority of current reported HP were from Asia.

Poisons

Table 2 illustrates the trend in reported poisons requiring extracorporeal elimination. Methanol, ethylene glycol, lithium, and salicylates remained among the most important ones on the list in every decade. This was also the case for paraquat, especially from Asia. Many poisonings that were prevalent in the 1950–1970s such as the barbiturates, ethchlorvynol, gluthethimide, and meprobamate are infrequently noted in recent years. Some poisonings were progressively more reported in later decades, notably organophosphorus pesticides after 1990, valproic acid after 2000, and dabigatran after 2010. Reported ECTRs for methylxanthines and tricyclic antidepressants peaked in the 1980–1990s and decreased thereafter.

Countries of publication

The large majority of publications are derived from the United States (831), then Germany (252), the United Kingdom (199), and China (197). The large majority of publications originated from either Europe or North America, with a lesser contribution from Asia. There were only nine publications from Africa and 20 from South America (Fig. 2).

Discussion

Extracorporeal treatments, such as HD and charcoal HP, are occasionally used to effectively increase the clearance of poisons. Unfortunately, aside from epidemiological data published from the United States (8), little is known on the trends of ECTR use in poisoning. Furthermore, data are sparse on the availability of ECTRs worldwide in poisoning contexts (12).

This review shows that the number of reports describing at least one patient undergoing an ECTR increased every decade, except in the 1990s. The decrease in reported ECTR observed in the 1990s is likely not explained by a fall in the incidence of poisonings worldwide; reported poisonings to the poison control centers in the United States increased significantly between 1985 and 1995 (13). A more likely contributor is an improved understanding of pharmacokinetics, limiting the misapplication of

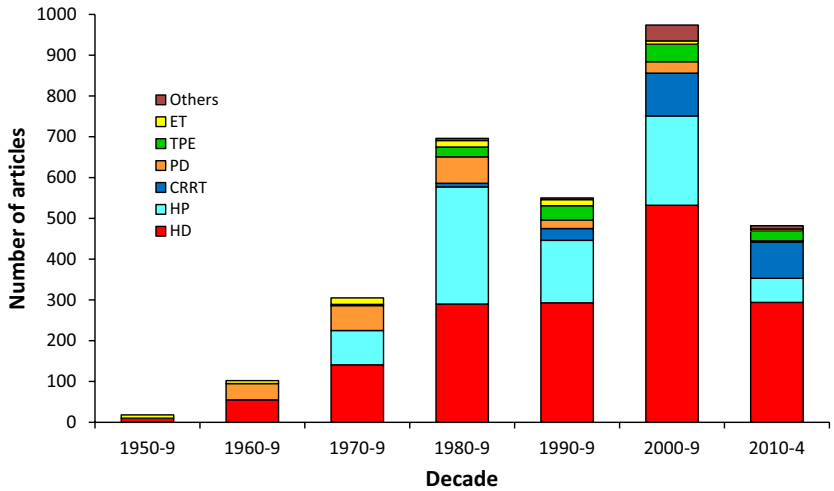

FIG. 1. Temporal trends, per decade, in the number of publications describing a case of an ECTR for the treatment of a poisoned patient. HD, hemodialysis; HP, hemoperfusion; CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; ET, exchange transfusion; PD, peritoneal dialysis. Others include sustained low efficiency dialysis, intermittent hemodiafiltration, cerebrospinal fluid exchange.

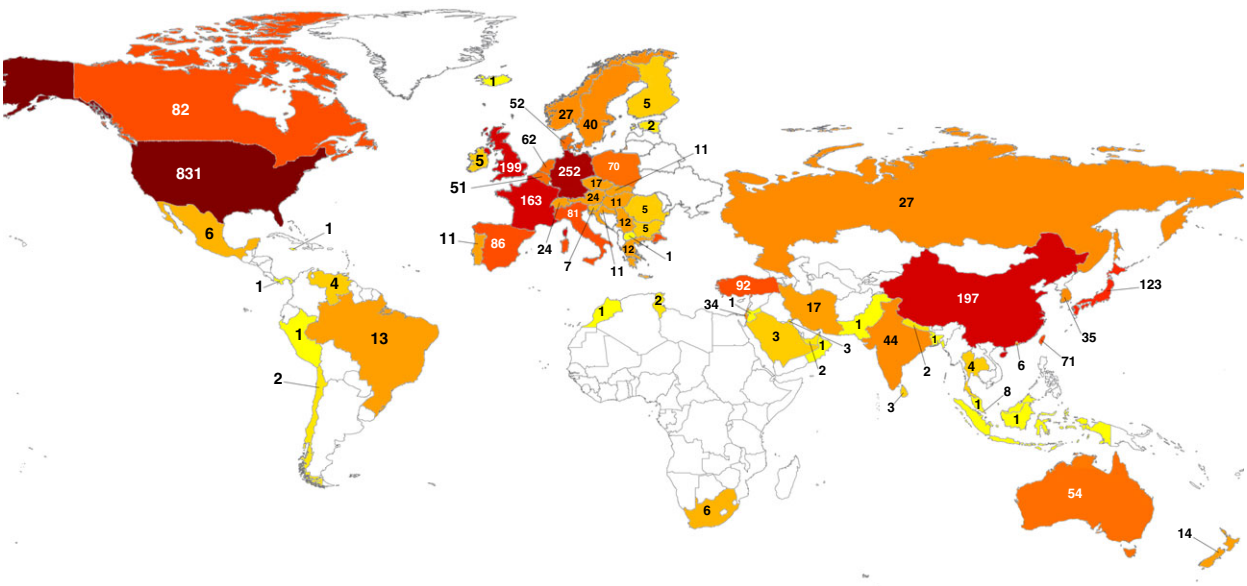

FIG. 2. Number of publications per country. The darker the color, the greater the number of publications originated from that country.

ECTRs. As noted in Table 2, prior to 1990, a number of poisons, not amenable to extracorporeal removal given their large volume of distribution, were treated with an ECTR, such as digoxin (14), tricyclic antidepressants, and quinine. After 1990, none of these were among the top 10 most reported. Another likely contributor to the changing application of ECTRs is improvements in supportive care and the advent of new antidotes (e.g., *N*-acetylcysteine, fomepizole) that may have rendered ECTR less crucial for some poisonings. Finally, when data supporting ECTR in a specific poisoning become sufficiently convincing and controversy is limited, new reports decline as they are not sufficiently novel or informative for publication. This is the case for salicylate poisoning, where most nephrologists would agree that ECTR may be life saving (15).

The trend of poisons subjected to ECTR has changed over time. The classical recommendations for ECTRs are toxic exposures to methanol, ethylene glycol, salicylates, lithium, and theophylline (16). Recently, with better understanding of toxicokinetics, newer indications for ECTRs have been postulated and applied in clinical practice. Examples include valproic acid, carbamazepine, dabigatran, and metformin; the interest in ECTR for poisoning with these medicines is also coupled with their increased use in clinical practice. Likewise, many

TABLE 1. Reported ECTR used per decade

	HD	HP	CRRT	TPE	ET	SLED	CSF exchange	PD	Albumin dialysis	IHDF
Year of first publication	1948	1964	1977	1967	1951	2005	1982	1947	2002	1985
Per decade										
1950–1959	10	0	0	0	8	0	0	0	0	0
1960–1969	55	1	0	1	7	0	0	40	0	0
1970–1979	141	84	1	3	16	0	0	61	0	0
1980–1989	290	287	9	24	16	0	1	65	0	4
1990–1999	293	153	29	35	15	0	2	21	0	2
2000–2009	532	219	105	43	8	4	4	28	20	11
2010–2014	294	59	89	24	5	2	2	3	2	2
Total[a]	1615	803	233	130	75	6	9	218	22	19

HD, hemodialysis; HP, hemoperfusion; CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; ET, exchange transfusion; SLED, sustained low efficiency dialysis; CSF, cerebrospinal fluid; PD, peritoneal dialysis; IHDF, intermittent hemodiafiltration.

[a]The total number of techniques reported exceeds the number of publications as patients who underwent more than 1 ECTR (in series or one following the other) may be duplicated

TABLE 2. List of the reported toxins most often requiring extracorporeal removal per decade

1950–1969	1970–1979	1980–1989	1990–1999	2000–2009	2010–2014
Barbiturate (43)	Paraquat (45)	Paraquat (77)	Ethylene glycol (66)	Methanol (97)	Metformin (75)
Salicylates (25)	Barbiturate (44)	Methyl xanthines (56)	Methyl xanthines (41)	Metformin (85)	Methanol (45)
Methanol (15)	TCAs (19)	Ethylene glycol (54)	Methanol (35)	Paraquat (83)	Ethylene glycol (45)
TCAs (7)	Amanita sp (19)	Methanol (49)	Lithium (35)	Ethylene glycol (80)	Lithium (28)
Quinine (5)	Lithium (17)	Lithium (45)	Paraquat (34)	Organophosphates (76)	Paraquat (28)
Isoniazid (4)	Digoxin (15)	Barbiturates (41)	Organophosphates (34)	Lithium (54)	Valproic acid (24)
Phenytoin (4)	Gluthetimide (14)	TCAs (30)	Amanita sp (18)	Valproic acid (45)	Dabigatran (22)
Gluthethimide (3)	Meprobamate (12)	Digoxin (26)	Acyclovir (18)	Acetaminophen (42)	Acetaminophen (18)
Ethchlorvynol (3)	Thallium (12)	Salicylates (22)	Salicylates (15)	Amanita sp (37)	Organophosphates (17)
Ethylene glycol (2)	Methanol (11)	Amanita sp (21)	Acetaminophen (13)	Salicylates (35)	Carbamazepine (16)

TCAs, Tricyclic antidepressants.

reported xenobiotics that required ECTR removal in the early study period are no longer listed. This is the case for certain sedatives like barbiturates, ethchlorvynol, meprobamate, and gluthetimide. The reason for this is their progressive replacement by safer drugs, like benzodiazepines, so prescribing is infrequent or even obsolete in some countries.

As previously mentioned, the earlier enthusiasm for several techniques like PD and ET has tailed off because of lower clearances compared with HD. Early clinical experience with HP suggested that it was more effective than either HD or PD, for poisons for which no antidote were available, such as barbiturates, and paraquat (17,18). The advantage of HP over HD for poison clearance appeared to be particularly convincing for theophylline and carbamazepine (19,20). This observation, based on clinical cases and measured clearances rather than controlled trials, was followed by the enthusiastic use of HP in some centers during the 1970s and 1980s. Apparent advantages of HP included clearances exceeding those of HD and not limited by a high degree of protein binding and a simpler extracorporeal circuit because no countercurrent dialysate was required. After 1990, however, there was a proportionally waning interest in HP in many countries, including the United States (8). This is also suggested in this review by the decreasing number of reported HP cases outside of Asia. The reasons for this are likely multifactorial and include a higher rate of complications compared with HD (21), a higher cost (22), saturation of cartridges, lack of renal replacement (23), and less availability (although data outside the United States are limited) (12). Furthermore, the advent of high-flux, high-efficiency dialysis filters has improved clearance of small, middle, and protein-bound molecules to such an extent that it remains unclear how much of an advantage, if any, remains for HP (24–26). These concepts are described in more detail in another article in this issue on HP.

However, there is ongoing enthusiasm for HP in Asian countries, as shown by the increasing number of publications from this region. For example, in China, India, and South Korea, HP is used for poisoning with pesticides and medicines (27–31). Since 2010, the EXTRIP workgroup identified more than 700 published cases worldwide in which HP had been administered; this is a likely underestimate of the actual number. Clinicians from these countries have reported favorable outcomes in uncontrolled observational studies and controlled trials for some poisons (28,32,33), but others have

called for ongoing clinical studies to better define the risk–benefit ratio (34). New resin-based HP columns are also being marketed, although information regarding their effectiveness in the treatment of patients with acute poisoning is extremely limited.

There are major limitations to this study. Firstly, although the methods were intended to capture a good representation of ECTR reporting worldwide, the only databases that were systematically accessed were PUBMED and EMBASE. Despite a conscious effort to translate every publication not in the English language, these databases yield reports mostly from North America and Europe. Although other databases were also accessed, the search strategy was not as exhaustive as the earlier two databases. Secondly, contrary to randomized trials and meta-analyses, there are no registries for case reports; their publication depends largely on the authors and editors' interest. If a case appears redundant or if the studied ECTR does not show any benefit, there is less chance that it will be reported and/or published. There is also a current trend to limit the acceptance of case reports in several journals. Similarly, new techniques or new xenobiotics (e.g., dabigatran) are more likely to be reported because they are novel, thereby overstating their contribution to the total number of cases subjected to ECTR. Consequently, the number of ECTRs reported will always underestimate and potentially misrepresent the number of ECTR performed. Finally, we could not eliminate all duplicate reports; we found similar patients reproduced in different journals and under a different name of the first author.

In conclusion, the trends in case reporting of poisoning necessitating extracorporeal elimination not only depend on the geographical availability of different ECTRs but also on the changing efficacy of these techniques, as well as on the modification in various agents capable of causing harm. Despite these factors, hemodialysis has consistently remained to this day the favoured ECTR in the treatment of poisoned patients throughout the years.

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