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Original Article

Availability and cost of extracorporeal treatments for poisonings and other emergency indications: a worldwide survey

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ABSTRACT

Background: Extracorporeal treatments (ECTRs) are used for different conditions, including replacement of organ function and poisoning. Current recommendations for ECTRs in various poisonings suggest that intermittent haemodialysis (IHD) is the most efficient technique. However, the practicality of these recommendations is poorly defined in view of limited information on availability and cost worldwide.

Methods: A survey invitation to an Internet-based questionnaire was emailed between January 2014 and March 2015 to members of international societies to determine the availability, time to initiation and cost of ECTRs (including filters, dialysate, catheter, anticoagulant and nursing/physician salary). The median cost ratio of every ECTR compared with IHD performed in the same institution were presented.

Results: The view rate was estimated at 28.1% (2532/9000), the participation rate was 40.1% (1015/2532) and the completion rate was 16.0% (162/1015). Respondents originated from 89 countries, and nearly three-fourths practiced in a tertiary care centre. A total of 162 respondents provided sufficient data for in-depth analysis. IHD was the most available acute ECTR (96.9%), followed by therapeutic plasma exchange (TPE; 68.3%), continuous renal replacement therapy (CRRT; 62.9%), peritoneal dialysis (PD; 44.8%), haemoperfusion (HP; 30.9%) and liver support devices (LSDs; 14.7%). IHD, CRRT and HP were the shortest to initiate (median = 60 min). The median cost ratios of each ECTR compared with IHD were 1.7 for CRRT and HP, 2.8 for TPE, 6.5 for LSDs and 1.4 for PD ($P < 0.001$ for all). The median cost ratio of a 4-h IHD treatment compared with 1 day in the intensive care unit was 0.6 ($P = 0.2$).

Conclusions: IHD appears to be the most widely available ECTR worldwide and is at least 30% less expensive than other ECTRs. The superior efficacy of IHD for enhanced elimination, added to its lower cost and wider availability, strengthens its preference as the ECTR of choice in most cases of acute poisoning.

Keywords: costing, CRRT, EXTRIP, hemodialysis, hemoperfusion

INTRODUCTION

Extracorporeal treatments (ECTRs) are primarily used to replace impaired organ function, such as intermittent haemodialysis (IHD) for acute kidney injury (AKI) or liver support devices (LSDs) for acute or acute-on-chronic liver failure [1, 2]. ECTRs may also enhance elimination of endogenous and exogenous toxins [3–6] and are used in 0.1% of all reported intoxications [7].

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup has published several systematic reviews on the use of ECTRs in various poisonings. The workgroup showed that IHD was the most efficient ECTR to enhance the elimination of most dialyzable poisons [8–13]. However, there are limited data comparing the worldwide availability of different ECTRs. In cases where efficacy between some ECTRs was relatively similar [e.g. IHD or haemoperfusion (HP) for carbamazepine or theophylline poisoning], ascertainment was based on presumed better

availability and lower costs of IHD. Published studies usually focus their analysis on availability and/or cost to a single country/region [1, 14–23] or a single ECTR [1, 14, 15, 17, 18, 24], thereby restricting comparison and generalizability. In addition, cost estimates of ECTRs are needed to evaluate their cost-effectiveness, especially in clinical conditions with equivocal indications (e.g. marginal toxicity from a lithium overdose).

To address these issues, in partnering with the International Society of Nephrology (ISN) we conducted an online survey to provide a global representation of the availability and costs of ECTRs used in the acute setting worldwide, especially those that may enhance the elimination of exogenous poisonings, including IHD, HP, continuous renal replacement therapy (CRRT), peritoneal dialysis (PD), LSD, therapeutic plasma exchange (TPE; plasmapheresis) and exchange transfusion (ET).

MATERIALS AND METHODS

Questionnaire development and content

A survey questionnaire was developed to maximize information quality and minimize the effect of variations in costing practices. Following a literature review, item generation was performed to identify and include all items that were considered pertinent ('sampling to redundancy'). The survey questionnaire was formatted to favour closed responses and adaptive questioning. The questionnaire was pretested by nephrologists within the EXTRIP workgroup to assess its content validity and a pilot version was then submitted to other participants for further iteration. Respondents were required to answer a question before proceeding to the next. Missing answers were not considered to be a negative response [25].

The questionnaire included the following items (Supplementary data, Table S1): (i) demographics of participants: country of practice, type of health care professional, type of dialysis centre and population of patients (adult, paediatric or both); (ii) availability of and time to initiation for IHD, CRRT, HP, LSD, PD and ET) in acute settings; (iii) costs for available ECTRs, including (a) costs related to the catheter installation: catheter, nursing or technician salary, physician salary, rental of ultrasound, related consumables and confirmatory x-ray (if required); (b) salary cost: fixed or hourly salary for nursing, technician and physician; (c) direct ECTR costs: machine rental, dialyzer/filter/columns, consumables, dialysate, replacement fluid, fresh frozen plasma, albumin, electrolyte supplementation and anticoagulant; (d) indirect ECTR costs: average daily cost (24 h) for admission to the emergency room, medical ward and/or intensive care unit (ICU). Costs related to machine maintenance and reverse osmosis water systems were not considered. The instructions of the survey questionnaire mentioned reporting actual costs, not fees to patients or reimbursements provided by private or national insurance schemes. Respondents were instructed to estimate costs for 24 h for CRRT and PD and for a 4-h session for other modalities to facilitate analyses and comparison.

We followed current recommendations for survey research methodology and reporting from recent systematic reviews [25, 26], special articles [27, 28] and guidelines [29, 30]. Each electronic invitation included a hyperlink access to an Internet-based survey on Fluidsurveys and was accompanied by a cover letter signed by the organizing team explaining the purpose of the survey. The cover letter mentioned that participation was anonymous unless respondents preferred acknowledgment of their contribution.

The survey questionnaire was available in English but could be translated if requested by participants. The ethics committee at Sacré-Coeur de Montréal Hospital waived the need for review due to the nature of the survey and consent to participate was implied by a response from the participant.

Respondents

Between January 2014 and March 2015, a worldwide Internet-based survey questionnaire was emailed to clinicians involved in referring or prescribing ECTRs. The questionnaire was emailed to each member of the following societies: CRRT Conference, ISN, Asia Pacific Association of Medical Toxicology (APAMT) and European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). In addition, the survey questionnaire was emailed to key contacts of other national and international nephrology societies. Finally, personal invites were sent to all EXTRIP workgroup participants and other clinicians (clinical toxicologists, emergency physicians, medical internists, nephrologists and nurses) through professional networks and each was encouraged to forward the questionnaire to their colleagues to maximize representativeness and participation.

Sample selection

We used a non-probability purposive sampling design to reach our target population since we could not reliably estimate the chance of any given individual being included in the sample [30] (i.e. the same clinician could have received more than one invitation from various sources) and because individuals were selected based on their likelihood of using any ECTR due to membership in a relevant professional society. As an incentive, respondents were offered compensation of US$40 for a fully completed questionnaire. At least two reminders were sent out to every participant. Since costs may vary between institutions within the same country, we surveyed participants from multiple centres in the same country. After a first review of the countries represented, personal invitations were subsequently sent out to include respondents from countries not already represented in the survey.

There was no predetermined sample size calculation. Any questionnaire that contained at least one completed item was included.

Analyses

As proposed from other sources [29], we identified respondents by their IP address provided by FluidSurvey and considered only the most recent entries for analysis. We defined the 'view rate' as the ratio of unique visitors to the first page of the Internet-based questionnaire divided by the number of unique survey invitees, the 'participation rate' as the ratio of unique responders who gave at least one response divided by the number of visitors to the first page of the Internet-based

questionnaire and the 'completion rate' as the number of responders submitting a complete questionnaire divided by the number of responders who gave at least one response [29]. Data extraction and analysis were conducted after the survey was closed to respondents. All costs were compiled in the respondents' currency and converted to US$ for comparison at the exchange rate available on the day of response (www.x-rates.com). We obtained the gross national income (GNI, formerly GDP) per capita for every country from World Bank data (www.data.worldbank.org) as of 1 July 2015.

We reported costs as absolute values and as ratios of each ECTR available relative to IHD at the same centre. Because we were also interested in the relative contribution of ECTR cost of managing poisoning, we also determined the cost ratio of a 4-h IHD to 1 day in the ICU (calculated at the same centre).

All continuous variables are presented as means with 95% confidence intervals (CIs) or medians with lower and upper quartiles (Q1–Q3) and compared using *t*-test or Mann–Whitney U test, respectively, where appropriate. Categorical variables are presented as proportions and compared with the chi-square or Fisher's exact test, where appropriate. Two-tailed P-values < 0.05 were considered significant. Statistical analyses were performed with SPSS Statistics 22 (IBM, Armonk, NY, USA).

RESULTS

A total of 1015 respondents completed at least one item of the Internet-based questionnaire, from which 162 answered it in its entirety (Table 1). The view rate was estimated at 28.1% (2532/9000), the participation rate was 40.1% (1015/2532) and the completion rate was 16.0% (162/1015).

Characteristics of respondents

Respondents originated from 89 countries (Table 2 and Figure 1) and three-fourths of them were from Europe or Asia. More than half of recipients practiced in a publicly funded facility only and nearly three-fourths practiced in a tertiary care centre. More than 85% were physicians practicing in an urban academic centre. The vast majority of respondents only treated adult patients.

Availability

A total of 758 respondents (75.0%) reported treating patients requiring acute dialysis, while 252 did not. Acute IHD was the most available ECTR (98.8%), followed by TPE, CRRT, ET, PD and HP. Only 14.7% of centres had LSDs available. IHD was significantly more available than any other ECTR (Table 3). Five respondents mentioned that although acute IHD was unavailable at their institution, other ECTRs were available: CRRT ($n = 3$), HP ($n = 1$), TPE ($n = 2$) and PD ($n = 1$).

The median GNI of countries where CRRT, ET, HP, ET, TPE and LSDs were available was significantly higher than that of countries where these ECTRs were unavailable (Figure 2). Inversely, the median GNI of countries where acute PD was available was significantly lower than where PD was unavailable.

Table 1. Description of survey sampling and responses

	Survey invitation sent	Internet-based questionnaire opened	At least one response given
International Society of Nephrology	8199	2532	
Continuous renal replacement therapy meeting list	9000	1636	
EXTRIP contacts	35	35	1015
APAMT	295	Unknown	
EAPCCT	243	Unknown	
Personal invitations	47	47	
National nephrology societies	42[a]	Unknown	

It is likely that there is major redundancy in e-mails sent out, as more than one survey invitation may have been sent to the same recipient.
[a]Survey invitations were sent directly to 42 societies, although it is unknown if they sent the survey to all members. EXTRIP, EXtracorporeal TReatments In Poisoning; APAMT, Asia Pacific Association of Medical Toxicology; EAPCCT, European Association of Poisons Centres and Clinical Toxicologists.

Table 2. Characteristics of respondents ($n = 1015$)

Characteristic	%
Profession	
Physician in practice	95.2
Pharmacist	0.6
Nurse	3.0
Fellow	0.3
Other/unspecified	0.9
Health care facility funding	
Public	56.6
Private	36.4
Combined	6.9
Profile of practice	
Academic	85.4
Non-academic	14.2
Both	0.4
Patient population	
Respondents that only treat adult patients	39.7
Adult patients treated, mean	80.7
Health care facility level of care	
Primary or secondary	12.2
Tertiary	72.7
Quaternary	11.6
Secondary/tertiary	1.7
Tertiary/quaternary	1.7
Location of health care facility**	
Urban	91.5
Suburban	1.5
Rural	6.9
Provenance of respondents	
Europe	53.4
Asia	23.6
North America	9.0
Central and South America	7.0
Oceania	3.1
Africa	2.7
Unknown	1.3

**A primary health care centre is often the first point of contact of a patient and is usually composed of family physicians and a limited number of specialists. A secondary care centre is where there is wider availability of care and a greater number of specialists. A tertiary care centre is a highly specialized medical care centre where advanced and complex procedures and treatments are available. A quaternary care centre is considered to be an extension of a tertiary care centre and has many up-to-date experimental procedures and highly specialized personnel and services (transplant, trauma, etc.).

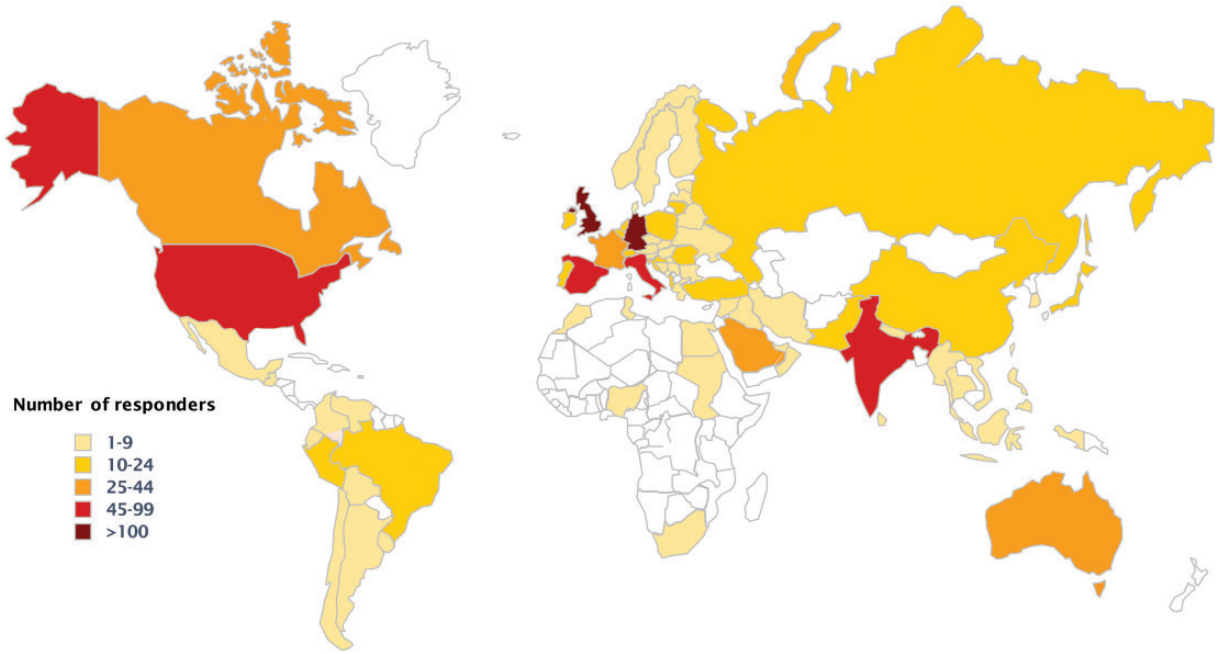

FIGURE 1: Country of practice of respondents.

Table 3. Availability, timing of initiation and cost of extracorporeal therapies

ECTR	Availability[a]		Timing of initiation[b]		Cost			
	Number of responses	%	Number of responses	Median time in minutes (Q1–Q3)	Number of complete responses	Median cost in US$ (Q1–Q3)	Median ratio ECTR/IHD[c] (Q1–Q3)	P-value*
IHD	162	96.9	119	60 (30–90)	112	314 (153–563)	N/A	N/A
CRRT	124	62.9	58	60 (30–120)	56	701 (383–1258)	1.71 (1.47–2.37)	<0.001
HP	123	30.9	27	60 (45–150)	22	699 (379–1240)	1.70 (1.43–2.60)	<0.001
TPE	120	68.3	56	120 (60–225)	48	980 (549–2081)	2.76 (1.52–6.10)	<0.001
LSDs	116	14.7	9	120 (60–270)	10	3519 (1,468–6258)	6.52 (1.47–17.00)	0.007
PD	116	44.8	41	120 (60–210)	36	454 (120–974)	1.37 (0.85–2.61)	0.003
ET	20	60.0	6	210 (98–450)	4	1897 (1,273–2241)	3.77 (2.49–7.06)	0.07

CRRT, continuous renal replacement therapy; ECTR, extracorporeal treatment; ET, exchange transfusion; HP, hemoperfusion; IHD, intermittent hemodialysis; LSD, liver support devices; PD, peritoneal dialysis; TPE, therapeutic plasma exchange; N/A, not applicable; Q1, lower quartile; Q3, upper quartile.

[a]IHD is more often available than all other ECTRs ($P < 0.001$).

[b]Time to start IHD, CRRT and HP were not statistically different but all three were faster than TPE, LSDs, PD and ET ($P < 0.01$).

[c]Ratios are performed by dividing the cost of an ECTR by IHD from the same centre.

*P-values <0.05 represent a ratio that is significantly different than 1.

Time to ECTR initiation

The median time to initiate acute IHD, CRRT and HP was 60 min, compared with 120 min for TPE, PD and LSDs and 210 min for ET (Table 3). The median time to initiate IHD was lower than for TPE, LSDs, PD and ET ($P < 0.01$) but was not different from CRRT and HP.

Comparative costs of ECTRs

The median cost of ECTRs is reported in Table 3. IHD was the least expensive (US$314) followed by PD (US$454), HP, CRRT, TPE, ET and LSDs (Table 3). When performing cost ratios of each ECTR relative to IHD at the same centre, the median cost ratios were 1.4 for PD, 1.7 for HP and CRRT, 2.8 for TPE, 3.8 for ET and 6.5 for LSDs (Figure 3). All ratios were significantly greater than 1, except for ET compared with IHD, due to the small number of ETs.

The median cost ratio of all expenses related to catheter installation (the catheter itself, disposables, nursing and physician salary) to the total median cost of IHD was 0.54. In comparison, the median cost ratio of the following items to the total cost of IHD was 0.10 for physician salary, 0.09 for nurse salary and 0.32 for disposables including filters, syringes, heparin, dialysate/effluent and water.

The median cost ratio of a 4-h IHD treatment over the total median cost of 1 day in the ICU (excluding that related to IHD and mechanical ventilation) was 0.59 ($P = 0.2$).

DISCUSSION

This survey is the first to report data on availability, time to initiation and cost of ECTR in an acute setting. From an availability perspective, we found that IHD was present in almost all centres,

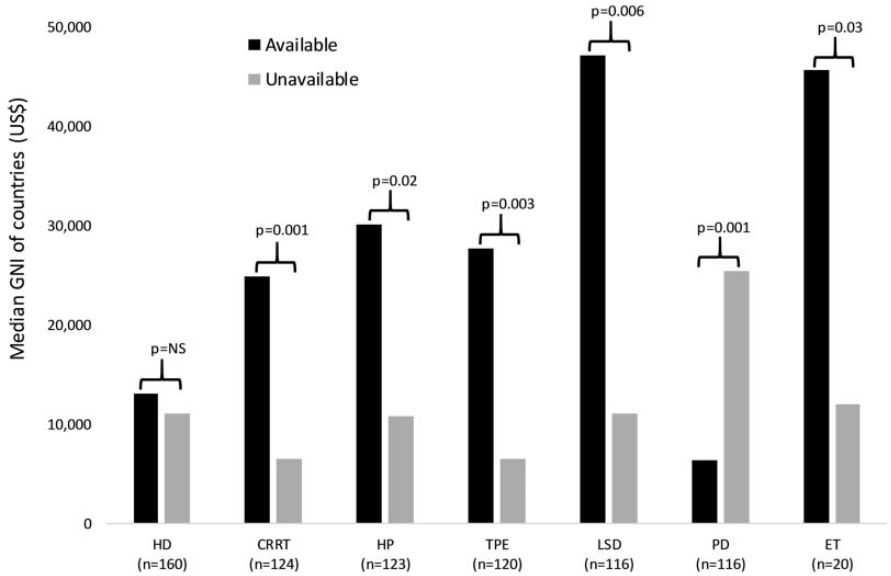

FIGURE 2: Availability of ECTRs according to gross national income. CRRT, continuous renal replacement therapy; ECTR, extracorporeal treatment; ET, exchange transfusion; HP, hemoperfusion; IHD, intermittent hemodialysis; LSD, liver support devices; PD, peritoneal dialysis; TPE, therapeutic plasma exchange.

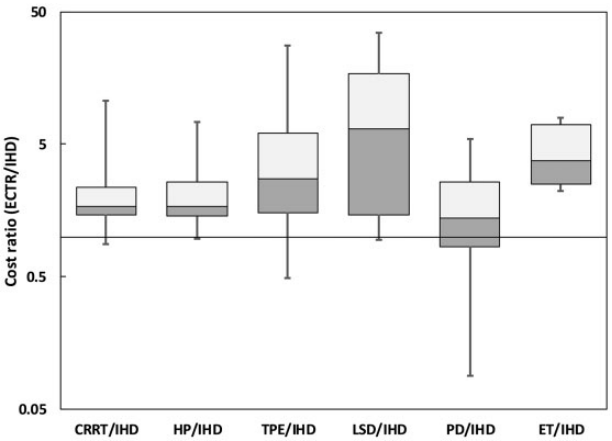

FIGURE 3: Cost ratio of ECTRs relative to IHD at the same centre. For all box plots, the central rectangle spans the first to the third quartile (the 'interquartile range'), the segment inside the rectangle represents the median and whiskers above and below the box show the minimum and maximum. CRRT, continuous renal replacement therapy; ECTR, extracorporeal treatment; ET, exchange transfusion; HP, hemoperfusion; IHD, intermittent hemodialysis; LSD, liver support devices; PD, peritoneal dialysis; TPE, therapeutic plasma exchange.

followed by TPE, CRRT, ET, PD, HP and LSDs. We also found that the accessibility of all techniques except acute PD was greater in countries with higher GNI; this observation is consistent with current data for AKI showing restricted access to IHD and CRRT in some regions of the world [14, 31], although decreasing costs of equipment have facilitated the use of these techniques in developing countries [16]. The most recent large survey, conducted in 2004 with 560 participants, showed that CRRT was available in 91% of participating centres, compared with 69% for IHD [24]. However, $>85\%$ of the participants originated from Europe (compared with 54% in our survey), limiting the generalizability of the former results. Other studies showed more limited availability of CRRT in resource-limited regions: CRRT was available in only 12% of hospitals in Malaysia, in 17% of paediatric nephrology centres in India [32] and in 23% of nephrology divisions in Latin America [18]. Factors other than cost can also account for variable CRRT availability; for example, in some ICUs, CRRT is preferred over IHD and may be the only option during late hours because of personnel limitations, local practices or physician preference [15, 33].

There is limited information on the availability of TPE, HP and ET around the world. One Spanish study reported that 62% of centres involved in apheresis had acute therapeutic apheresis available [34], while TPE is neither readily available nor affordable in many parts of Africa [35]. As for HP, our data suggest that it is still available in many countries despite reports to the contrary in the USA (HP cartridges could be found in only 29% of dialysis units in New York) [36] and in Malaysia (found in 16% of hospitals) [16]. Even when available, IHD is currently performed ~50 times more often than HP for poisonings in the USA, and this technique has become almost obsolete in Canada, the UK and Denmark [37]. However, HP remains favoured in certain regions of Asia for specific poisonings like paraquat and organophosphates [38, 39], where data appear to suggest a survival benefit for HP [40, 41]. ET was available in 60% of centres, albeit on a restricted number of responses, whereas it was available in 32% of centres in Malaysia [16]. At present, limited indications for ET include massive haemolysis [42], poison removal in infants [43] and poison-induced methemoglobinaemia [44], but because it can be performed without a complicated or expensive apparatus, it is not surprising that it is found in a relatively large percentage of centres.

The availability of acute PD was 45% overall and was greater in countries with lower GNI. This result is not surprising considering that PD is often the only technique available to treat AKI in resource-limited countries, as it does not require an extracorporeal circuit. In developed countries, except for infants, acute PD is uncommonly used: a previous survey

distributed to attendees at three PD meetings showed that PD was used to treat AKI in 46% of centres in Asia compared with 19% and 12% of centres in Europe and North America, respectively [45]. According to the aforementioned large survey mainly consisting of European participants, acute PD was available in 23% of centres [24], and as low as 2% in the UK [15]. In comparison, acute PD was available in 51% of centres in Malaysia [16] and in 30% of nephrology divisions in Latin America [18].

We found that IHD, HP and CRRT could be initiated significantly faster than other ECTRs. Nevertheless, all ECTRs except ET could usually be initiated within 3 h after prescription. These relatively small differences in delays are unlikely to affect outcomes for most poisonings; however, if these delays are added to time required for interhospital transfer, which by itself is directly dependent on the availability of ECTR, then IHD stands out as the fastest ECTR to initiate. Regarding HP, many centres may have the capability and personnel to perform this technique but may not routinely stock the adsorptive cartridges, which can affect the reported time for initiation [36].

We report data on costs of various ECTRs from 52 countries. We found that costs vary greatly between and even within countries, especially when both private and public health care systems are present. Nevertheless, our results suggest that IHD is the least expensive ECTR worldwide. This remains true even when comparing cost ratios within the same centre, excluding confounding from non-comparable and heterogeneous regions. We found that CRRT was more expensive than IHD, with a cost ratio of 1.7. This is comparable to other studies: to our knowledge, the largest survey, which was performed 15 years ago, from 23 countries reported a median cost difference of US$289.60 for CRRT. CRRT:IHD cost ratios reported elsewhere also compare to ours: 1.9 in the USA [46], 1.4–1.7 in Canada [47], 1.6 in Switzerland [21] and 1.1 in Italy [48]. These findings confirm the validity of our findings and show that even nearly three decades following the implementation of CRRT, the relative costs associated with this modality remain universally higher than IHD [23, 49].

Our study also provides information on relative costs of acute PD, HP, TPE and LSDs for which there are very limited data worldwide. For acute PD, we found that the costs were higher than IHD (cost ratio 1.4), as opposed to previous findings from Italian and African studies [50, 51], which reported cost ratios of 0.5–1.0, possibly due to greater relative costs of consumables and salaries. We reported a cost ratio of 1.7 for HP compared with IHD; in a Russian study, that ratio was > 3 [52]. For TPE, we found a median cost ratio of 2.8 over IHD and a median cost of US$980. Unsurprisingly, costs for TPE vary greatly in the literature, from US$213 per session in 2001 in India [53], US$500 in France in 2000 [54] and US$4150 in 2010 in the USA [55], but also seem to be consistently greater than IHD for any given country. For LSDs, we reported a median cost ratio of 6.5; extrapolating existing data for LSDs [56] and comparing with IHD from another source during the same period [46], an LSD:IHD cost ratio may be estimated at 7.1–8.9 in the USA. Both TPE and LSDs have limited clinical application, especially in acute poisonings, where they may be considered only for removal of highly protein-bound poisons [8].

We found that more than half of the costs related to IHD were attributed to catheter installation and about a third to disposables. In comparison, costs related to supplies and the machine represented 25.9% of the cost of one IHD session in a Canadian study more than a decade ago [47], which did not include costs related to catheter insertion. Our results show that the cost of one IHD session is lower than one average day in an ICU, although the results were not statistically significant. A proper cost-efficiency analysis would be ideal to evaluate the benefit of ECTR to reduce ICU costs and length of stay in, for example, non-lethal poisonings, which can cause prolonged admission in the ICU (e.g. carbamazepine and barbiturates).

The relevance and scope of our data are most pertinent for situations where exogenous toxin removal is required, as more than one ECTR is usually available and potentially effective. In acute poisonings, IHD appears to provide the best poison clearance for most toxins and is currently favoured for poisonings with salicylate [10], lithium [13], methanol [57], metformin [58], phenytoin [59], valproic acid [11] and carbamazepine [12]. It is likely that the present data strengthen the preference and justification for IHD over other ECTRs when efficacy is comparable.

Our survey has several limitations. First, the completion rate was relatively low (16%), although the absolute number of comprehensive responses compares favourably with other studies. Furthermore, our results may have overestimated the true availability of some ECTRs, as most of our respondents originated from specialized centres; for example, the percentage of centres with LSDs (15%) seems relatively high. A survey targeting emergency physicians or general physicians/internists may have shown differing data on the availability of ECTRs, particularly in centres without on-site nephrology support. Also, results may have differed if we had specifically targeted intensivists for this survey. However, this limitation remains true for previous surveys and does reflect the availability of various ECTRs within a nephrology-centred practice. Second, the response rate could not be reliably estimated, as some recipients may have received more than one invitation because of potential overlap in mailing lists. It is also possible (but not likely) that one individual at a single institution provided data on behalf of multiple colleagues who were e-mailed the survey invitation. In both of the latter cases, the apparent response rate is likely to under-reflect the true response rate. Third, due to the objective and quantitative nature of the data surveyed, reliability assessment was not performed [25, 30]. Fourth, our results relied on self-reported data and the data collected depended upon the knowledge of the respondents or their willingness to respond accurately. However, our results are in accordance with those from the literature, reinforcing the quality of our data. Finally, this survey is not exhaustive and responses from certain regions were underrepresented (Africa and South America), so we cannot claim to have accurate data from every country. Therefore, in countries for which there are no data, or if individuals believe that data for their institution differ from that presented here, we encourage them to report their findings for the purpose of improving knowledge and accuracy of the costs related to ECTR.

CONCLUSION

Our findings confirm the lower cost, shorter time of initiation and wider availability of IHD compared with other ECTRs. These advantages strengthen the preference for IHD over other ECTRs in the majority of acute indications, in particular poisonings, when their benefits are comparable. Future research on the use of ECTRs in acute settings should focus not only on the efficacy, but also on the cost-effectiveness of using ECTRs in these conditions.

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All responses were kept confidential and anonymous unless respondents waived anonymity.

CONFLICT OF INTEREST STATEMENT

None declared.

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