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Construction of a Mathematical Model for Conventional Haemodialysis and Continuous Renal Replacement Therapy in Subjects with Hyponatraemia or Hypernatraemia and/or hyperkalaemia

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Abstract

Background:

Dialysis in patients with dysnatraemia and hyperkalaemia is generally difficult because needing to minimize [Na] correction while ensure rapid [K] correction, and thus a need for mathematical model.

Methods:

A model was derived with 80 regular ESRD dialysis sessions and 10 acute dialysis (AD) sessions. Clinical audit was performed assessing error of this model with new set of 33 AD of HD and CRRT with [Na] <=130 or >=150mmol/L pre-dialysis.

Results:

Na prediction could be derived with dialysate flow rate (Qd) clearance calculation and solute transport, assuming that all plasma flow is changed to the dialysate Na concentration, i.e., Qd with limit by plasma flow rate. However, a refined calculation was for intracellular solute such as K and urea, for Qd being multiplied by the factor of: Blood water flow rate / (blood water flow rate + dialysate flow rate), i.e., BWFR/ (BWFR+Qd).

And, because of varying "volume of distribution", the total body water (TBW) needs to be adjusted with fuzzy factor, namely f_{Na}, f_K, and f_{urea}, which were determined as 0.846, 1.931, and 1.128 respectively (of Watson TBW). Extracellular electrolyte has lower fuzzy factor than predominant intracellular electrolyte.

The errors in absolute number for serum Na, K, urea and osmolarity estimation prediction were 1.8 ±1.3, 0.32 ±0.34, 2.3 ±1.9 and 3.8 ±3.2 mmol/L, respectively. Good reliability and correlation were shown between predicted and measured parameters.

Conclusion:

Model substantiates fuzzy factor correction for TBW, and also dialysis clearance calculation with Qd limit by plasma flow rate for extracellular electrolyte, and in contrast, the need of Qd dilution by factor of (BWFR/(BWFR+Qd)) for intracellular electrolyte. Low errors in absolute number between predicted and actual electrolyte were shown.

KEYWORDS: Haemodialysis, Continuous Renal Replacement Therapy, Hyponatraemia, Hypernatraemia, Hyperkalaemia, Acute Kidney Injury, End Stage Kidney Disease

Plain Language Summary:

Dialysis in patients with dysnatraemia and hyperkalaemia is generally difficult because needing to reduce [Na] correction while ensuring timely adequate [K] removal. A mathematical model was created, with derivation cohort, followed by validation cohort in patients with dysnatraemia to ascertain the reliability of the model. This model might serve as potential tool to construct future dialysis regime.

INTRODUCTION

Continuous renal placement therapy (CRRT) and Haemodialysis (HD) for patients with hyponatraemia or hypernatraemia could be difficult because of the danger of too rapid correction of the serum sodium level [1,2]. On the other hand, hyperkalaemia would need rapid correction with dialysis and thus concurrent dysnatraemia and hyperkalaemia would pose dilemma for clinicians in prescribing dialysis. Currently, there was not yet any validated mathematical model for dialysis clearance and solute transport in counter current flow to predict serum Na and K changes during dialysis.

A mathematical model was derived from a previously published model for management of these patients to create a mathematical model to safeguard CRRT management and haemodialysis [3,4]. In brief, it is assumed that serum electrolyte changes during dialysis are correspondent to flow rate of blood pump and dialysate electrolyte concentration, in the calculable efficacy mimics intravenous drip electrolyte concentration; and thus by adding in mathematical model derived intravenous drip with appropriate electrolyte concentration, one can safeguard the dialysis process, not to overcorrect [Na] while ensure [K] reaching target level.

METHODS

It was assumed that sodium and calcium ions are moving speedily across the filter membrane as they are predominantly **extracellular electrolytes (ec)**, while potassium and urea are moving slower across the filter membrane as they are distributed significantly **intracellular electrolytes (ic)**.Therefore, differences were existed in formulae 1, 3, 5, 9, 10, 11 stated below. **This is because extracellular electrolyte is readily crossing over filter membrane during dialysis, and thus dialysis clearance calculation with Qd merely limit by plasma flow rate; but intracellular electrolyte needs to cross over cellular membrane, before crossing over filter membrane. Thus, there was a dilution necessary for dialysis clearance and effective solute flow rate of dialysate for intracellular electrolyte, i.e., Qd being multiplied by the factor of:**

***blood water flow rate / (blood water flow rate + dialysate flow rate)*,**

(BWFR / (BWFR+Qd))

because intracellular electrolyte is crossing over compartment from intracellular to extracellular, before diffusion movement across dialysis filter membrane.

And, because of varying "volume of distribution", due to varying intracellular concentration, the total body water (TBW) needs to be adjusted with fuzzy factor for [Na], [K], and [urea], namely f_{Na}, f_K, and f_{urea}.

Calculation of plasma clearance

Plasma flow rate, PFR = (Qb (ml/min) x 69 (ml/hour) x (1-HCT) (Formula 1.1)

where Qb represents blood pump rate and HCT represents hematocrit

Blood water flow rate, $BWFR_{ic}$(ml/hour) = Qb (ml/min) x 60(ml/hour) x [(1 - HCT) x 0.93 + HCT x 0.72]

(Formula 1.2, applicable for potassium and urea with significant intracellular concentration (ic).)

Blood water flow rate for sodium and calcium, $BWFR_{ec}$(ml/hour) = PFR

(Formula 1.3, applicable for sodium and calcium with mainly extracellular concentration (ec).)

Filter fluid inflow rate, FFIR = PFR + PBP + PRE (Formula 2)

where PBP is defined as preblood pump dilution flow rate,

PRE is defined as prefilter replacement flow rate,

Dialysis clearance, Kd_{ic} = Qd x ($BWFR_{ic}$ / ($BWFR_{ic}$ +Qd)) (Formula 3.1)

Dialysis clearance, Kd_{ec} = Dialysate flow rate (Formula 3.2)

Diafiltration clearance, DFC (ml/hour) = (UF + Kd) x (BWFR / (BWFR + PBP + PRE)) (Formula 4)

In consideration of high dialysate flow beyond the rate of remaining plasma flow rate being dialyzed, one can apply this formula for extracellular electrolyte:

If Dialysate flow rate >= (Plasma flow rate – SPBP – SPRE – Post Replacement),

then effective clearance flow rate for Dialysate (Kd_{ec}) = Plasma flow rate – SPBP - SPRE - POST. (Formula 5)

where POST represents post filter replacement flow rate.

Blood water flow rate is as in literature [5].

Calculation of electrolyte changes

The sodium, potassium and calcium ion delivery are calculated with:

Electrolyte delivery (μmol/hr)

= electrolyte concentration (mmol/L x effective flow rate (ml/hour) (Formula 6)

$$\text{Effective Solute Flow Rate of Prebloodpump-Dilution, SPBP} = \text{PBP x } \frac{\text{BWFR}}{\text{BWFR+PBP}} \text{(Formula 7)}$$

$$\text{Effective Solute Flow Rate of Pre-Dilution, SPRE} = \text{PRE x } \frac{\text{BWFR- PBP}}{\text{BWFR-PBP+PRE}} \text{(Formula 8)}$$

$$\text{Effective Solute Flow Rate of Dialysate, Sdialysate}_{ic} = \text{Qd x } \frac{\text{BWFR}_{ic}\text{- PBP - PRE}}{\text{BWFR}_{ic}\text{-PBP-PRE + Qd}} \text{(Formula 9)}$$

Effective Solute Flow Rate of Dialysate, $Sdialysate_{ec}$= Qd, (Formula 10)

but if Qd> PFR – PBP – PRE – POST, then:

$Sdialysate_{ec}$ = PFR – SPBP –SPRE – POST (Formula 11)

CRRT or HD Solute Flow Rate, SRRT = SPBP + SPRE + POST + SDialysate (Formula 12)

Effective Solute Concentration for CRRT or HD (mmol/L), as for sodium,

$$[Na]_{RRT} = \frac{SPBP \text{ x } [Na]_{PBP} + SPRE \text{ x } [Na]_{PRE} + POST \text{ x } [Na]_{POST} + Sdialysate \text{ x } [Na]_{Dialysate}}{SRRT}$$

(Formula 13)

Recirculation adjusted, SRRT' = SRRT x (1 – recirculation rate) (Formula 14)

Effective Solute Concentration for CRRT (or HD) & Intravenous Drip in mmol/L, as for sodium,

$$[Na]_{RRT\,\&\,IVD} = \frac{SRRT' \text{ x } [Na]_{CRRT} + IVD \text{ x } [Na]_{IVD}}{SRRT'+IVD} \text{(Formula15)}$$

In which IVD = rate of Intravenous drip flow rate

Next, total body water (TBW) was assessed with 2 formulae: i) Watson formula. ii) Fractional water ratio: 0.6 in male adult, and 0.5 in female adult; 0.5 in male elderly and 0.45 in female elderly; 0.6 in all children of body weight. Calculation of fluid status was detailed and was adjusted for dehydration as in Appendix A.

$$\text{Effective Ultrafiltration Rate, EUF} = \text{Ultrafiltration Filtration Rate x } \frac{\text{BWFR}}{\text{BWFR} + \text{PBP} + \text{PRE}}$$

Expected Changes in Serum [Na] after 1 hour,

$$[\text{Na}]_{\text{change}} = \frac{[\text{Na}]_{\text{RRT\&IVD}} - [\text{Na}]_{\text{baseline}}}{f_{\text{Na}} \text{ x TBW} + \text{Net Fluid Change Rate}} \text{ x (SRRT'+IVD + EUF)/1000} \quad \text{(Formula 16.1)}$$

$$[\text{Na}]_{\text{expected}} = [\text{Na}]_{\text{baseline}} + [\text{Na}]_{\text{change}}$$

All these formulae are also applicable for [K], [Ca] and [urea], besides [Na]. Total body water (TBW) was corrected with various fuzzy factors (f):

Corrected TBW = f x TBW with f_{Na}, f_K and f_{urea}.

Fuzzy factor was derived with formulae in Appendix B. In order to determine fuzzy factor adjustment of total body water (TBW) for [K] and [urea], f_K and f_{urea}, study was performed on 80 dialysis session of 41 local end stage renal disease (ESRD) patients on regular 3x/week haemodialysis in the hospital, over 2 HD sessions 3 months apart, measuring [K] and [urea] pre and 3-5 minutes post haemodialysis. (Average urea regeneration rate of this ESRD cohort is 0.38 mmol/L/hr.)

For the fuzzy factor of [Na], f_{Na} was assessed in 10 acute dialysis sessions in which patients had measured [Na] changes > 5 mmol/L and were euvolemic as determined with clinical examination, chest X-ray, and ultrasound of inferior vena cava.

It was also assumed that the recirculation rate of temporary catheters is 13.1% with femoral catheter, or more specifically 8.3% for catheter length >=20cm and 26.3% for <20cm, while it is 0.4% with internal jugular catheters, based on published data [6].

Effective ultrafiltration is adjusted with recirculation rate, EUF' = EUF x (1 – recirculation rate)

Because all dialysis process that were pictured by these mathematical mechanism formulae were on-going all the while, thus, one could do logarithm calculation:

Logarithm calculation for prediction of serum [Na] and [K]

The sodium ion delivery is calculated with: Solute flow rate, SFR = SRRT' + IVD Based on Appendix B approximation, and considering that

UF may further shift the serum [Na] in the same magnitude from $[Na]_0$ to $[Na]_{CRRT\&IVD}$, it is postulated that the trend of serum [Na] getting closer to $[Na]_{CRRT\&IVD}$ is with the gradual gradient of being changed in t hour with:

$$\ln\left(1-\frac{[Na]_t-[Na]_0}{[Na]_{RRT\&IVD}-[Na]_0}\right)=-\left(\frac{(SFR+EUF')\ x\ t}{f_{Na}\ x\ TBW+Net\ Fluid\ Change\ Rate\ x\ t}\right)$$

(formula 17)

where $[Na]_0$=[Na] at time 0; $[Na]_t$=[Na] at time t;EFR is to be converted to L/hour;and EUF' is the ultrafiltration flow rate in L/hour (adjusted with recirculation rate), not total ultrafiltration in one dialysis session.

$$[Na]_t = [Na]_0 + ([Na]_{RRT\&IVD} - [Na]_0)\ x[1- e^{-\left(\frac{(SFR+EUF')\ x\ t}{f_{Na}\ x\ TBW\ +\ Net\ Fluid\ Change\ Rate\ x\ t}\right)}]$$

(Formula 18)

$$[K]_t=[K]_0+([K]_{RRT\&IVD} - [K]_0)\ x[1- e^{-\left(\frac{(SFR+EUF')\ x\ t}{f_{K}\ x\ TBW\ +\ Net\ Fluid\ Change\ Rate\ x\ t}\right)}]$$

(Formula 19)

Formulae 18 and 19 are taken as the standards, and thus are applied in all the analysis of this model.

Appendix B shows the derivation formulae for fuzzy factors, and Appendix C shows formulae to determine regime modification needed to achieved desirable [Na]; while Appendix D showed calculation to predict urea level. Fluid overload delays electrolyte concentration changes, and adjustment is needed based on the ratio of the subject's current weight over usual weight (Please refer 1st statement of in footnote of Appendix D). These adjustments were ascertained on based on the accuracy test of the formula in case series.

The subsequently derived formulae are the theoretically most accurate formulae:

$$[\mathrm{Na}]_t = [\mathrm{Na}]_0 + ([\mathrm{Na}]_{\mathrm{RRT\&}IVD} - [\mathrm{Na}]_0)\ \mathrm{x}[1 - e^{-\left(\frac{(\mathrm{SFR}+\mathrm{EUF'})\ \mathrm{x}\ t}{f_{\mathrm{Na}}\ \mathrm{x}\ \mathrm{TBW} + \mathrm{Net\ Fluid\ Change\ Rate\ x}\ t}\right)}]$$

(Formula 18)

$$[\mathrm{K}]_t = [\mathrm{K}]_0 + ([\mathrm{K}]_{\mathrm{RRT\&}IVD} - [\mathrm{K}]_0)\ \mathrm{x}[1 - e^{-\left(\frac{(\mathrm{SFR}+\mathrm{EUF'})\ \mathrm{x}\ t}{f_{\mathrm{K}}\ \mathrm{x}\ \mathrm{TBW} + \mathrm{Net\ Fluid\ Change\ Rate\ x}\ t}\right)}]$$

(Formula 19)

A software spreadsheet was created based on the derived formulae; requiring inputs of serum Na, serum K, serum urea level, weight, height, blood flow rate, dialysate flow rate, duration of dialysis, and concurrent fluid infusion, to determine the expected serum Na, serum K and serum urea level, after the dialysis session.

Procedures

For CRRT, equipment included Prismaflex machines (Baxter), Prismaflex M100 hollow-fiber dialysers (M-100; 0.9 m^2; AN69; Baxter), with Prismasol® solution and also concentration modified solution, as proposed by this mathematical model. As the hospital only has pints of half saline (NaCl 0.45%, 77 mmol/L) or Hartmann solution of 500ml, a 3 way tap was used to add on additional solution.

For HD, Fresenius 4008S machines with Almedico polyethersulfone (PES) dialyzer SA-DL-1.8HF 1.8m^2 (ISO9001/ISO13485) were used for adults, while Fresenius Polysulfone® F6 HPS 1.3m^2 dialyzers were used for children; with solution of Renacid® AK5 and Renacab® BK2, and [Na+] dialysate adjusted accordingly; as well as concurrent fluid infusion with electrolyte level proposed by the later built mathematical model. Potassium concentration of dialysate is 1.9 mmol/L.

This mathematical model was assessed for patients needing acute dialysis with serum sodium <= 130 or >= 150 mmol/L before dialysis. Hyperkalaemia is defined as serum potassium >= 6 mmol/L.

Reliability testing was performed by calculating Cronbach's alpha for assessment of internal consistency, and Pearson's correlation was determined between predicted and measured sodium level and their changes over time.

Laboratory tests are as shown in Appendix E. Estimated changes in serum osmolarity before and after dialysis sessions were derived with the below formula:

Serum osmolarity = ([Na] + [K]) x 2 + urea

IBM SPSS version 21 and Microsoft excel were used to perform statistical analysis. Mean ± standard deviation were shown.

This research is registered with National Medical Research Register, Ministry of Health Malaysia with registered ID NMRR-21-1585-61141. The study has gained approval from medical research ethical committee.

RESULTS

This mathematical model was initially assessed on 10 acute dialysis sessions from derivation cohort to derive fuzzy factors, followed by validation assessment on 33 dialysis sessions from validation cohort in Intensive Care Unit and the General Medical Ward of the hospital over 2 years period. Two case of acute dialysis with predialysis mathematical modelling and good outcome were excluded because of blood sampling issues. All patients were dialyzed using temporary venous dialysis catheters via the internal jugular vein or femoral vein.

There were 24 patients included: 6 patients in derivation cohort, 21 patients in validation cohort; 3 patients were having dialysis sessions both during the mathematical model derivation period and also validation period. The age ranged from 13.6 to 78.2, mean 49.5 ± 20.5 years. Their weight ranged from 36 to 90 kg with mean of 58 ± 11 kg. There were altogether 34 dialysis sessions with baseline [Na+] <=130mmol/L and 9 dialysis sessions with baseline [Na+] >= 150 mmol/L. In total, 11 CRRT and 32 HD sessions were studied. Analysis was based on formula 18 and for $[K]_t$ and $[urea]_t$, formulae 19 and 23 were used.

In order to determine fuzzy factor for TBW correction, with the help of formulae of 18.1, 19.1 and 23.1, putting in the pre and post dialysis electrolyte level, the average of f_{Na}, f_K and f_{urea} were taken from 10 euvolemic acute dialysis patients for sodium level, and also 80 dialysis sessions of 41 ESRD patients for potassium and urea level (with 2 dialysis sessions per person, Two dialysis sessions were not included because of sampling error, 82 – 2 = 80). Thereby, the fuzzy factor for corrections of TBW of Watson, and fractional water ratio was determined as:

f_{Na} are 0.846 and 0.913

f_K are 1.931 and 2.144

f_{urea} are 1.128 and 1.258

Table 1 Dialysis Regime of Acute Dialysis for patients with dysnatraemia with or without hyperkalaemia

HD*		Median	Minimum	Maximum
Blood Flow Rate	ml/min	200	150	300
Dialysate Flow Rate	ml/min	500	500	@800
Dialysate [Na]	mmol/L	140	130	145
Gross Extraction~	ml	2000	300	6000
Duration	hour	3	2	7
CRRT				
Blood Flow Rate	ml/min	190	150	200
Dialysate Flow Rate	ml/hour	700	500	1000
Dialysate [Na]#	mmol/L	135	118	167
Pre Blood Pump Dilution^	ml/hour	800	500	1100
Post Replacement^	ml/hour	300	300	300
Extraction	ml/hour	20	0	150
Duration**	hour	10	4	24
DiaFiltration Clearance per Weight	ml/kg/hr	30	23	32

*Among 26 HD sessions for hyponatraemic patients, concurrent IV D5% is given in 15 sessions, with the rate ranging from 200 to 1000 ml/hour during HD time and median of 500 ml/hr, while extracting the extra infusion volume with HD, in order to achieve desirable serum [Na]; whereas among 6 HD patients with hypernatraemia, IV NaCl 3% of 125, 200, 200 and 500 ml/hour were given in 4 patients.

@Dialysate flow of 800 ml/min is applied for patients with hyperkalaemia, accompanied by infusion of IV D5% or D10% at >=40 ml/hour, or IV D50% 10ml/hour to prevent hypoglycemia if no glucose in infusion and dialysate.

~Gross extraction includes priming volume and concurrent infusion of fluid with calculated electrolyte, besides originally intended extraction volume.

#In dialysate flow of CRRT for dysnatraemia patients, out of 11 sessions, 3 sessions required half saline with Na 77 mmol/L, another 3 sessions require Na 104 mmol/L, with combination of hartmann's solution Na 131 mmol/L and half saline Na 77 mmol/L, while the remaining 5 sessions were with Prismasol.

^Prismasol was used for Pre Blood Pump Dilution and Post Replacement in CRRT. By diluting NaCl3% 400 ml for 10 hours, 250 ml for 24 hours, then 120 ml for next 24 hours into 5 L of prismasol, a patient with hypernatraemia was smoothly brought out from hypernatraemia and rhabdomyolysis critical condition. Similarly, hyponatraemia could be treated with D5% dilution.

**Duration of CRRT reveals the time of a regime before next modification, not the total duration of CRRT.

Table 2 Average error in absolute number between predicted and measured parameters of subjects post-dialysis

Cohort		End stage renal disease patients on regular dialysis						Acute dialysis patients						
Flow in model		Qb	PFR	$BWFR_{ic}$				PFR				$BWFR_{ic}$		
TBW in model	mmol/l	Wat	Wat	Wat	Wat	Fr	Fr	Wat	Wat	Fr	Fr	Wat	Fr	Fr
Fuzzy factor	Applied	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No
[Na]	mmol/l							**1.8**	2.3	1.8	2.5			
[K] without Qd refined calculation *	mmol/l	0.31	0.29	0.27		0.31								
[K] with Qd refined calculation *	mmol/l	0.31	0.28	**0.27**		0.31						**0.32**	0.33	0.98
[Urea] without Qd refined calculation*	mmol/l			**1.23**	3.69	4.92	5.071							
[Urea] with Qd refined calculation *	mmol/l			**1.19**	1.35	5.42	5.53					**2.3**	2.4	4.3

Abbreviation: ESRD, end stage renal disease patients on regular dialysis; AD, acute dialysis patients; Qb, blood pump; $BWFR_{ic}$, blood water flow rate for intracellular electrolyte; PFR, plasma flow rate; TBW, total body water; Wat, Watson; Fr, Frational TBW, i.e., TBW: Age <=12: 0.6, Age >=65: Male 0.5, Female 0.45, otherwise for general population Male 0.6, Female 0.5.

*Qd refined calculation: In order to calculate dialysis clearance and solute flow rate for intracellular electrolyte, Qd is to be multiplied with factor of BWFR / (BWFR + Qd).

Based on this evaluation, fuzzy factor correction for TBW is needed to reduced error. For [Na] estimation, model with PFR and Watson TBW is chosen as the error is the lowest, 1.8 ± 1.3mmol/L in AD; For [K] estimation, model with $BWFR_{ic}$ and Watson TBW and with adjustment for Qd is chosen as the errors are lowest, 0.32 ± 0.34mmol/L in AD and 0.27 ± 0.31 mmol/L in ESRD; For [urea] estimation, model with $BWFR_{ic}$ and Watson TBW and with adjustment for Qd is chosen as the errors are low, 2.3 ± 1.9 mmol/L in AD and 1.2 ± 1.2 mmol/L in ESRD. Error of changes in osmolarity with dialysis is 3.8 ± 3.2 mmol/L with these chosen parameters estimation in AD.

Take note that the maximum for errors in [K] prediction with Qd adjustment in ESRD regular subjects was 2.084, lower than model without Qd adjustment 2.142, and the variance of errors in [K] prediction with Qd adjustment was 0.094, lower than model without Qd adjustment 0.104. Thus, Qd adjustment was necessary for intracellular electrolyte.

It was shown that f_{Na} was lowest, followed by f_{urea} and f_K because sodium was distributed extracellular predominantly, while potassium was distributed intracellular predominantly, whereas urea was distributed significantly in both intra and extracellular compartments.

Acute Dialysis Regime was as shown in table 1. Average error in absolute number for difference between predicted and measured [Na], [K] and urea was as shown in table 2 with 33 acute dialysis sessions from validation cohort.

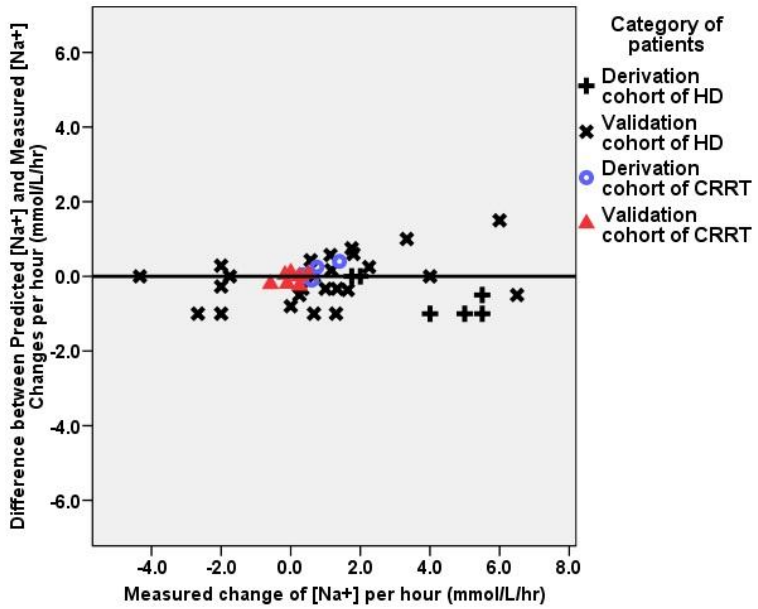
It is shown that Na prediction could be derived with dialysate flow rate clearance calculation, assuming that all plasma flow is changed to the dialysate Na concentration, with limit by flow rate of dialysate (Qd).

It is also shown that refined calculation of dialysis clearance and effective solute flow rate of dialysate for [K] and [urea] need to be performed with Qd being multipled by the factor of: Blood water flow rate / (blood water flow rate + dialysate flow rate).

Besides, as shown in table 2, TBW that was estimated with Watson formula, was of lower error than fractional TBW. However, fuzzy factor correction was still needed to further reduce the absolute error in the [Na] level estimation. And thus fuzzy factor correction was needed to improve the accuracy of post dialysis serum [Na] prediction. Similarly, this was warranted for [K] and [urea] prediction.

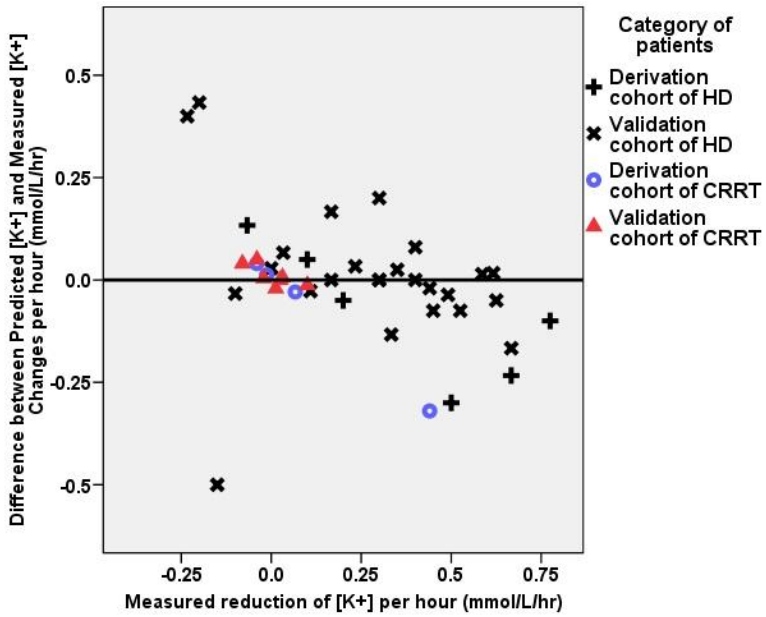
Close approximation was found between the predicted and measured changes in sodium, potassium, urea and estimated osmolarity level, with good reliability test and Pearson's correlation as shown in Figure 1, 2, 3 and 4.

Figure 1: Bland Altman plot of difference between expected change in serum [Na+] and measured change in serum [Na+] in acute dialysis patients with dysnatraemia



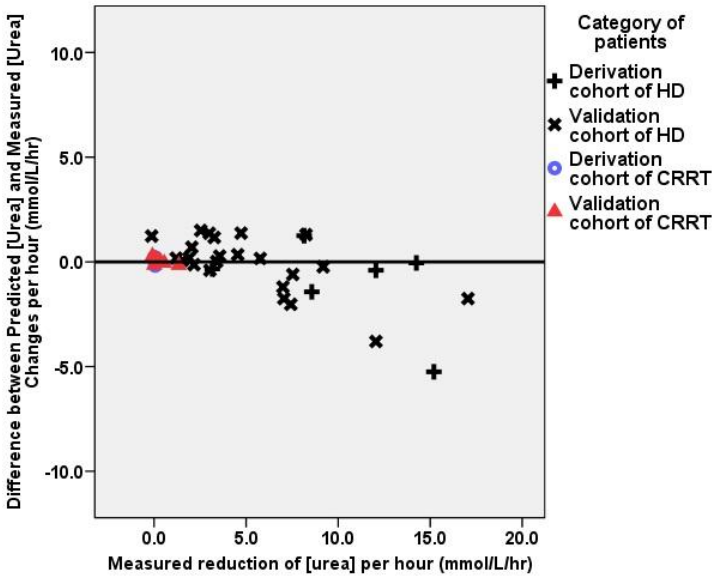
Difference between expected [Na+] and measured change in serum [Na+] in acute dialysis patients is -0.1 ± 0.6 mmol/L/hr, Reliability test Cronbach's alpha = 0.982, Two-tailed Pearson correlation, r^2=0.966 (p<0.001) for validation cohort.

Figure 2: Bland Altman plot of difference between expected change in serum [K+] and measured change in serum [K+] in acute dialysis patients with dysnatraemia



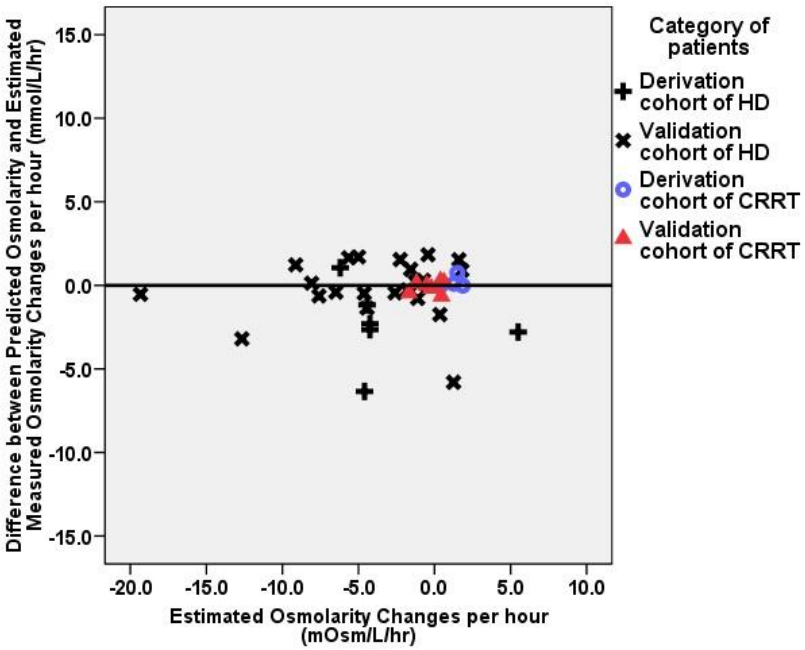
Difference between expected [K+] and measured change in serum [K+] in acute dialysis patients is 0.0 ± 0.2 mmol/L/hr, Reliability test Cronbach's alpha = 0.905, Two-tailed Pearson correlation, r^2=0.827 (p<0.001) for validation cohort.

Figure 3: Bland Altman plot of difference between expected change in serum [urea] and measured change in serum [urea] in acute dialysis patients with dysnatraemia



Difference between expected [urea] and measured change in serum [urea] in acute dialysis patients is -0.2 ± 1.3 mmol/L/hr, Reliability test Cronbach's alpha = 0.976, Two-tailed Pearson correlation, r^2=0.963 (p<0.001) for validation cohort.

Figure 4: Bland Altman plot of difference between expected and measured change in osmolarity based on [Na], [K] and [urea] with acute dialysis with dysnatraemia



Difference between expected osmolarity and measured change in estimated osmolarity in acute dialysis patients is -0.4 ± 1.8 mmol/L/hr, Reliability test Cronbach's alpha = 0.973, Two-tailed Pearson correlation, r2=0.948 (p<0.001) for validation cohort.

Additional feature in model for rapid rise of [K]

And, in critical case of rapid rising of predialysis [K] ($[K]_{rise}$) >= 0.08mmol/L/hour, such as in this cohort, a case of rhabdomyolysis with $[K]_{rise}$ 0.43 mmol/L/hour and a case of post-surgery total parathyroidectomy with $[K]_{rise}$ 0.08 mmol/L/hour, the formula 19.2 should be used to ensure good predictability and thus survival:

$$[K]_t = [K]_0 + [K]_{rise} + ([K]_{RRT\&IVD} - [K]_0 - [K]_{rise}) \text{ x}[1 - e^{-(\frac{(SFR + EUF')}{f_K \text{ x TBW} + \text{Net Fluid Change Rate}})}]$$

(Formula 19.2)

The above formula is to be repeated hourly substituting $[K]_0$ of next hour with $[K]_t$ of last hour.

Alternatively, one can apply for easier single approach:

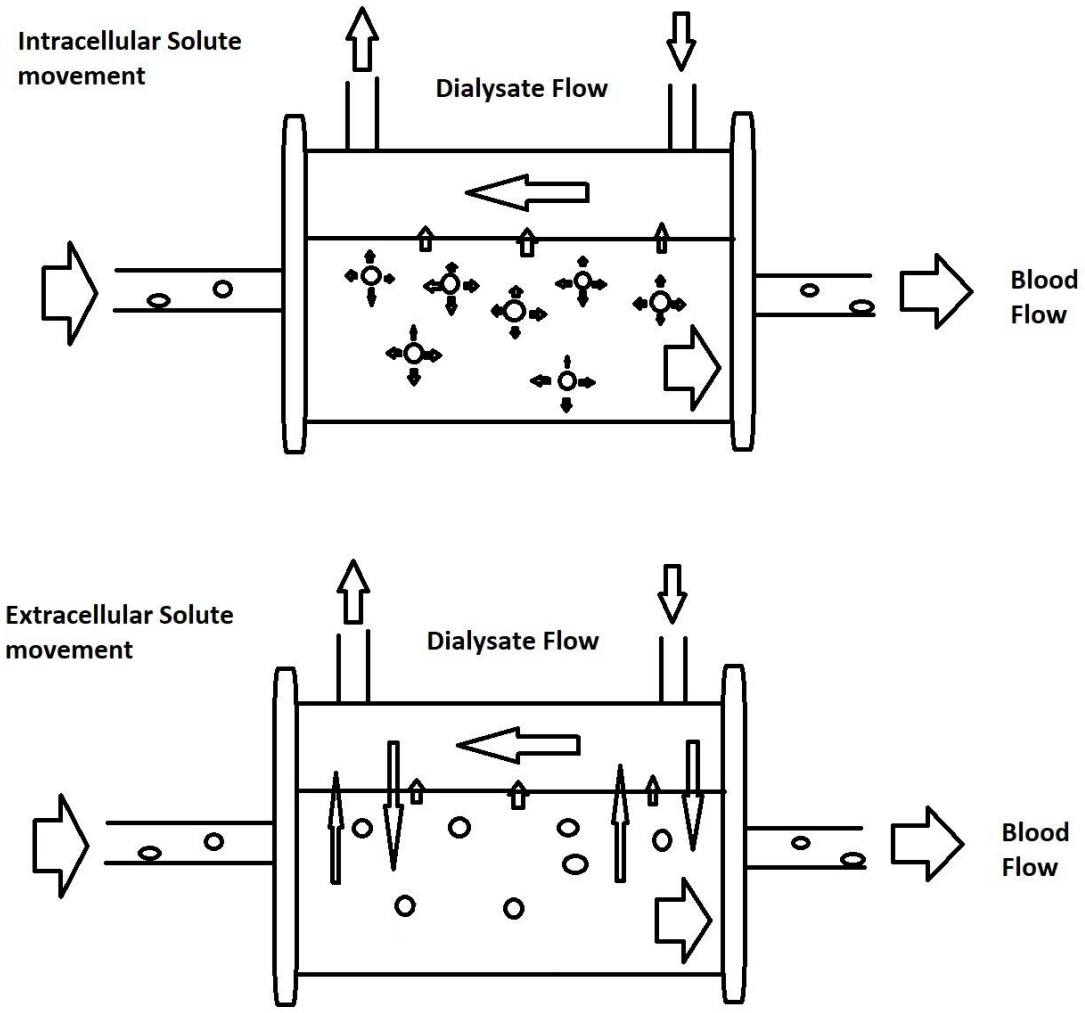
$$[K]_t = [K]_0 + [K]_{rise} \text{ x } t + ([K]_{RRT\&IVD} - [K]_0 - [K]_{rise} \text{ x } t) \text{ x}[1 - e^{-(\frac{(SFR + EUF') \text{ x } t}{f_K \text{ x TBW} + \text{Net Fluid Change Rate x } t})}]$$

(Formula 19.3)

However, formula 19.3 might underestimates the intrinsic rise of potassium level, because this formula assumes the intrinsic rise of potassium level occurring all at the beginning of dialysis, but obviously it occurs every hour throughout dialysis; thus, formula 19.2 is found to be more accurate especially in hyperkalaemia related to on-going lysis.

A brief explanation for solute movement during haemodialysis based on the finding of this study is documented in figure 5. And the mathematical model was incorporated to a software as shown in website of figure 6.

Figure 5: Diagram of solute movement during haemodialysis



During counter current haemodialysis flow, intracellular potassium ion and urea are slower in diffusion to extracellular fluid compartment, and subsequently crossing over dialysis membrane, and thus, its solute calculation mimic the mere dilution of blood water flow rate by dialysate; while extracellular electrolyte such as sodium ion is fast in diffusion movement, and thus it could be assumed that all plasma flow is changed to sodium concentration of dialysate solution, limited by dialysate flow rate.

Figure 6: Mathematical software for HD, CRRT or SLEDD-f of subjects with dysnatraemia and/or dyskalaemia

A spreadsheet software was created freely provided to all clinicians with open access as a non-profit charity project, based on formulae presented in this article, in which clinicians could download the 1empty…xlsx file. Clinicians could just amend the Na and K dialysate value of the software, changing to the value that is available in respective local setting.

Concurrent IV D5% with calculated flow could be given for subjects with hyponatraemia going through acute dialysis, while IV NaCl3% likewise could be given for subjects with hypernatraemia going through acute dialysis, to minimize the [Na] changes, while achieving target of potassium or other uraemic related toxin removal. Additional features include the calculation of concurrent flow needed with dextrose or HCO3 or lactate containing solution, to overcome the issues of shortage of glucose, HCO3 or lactate in dialysate.

DISCUSSION

Patients with deranged sodium levels are at risk of complication with drastic correction: Patients with hyponatraemia may develop osmotic demyelination syndrome (ODS) when conventional HD is performed [9,10]. Slower rate of correction of [Na+] has been proposed to minimize this complication [11,12], in line with the recommendation by the European panel [12], the American panel [13] and other recommendations [14,15,16].

There was a great need for mathematical model for counter current flow dialysis clearance and solute transport calculation. Until now, there was not yet any model available for such purpose. The investigators in this study sought to create a mathematical to predict Na, K and urea with counter current flow dialysis.

As an advancement from model presented by past literature [3] with only calculation on continuous veno-venous haemofiltration, this current mathematical model has extended into the territory of continuous haemodiafiltration as well as haemodialysis, and described about calculation of [K] besides [Na] and [urea], and also their different correction factors from total body water, related to varying intra and extracellular distribution. Yessayan et al has published a very constructive method to dialyze these patients with continuous haemofiltration [11]. Current paper has utilized both haemofiltration as well as haemodialysis as dialysis modality. Furthermore, this study has shown that haemodialysis changes electrolyte concentration not in the same principle as haemofiltration because it is of counter current flow; and intracellular and extracellular distribution of solute do play significant role changing the final result of post-dialysis value as described in formulae 1, 3, 5, 9 to 11. The reason was explained in first paragraph of method section.

In the other word, there is a continuum for calculation of efficacy of dialysis clearance and solute transport from need of being multiplied by BWFR/(BWFR+Qd) for intracellular compound such as potassium and urea, to another calculation with PFR limited by Qd for

extracellular predominant electrolyte such as sodium, in order to get to the closest approximation for the achievement of post-dialysis level.

Note: BWFR/(BWFR+Qd) is abbreviation for blood water flow rate / (blood water flow rate + dialysate flow rate; PFR, plasma flow rate.

Reasonable reliability of the expected Na, K, and urea were shown with eventual serum measurement.

In advance clinical setting, dialysate of varying sodium content could be easily available, either prepared on-line or pre-mixed with varying outcome on HD patients [17]. Anyway, in majority of the countries worldwide, because of limited resources, most HD machines were only equipped to provide range of sodium dialysate within 10 mmol/L from baseline of 140 mmol/L. Thus, this mathematical model serves to be a platform for invention of future dialysis model to handle patients with extreme sodium derangement, with new idea of concurrent intravenous drip of calculated electrolyte fluid.

Recently Markus Pirklbauer has performed a good review on dialysis for patients with hyponatraemia and hyperkalaemia [18]. Due to the limitation in lowest on-line constitution of dialysate sodium available, lower Qb and low dialysate flow rate are advocated for hyponatraemia patients going for HD.

However, in patients with concurrent hyponatraemia and hyperkalaemia, removal of potassium would be inefficient with low Qb and low dialysate flow rate. This mathematical model provided a frame work that allowing high Qb, high dialysate flow rate and concurrent dextrose or other calculated electrolyte infusion to remove potassium efficiently. The outcome of this approach would be presented in future paper.

In conclusion, this model serves as a potential tool for future prescription of HD, SLEDD-f and CRRT for hypo or hypernatraemia patients and/or hyperkalaemia. Model proposes different distribution of extra and intracellular electrolyte for total body water, and also calculation of dialysis clearance with Qd limit by plasma flow rate for extracellular electrolyte, and in contrast, the need of Qd dilution by factor of (BWFR / (BWFR + Qd)) for intracellular electrolyte, for calculation of achievement of serum electrolyte with time, Low error in absolute number in difference between predicted and actual electrolyte were shown with the final model, in comparison to traditional model without correction by fuzzy factor and dilution with BWFR/(BWFR + Qd) for dialysis clearance and solute transport. Limited by margin of current paper, the outcome of this approach would be presented in future paper.

Finally, this mathematical model substantiates that, because of sodium, potassium, and urea distributed varying intracellular and extracellular, therefore different fuzzy factors should be applied as correction for TBW; and there are also different calculation methods for dialysis clearance for intracellular and extracellular significant electrolytes, going through dialysis filter environment with counter current flow between blood and dialysate.

Of course, models of artificial kidney filters were trying to mimic the kidneys that God has created, but even the Creator behind this practical science was definitely not the author, but God himself, “For since the creation of the world God’s invisible qualities—his eternal power and divine nature—have been clearly seen, being understood from what has been made, so that people are without excuse.” (Romans 1:20)

Limitation

This model sought to get towards closest approximation with the actual level. Cohort with larger sample size with varying extreme clinical parameters might be needed in order to verify its reliability in diversified clinical scenarios. Theoretically Na, K and urea being small in molecular weight should be easily transported across different type of membranes with similar rate, and thus different type of dialysis filter should not affect the model prediction, as partially substantiated by current study; yet it would be ideal to verify the result with other type of filters in future study.

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Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A: Calculation of body water in subjects

Fluid Loss = Urine output + Gastrointestinal loss + Fluid Removal Rate of RRT + Other loss

Net fluid change Rate (L/hr) = (IV Drip + Nasogastric gain – Fluid Loss)/1000

Total Body Water (Litre), TBW is derived with:

First option of TBW: Watson equation [7]: If height is not available, clinicians estimate the height with chart modified from cross sectional study of local population [8].

Second option of TBW:

TBW (L) = body weight (kg) x fractional ratio

Frational ratio of TBW for adult: male is 0.6 and female is 0.5, while in elderly: male is 0.5 and female is 0.45, and in children: all 0.6.

Note on dehydration adjustment:

As Na is considered a predominantly extracellular electrolyte and thus its changes are greatly subjected to dehydration, and Na change is drastically accelerated by intravascular depletion,

fuzzy factor of Na is further corrected with percentage of intravascular depletion related to dehydration in patients with dehydration or acute blood loss, with below formulae:

For patient with hypernatraemia, Percentage of dehydration could be estimated with:

Dehydration (%) = ([Na] – 140) / 140 x 100%

Intravascular compartment depletion = (Dehydration portion)^(1/3)

in which dehydration portion = Dehydration(%) / 100%

For patient with acute blood loss, Percentage of intravascular compartment depletion could be estimated with:

Intravascular compartment depletion = (Baseline HCT – Current HCT) / 100%

f_{Na}' = f_{Na} x (1 – Intravascular compartment depletion)

Because of significant intracellular concentration, potassium and urea are not affected by such rules.

Nevertheless, the clinicians are free to decide the appropriate dehydration status and intravascular compartment depletion based on their clinical assessment.

Appendix B: Formulae to derive fuzzy factors

In order to determine fuzzy factor, from formula 18 and 19, we are getting:

$$[Na]_t - [Na]_0 = ([Na]_{RRT\&IVD} - [Na]_0)\ x[1 - e^{-(\frac{(SFR + EUF')\ x\ t}{f_{Na}\ x\ TBW + Net\ Fluid\ Change\ Rate\ x\ t})}]$$

$$f_{Na} = \frac{-\frac{(SFR + EUF')\ x\ t}{\ln(1 - \frac{[Na]_t - [Na]_0}{[Na]_{RRT\&IVD} - [Na]_0})} - Net\ Fluid\ Change\ Rate\ x\ t}{TBW}$$

(Formula 18.1)

$$[K]_t = [K]_0 + ([K]_{RRT\&IVD} - [K]_0)\ x[1 - e^{-(\frac{(SFR + EUF')\ x\ t}{f_K\ x\ TBW + Net\ Fluid\ Change\ Rate\ x\ t})}]$$

$$f_K = \frac{-\frac{(SFR + EUF')\ x\ t}{\ln(1 - \frac{[K]_t - [K]_0}{[K]_{RRT\&IVD} - [K]_0})} - Net\ Fluid\ Change\ Rate\ x\ t}{TBW}]$$

(Formula 19.1)

Appendix C Formulae to determine regime modification needed to achieved desirable [Na]

In order to calculate regime modification needed to achieve desired serum [Na], there are options as below:

1. For HD in any patient with dysnatraemia, to aim for Desired serum [Na], to determine the flow rate of IVD with the M fluid with $[Na]_M$ sodium concentration, the equation to determine the flow rate of M fluid is as below:

Flow rate of M = Current SFR x ($[Na]_0$– Desired serum [Na]) /(Desired serum [Na] – $[Na]_M$)

The M fluid that is used to modify patient serum [Na] is either D5% or half saline (Na 77 mmol/L) or other fluid solution for hyponatraemia patients, or NaCL 3% (510 mmol/L) for hypernatraemia patients.

2. For CRRT in any patient with dysnatraemia, to aim for Desired serum [Na], to determine the flow rate of additional CRRT dialysate M fluid with $[Na]_M$ sodium concentration, the equation to determine the flow rate of M fluid is as below:

Flow rate of M = Current SFR x ($[Na]_0$– Desired serum [Na]) /(Desired serum [Na] – $[Na]_M$) x 100 / (1 – recirculation rate)

3. For CRRT in any patient with dysnatraemia, the amount of additional $[Na]_M$ to be diluted into 1 bag of CRRT, in order to achieve Desired serum [Na], is calculated with this formulae:

Ideal $[Na]_{RRT}$= (Current $[Na]_{RRT\&IVD}$ x Current SFR) / SRRT'

Amount of additional $[Na]_M$ to be diluted into 1 bag of CRRT

= CRRT volume x (Ideal $[Na]_{RRT}$ – Current $[Na]_{CRRT}$) / ($[Na]_M$ – Ideal $[Na]_{RRT}$)

4. For HD in patients with hyponatraemia, in aim for isonatraemia, the equation to determine the flow rate of IVD D5% is as below:

Additional IVD D5% = Current SFR x (Current $[Na]_{RRT\&IVD}$ – $[Na]_0$)/$[Na]_0$

And, to aim for a Desired Rise of serum [Na](usually within 0 to 6 mmol/L), the equation to determine the flow rate of IVD D5% is as below:

Ideal concentration of $[Na]_{RRT\&IVD}$

= Desired Rise of serum [Na] /(1 – $e^{-((SFR+EUF')x\ t\ /\ (fNa\ x\ TBW\ +\ Net\ Fluid\ ChangeRate\ x\ t))}$) + current serum [Na]

Additional IVD D5% = Current Electrolyte delivery /Ideal concentration of [Na]RRT&IVD – Current SFR

Current formulae were derived as described in methods above (3), with help of software to speedily derive modification needed.

Appendix D: Logarithm calculation for prediction of serum [urea]

As similar principle as formula 18,

Urea prediction without considering urea regeneration rate, i.e., the lowest achievable urea level:

$$[Urea]_t = [Urea]_0 + (0 - [Urea]_0)\ x[1 - e^{-(\frac{(SFR + EUF')\ x\ t}{f_{urea}\ x\ TBW + Net\ Fluid\ Change\ Rate\ x\ t})}]$$

in which f_{urea} represents fuzzy factor for urea.

$$[Urea]_t = [Urea]_0\ x\ e^{-(\frac{(SFR + EUF')\ x\ t}{f_{urea}\ x\ TBW + Net\ Fluid\ Change\ Rate\ x\ t})} \qquad \text{(Formula 22)}$$

However our body is constantly producing urea, thus:

$$[Urea]_t = ([Urea]_0 + UGR\ x\ t)\ x\ e^{-(\frac{(SFR + EUF')\ x\ t}{f_{urea}\ x\ TBW + Net\ Fluid\ Change\ Rate\ x\ t})} \qquad \text{(Formula 23)}$$

Urea regeneration rate (UGR) is increment of urea over time in mmol/L/hour.

Note: Urea regeneration rate is estimated based on the increment of urea level just before dialysis, and in most cases it is not known, so clinicians used the average urea regeneration rate of 41 ESRD patients on regular haemodialysis, to estimate urea regeneration rate of acute dialysis patients with below formulae.

Optimal urine output of a subject = 1.5 ml/kg/hour

Urea regeneration rate of patient = [(optimal urine output - current urine output) / optimal urine output]

x average urea regeneration rate of end stage renal failure patients in local population.

Note:

1. If current weight of patient is above normal (or usual) weight because of fluid overload, then all fuzzy factors need to be adjusted by ratio of current weight over normal weight by power of 4, due to double compartment fluid calculation:

$f_{Na}' = f_{Na}$ x (current weight / normal weight)^4

$f_K' = f_K \times (\text{current weight} / \text{normal weight})^4$

$f_{urea}' = f_{urea} \times (\text{current weight} / \text{normal weight})^4$

Take note that this normal weight is not dry weight of patient, but the usual weight of patient in which patient is in well stable equilibrated electrolyte state.

2, In order to determine f_{urea}, from formula 23, we are getting:

$$[Urea]_t = ([Urea]_0 + UGR \times t) \times e^{-\left(\frac{(SFR + EUF') \times t}{f_{urea} \times TBW + \text{Net Fluid Change Rate} \times t}\right)}$$

$$f_{Urea} = \frac{-\frac{(SFR + EUF') \times t}{\ln\left(\frac{[Urea]_t}{[Urea]_0 + UGR \times t}\right)} - \text{Net Fluid Change Rate} \times t}{TBW}$$

(Formula 23.1)

Appendix E: Laboratory tests

Serum sodium and potassium were routinely tested with indirect ion-selective electrode (ISE) method, while for Covid-19 and those in patients under investigation for Covid-19, direct ISE method are employed.

Urea was measured with Enzymatic Urease: The ammonia and α-oxoglutarate are converted to glutamate in a reaction catalyzed by L-glutamate dehydrogenase (GLDH).

Creatinine was measured with kinetic Jaffe test, using picrate acid into alkaline solution, 20-80 seconds and measured with spectrophotometry.

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