Sugar or salt: the use of 5% dextrose in the adult, non-diabetic haemodialysis population

Glenda Rayment, Susana San Miguel & Josephine Chow

Abstract
Background: There is a lack of evidence in assisting renal clinicians in determining the optimal strategy for preventing the need for rapid ultrafiltration during haemodialysis (HD).

Aim: This study aimed to compare the effectiveness of 5% dextrose for priming, reinfusion and treatment of intravascular volume depletion symptoms against 0.9% saline in non-diabetic people receiving HD.

Objectives: The primary objective was to reduce interdialytic weight gain, thereby preventing rapid ultrafiltration during HD. The secondary objective was to minimise symptoms of intravascular volume depletion (hypotension, dizziness and cramping) during HD treatments.

Method: The study used 0.9% saline for priming, reinfusion and treatment of intravascular volume depletion symptoms during HD for the first three months. The study then converted to using 5% dextrose for the following six months.

Subjects: A total of 38 adults who had been receiving HD for a minimum of six months with a permanent vascular access were recruited with 30 participants completing the study.

Results: Analysis of the data showed no difference in the interdialytic weight gain from baseline to week 11. However, from week 12 to week 20 interdialytic weight gain was found to be significantly reduced. Cramping during dialysis decreased from baseline and week 12 compared to subsequent weeks; however, this was not statistically significant (p=0.07). The pre-dialysis blood pressure was found to be elevated in participants following conversion.

Conclusion: This study showed that the use of 5% dextrose can reduce interdialytic weight gain and the incidence of cramping during HD which can assist clinicians in optimising fluid removal on HD.

Keywords
Haemodialysis, hypovolaemia, blood volume, interdialytic weight, hypotension, dry weight.

Background
Haemodialysis (HD) is the most common form of renal replacement therapy used in dialysis units around the world. Although HD is effective in removing excess solutes and fluid, it is frequently accompanied by intradialytic complications such as hypotension, muscle cramps, dizziness and light-headedness (Henrich, 2012; Holley, 2012; Nette, Krepel, van den Meiracker, Weimar, & Zietse, 2002). Hypotension occurs in approximately 25 to 55% of HD treatments whilst intradialytic cramping has been reported as occurring in 5 to 20% of HD treatments (Holley, 2012). These complications are generally caused by multiple underlying factors. These factors include an excessive reduction in blood volume due to rapid fluid removal; the need for a high ultrafiltration rate (UFR) due to excessive interdialytic weight gain (IDWG); target weight set too low; intake of food during treatments; ingestion of antihypertensive medications prior to treatment; and poor contractility due to age and/or cardiac disease (Henrich, 2012; Holley, 2012;
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Sherman, Daugirdas, & Ing, 2007). These complications often occur simultaneously. Hypotension is usually accompanied by cramping, light-headedness, and sometimes nausea and vomiting (Sherman et al., 2007). In addition, hypotension causes inadequate tissue perfusion thus predisposing individuals to cardiac and cerebral ischaemia (Robbins, Amato, Hlebovy, King & Salai, 2008). People who are most prone to hypotensive episodes during HD are the elderly and those with a compromised cardiovascular system (Berns, 2012).

An important contributing factor for these complications is hypovolaemia due to the removal of fluid from the intravascular space during the HD treatment and the inadequate refilling from the extravascular compartment (Nette et al., 2002). Other contributing factors include the inadequate constriction of the venous and arterial vascular beds and dysfunction of the autonomic nervous system (Nette et al., 2002; Schroeder, Sallustio, & Ross, 2004). The treatment of hypotension includes placing the patient in the trendelenburg position, the administration of a bolus dose of 0.9% saline and reducing as near to zero as possible the UFR (Daugirdas, Blake, & Ing, 2007). These treatments, however, lead to decreased dialysis efficiency, inadequate fluid removal and consequently increased morbidity and a decreased quality of life (Henrich, 2012; Holley, 2012). Hypotensive episodes can also be treated with the administration of hypertonic fluids such as hypertonic saline, hypertonic glucose, or mannitol. However, these agents must be used with caution due to their potential side effects such as thirst, IDWG and hypertension (Robbins et al., 2008).

Two studies (Nette et al., 2002; Van Der Sande, E.M., Luik, A.J., Kooman, J.P, Verstappen, V., & Leunissen, M.L., 2000) have compared various intravenous solutions such as albumin, hydroxyethyl starch, 3% hypertonic saline, 20% mannitol, 7.5% hypertonic saline, 23% saturated hypertonic saline, 7.5% hypertonic saline with 6% dextran, 5% dextrose, 20% dextrose, and 0.9% saline to treat hypovolaemia. The studies examined the effects of these various intravenous solutions on relative blood volume (RBV), blood pressure (BP) and the relief of symptoms of volume depletion in people receiving HD treatment. Both of these studies confirmed that the use of hypertonic solutions increased blood volume (thus increasing BP) in hypotensive-prone individuals. However, these studies did not examine the effects of these solutions in regard to IDWG.

A study by Nette et al. (2002) compared the specific effects of 20% dextrose, 20% mannitol, 0.9% saline & 5% dextrose on blood volume during HD. The results showed that an increase in RBV was greater after the infusion of 20% dextrose than with other solutions (p<0.05). A major limitation of this study was the sample size. Only six clinically stable participants were included in the study and the study duration was six consecutive weeks. Again, this study did not include the effects of the solutions in regards to IDWG.

Normal saline (0.9%) has traditionally been used as the priming fluid for extracorporeal circuits, to relieve symptoms of volume depletion (cramps, hypotension, dizziness) and for reinfusion at the end of HD (Robbins, et al., 2008). This paper reports a study that examined the use of 5% dextrose, instead of 0.9% saline, in the priming and reinfusion of the extracorporeal circuit and to relieve symptoms of volume depletion, thus reducing IDWG in non-diabetic people receiving HD treatment. The study protocol has been previously published (see San Miguel, Rayment, & Chow, 2011).

Hypothesis
The use of 5% dextrose instead of 0.9% saline for priming the extracorporeal circuit in HD will reduce the IDWG, thus reducing the need for high UFR and preventing subsequent episodes of intravascular depletion during HD.

Aim
To compare the effectiveness of using 5% dextrose for priming, reinfusion of the extracorporeal circuit and treatment of intravascular volume depletion symptoms against 0.9% saline in non-diabetic people receiving HD treatment.

Objectives
- To minimise/reduce symptoms of intravascular volume depletion during HD treatments.
- To minimise/reduce IDWG, thereby preventing rapid ultrafiltration during HD.

Methodology
This was a nine-month, prospective, self-controlled, interventional study of 38 participants, examining the use of 5% dextrose for priming, reinfusion of the extracorporeal circuit and for the treatment of intravascular volume depletion symptoms and in reducing the incidence of hypotension and cramps in people receiving HD treatment. A randomised controlled trial was not considered for the study design as there would not be sufficient potential eligible participants due to the rigorous exclusion criteria. Ethics approval was obtained prior to commencement of the study.

Study setting and sample
Participants were recruited from five HD units located within one Local Health District in New South Wales. A convenience sample size of 38 participants was eligible for the study and a power calculation was not attended. This sample size was based on the number of people who met the selection criteria and who would consent to participate in the study.

Inclusion criteria
Participants were included in the study and met the following criteria:
- Age 18 years or above at entry to the study.
- Ability to provide informed consent.
- Receiving maintenance HD for at least six months.
- Permanent HD vascular access (that is, native arteriovenous fistula or graft).
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Exclusion criteria
Participants were excluded if they had:

- Vascular catheters, either tunnelled or non-tunnelled.
- Acute HD (that is, patients receiving dialysis in intensive care unit and coronary care unit).
- Diabetes mellitus (insulin-dependent and non-insulin dependent).
- Receiving haemodiafiltration.

Study design
Participants recruited to the study were to continue to receive their usual treatment (that is, 0.9% saline for priming, reinfusion of the extracorporeal circuit and treatment of the intravascular volume depletion symptoms during HD treatments) for the first three months. There was no washout period prior to the change to 5% dextrose as these subjects had been using 0.9% saline for their previous dialysis sessions. Following the two-day break from HD, participants were then changed to 5% dextrose for priming, reinfusion of the extracorporeal circuit and treatment of the intravascular volume depletion symptoms during HD treatments for the following six months. Treatment effects were compared for the entire study periods. Data collection included:

1. IDWG — the difference in weight between the previous and the next HD treatment (midweek treatment comparison).
2. Vital signs (these included BP, pulse and temperature) at the commencement and at the end of the HD treatment.
3. Symptoms of intravascular volume depletion — which included signs of dizziness, cramps, hypotension (that is, blood pressure of less than 90/60).
4. RBV — monitored via the Fresenius BVM™ module once during the midweek dialysis session, noting the minimum RBV percentage (mRBV%) at the end of the HD treatment.
5. Blood glucose levels using a glucometer at a random time during the midweek dialysis session. Blood was aseptically collected from the arterial line.
6. Monthly full blood count and biochemistry (including random glucose level) collected during the study.

Adverse events were tracked, recorded and monitored. All hospital care was recorded routinely on the case report forms at study visits.

Statistical analyses
Data was compared at baseline and week 12 (conversion to 5% dextrose) to subsequent visits at weeks 13, 14, 15, 16, 20, 24, 28, 32 and 36. Continuous data was analysed using paired t-tests and nominal data was analysed using McNemar’s test. SPSS Version 14 software (Inc, 2005) was used for data analysis with the statistical significance value set at p<0.05.

Safety evaluations
Participant safety was monitored through the evaluation and monitoring of any changes to IDWG, frequency of hypotensive episodes, pre- and post-dialysis BP readings, mRBV%, and blood glucose level. Any changes detected were discussed with the participant’s medical physician and the participant withdrawn from the study at the direction of the medical physician if necessary.

The following safety evaluations were performed during the study to measure, monitor and evaluate the use of 5% dextrose for priming, reinfusion of the extracorporeal circuit and treatment of intravascular volume depletion symptoms such as hypotension, cramps and dizziness during HD treatments: vital signs, changes to patients’ IDWG, mRBV% at end of dialysis, and blood glucose level. All adverse events occurring during the study period were reported and investigated. All persisting adverse events at the study completion were followed until a clinically stable resolution was achieved.

Results
Thirty-eight participants were recruited, with 30 participants completing the study. Data was collected and analysed from the number of participants remaining in the study at the study visit. No data was collected once a participant had withdrawn from the study. Five participants withdrew from the study, two participants were deceased and one participant changed to haemodiafiltration shortly after consent. The reasons for withdrawal included: patient choice, transfer to another non-participating hospital, adverse event unrelated to study intervention, hospitalisation unrelated to study intervention and protocol violation (participant transferred during dextrose phase and dextrose was not continued for priming and reinfusion). The study intervention was unrelated to the two participants who were deceased, with their deaths occurring during the saline phase of the study.

Demographics
The mean age of the study participants was 66.47 (SD 15.32) years who had been receiving HD for a mean duration of 5.99 (SD 5.55) years. Gender was evenly distributed in the group with 50% being male. The largest racial group was Caucasian (n=22) followed by Vietnamese (n=7), Chinese and Samoan (n=5), Arab and Indian (n=2). The morbidities of the participants are listed in Table 1. The participants were dialysed using Model 4008SM™ and 5008HTM™ dialysis machines from Fresenius Medical Care, with the majority of participants (97%) dialysing three sessions per week.

Ideal body weight (IBW) and IDWG
IBW was documented at each study visit. The mean IBW at baseline was 65.59 (SD 17.29) kg and at week 36 was 64.43 (SD 15.1) kg. There were no statistically significant differences from the baseline and week 12 visit to any subsequent study visits during the follow-up period.
The IDWG was also documented at each study visit. This was calculated by measuring weight gain from the previous dialysis session’s post-dialysis weight to the pre-dialysis weight for the next dialysis session. Midweek dialysis sessions were compared. Paired t-testing found there was no difference in the IDWG from the baseline visit to subsequent visits. However, when comparing week 12 (conversion visit) with subsequent study visits, there was a significant decrease in IDWG at week 13 (mean IDWG 1.8 (SD 1.3) kg, p<0.001), week 14 (mean IDWG 1.6 (SD 1.1) kg, p=0.001), week 15 (mean IDWG 1.7 (SD 0.9) kg, p=0.024) and week 16 (mean IDWG 1.7 (SD 1.0) kg, p=0.005) as shown in Graph 1. From week 20 there was no significant difference between the saline and dextrose phase with the IDWG.

BP and pulse
BP was measured and documented in sitting and standing positions both pre- and post-dialysis. The sphygmomanometer used was part of the Fresenius Model 4008™ and 5008H™ dialysis machines. A statistically significantly increase in BP was noted in the pre-dialysis sitting systolic readings from baseline measurements (mean systolic BP 137 (SD 22) mmHg) compared to week 28 (mean systolic BP 149 (SD 21) mmHg, p=0.017), week 32 (mean systolic BP 148 (SD 22) mmHg, p=0.024) and week 36 (mean systolic BP 147 (SD 22) mmHg, p=0.003). A statistically significantly increase in BP was also noted in pre-dialysis sitting diastolic readings from baseline measurements (mean diastolic BP 60 (SD 12) mmHg) compared to week 28 (mean diastolic BP 67 (SD 13) mmHg, p=0.009), week 32 (mean diastolic 69 (SD 15) mmHg, p=0.024) and week 36 (mean diastolic BP 66 (SD 15) mmHg, p=0.003) as shown in Graph 2. There were no differences from baseline and week 12 visit to subsequent visits for pre-dialysis standing, post-dialysis sitting and standing BP. The pulse rate was also measured and documented pre- and post-dialysis. There were no significant differences with pre- or post-dialysis pulse rates during the study visits.

Intradialytic complications
The number of participants experiencing hypotensive episodes, dizziness or cramping during the 36-week follow-up period was collected at each study visit following review of the dialysis records. If dialysis intradialytic complications were reported, this was documented as a ‘yes’ or ‘no’ response in the case report form.

### Table 1: The comorbidities of the study group

<table>
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<th>Comorbidities</th>
<th>Cerebral vascular disease</th>
<th>Peripheral vascular disease</th>
<th>Chronic lung</th>
<th>Coronary artery disease</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>22.20%</td>
<td>13.90%</td>
<td>11.10%</td>
<td>30.60%</td>
</tr>
<tr>
<td>No</td>
<td>77.80%</td>
<td>86.10%</td>
<td>88.90%</td>
<td>69.40%</td>
</tr>
</tbody>
</table>

Graph 1: Comparison of IWG

*Graph 1: Comparison of IWG

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As the time between study visits was not consistent, the intradialytic complications were grouped and a McNemar’s test was calculated at weeks 12, 24 and 36. The number of participants experiencing hypotensive episodes (week 12 n=5, week 24 n=8, week 36 n=8) and dizziness (week 12 n=5, week 24 n=9, week 36 n=9) increased during the dextrose phase of study. The number of study participants was small and there was not a statistically significant difference between the groups. The number of participants experiencing cramping decreased during the dextrose phase; however, this was not statistically significant. At week 12, 13 participants experienced cramping when 0.9% saline was used for priming and reinfusion compared with 10 participants at week 24 and six participants at week 36 (p=0.07) during the dextrose phase as shown in Graph 3.

**Blood sugar levels**

A random blood sugar level was obtained at each study visit. The blood was collected aseptically from the arterial port of the dialysis line and was analysed using the Optium Xceed™ glucometer (Abbott Diabetes Care) as per hospital policy. The timing was random. Analysis of the blood sugar levels for the total participants found there were no significant differences between baseline and subsequent study visits. At baseline the mean was 88.49 (SD 6.26) % and at week 36 the mean was 87.21 (SD 6.10) %.

**Haematology and biochemistry markers**

The routine monthly blood results were used for the duration of the study to examine differences between the saline and dextrose phase. The parameters examined include haemoglobin, sodium, potassium, albumin, protein and glucose. There were no differences between baseline and week 12 visit with subsequent study visits with serum haemoglobin, potassium and albumin levels. The serum sodium level at week 36 (mean 137.51 (SD 3.94) mmol/L) was significantly increased (p=0.024) from baseline (mean 136.75 (SD 3.72) mmol/L) as shown in Graph 4. The serum glucose level was found to be significantly lower at week 24 (mean 4.88 (SD 1.54) mmol/L) compared to baseline (mean 5.66 (SD 1.34) mmol/L, p=0.009) as shown in Graph 5. The serum protein levels were also found to be significantly decreased compared to baseline (mean protein level 73 (SD 9) g/L) at week 24 (mean protein level 69 (SD 5) g/L, p=0.017), week 28 (mean protein level 69 (SD 5) g/L, p=0.002), week 32 (mean protein level 70 (SD 5) g/L, p=0.018) and week 36 (mean protein level 69 (SD 7) g/L, p=0.001).

**Adverse events**

Adverse events were collected during the follow-up period. A total of 64 adverse events occurred during the study, 18 during the saline phase and 46 during the dextrose phase. Twenty-eight of these adverse events were attributed to dialysis therapy. There were nine events during the saline phase and 19 during dextrose phase. These events are listed in Table 2.
Study limitation
This study only included non-diabetic adult HD population with permanent vascular access. Considering that the leading cause of end-stage renal disease is diabetes mellitus (McDonald, Excell, & Dent, 2009), this study excluded the majority of the HD population. In addition, this study excluded patients with vascular catheters (either tunnelled or non-tunnelled) to reduce the variable in the patients’ hypovolaemic episodes. Vascular catheters have been known to increase the chance of septic episodes amongst these patients (VAS, 2002), thus leading to vasodilatation and hypotensive episodes that could or could not be related to high UFR. Unfortunately, the dialysis units involved had a high incidence of vascular catheters use for patients who are unsuitable to have an arteriovenous fistula (AVF) or arteriovenous graft (AVG) created or patients who had had multiple access failure. This accounted for approximately 20% of the current HD population within the Local Health District. The dichotomous data collection for intradialytic complications was also a limitation of the study. Each intradialytic complication should have been accounted for rather than one ‘yes’ or ‘no’ response. Another limitation of the study is the small sample size and the non-randomisation of the intervention.

Discussion
The study examined whether the use of 5% dextrose would minimise and/or reduce IDWG. This study is novel in that it is the only study so far that has examined the effect of both isotonic solutions (0.9% saline and 5% dextrose) on IDWG. Other studies (Nette et al., 2002; Van Der Sande et al., 2000) have compared the effect of isotonic and hypertonic solutions on blood volume and BPs. There was a short positive response of eight weeks (where IDWG decreased significantly) following conversion to 5% dextrose with no change in BP during this period. IDWG has increased from week 20 until the end of the study, although not statistically significant. This correlates with the significant increase in pre-dialysis sitting BP from week 28 to week 36. Isotonic saline (0.9%) or hypertonic saline (3%) are widely used in clinical practice to treat symptoms of hypovolaemia. The use of hypertonic solution such as 3% saline has the detrimental effect of increased thirst, consequently leading to increased IDWG and elevated BP (Nette et al., 2004).
necessitating higher UFR. Both 5% dextrose and 0.9% saline used in this study are isotonic solutions so the increase in IDWG towards the end of the study is unexplainable.

The study also examined whether the use of 5% dextrose would reduce symptoms of intravascular volume depletion during HD. Participants were monitored during the study for hypotensive episodes (BP <90/60 mmHg), dizziness and cramping. Results showed episodes of hypotension and dizziness increased following conversion to 5% dextrose. Several factors can contribute to hypotension such as (but not limited to) ingestion of antihypertensive medication before dialysis, inaccurate target weight, high UFR, autonomic neuropathy, eating during or just before dialysis, diminished cardiac reserve and tissue hypoxaemia causing the release of potent vasodilator adenosine (Henrich, 2012; Robbins, et al., 2008) However, cramping decreased following conversion which was statistically significant (p=0.07). This correlates to decreased IDWG on conversion to 5% dextrose. Most literature suggests that avoidance of large IDWG can avoid rapid reduction in plasma osmolality that mainly occurs due to high UFR (Holley, 2012; Henrich, 2012).

There was a staggered approach to the study commencement at the dialysis units. When the first unit reached the conversion visit at week 12 and commenced using 5% dextrose, it was observed that the blood sugar level from the random glucometer readings had increased in eight participants (Graph 5). The observed increase in blood sugar levels was reviewed by the nephrologists who decided that there were too many variables such as the glucose in the dialysate, food intake and timing of glucometer reading to consider the higher readings to be related to the study intervention. Literature suggests that uremic patients, either diabetic or non-diabetic, have decreased insulin secretion and diminished tissue response to insulin (Tzamaloukas, Leehey & Friedman, 2007). One nephrologist suggested an endocrinology review for some of the participants who were not diabetic but may have a degree of glucose intolerance which warranted further investigation. At the completion of the study, the blood glucose levels from the glucometer readings and monthly blood tests were analysed and found that the glucose level from baseline visit and week 24 visit was significantly lower than baseline (p=0.009) indicating that the use of 5% dextrose did not increase the blood sugar levels of the study participants.

A concern expressed prior to the study by one nephrologist was whether there would be a decrease in the blood sodium level following conversion to 5% dextrose. Blood sodium levels were collected during the study visits using the regular monthly blood collection. Analysis of the sodium level was found to be unchanged during the study until week 36 when the mean was significantly higher (137.5 (SD 3.9) mmol/L) when compared to baseline (136.7 (SD 3.7 mmol/L), although still within normal range (Longmore, Wilkinson & Torok, 2002).

The number of dialysis-related adverse events were evenly distributed as there were nine events for the 12-week 0.9% saline phase and 19 events for the 24-week 5% dextrose phase. Of concern is the number of severe hypotensive episodes: there was one in the saline phase and four in the dextrose phase. However, there was no clear explanation for these findings. As previously discussed, causes of hypotension during dialysis are multifactorial (Henric, 2012; Robbins, et al., 2008) and as such, clinicians have to accurately assess individuals before and after dialysis to prevent reoccurrence of hypotensive episodes.

Conclusion

HD has limitations and disadvantages due to complications that could occur during treatment. People receiving HD can suffer symptoms of volume depletion such as hypotension, muscle cramps, dizziness, nausea and vomiting during their treatment. Hypotension is the most common intradialytic complication
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Graph 5: Comparison of serum glucose level (mmol/L)

*\( p=0.009 \) Baseline versus week 24

Graph 6: Comparison of blood glucose level

in dialysis. The cause of this is multi-factorial, such as high UFR, and/or inaccurate assessment of dry weight. Preventing or minimising these complications is one of the goals of HD. This study showed that the use of 5% dextrose can reduce IDWG and the incidence of cramping during HD following conversion from 0.9% saline even though only for a brief period of time. This is only a small study but has provided evidence to assist renal clinicians in determining the optimal strategy for preventing rapid ultrafiltration and the subsequent complications during HD. Further study should be conducted on a bigger scale that includes people with those with diabetes and vascular catheters, which would better represent the current HD population.

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