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Full Title

A meta-analysis of sodium profiling techniques and the impact on intradialytic hypotension.

Running Head

Meta-analysis of sodium profiling techniques

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Haemodialysis, intra-dialytic hypotension, meta-analysis, renal hypotension, sodium profiling.

Abstract

Aims

To assess the effectiveness of haemodialysis sodium profiling techniques

Background

Haemodialysis has improved in recent years, however, despite such improvements, intra-dialytic hypotensive episodes still persist which can lead to a reduction in the overall effectiveness of the treatment. Profiling sodium levels during dialysis can improve vascular refilling and therefore may prevent hypotensive events. A number of profiling methods exist and this meta-analysis set out to examine the effectiveness of these methods.

Design

A review and meta-analysis analytical framework was used.

Methods

A search was conducted using Medline, Embase and CINAHL, Scopus and Web of Knowledge between 1946 and 2014 of published English-language peer reviewed randomised control studies. In total 10 articles were retrieved and included in the review. All data was abstracted with a standardised data collection form.

Review Methods

Stata 11.2 (Stata Corp) was used to analyse the data. Actual numbers of hypotensive events were pooled between studies. Analysis of subgroups was performed on sodium profile type. The data were further investigated using meta-regression. Publication bias was also tested.

Results

Stepwise profiling was shown to be statistically significantly effective in reducing intradialytic episodes. Results demonstrated that linear sodium profiling was not effective in reducing hypotensive events during dialysis.

Conclusion

This review has shown that using stepwise profiling is more effective at reducing intra-dialytic symptoms than other profiling methods. There was no evidence that linear profiling method was any more effective than conventional dialysis and in fact the results showed the reverse.

Body of Article

INTRODUCTION

End stage renal failure (ESRF) is the result of deterioration in kidney function [(1)]. Kidney transplantation is the most effective treatment for end stage renal failure [(2)]. However, due to the limited number of organ donors and difficulties with tissue matching, patients with ESRF may require medical management with dialysis for some time.

Dialysis treatment has improved in recent years with machines that allow profiling of ultra filtration and sodium (tailoring dialysis treatment to individual needs) and more choices in dialysate fluid composition for removal of toxins [(3)]. Despite such improvements in care delivery, treatment is not asymptomatic for all patients and symptoms of hypotension are common in up to 20% of dialysis sessions [(4)]. Hypotensive episodes during dialysis can lead to shortening of treatment sessions reducing the effectiveness of the overall treatment. There is evidence to suggest that survival of dialysis patients is related to the delivered dose [(5-9)], and therefore it is essential that effective dialysis treatment is maintained.

Conventional dialysis uses constant sodium levels throughout the dialysis session. Profiling involves altering the sodium level during the course of dialysis treatment. Profiling sodium levels during dialysis can improve vascular refilling and therefore may prevent hypotensive

events during dialysis [10]. A number of profiling methods are used in clinical practice; however the UK Renal Association [11] recommends that the stepwise method be used in preventing symptomatic dialysis.

There have been a number of randomised trials that have tested whether sodium profiling can reduce intradialytic hypotensive episodes; however some of these trials have been small [12, 13] and some have failed to show any statistical significance [14-16]. Issues of selecting participants that are not prone to hypotensive episodes during dialysis also exists. There is some uncertainty if the effect estimates are influenced by the recruitment of only haemodynamically stable patients as included in two studies [12, 17]. It would seem plausible that if these patients do not usually have hypotensive episodes during conventional dialysis then this is unlikely to change during profiled dialysis.

The review

AIM

The aim of this review and meta-analysis was to synthesize the findings of primary research comparing sodium profiling techniques in minimising intradialytic hypotensive episodes. Using a PICOS framework [18] the review components were – Population: patients requiring haemodialysis, Intervention: sodium profiling techniques; Comparison: conventional dialysis; Outcome: number of intra-dialytic hypotensive events; Study design: meta-analysis.

METHODS

Design

A review and meta-analysis analytical framework was used. Summary statistical data were obtained from a set of studies and effect sizes and variance were calculated. Effect sizes were weighted inversely according to their variance.

A search was conducted using Medline, Embase and CINAHL, Scopus and Web of Knowledge (1946 to 2015) using the keywords: dialysis, haemodialysis, hypotension, intradialytic hypotension, sodium profile, stepwise profile, linear profile. These keywords were used in combination using 'OR' and 'AND' to identify all relevant papers. The search was limited to primary peer reviewed published manuscripts in English language. Only studies with a control or referent group were included in the review. There was no restriction based on dialysis prescription, gender, age or ethnicity. All sodium profiling techniques that could be found were included in the review. Publications had to include the number of intra-dialytic hypotensive episodes. There were no date restrictions. Reference lists from published papers were also manually assessed for further relevant papers. Hand searches of specific Journals were not conducted.

After duplicate papers were discarded, a total of 146 papers were assessed for relevance (Figure 1). Screening of articles was performed by reviewing the title and abstract. A copy of the articles that met the inclusion criteria based on the title and abstract screen were obtained for the full review. Full text eligibility was then screened with reasons for exclusion annotated and tracked.

Search outcome

In total ten articles were found and included in the meta-analysis [12-17, 19-22].

Quality Appraisal

The methodological quality of the studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Table 1). The ten papers were subjected to a quality appraisal process to ensure minimum research criteria were met[23]. Sodium profile findings from three papers [13, 19, 22] were considered separately for outcomes as two interventions were tested against the control.

Outcome measurements and sensitivity analysis

Data was collected by one researcher. Outcomes were analysed on an intention-to-treat basis. The primary outcome was number of hypotensive events. Sensitivity analysis assessing the robustness of the results included heterogeneity analysis and subgroups analyses of sodium profile types.

As regards profile type, the most commonly used were linear, stepwise and alternate; therefore the other methods were combined to have four profile types in the analysis. All studies were randomised cross over trials. [17], [22] and [21] satisfied all 12 quality criteria. Two studies satisfied 11 of the 12 quality criteria [13, 19], four studies met 10 of the 12 quality criteria [12, 14, 16, 20] and one study met 9 of the 12 quality criteria [15], as a result, no studies were excluded from the review.

Data Abstraction

All data were abstracted with a standardised data collection form. The following data were collected for each trial: type of randomization, sample size, sequence generation, allocation concealment, blinding, incomplete outcome data, attrition, analysis consideration, free of selective reporting, washout, profile type. Confounding factors, such as washout used in cross over trials and hypotensive prone patients included were also recorded.

Synthesis

Stata 11.2 (Stata Corp) was used to analyse the data using the random effects method and for comparison and sensitivity analysis, the generic inverse variance method [24] . Actual numbers of hypotensive events were pooled between studies and odds ratios have been used for the meta-analysis. Further analyses of subgroups were performed on sodium profile type. Forest plots have been presented to show the extent of the variation in the studies and the I^2

statistic used to test heterogeneity. The data were further investigated using meta-regression. In particular, meta-regression was used to test the hypothesis around the effect of profile types on outcomes. Publication bias was tested using the Egger's test [25] and a funnel plot has also been presented.

RESULTS

Characteristics of the studies

Each paper was analysed for the patient type and dialysis treatment for comparison (Table 2). The mean age of patients ranged from 45 to 71 with the exception of Sadowski [22] whose participants were aged between 16-32 years of age. The majority of papers used a dialysis protocol of 4 hour consecutive dialysis sessions of between 6-12 sessions (thrice weekly) again with the expectation of one paper [22] that had a protocol of 1.5-3 hour dialysis session according to kinetic modelling. One paper [13] did not state the length of each dialysis session or the frequency of dialysis treatments. As regards dialysate, most studies had similar dialysate compositions, only one study [14] did not state the dialysate used.

Afferent and efferent dialysate sodium levels were included in only two studies [12, 17]. Sodium levels were measured using ion selective electrodes, however three studies did not state their method of sodium analysis [14, 19, 20]. Only six studies analysed pre-dialysis sodium levels [12, 13, 15-17, 21].

There is a tendency for thermal energy to accumulate during dialysis and therefore temperature needs to be controlled. Heat removal is generally controlled by dialysate and patient temperatures [26]. Dialysate temperatures have been provided by seven authors [12, 13, 15, 16, 19-21]. As low body temperatures are common it is recommended that dialysate temperatures are less than 36°C to maintain reasonable temperature gradients [27], however

the studies that presented this data, reported dialysate temperatures between 36-37°C, however it can be argued that dialysis treatment itself can provide cooling even with dialysate temperatures of 37°C. Extracorporeal blood flow assists with thermal regulation, however data were only found in seven of the ten studies and flow ranged from 200-400mls/min [12, 13, 16, 17, 19, 20, 22].

Most studies declared that they had excluded patients with co-morbidities with two exceptions [14, 19], however they were all cross over trials with the patients being their own control. Most studies recruited participants that had diabetes [13-16, 19-21], however did not state whether they had accounted for the glucose effect

There was limited information from some studies as regards chemistries and bioimpedance data was limited from most of the studies, those data that were found are presented for comparison (Table 3).

Within study definitions of symptomatic hypotension were similar across studies (Table 4) with some exceptions [14, 19, 21, 22].

The characteristics of the studies included in the meta-analysis can be found in Table 5. As some studies investigated more than one sodium profile type and compared the results to the control, there are 13 datasets that have been included in the meta-analysis.

All the studies included in the meta-analysis were cross over design trials, however all but four studies [16, 20-22] had a washout period between treatment and control. Two studies had only participants that were not prone to hypotensive events [12, 17], seven studies included those who were prone to hypotensive events during dialysis [13-16, 19-21]. One study did not stipulate haemodynamic status in the inclusion criteria [22] and this study had age ranges from

16 to 32 (young adults) who did not have diabetes or cardiovascular disease. The other studies did not make this stipulation in the inclusion criteria.

Meta-analysis

The number of haemodialysis sessions from the control phase of all the studies was 1,847 and from the intervention phase was 1,813, making 3,660 total dialysis sessions from all the studies combined.

The risk difference was calculated for each study and ranged from reducing the risk of having a hypotensive event from 1.25 percentage points to 12 percentage points. Two studies found that the risk of having a hypotensive event on intervention increased and ranged from 1.08 percentage points to 8.6 percentage points.

Odds ratios from the individual studies ranged from 0.15 to 2.57 (Figure 2). Two studies had estimates that suggested increased hypotensive events with sodium profiling [20, 22]. The overall benefit of sodium profiling had a combined odds ratio of 0.71 (95% CI: 0.60 to 0.85) using the inverse variance fixed effects method, and 0.73 (95% CI: 0.56 to 0.95) using the random effects method. There was moderate heterogeneity between the studies (I^2: 47.2%; p=0.030).

Type of profile was sub divided into groups (Figure 3). The 'other' profile group had a pooled odds ratio of 0.48 (95% CI: 0.30 to 0.78), the stepwise group had pooled odds ratio of 0.58 (95% CI: 0.44 to 0.76), the linear group had pooled odds ratio of 1.01 (95% CI: 0.77 to 1.32) and alternate 0.67 (95% CI: 0.25 to 1.74). Performing linear and alternate profiling did not consistently demonstrate reduction of hypotensive events during dialysis and two studies were found to favour control (conventional dialysis) over linear profiling. Overall, using

another type of profile method other than linear was shown to be beneficial, although some studies did cross the line of no effect.

Performing stepwise and other profile type did show overall reduction in hypotensive events compared to standard dialysis; however some studies did cross the line of no effect. The test of interaction based on this grouping was significant (p=0.012).

Heterogeneity between the studies was expected as the studies differed in treatment, design and participants' age ranges. There were in total six different profile types (two were grouped into one category labelled 'other' for ease of analysis). When these studies were grouped into profile type, considerable heterogeneity was found (p=0.012).

Publication bias

Publication bias was tested using the Egger's plot [25] and showed some symmetry (Egger's bias coefficient =0.322; 95% CI: -2.69 to 3.34; p=0.82). The funnel plot (Figure 4) demonstrates the smaller studies are closer to the bottom and further from the central line as expected. The larger studies are closer to the central line. Therefore there was no evidence of overestimation of the intervention effect in the meta-analysis and little evidence of publication bias.

DISCUSSION

Maintaining effective dialysis regimes has been shown to reduce mortality rates [8] and therefore it is important to discover techniques which aid in this treatment. This meta-analysis has demonstrated that some profiling methods reduced intradialytic hypotensive events compared to conventional dialysis. Using stepwise profiling is better at reducing intradialytic symptoms than linear or alternate profiling. There was no evidence that linear profiling method was better than conventional dialysis and in fact the results showed that

conventional dialysis was the better method (p=0.026), with two studies showing increased intradialytic hypotensive events during the linear profile phase.

Donnan coefficient profiling method and the exponential profiling method (the two studies that were grouped into the 'other' category) were also shown to be of benefit; however one of these studies used only haemodynamically stable participants that were not prone to intradialytic hypotensive events and this may have impacted on the results.

This meta-analysis showed considerable heterogeneity of the studies. This though makes it difficult to compare and combine studies and to pool their data to perform a meta-analysis. It may have been beneficial to have concentrated on one sodium profile type.

It has been questioned that sodium profiling could lead to sodium loading [28] which is associated with increased interdialytic weight gain (IDWG), however with most studies sodium plasma levels did not change significantly pre and post dialysis (table 3). It is unclear as to the degree which IDWG can impact on health outcomes [29] however only one study had shown an increase in IDWG using a profiled techniques [13].

The results of this meta-analysis may have implications to clinical practice. Currently it is accepted that profiling sodium levels are of benefit above conventional dialysis in those patients that are prone to intradialytic hypotensive events, however this may not be the case with all sodium profile methods and this needs to be highlighted. An effective method that is supported by the UK Renal Association [11] is stepwise profiling and this should be adopted above linear in clinical practice.

One issue that was not discussed by any of the studies included in this meta-analysis was the patient experience. It may be that hypotensive events are reduced, but if other symptoms are

produced by profiling that may adversely impact on the overall treatment experience, then this needs to be considered when deciding on treatment options.

Limitations

A limitation of this meta-analysis was using cross over design studies as they are inherent with problems of pooling data for meta-analysis [30]. However no studies could be found, using the search criteria outlined earlier, that were not cross over in design. Another limitation was that in some studies two intervention groups were compared to their own control and these were then taken and used as separate studies for this meta-analysis. This could have altered the results due to the carry-over effect, however all studies that did not have a washout period detailed minimising the carry-over effect during their trial. Having repeated measures on one individual can lead to unit of analysis error. This can be overcome by using tests that account for this such as paired analysis or Crossover ANOVA [30] as all but one of the studies used.

CONCLUSION

Dialysis regimes can contribute to episodes of intra-dialytic hypotension which can reduce the effectiveness of the treatment regime and lead to poor health outcomes. To ensure that treatment is manged effectively, sodium profiling techniques need to be assessed to determine if they have a positive impact on patient outcomes. However, there has been little evaluation of sodium profiling techniques to determine their impact on patient outcomes. This review found that there are a number of sodium profiling techniques used in dialysis units but there is variability in the effectiveness of these techniques. The techniques found to be most effective were the stepwise method, the Donnan coefficient and the exponential profiling technique. Recommendations from this review are that stepwise profiling should be adopted in clinical practice.

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Figure Legends

Figure 1. Inclusion and exclusion diagram for articles selected for meta-analysis

Figure 2. Forest plot showing odds ratios of sodium profiling on hypotensive events using inverse variance fixed effects method and random method.

Figure 3. Forest plot showing odds ratios of subgroups of profile types.

Figure 4. Funnel plot with pseudo 95% confidence limits

Study	Design	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Attrition rate	Analysis consideration	Free of selective reporting	Other sources of bias	Quality score
De Paula 2004	Prospective non-randomised cross over trial	No	No	'Participants not aware of modification in dialysate Na+'	No	0%	ITT analysis is followed in those excluded from trial	Yes	Unclear	Good
Meira 2010	Prospective randomised cross over trial	Simple number drawing	Unclear	Unclear	No	0%	Results included all participants	Yes	No	Good
Meira 2007	Prospective cross over trial	Unclear	Unclear	Unclear	Yes	22% Study reports 3 lost but number does not match number analysed	Unclear	Yes	Unclear	Fair
Moret 2006	Prospective randomised cross over trial	No	Unclear	Unclear	No	16% Reasons for missing data unlikely to be related to true outcome	No. Conducts only a per protocol analysis with ≤95% of randomised patients analysed in allocation group	Yes	Unclear	Fair
Zhou 2006	Prospective randomised cross over trial	'performed random allocation'	Unclear	Unclear	Yes- 11 sessions missing as did not meet criterion for interdialytic weight	0%	Unclear	Yes	No	Fair
Straver 2002	Prospective cross over trial	No	No	Unclear	No	0%	Results included all participants	Yes	Unclear	Fair
Hamzi 2012	Prospective cross over trial	No	No	Unclear	Missing data not mentioned	22%	Unclear	Yes	Unclear	Fair
Oliver 2001	Prospective randomised cross over trial	Random number tables	Unclear	Yes- 'both staff and patients were blinded'	Unclear	3%	As per study protocol. ITT analysis not followed	Yes	No	Good
Sadowski 1993	Prospective randomised cross over trial	'Random allocation'	Unclear	'Patients blinded'	Yes	11%	ITT analysis followed	Yes	No	Good
Song 2005	Prospective randomised cross over trial	'Random allocation'	Unclear	Unclear	No	27%	ITT analysis followed	Yes	No	Fair

Table 1. Adapted Cochrane Collaboration's tool for assessing risk of bias

Author	Mean Age	Co-morbidity scores	Dialysis treatment	Pre dialysis weight (kg) (mean. SD)	Adequacy	Dialysate mmols/l	Dialysate temperature
de Paula 2004	46±14	Stable condition	9 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Not stated	Kt/V >1.2	HCO_3- 33 K^+ 2.0 Ca 1.75 Mg 0.5	Not stated
Meira 2010	61.2±15.2	Not stated	12 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Control 73.7±15.9 Stepwise 74.1±16.4 Linear 74.5±16.4	Kt/V >1.2	HCO_3- 33 K^+ 2.5 Ca 3.5 Mg 0.5	36-36.5°C
Meira 2007	59.9±12.6	Not stated	12 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Not stated	Not stated	Not stated	Not stated
Moret 2006	71±11	Included patients with CHF and diabetes who were in a stable condition	11 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Not stated	Kt/V >1.2	HCO_3- 32 K^+ 2.0 Ca 1.5 Mg 0.5	36°C
Zhou 2006	52±9	Patients with co-morbidities excluded	10 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	56.5± 8.0	Kt/V >1.2	HCO_3- 33 K^+ 2.5 Ca 1.75 Mg 0.5	37°C
Straver 2002	63±6	Haemodynamically stable	1, 4 hour dialysis session for each phase conducted on the same day each week	Not stated	Kt/V 1.07±0.02	Bicarbonate buffer	37°C
Hamzi 2012	45.2±11.4	Stable condition Co-morbidities excluded	10 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Control 62.14±7.5 Profile 62.02±7.3	Kt/V >1.14	HCO_3- 29 K^+ 2.0 Ca 1.50 Mg 0.5	37°C
Oliver 2001	69.47	Stable condition	6 consecutive 4 hour dialysis sessions for each phase (thrice weekly)	Control 71.7 Profile 72.1	URR 69.9	HCO_3- 35 Ca 2.5	36.5
Sadowski 1993	19	Stable condition	6 consecutive 1.5-3 hour dialysis sessions (determined by kinetic modelling) for each phase (thrice weekly)	Not stated	Kt/V 1.29±0.25	Bicarbonate based dialysate	Not stated
Song 2005	54±9	Stable condition	6 week treatment period	49.1±8.9	Kt/V 1.23±0.11	HCO_3- 30 K^+ 2.5 Ca 1.75 Mg 0.75	37°C

Table 2. Within study patient characteristics and treatment characteristics

Author	IDWG (mean, SD)	Pre dialysis BP (mean, SD)		Post dialysis BP (mean, SD)		Pre dialysis plasma Sodium (mean, SD)		Post dialysis plasma sodium (mean, SD)		Sodium concentration (mmols/l)		Hb (g/dl) (mean, SD)	Protein (g/dl) (mean, SD)	Albumin (g/dl) (mean, SD)	Hypotensive events (%)	
		Control	Profile	Control	Profile	Control	Profile	Control	Profile	Control	Profile				Control	Profile
de Paula 2004	Control 2.91±0.87 Profile 2.29±0.87	147±19/85±13	146±19/85±12	124±15/73±11	123±17/ 74±9	134.0±1.4	134.0±1.5	135.9±2.0	133.1±2.6	138	Initial 138 End 126	Not stated	Not stated	Not stated	9	2
Meira 2010	Control 3.00(1.98-4.34 Stepwise 2.96 (2.00-4.13) Linear 2.91 (1.93-4.41)	149±18/85±13	Stepwise 148±22/83±13 Linear 147±21/82±12	128±21/75±11	Stepwise 127±20/ 74±11 Linear 123±22/ 73±12	Not stated	Not stated	Not stated	Not stated	139	147-stepwise 138-linear	Control 121±20 Stepwise 117±15 Linear 117±16	Not stated	Not stated	25.8	Stepwise 13.6 Linear 22.7
Meira 2007	Control 2.78±1.0 Profile 2.5±1.1	149.5±23.5/84.1±12.2	154.5±25.4/86.4±13.4	136.8±22.3/ 80.3±11.4	140.7±23.4/ 78.2±10.7	Not stated	Not stated	Not stated	Not stated	139	Initial 147 End 139	Not stated	Not stated	Not stated	67.7	53.2
Moret 2006	Control 2.0±1.0 Profile 2.1±1.0	Systolic 146±26	Systolic 144±22	Not difference between various modalities		138±2	139±3	Not stated	Not stated	140	Initial 150 End 140	Not stated	Not stated	3.82±3.8	16	14
Zhou 2006	Control 2.91±0.6 Profile 2.96±0.81	MBP- 100.78±10.32	MBP- 99.10±10.05	Greater stability of MBP in the profile group		138.00±2.7	137.17±1.8	138.75±2.3	137.65±1.9	138	Initial 148 End 131	10.57±1.6	7.26±1.19	3.32±0.9	20	18.75
Straver 2002	Not stated	MBP 94±7	MBP 97±4	MBP 79±5	91±3	140.1±0.7	140.0±0.7	Not stated	Not stated	141	Initial 152 End 130	Not stated	Not stated	Not stated	25	0
Hamzi 2012	Control 2.09±0.5 Profile 2.2±0.47	134±13/66±12	138±16/64±12	128±16/65±10	128±17/ 60±19	Not stated	Not stated	Not stated	Not stated	139	Initial 147 End 131	Not stated	Not stated	Not stated	9	15
Oliver 2001	Not stated	151/79	149/78	134/74	137/76	137	137.3	139.7	141.0	142	Initial 152 End 142	11.5	Not stated	3.647	20	13
Sadowski 1993	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	138	Initial 148 End 138	Not stated	Not stated	Not stated	26.3	Stepwise 17.0 Linear 27.1
Song 2005	Control 2.7±0.6 Stepwise 3.9±0.6 Alternate 3.5±0.5	148±17/85±8	Stepwise 149±19/86±10 Alternate 144±16/84±8	126±15/75±9	Stepwise 137±20/ 77±10 Alternate 136±19/ 75±10	138.1±0.3	Stepwise 138±0.5 Alternate 138.1±0.7	138.1±0.1	Stepwise 140.4±0.4 Alternate 138.6±0.4	138	Initial 148 End 138	8.7±1.1	6.8±0.5	3.4±0.3	36.4	Stepwise 18.2 Alternate 18.2

Table 3. Pre, post and intradialytic chemistries and measurements

Author	Working definition of symptomatic intradialytic hypotension
de Paula 2004	Rapid changes in BP (within 15mins) accompanied by symptoms requiring nursing interventions, or a brisk fall in BP >40mmHg systolic or >20mmHg diastolic
Meira 2010	No definition provided other than intradialytic symptomatic hypotension
Meira 2007	No definition provided
Moret 2006	Decline in systolic BP to <100mmHg or decline in systolic BP >30mmHg together with symptoms necessitating nursing interventions
Zhou 206	Decrease in supine systolic BP of >30mmHg or an absolute systolic BP of <90mmHg during dialysis, accompanied by hypotensive symptoms such as dizziness, frequent yawning or perspiration
Straver 2002	Decrease in supine systolic BP of >30mmHg or an absolute systolic BP of <90mmHg during dialysis, accompanied by hypotensive symptoms such as dizziness, frequent yawning or perspiration
Hamzi 2012	Decrease in systolic BP >30mmHg
Oliver 2001	Systolic BP <100mmHg, or dizziness, cramps, nausea, headache or other
Sadowski 1993	Decrease in BP temporally associated with symptoms
Song 2005	Systolic BP <90mmHg or a decrease of >30mmHg or an event that required immediate intervention

Table 4. Definitions of symptomatic hypotension

Author Year	Trial	Washout	Hypotensive prone patients included	Profile type	Control		Intervention		RD*	NNT†
					Hypo-tensive events	Total HD sessions	Hypo-tensive events	Total HD sessions		
De Paula (2004)	1	Yes	No	Other	23	333	6	333	-5.1%	19.6
Meira (2010)	2	Yes	Yes	Stepwise	68	264	36	264	-12%	8.3
	3	Yes	Yes	Linear	68	264	60	264	-3.3%	30
Meira (2007)	4	Yes	Yes	Stepwise	63	204	42	177	-7.2%	13.8
Moret (2006)	5	Yes	Yes	Linear	18	110	16	110	-1.45%	68.9
Zhou (2006)	6	No	Yes	Linear	16	80	15	80	-1.25	80
Straver (2002)	7	Yes	No	Alternate	2	8	0	8	-25%	4
Hamzi (2012)	8	No	Yes	Linear	9	140	21	140	+8.6%	11.62
Oliver (2001)	9	No	Yes	Other	37	188	24	181	-6.4%	15.6
Sadowski (1993)	10	No	Yes	Linear	25	95	26	96	+1.08	92.6
	11	No	Yes	Stepwise	25	95	16	94	-8.9%	11.23
Song (2005)	12	Yes	Yes	Stepwise	13	33	11	33	-5.6%	17.8
	13	Yes	Yes	Alternate	13	33	11	33	-5.6%	17.8

Table 5. Characteristics of the studies included in the Meta-Analysis (* Risk difference; †Numbers needed to treat)