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Biofeedback dialysis for hypotension and hypervolemia: a systematic review and meta-analysis

Gihad E. Nesrallah[1,2,3], Rita S. Suri[1,4], Gordon Guyatt[2], Reem A. Mustafa[2], Stephen D. Walter[2], Robert M. Lindsay[1] and Elie A. Akl[4,5]

[1]Department of Medicine, The University of Western Ontario, London, Canada, [2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada, [3]Department of Nephrology, Humber River Regional Hospital, Toronto, Canada, [4]Department of Clinical Epidemiology and Biostatistics, The University of Western Ontario, London, Canada and [5]Department of Medicine, State University of New York at Buffalo, NY, USA

Correspondence and offprint requests to: Gihad E. Nesrallah; E-mail: gnesrallah@hrrh.on.ca

Abstract

Background. Intradialytic hypotension (IDH) is associated with morbidity and mortality. We conducted a systematic review to determine whether biofeedback hemodialysis (HD) can improve IDH and other outcomes, compared with HD without biofeedback.

Methods. Data sources included the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and ISI Web of Science. We included randomized trials that enrolled adult patients (>18 years) with IDH or extracellular fluid expansion and that used biofeedback to guide ultrafiltration and/or dialysate conductivity. Two authors assessed trial quality and independently extracted data in duplicate. We assessed heterogeneity using I^2. We applied the GRADE framework for rating the quality of evidence.

Results. We found two parallel-arm randomized controlled clinical trials and six randomized crossover trials meeting inclusion criteria. All trials were open-label and at least four were industry-sponsored. Studies were small

(median $n = 27$). No study evaluated hospitalization and the evidence for effect on mortality was of very low quality. Three studies assessed quality of life (QoL); none demonstrated benefit or harm, and quality of evidence was very low. Biofeedback significantly reduced IDH (risk ratio 0.61, 95% confidence interval 0.44–0.86; $I^2 = 0\%$). Quality of evidence for this outcome was low due to risk of bias and potential publication bias.

Conclusions. Biofeedback dialysis significantly reduces the frequency of IDH. Large and well-designed randomized trials are needed to assess the effects on survival, hospitalization and QoL.

Keywords: biofeedback dialysis; clinical trials; intradialytic hypotension; meta-analysis; systematic review

Introduction

End-stage renal disease (ESRD) is associated with chronic accumulation of extracellular fluid (ECF) resulting in symptoms of hypervolemia, ventricular hypertrophy and premature death [1]. Attempts to correct ECF expansion often result in intradialytic hypotension (IDH), which affects up to 50% of all conventional hemodialysis (HD) sessions [2]. IDH is defined as a reduction in a systolic blood pressure (SBP) of >20 mmHg, associated with symptoms such as dizziness, syncope, nausea, vomiting and muscle cramps [3].

The etiology of IDH is multifactorial. During ultrafiltration, there is a drop in effective circulating volume, which is normally compensated by translocation of fluid from the interstitial and intracellular spaces into the intravascular compartment—so-called 'plasma refilling'. A significant mismatch between ultrafiltration and plasma refilling rates results in IDH, especially if compensatory mechanisms that increase cardiac output and peripheral resistance are impaired. Such factors include poor cardiac function, the use of antihypertensive medications and autonomic neuropathy. Acute repeated drops in tissue perfusion due to IDH could result in chronic organ injury over time, potentially contributing to the high morbidity and mortality of HD patients [4]. Strategies that maintain hemodynamic stability during dialysis are needed.

Longer and more frequent HD may improve hemodynamic stability [5, 6], but these therapies are not widely available. Several other strategies, including cool temperature dialysis [7, 8], α-adrenergic agents [9], dialysate sodium ramping [10] and high dialysate calcium [11], have had variable success in reducing IDH. Biofeedback technology may offer improved hemodynamic stability, which could translate into improved patient outcomes. Many such devices have become widely available and are included as standard equipment on modern HD machines from a wide range of manufacturers. Most biofeedback devices continuously monitor blood pressure (BP) or infer plasma refilling from the relative blood volume. Calibrated software can then automatically adjust dialysate conductivity and/or ultrafiltration rates to optimize the balance between fluid removal and preservation of intravascular volume [12]. Integrated mathematical modeling software can also be used to achieve neutral or negative sodium balance.

Such technologies have been evaluated in small clinical trials with limited statistical power. We therefore conducted a systematic review and meta-analysis of randomized studies to determine whether HD using biofeedback-guided ultrafiltration and/or modulation of dialysate conductivity improves outcomes in patients with chronic fluid overload or symptomatic IDH, compared with constant ultrafiltration and conductivity.

Materials and methods

Protocol and registration

Our review adhered to a pre-specified protocol and analytical plan. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42011001133) [13].

Eligibility criteria

Types of studies. We included randomized controlled clinical trials (RCTs) and randomized crossover trials. Full-text published articles, abstracts and unpublished data were eligible for inclusion. Studies required a minimum definition for IDH of at least 10 mmHg drop in SBP or SBP < 100 mmHg during HD that was associated with muscle cramps, dyspnea, nausea, vomiting or dizziness. Studies of hemofiltration, hemodiafiltration, continuous renal replacement therapy, acute renal failure and hospitalized patients were excluded.

Types of participants. We included studies with adult patients (>18 years at dialysis initiation) undergoing three times weekly HD ('conventional HD') for at least 90 days and experiencing chronic fluid overload or symptomatic IDH. Chronic fluid overload was defined as either: (i) ECF volume >45% of total body water by bioimpedance spectroscopy; (ii) clinically apparent edema or (iii) clinical or radiographic evidence of pulmonary edema.

Types of interventions. Trials evaluating biofeedback technologies that used modulation of dialysate conductivity and/or ultrafiltration rates were included. Input variables for biofeedback algorithms included measurements of relative blood volume monitoring (BVM) or other indices of hemodynamic stability (BP). BVM with dialysate conductivity control was defined as biofeedback dialysis in which the primary input variable for the biofeedback algorithm was relative blood volume and in which dialysate conductivity was manipulated without directly measuring blood-side conductivity (e.g. Hemocontrol™, Hospal-Gambro, Quebec, Canada). BVM with plasma conductivity-controlled dialysis was defined as biofeedback dialysis in which plasma conductivity was measured directly (in the blood lines), and served as an input variable in the biofeedback algorithm, along with relative blood volume (e.g. Diacontrol™, Hospal-Gambro). The control intervention consisted of thrice-weekly HD with constant dialysate conductivity and ultrafiltration ('conventional HD').

Types of outcomes. Primary outcomes were quality of life (QoL) [generic (SF-36) and disease-specific (KDQOL-36 and Dialysis Somatic Symptoms Questionnaire)] scales, hospitalization for any cause and mortality. The pre-specified patient-important [14] secondary outcome was the frequency of symptomatic IDH (muscle cramps, fatigue, dizziness, nausea, vomiting, dyspnea, chest pain, in association with IDH). Secondary safety outcomes were evidence of sodium-loading (increases in predialysis SBP, antihypertensive medications, interdialytic fluid gain, edema or shortness of breath), electrolyte abnormalities (hypo- and hypernatremia), reduced delivered dialysis dose and reduced delivered dialysis time.

Information sources

We searched: (i) The Cochrane Central Register of Controlled Trials (CENTRAL—Issue 1 of 4, January 2011) [15]; (ii) MEDLINE (1966 to January 2011 including in-process and other non-indexed citations); (iii)

EMBASE (1980 to January 2011); and (iv) ISI Web of Science (1976 to January 2011). We also searched the Cochrane Database of Systematic Reviews (CDSR), PubMed (1966 to January 2011), the Database of Abstracts of Reviews and Effects (DARE) and ISI Web of Science for relevant review articles.

We hand-searched conference proceedings and abstracts of the annual meetings of the American Society of Nephrology, Canadian Society of Nephrology, International Society of Nephrology, National Kidney Foundation (USA), European Dialysis and Transplant Association and American Society of Artificial Internal Organs meetings, from January 2005 to March 2011. Finally, we requested unpublished data and abstracts from the leading biofeedback dialysis equipment manufacturer (Hospal-Gambro).

Search

We developed search strategies in consultation with a Health Sciences Information Specialist (Supplementary Appendix). Subject headings and keywords included: dialysis- or dialysis-induced hypotension, hypotension, intradialytic hypotension, IDH, edema, extracellular fluid (or expansion or space), interdialytic weight or fluid gain, biofeedback dialysis, feedback dialysis, blood-volume (or BV) or plasma conductivity (or PC) combined with dialysis or feedback or technology or any of the biofeedback dialysis equipment brand names (Hemocontrol™ or Diacontrol™, Hospal-Gambro; Supplementary Appendix). We applied a highly sensitive search strategy developed for the Cochrane Collaboration for the identification of clinical trials, including crossover studies [16]. We placed no limits on publication language. We used similar search strategies to identify relevant systematic reviews and meta-analyses.

Study selection

We downloaded all identified citations into a reference manager software application (Endnote X4 for Macintosh, Thomson-Reuters Inc., San Francisco, CA). Duplicate records were deleted. One reviewer (G.E.N.) assessed all titles and abstracts for potential eligibility and retrieved full-texts of relevant citations ($n = 69$). Two reviewers (G.E.N. and R.S.S.) screened these in duplicate and independently for eligibility using a standardized and pilot tested form. Disagreements were resolved by consensus. Abstracts or other gray literature reports were cross-referenced with corresponding full-text articles representing the same studies.

Data collection process

Two authors (G.E.N. and R.S.S.) extracted data in duplicate and independently using a standardized form. We grouped multiple reports of the same study as a single unit for data extraction and analysis. Disagreements were resolved in consultation with a third reviewer (R.M.L.). We also attempted to contact corresponding authors for additional information or to clarify discrepancies between published reports. Detailed data abstraction forms were pilot tested with two studies, then modified as required.

We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for assessing the quality of evidence for each outcome [17].

Statistical analysis

Data were entered into Review Manager 5.1 for Macintosh [18]. Summary measures were pooled using a random-effects model. When only two studies were available for pooling, a fixed-effects model was used. We used the inverse variance and generic inverse variance methods as appropriate for pooling treatment effects. Parallel and crossover studies were meta-analyzed separately and in aggregate. Heterogeneity between studies was examined using a χ^2 and I^2 (the estimated proportion of variability in the study-specific values of the treatment effect that is associated with characteristics of the studies rather than within-study error).

We converted count data into rates using the reported follow-up times. We then calculated natural logarithms of rate ratios for pooling with the generic inverse variance method. The natural logarithm of the standard error of the rate ratio was estimated as $\ln(\mathrm{SE}) = \sqrt{1/E_\mathrm{T} + 1/E_\mathrm{C}}$, where E_T and E_C are event counts for the treatment and control groups, respectively; where required, we computed these values from reported rate data. The rate difference was computed as $(E_\mathrm{T}/T_\mathrm{T}) - (E_\mathrm{C}/T_\mathrm{C})$ with standard error = $\sqrt{\mathrm{E_T}/T_\mathrm{T} + E_\mathrm{C}/T_\mathrm{C}}$, where T_T and T_C represent time units in dialysis sessions for the treatment and control groups, respectively [19]. For continuous data, we recorded sample sizes, mean values and standard deviations for use with the inverse variance method.

We could not use formal methods such as funnel plots to assess publication bias, given the small number of included studies. However, as most included studies were primarily industry-funded, we considered all analyses to be at high risk of publication bias [20].

Finally, we were not able to undertake any of our pre-specified subgroup analyses to explore potential sources of heterogeneity, as individual patient-level data were not available, and none of the included studies reported outcomes by subgroup.

Results

Study selection

We identified 939 studies with our initial search (Figure 1). Of these, 80 were duplicates. We excluded 790 studies based on the title and abstract, and an additional 58 after reading full-texts (Figure 1). This left 11 reports (3 abstracts [21–23] and 8 full-text publications) of 8 studies [24–31]. We achieved excellent agreement ($\kappa = 0.89$) between reviewers.

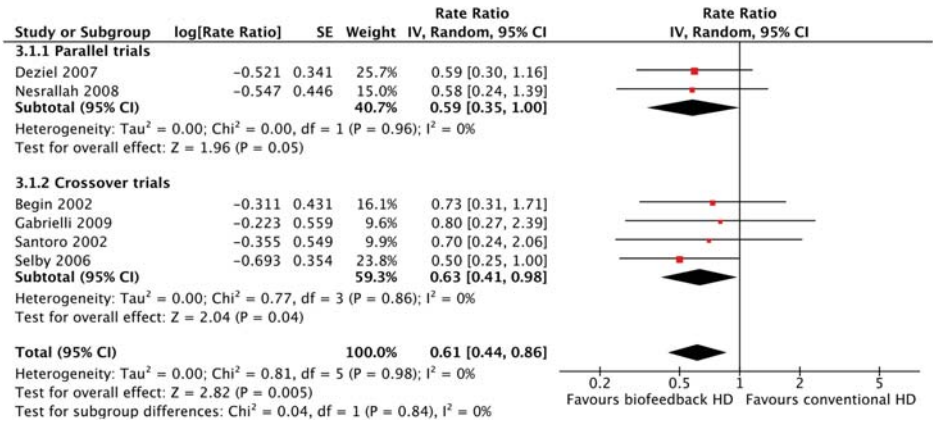

Fig. 1. Study selection flow diagram.

Study characteristics

Among the eight included studies, two were parallel-arm RCTs of 6-month duration (Table 1) [26, 29]. Six were crossover studies with random allocation to the sequence of interventions. Study periods ranged 2–6 weeks, with two [24, 27, 30], three [25], or four [28, 31] crossover periods per study. One study was conducted at nine sites in eight countries (Italy, Israel, Sweden, France, the Czech Republic, Sweden, Norway and Germany) [27], and another at 10 facilities in Italy [31]; all other studies were conducted at a single center.

Seven of eight studies (88%) enrolled patients with frequent IDH (20–33% of sessions), while one enrolled patients on the basis of ECF expansion [29]. Studies assessed one of four available biofeedback devices (Table 1): one device used automated BP measurements as a measure of hemodynamic stability and adjusted ultrafiltration rate [24], while the three other biofeedback platforms used relative blood volume as an input variable to adjust dialysate conductivity and/or ultrafiltration rate. Six out of eight (75%) studies used a biofeedback device that manipulated the dialysate conductivity in conjunction with ultrafiltration rate to improve hemodynamic stability during dialysis.

Risk of bias within studies

One study blinded participants [31], while none blinded nurses, physicians or other care providers. Whether data analysts and outcome adjudicators were blinded was unclear. Although all studies used random sequence generation, only three of eight (38%) studies specified the use of computer-generated sequences. Completeness of follow-up ranged from 77 to 100%, with most study exit events due to changes in dialysis modality, transplantation or relocation to a new dialysis facility. Both parallel RCTs adhered to the intent-to-treat principle [26, 29].

Reasons for patient exclusion varied across studies and included: reduced life-expectancy, severe anemia, pregnancy and cardiac arrhythmia. Only patients with follow-up data reported were included in analyses. None of the included studies reported previously published protocols. Four studies (50%) were industry-funded [25–27, 29], while one was university-funded [24]. Three studies did not specify funding sources [28, 30, 31], but used a commercial biofeedback software product (Hemocontrol™, Hospal-Gambro).

Synthesis of results

Mortality and hospitalization. Since we could not exclude the possibility of carry-over effects, we did not include crossover studies in the analysis of all-cause mortality. We pooled mortality data from the two parallel RCTs (Figure 2) with a total of 104 patient-years of follow-up. Two deaths occurred in patients undergoing biofeedback HD, when compared with six deaths among patients undergoing conventional HD. The pooled effect estimate did not rule out a beneficial or harmful effect of biofeedback dialysis risk ratio (RR) = 0.37 [95% confidence interval (CI) 0.07–2.01; $I^2 = 0\%$]. The quality of evidence for that outcome was very low, due to risk of publication bias and imprecision. No studies reported hospitalization data.

Quality of life. QoL was reported in three studies, but heterogeneity in measures and reporting precluded pooling. The study by Deziel *et al.* [26] detected no changes in any individual components of the Kidney Disease-Specific Short Form (KDQOL), and summary scores were not available for pooling. A second parallel trial that measured QoL with the Dialysis Somatic Symptoms Questionnaire [32] also found no significant between-group differences [29]. Finally, a crossover study reported 'a significant reduction in symptoms' of 10%, $P < 0.001$, in patients crossing over from conventional to biofeedback dialysis [31]. Details of the measurement and validity of this outcome were not provided.

Intradialytic hypotension. The frequency of IDH was lower among patients receiving biofeedback dialysis in all six studies that reported this outcome (Figure 3a) [25–27, 29, 30]. Three studies reported the number of 'sessions' complicated by IDH [25–27] while three included all episodes of IDH (including multiple episodes per session) during follow-up [29–31]. The pooled rate ratio for symptomatic IDH was 0.61, 95% CI 0.44–0.86, $I^2 = 0\%$ with a rate difference of −0.10, 95% CI −0.13 to −0.08, $I^2 = 0\%$, favoring biofeedback dialysis. The quality of evidence for that outcome was low, rated down for potential bias from lack of blinding and possible publication bias (Table 2).

Blood pressure. BP medications did not change in any study. Four studies specified that BP medications were held constant during follow-up [24–26, 30]. Pre-dialysis SBP (Figure 4), as reported in seven of eight studies, did not change (mean difference = 3, 95% CI −2 to 7 mmHg; $I^2 = 0\%$). Post-dialysis systolic BP (Figure 4b) was reported in three of eight studies, with a mean difference of 7 mmHg (95% CI 5–19; $\chi^2 = 10.52$, $P = 0.005$, $I^2 = 81\%$). However, statistical heterogeneity may have resulted from different follow-up times and patient characteristics. The quality of evidence for pre- and post-dialysis SBP was very low, due to potential publication bias, imprecision and inconsistency (post-dialysis SBP $I^2 = 81\%$).

Other outcomes. Three studies measured pre- and post-dialysis sodium levels and reported no changes in this measure. Three studies reporting measures of urea clearance as equilibrated K_t/V [27] and single-pool K_t/V [29, 31] showed no between-group differences in these outcomes. One study reported fewer post-dialysis regional wall motion abnormalities by two-dimensional echocardiography with biofeedback when compared with conventional HD [30].

Table 1. Characteristics of included studies

Study	Methods				**Intervention**[b] Study periods in weeks	Patient characteristics			Outcomes[c]	Comments
	Design[a]	Randomization method	Allocation concealment/ blinding	% enrolled patients included in analysis		Inclusion criteria	Exclusion criteria	Sample size Mean age (years) Mean Vintage (years) % Female		
Begin *et al.* [25]	Crossover (ABABAB/ BABABA)	Not specified	Not specified/ open label	86	**Hemocontrol™ versus CHD** Run-in: 0 Wash-out: 0 Period length: 2 Total duration: 12	Symptomatic and asymptomatic IDH during ≥30% of HD over 3 months	Bleeding or severe anemia; arrhythmia	$n = 7$ Mean age = 76 Vintage>0.5 % Female = 43	'Event-free HD'—Events: IDH, delay in leaving dialysis; BP	Industry-funded; BP medications held on HD days; BP medications held constant
Coli *et al.* [24]	Crossover (AB/BA)	Not specified	Not specified/ open label	100	**Profiled dialysate conductivity with BP monitoring (manufacturer not specified) versus CHD** Run-in: 0 Wash-out: 0 Period length: 1 Total duration: 2	Mean BP <80 mmHg at start of HD with decreasing trend during HD	None specified	$n = 20$ Mean age = 62 Vintage>4.8 % Female NR	SBP changes during HD	University-funded; BP medications held constant
Deziel *et al.* [26]	Parallel	Computer-based	Not specified/ open label	87	**Hemocontrol™ versus CHD** Run-in: 4 Total duration: 24	IDH requiring intervention[d] during ≥30% of HD during run-in	None specified	$n = 44$ Mean age = 65 Vintage>3.5 % Female = 48	KDQOL™ [34]; IDH; home BP; mortality	Industry-funded; BP medications held constant
Gabrielli *et al.* [27]	Crossover (AB/BA)	Not specified	Not specified/ open label	77	**BVM (Fresenius Medical Care, Bad Homburg, Germany) versus CHD** Run-in: 6 Wash-out: 0 Period length: 6 Total duration: 12	Symptomatic IDH during ≥33% of HD sessions over 6 wk	None specified	$n = 34$ Mean age = 65 % Female = 35	IDH; BP	Industry-funded
Moret *et al.* [28]	Crossover	Not specified	Not specified/ open label (random sequence of A, B, C, D)	83	**Diacontrol™ versus Hemocontrol™ versus linear Na profiling (15.0 mS → 14.0 mS) versus CHD** Run-in: 2–3 Wash-out: 1 Period length: 11 HD sessions Total duration: >6	Decline in SBP to <100 mmHg or a drop of >33 mmHg with IDH symptoms[d]	None specified	$n = 12$ % Female = 33 Mean age = 71	IDH; BP	Funding source not specified

Continued

Table 1. *Continued*

Study	Methods				**Intervention**[b] Study periods in weeks	Patient characteristics			Outcomes[c]	Comments
	Design[a]	Randomization method	Allocation concealment/ blinding	% enrolled patients included in analysis		Inclusion criteria	Exclusion criteria	Sample size Mean age (years) Mean Vintage (years) % Female		
Nesrallah *et al.* [29]	Parallel	Computer-based	Not specified/ open label	94	**Hemocontrol™ versus CHD** Run-in: 4 Total duration: 24	ECFV >45% of total body water by bioimpedance spectroscopy	Anemia; pregnancy; arrhythmia; life expectancy <3 months	$n = 60$ Mean age = 65 % Female = 38	'DSSQ'; BP; IDH; mortality	Industry-funded
Selby [30]	Crossover (AB/BA)	Not specified	Not specified/ open label	100	**Hemocontrol™ versus CHD** Run-in: 1 Wash-out: 1 Period length: 1 Total duration: 4	IDH during ≥20% of HD sessions and LVMI>51g/m^2	None specified	$n = 10$ Mean age = 68 % Female = 0	IDH; BP	Funding source not specified; BP medications held constant
Santoro *et al.* [31]	Crossover (ABAB/ BABA)	Computer-based	Not specified/ participants blinded	89	**Hemocontrol™ versus CHD** Run-in: 2 Wash-out: 0 Period length: 4 Total duration: 16	IDH during 20–80% of HD sessions for 2 months before enrolment	Bleeding or severe anemia	$n = 36$ Mean age = 67 % Female = 50	IDH; number of interdialytic symptoms[c]	Funding source not specified

IDH, intradialytic hypotension; HD, hemodialysis; CHD, conventional hemodialysis (with constant ultrafiltration and conductivity profiles); DSSQ, Dialysis Somatic Symptoms Questionnaire; ECFV, extracellular fluid volume; ITT, intent-to-treat; ESRD, end-stage renal disease; BVM, blood volume monitoring; KDQOL™, Kidney Disease Quality of Life questionnaire; LVMI, left ventricular mass index; BP, blood pressure; ESRD, end-stage renal disease; 'wk', week.

[a]'A' and 'B' denote study periods (intervention and control) respectively. See 'Intervention' for study period duration.

[b]Conventional HD (CHD) is defined as thrice-weekly hemodialysis with constant dialysate sodium and conductivity.

[c]Typical symptoms associated with IDH can include: dizziness, cramps, fatigue, yawning, nausea, vomiting, chest pain and dyspnea.

[d]Nursing interventions include: infusion of isotonic saline, prompt reclining of dialysis chair or manual reduction of the ultrafiltration rate and/or blood flow rate.

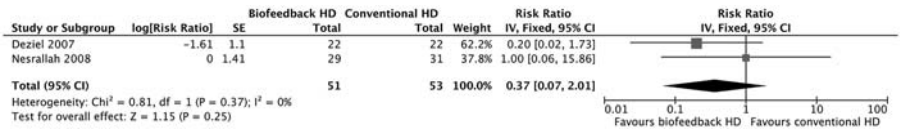

Fig. 2. Biofeedback HD versus conventional HD with constant dialysate conductivity and ultrafiltration rate; outcome: all-cause mortality.

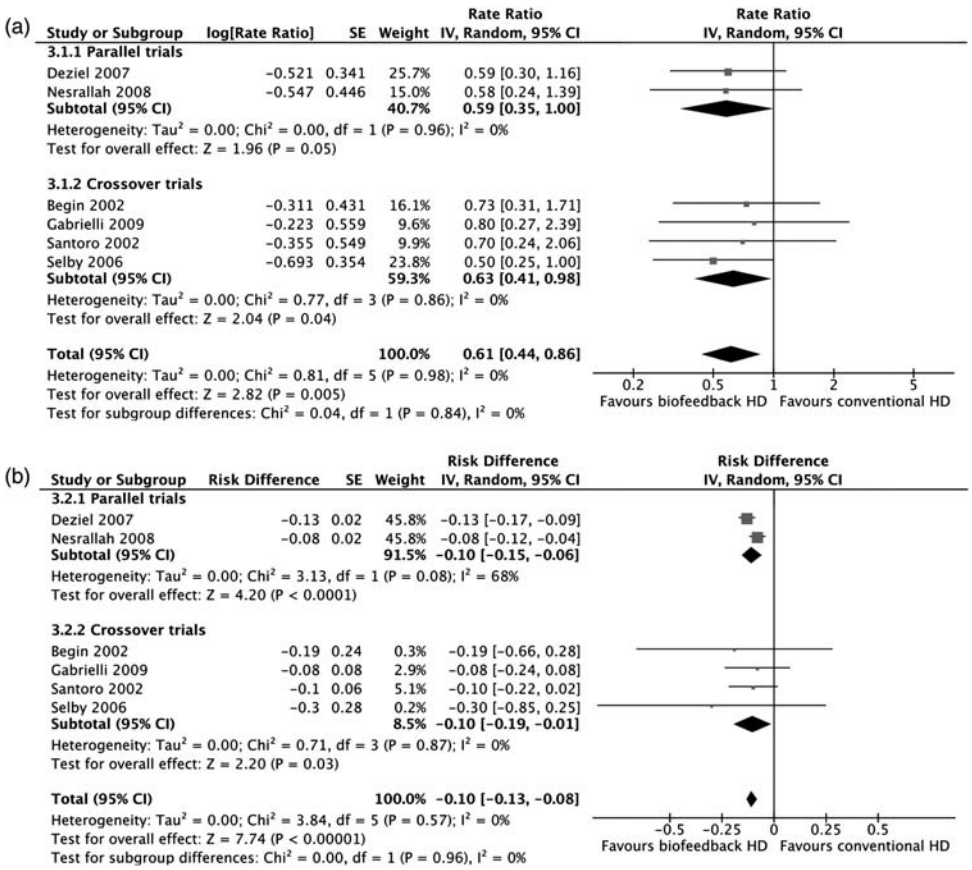

Fig. 3. (**a**) Biofeedback HD versus conventional HD with constant dialysate conductivity and ultrafiltration rate; outcome: IDH. Relative treatment effect estimate (rate ratio). (**b**) Biofeedback HD versus conventional HD with constant dialysate conductivity and ultrafiltration rate; outcome: IDH. Absolute treatment effect estimate (rate difference).

Discussion

Summary of evidence

Biofeedback dialysis is associated with a statistically and clinically significant reduction in the frequency of symptomatic IDH, with an absolute rate difference of 10% (95% CI 8–13%). Whether this translates into fewer hospitalizations or improved survival, however, cannot be ascertained from the current literature. Despite reduced IDH, two studies found no statistically significant improvement in disease-specific health-related QoL measures, while one found a 10% difference in interdialytic symptoms. Details of dialysis-related symptoms such as muscle cramps were not reported. No significant differences in pre- or post-dialysis SBP were evident, although pooled effect estimates had wide confidence intervals.

Physiological considerations

Biofeedback dialysis technology can modulate the ultrafiltration rate to allow BP or relative blood volume to improve, or alternatively, they modulate the dialysate sodium to directly increase plasma refilling. Among the eight studies included in this meta-analysis, six used a biofeedback platform that manipulated dialysate conductivity in conjunction with ultrafiltration rate to optimize plasma refilling. Although these devices are based on the 'isonatremic principle' (maintenance of neutral sodium balance) [33], there is a theoretical risk of inadvertent sodium loading due to measurement error. However, the observed reduction IDH in our meta-analysis was not associated with increased pre-dialysis BP, dry weight, interdialytic weight gain or post-dialysis sodium levels. Hence, it does not appear that biofeedback dialysis resulted in clinically significant sodium loading.

Table 2. Summary of findings for studies comparing biofeedback with conventional HD

Biofeedback dialysis for intradialytic hypotension or hypervolemia					
Patient or population: patients with intradialytic hypotension or hypervolemia					
Settings: in-center hemodialysis units					
Intervention: biofeedback dialysis					
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Biofeedback dialysis			
Mortality Rate ratio Follow-up: 6 months	Given the small overall number of patients and events, a valid illustrative comparative risk scenario could not be provided		**RR 0.37** (0.07–2.01)	104 (2 studies)	⊕◯◯◯ **very low**[b,c,d]
Hospitalization Rates	Not reported in included studies		—	—	—
Health-related Quality of Life Any quality of life scale Follow-up: 4–6 months	2/3 studies measuring quality of life using the KDQOL and DSSQ reported no statistically significant differences between groups. Baseline scores were not reported. One study reported a 10% decrease in 'interdialytic symptoms' ($P < 0.001$) after switching to biofeedback HD		—	(3 studies)	⊕◯◯◯ **very low**[d,e,f]
Intradialytic hypotension Follow-up: 1–6 months	**659 per 1000**	**402 per 1000** (290–567)	**RR 0.61** (0.44–0.86)	266 (6 studies)	⊕⊕◯◯ **low**[d,g]
Pre-dialysis systolic blood pressure mmHg Follow-up: 1–6 months		The mean pre-dialysis systolic blood pressure in the intervention groups was **3 higher** (2 lower to 7 higher)		266 (6 studies)	⊕◯◯◯ **very low**[d,h,i,j]
Post-dialysis systolic blood pressure mmHg Follow-up: 1–6 months		The mean post-dialysis systolic blood pressure in the intervention groups was **7 higher** (5–19 higher)		266 (6 studies)	⊕◯◯◯ **very low**[d,h,i,k]

CI, confidence interval; RR: risk ratio. GRADE Working Group grades of evidence: High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

[a]The basis for the 'assumed risk' (e.g. the median control group risk across studies) is based on pooled estimates. The 'corresponding risk' (and its 95% confidence interval) is based on the assumed risk in the comparison group and the 'relative effect' of the intervention (and its 95% CI).

[b]Although studies were open-label, lack of blinding was not likely to impact on the adjudication of all-cause mortality.

[c]Included studies suffered from imprecision due to small sample sizes and low event rates overall.

[d]Due to a small number of included studies, we could not assess risk of publication bias computationally, or by funnel plots; most studies were small and industry-funded, which increases the risk of publication bias.

[e]All studies were open-label, and none specified that outcome adjudicators or data analysts were blinded to treatment allocation.

[f]Different methods of QoL assessment were used across studies (see text). Heterogeneity in measures and reporting precluded pooling of summary scores.

[g]Lack of blinding to treatment group allocation may have biased reporting and adjudication of this outcome.

[h]Although studies were open-label, the potential impact of unblinding on blood pressure measurements was likely insignificant.

[i]Pre-dialysis SBP is a surrogate marker of uncertain prognostic significance; therefore, its importance in decision-making is unclear.

[j]Confidence interval included both benefit and no effect.

[k]I^2 for this outcome was 81%.

Strengths and limitations

We employed a number of strategies to optimize the validity of the inferences drawn from this review. We used a detailed search strategy and imposed no restrictions on language of publication. We limited studies to those in which treatment group allocation was randomized. We conducted a rigorous evaluation of risk of bias and interpreted our findings in light of these limitations. In addition, we limited our meta-analyses, primarily to patient-important outcomes. As such, we present a relatively conservative assessment of the risks and benefits of biofeedback dialysis.

Unfortunately, data from published randomized studies of biofeedback dialysis lacked sufficient power to evaluate

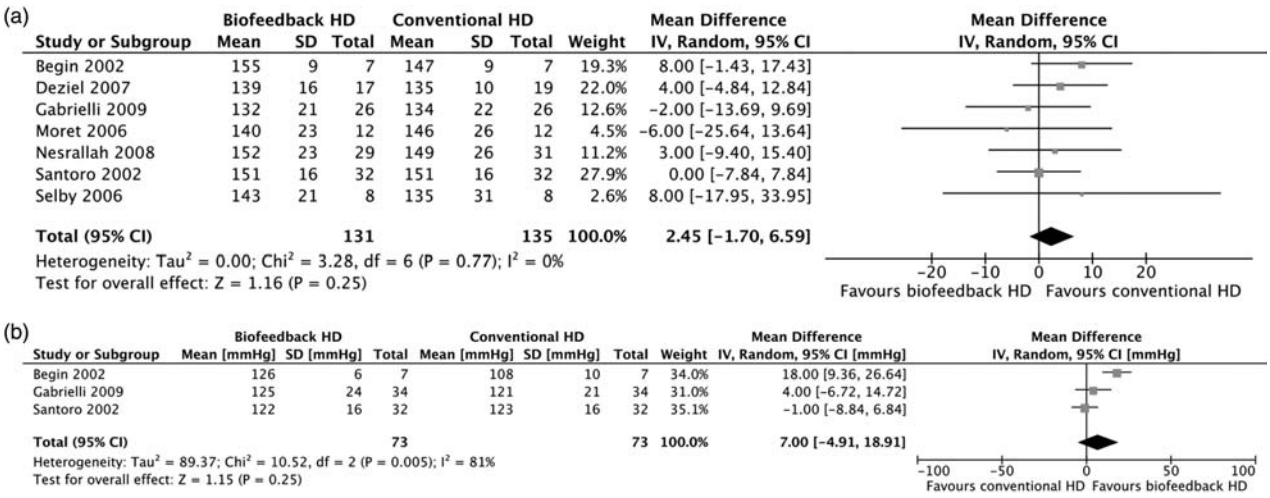

Fig. 4. (**a**) Biofeedback HD versus conventional HD with constant dialysate conductivity and ultrafiltration rate; outcome: pre-dialysis systolic blood pressure. (**b**) Biofeedback HD versus conventional HD with constant dialysate conductivity and ultrafiltration rate; outcome: post-dialysis systolic blood pressure.

its impact on major outcomes such as survival and hospitalization rates. Although biofeedback dialysis reduced IDH frequency, validated QoL measures were not improved in two studies that reported them. However, it is noteworthy that neither scale (KDQOL or DSSQ) has been previously validated in studies of hemodynamic stability or IDH. It is therefore possible that these instruments did not possess the appropriate measurement characteristics to capture changes in QoL related to biofeedback dialysis.

Finally, important sources of bias within studies included lack of blinding of all participants, study personnel and possibly outcome adjudicators and analysts. Furthermore, publication and selective reporting bias could not be excluded.

Conclusions

Implications for practice

Biofeedback reduces the frequency of IDH. This may translate into improvements in important clinical outcomes over the long term, although further study is needed to confirm this assertion. In addition, we did not detect any evidence of harmful effects, such as sodium loading with modulation of dialysate conductivity. Where feasible, this therapy should be considered for patients with IDH and possibly those with expanded ECF volume.

Implications for research

The potential impact of biofeedback dialysis on major clinical outcomes awaits further study. A larger clinical trial is warranted. Rigorous methods, including treatment allocation concealment and blinding, should be used. In addition, cost-effectiveness analyses will be useful in informing future use of this potentially promising therapy.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

Conflict of interest statement. G.E.N., R.S.S. and R.M.L. served as co-principal investigators in a clinical trial included in this review.

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