Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review

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Abstract

Background. Dialysis-induced hypotension is an important complication of haemodialysis. Midodrine is an oral α-1 agonist that has been used in several small studies to prevent intradialytic hypotension (IDH).

Methods. The authors searched MEDLINE, EMBASE, ASN conference proceedings, and references of potentially relevant articles, and contacted industry (Shire Pharmaceuticals) for unpublished data. Observational studies, randomized controlled trials, crossover studies and pre- and post-intervention design studies with ≥5 haemodialysis patients were included. Study outcomes assessed were: hypotensive symptoms, changes in systolic and/or diastolic blood pressure, dry weight and length of stay after treatment. Data were abstracted on: study design, patient characteristics, intradialytic changes in blood pressure, nadir blood pressure and symptom improvement with midodrine. Thirty-seven full text articles were retrieved and nine met the selection criteria, in addition to one unpublished study. Midodrine dosing regimens ranged from 2.5 to 10 mg of midodrine given 15–30 min before dialysis.

Results. Post-dialysis systolic blood pressure was higher by 12.4 mmHg [95% confidence interval (CI) 7.5–17.7] and diastolic pressure was higher by 7.3 mmHg (95% CI 3.7–10.9) during midodrine treatment vs control. Likewise, the nadir systolic blood pressure was higher by 13.3 mmHg (95% CI 8.6–18.0), with a difference in nadir diastolic pressure of 5.9 mmHg (95% CI 2.7–9.1). Six of 10 studies report improvement in symptoms of IDH, and there were no reported serious adverse events ascribed to midodrine.

Conclusions. This systematic review would suggest that midodrine has a role in the therapy of haemodialysis patients experiencing IDH. This conclusion must be viewed with caution, however, given the quality and sample size of the studies included in this review.

Keywords: adrenergic α-agonists; blood pressure; hypotension; midodrine; renal dialysis; review, systematic

Introduction

Intradialytic hypotension (IDH) is often defined as a systolic blood pressure <100 mmHg or a blood pressure drop of >20 mmHg with concomitant symptoms (dizziness, blurred vision, cramps and fatigue) [1]. IDH is a significant problem in haemodialysis units, complicating up to 20% of treatments [2]. IDH may interfere with the delivery of adequate dialysis, as patients suffering IDH are more prone to interrupt their treatment [3], and suffer significant impairment of well-being [4]. Hypotension may also induce or aggravate cerebral, mesenteric or cardiovascular hypoperfusion, leading in turn to more dire consequences [5]. Several methods have been suggested to prevent IDH which include: withholding antihypertensive agents on dialysis days, avoiding eating on dialysis, increasing dialysate sodium concentrations or sodium ramping, and cooling the dialysate [6].

Midodrine is the prodrug of the specific α-1 adrenergic receptor agonist, desglymidodrine. This metabolite induces constriction of both arterial and venous capacitance vessels and prevents venous pooling of the blood while increasing blood pressure [7]. Peak levels of the active metabolite in serum are achieved in 1 h and its half-life is 3 h as measured in individuals with orthostatic and other secondary causes of hypotension [8].

Midodrine has been suggested to be of benefit in preventing or ameliorating the symptoms and severity of IDH. While a number of studies have attempted to address this issue, each study contains a small number of patients. We conducted a systematic review of the
literature to determine the efficacy and safety of midodrine use for IDH.

Subjects and methods

Study identification

A literature search was performed in MEDLINE and EMBASE using the following search terms: renal dialysis or hemodialysis or haemodialysis, hypotension or low blood pressure, and midodrine or amatine or gutron. The time frame of the literature searched included 1965 to September 2003. A full search strategy is available from the authors on request. An experienced librarian reviewed the search strategies, and citations were screened independently for relevance by two observers. Every potentially relevant citation was retrieved. Other methods of study identification included searching authors’ names of relevant studies, searching American Society of Nephrology conference proceedings for the years 1996–2002, contacting industry for unpublished data and reviewing the reference lists of all potentially relevant articles. At no time did industry influence the conduct or reporting of this study.

Study selection

Prospective and retrospective observational studies, pre- and post-intervention design, and randomized controlled trials including crossover studies were included. The study was required to contain at least five patients on chronic haemodialysis experiencing IDH who were treated with oral midodrine. This requirement was designed to exclude very small case series or case reports. Objective outcomes of interest were changes in systolic and diastolic blood pressure during dialysis, which would enable quantification of effect and statistical analyses, while more subjective outcomes included adverse effects, intradialytic symptoms including prolonged stay after dialysis or treatment with saline. Two observers assessed study inclusion independently, and disagreements were resolved by consensus. Five potentially relevant non-English articles were translated to assess for inclusion (French, German, Japanese and Spanish).

Data abstraction

One reviewer, using pre-prepared forms, abstracted data on blood pressures, and the second reviewer carefully verified the results. Several primary authors were contacted to obtain additional data from individual subjects, but it was not possible to retrieve this information.

Statistical analysis

The kappa statistic was used to calculate interobserver agreement for study inclusion. Weighted means for available outcomes of interest were calculated together with ranges. Forrest plots were constructed using the mean from each study, and the 95% confidence intervals (CIs) were calculated where possible based on availability of variance estimates. These variance estimates were also used in a fixed effects model to estimate the pooled standard deviation (SD) for post-dialysis and nadir blood pressures. The weighted means of these outcomes were then compared between midodrine and control by independent samples t-test using Clinstat (St George’s Hospital Medical School). All outcomes compared were before and after or crossover in nature; however, a paired analysis was not possible without access to raw data from all individual subjects. Hence, a more conservative comparison using an independent samples t-test was performed.

Results

Study identification, selection and description

Thirty-seven citations were obtained using the search strategy and all 37 full text articles were retrieved. Nine of these studies met the predefined inclusion criteria. Raw data from an unpublished study provided by Shire Pharmaceutical Development Inc. (Rockville, MD) accounted for the tenth study. Agreement beyond chance for article inclusion was 0.93 between the two observers. The total number of patients included in all studies was 117.

Study characteristics

A summary table (Table 1) is provided which includes study design, sample size, dose of midodrine and relevant outcomes. Two of the studies employed a crossover design [9,10]. Three studies used a placebo control group [9,11,12]. The remainder of the studies were pre- and post-intervention design, and the number of patients in each study was small. Two studies that utilized small control groups did so in addition to a pre- and post-intervention group, not in a classic parallel group design, and these control group data did not lend themselves to inclusion in this analysis [11,12]. There were no published randomized controlled parallel group trials. Study patients were blinded to their treatment in a single study [9]; in the same study, the health provider remained blinded, and in none of the studies were the assessors of outcomes blinded. Seven studies reported on the use of other means to prevent IDH and stated that the co-interventions were applied equally in the midodrine and non-midodrine phases of treatment [1,7,10,12–15]. Co-interventions were not commented on in the three remaining studies [9,11,16]. With specific reference to cool dialysate, no studies reported its use in the control period.

Patient characteristics

The majority of studies listed the following as their inclusion criteria: symptoms of dizziness, blurred vision, nausea, vomiting, fatigue along with a blood pressure <100/60 mmHg [9]; systolic blood pressure <100 mmHg or decreased by 20 mmHg [1,7,10,12–16]; or a decrease of 25% [7]. Exclusion criteria were: all patients on antihypertensive agents [7,9]; active medical conditions, vascular access dysfunction, dialysis with catheter [16]; pericardial effusions, impaired left
Table 1. Summary of studies and outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Sample size</th>
<th>Midodrine dose</th>
<th>Mean Δ SBP (C)</th>
<th>Mean Δ SBP (M)</th>
<th>Mean Δ DBP (C)</th>
<th>Mean Δ DBP (M)</th>
<th>Mean nadir SBP (C)</th>
<th>Mean nadir SBP (M)</th>
<th>Mean nadir DBP (C)</th>
<th>Mean nadir DBP (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, 2003 [12]</td>
<td>Pre- and post-intervention design</td>
<td>12</td>
<td>5 mg p.o. 30 min prior to HD x 4 weeks</td>
<td>N/A</td>
<td>6.0</td>
<td>N/A</td>
<td>8.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cotera, 2002 [9]</td>
<td>Double-blind crossover design</td>
<td>10</td>
<td>10 mg p.o. x 5 HD treatments</td>
<td>23.4</td>
<td>19.3</td>
<td>11.1</td>
<td>7.3</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hoeben, 2002 [15]</td>
<td>Observational pre- and post-intervention design</td>
<td>6</td>
<td>10 mg p.o. 15-30 min prior to HD</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cruz, 1999 [10]</td>
<td>Prospective crossover design</td>
<td>11</td>
<td>10 mg p.o. 15-30 min prior to HD</td>
<td>23.7</td>
<td>19.2</td>
<td>11.3</td>
<td>9.0</td>
<td>90.6</td>
<td>103.9</td>
<td>54.9</td>
<td>62.3</td>
</tr>
<tr>
<td>Cruz, 1998 [1]</td>
<td>Observational pre- and post-intervention design</td>
<td>13</td>
<td>10 mg p.o. 30 min prior to dialysis</td>
<td>19.0</td>
<td>11.0</td>
<td>9.4</td>
<td>8.9</td>
<td>97.5</td>
<td>115.4</td>
<td>54.4</td>
<td>62.6</td>
</tr>
<tr>
<td>Lim, 1997 [7]</td>
<td>Pre- and post-intervention design</td>
<td>12</td>
<td>2.5 mg p.o. 30 min prior to HD (increased by 2.5 mg as needed)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>68.7</td>
<td>84.7</td>
<td>42.8</td>
<td>52.7</td>
</tr>
<tr>
<td>Cruz, 1997 [13]</td>
<td>Pre- and post-intervention design</td>
<td>10</td>
<td>5 mg p.o. 30 min prior to HD (one patient received 10 mg)</td>
<td>18.1</td>
<td>7.4</td>
<td>6.4</td>
<td>3.5</td>
<td>96.6</td>
<td>114.7</td>
<td>53.2</td>
<td>59.0</td>
</tr>
<tr>
<td>Flynn, 1996 [16]</td>
<td>Pre- and post-intervention design</td>
<td>21</td>
<td>2.5 mg p.o. prior to HD increased by 2.5 mg to maintain SBP &gt;100</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>93.1</td>
<td>107.1</td>
<td>52.3</td>
<td>57.9</td>
</tr>
<tr>
<td>Fang, 1996 [14]</td>
<td>Pre- and post-intervention design</td>
<td>10</td>
<td>2.5 mg bid on HD days, 1.25 mg bid on non-HD days</td>
<td>8.1</td>
<td>9.0</td>
<td>11.4</td>
<td>5.2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Shire Pharmaceuticals unpublished data [11]</td>
<td>Pre- and post-intervention design</td>
<td>12</td>
<td>Prior to HD: 5 mg (n=4), 10 mg (n=4), 15mg (n=4)</td>
<td>26.3</td>
<td>18.7</td>
<td>7.4</td>
<td>6.8</td>
<td>101.9</td>
<td>102.2</td>
<td>57.6</td>
<td>56.1</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; N/A = data not available, M = midodrine, C = control; HD = haemodialysis, Δ = pre-dialysis minus post-dialysis measurement. All blood pressures are in mmHg.
ventricle (documented by echocardiography) [7,15]; and those with diabetes [15].

**Blood pressure and symptoms**

Midodrine dosing regimens were considered together, and ranged from 2.5 to 10 mg given orally 15–30 min prior to onset of the dialysis treatment. Six out of 10 studies reported improvement in symptoms of IDH [1,7,10,12,13,15], one reported no change in symptoms [9] and the remainder did not comment on symptom improvement [11,14,16]. Two studies reported pre- and post-dialysis weights, and both showed no difference between the midodrine and placebo groups [10,14]. Two studies commented on the amount of fluid ultrafiltrated and both reported no statistical difference between the control and midodrine arms [10,16]. Four studies noted a decrease in the need for saline infusions [7,10,13,14], while one study found no difference in the need for saline between the control and midodrine phases [1]. Four studies reported adverse events including: scalp paraesthesias, heartburn, flushing, headache, neck soreness and weakness [7,12,13,15].

The weighted means and ranges of pre-dialysis, post-dialysis, pre- to post-dialysis delta and nadir systolic and diastolic blood pressures, in mmHg, are shown in Table 2 for both control and midodrine periods. In the primary studies, it was not clear at what time the pre-dialysis blood pressure was recorded. For most studies, it was likely that this represented the blood pressure immediately prior to commencement of dialysis, while midodrine was taken 15–30 min before this point. Blood pressures were not available prior to the administration of midodrine.

Estimates of variance, SD and/or SEM were available for most studies for the outcomes of post-dialysis (n = 101 subjects) and nadir (n = 79 subjects) blood pressure. This allowed the statistical comparison using a fixed effects model provided in Table 3. For every outcome, it appeared that midodrine held a clinically and statistically significant advantage. This is depicted graphically in the Forrest plots provided in Figure 1. Given the small number of studies and hence subjects, a formal test of heterogeneity was not undertaken, given the limited power inherent in such a test. However, inspection of the Forrest plots would suggest that each study was measuring a similar underlying magnitude and direction of effect.

**Discussion**

In this systematic review, both the data from individual studies and the combined data indicate that midodrine blunted the drop in blood pressure during dialysis. There was also a decrease in symptoms of IDH with midodrine and very few adverse side effects.

The biggest limitation of this systematic review is the quality of the studies. At best, two of the studies were crossover in design but the remainder were pre- and post-intervention. There were no published randomized controlled parallel group trials and the number of patients in each study was small. While it is reasonable to question the wisdom and indeed the validity of mathematically combining results from such studies, the authors felt that such an attempt was warranted, at the very least to provide a crude estimate of the likely effect of midodrine for IDH, to suggest the sample size of a future definitive randomized controlled trial. By way of example, if nadir systolic BP was chosen as primary outcome measure, for which our analysis suggested an advantage of midodrine of 13.3 mmHg (95% CI 8.6–18.0), the sample sizes required for a parallel group, placebo-controlled trial to demonstrate a 10 mmHg effect size with 80% power would be 36 patients per group. For pooled estimates, the P-values and 95% CIs could not be calculated for all outcome variables as many of the necessary elements (raw data, measures of variance or error) were not available to the investigators, nor could pooled estimates of SD be calculated for several variables, preventing their pre-and post-intervention comparison.

An important question that this systematic review cannot answer is whether or not midodrine offers any added advantage to such IDH-preventing strategies as cool dialysate, thermoneutral and/or isothermic dialysis [17]. Our systematic review included two articles which compared cool dialysate, midodrine

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**Table 2. Summary of pooled results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of subjects</th>
<th>Control mean (range)</th>
<th>Midodrine mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre SBP (mmHg)</td>
<td>5</td>
<td>56</td>
<td>123.2 (73.0–135.2)</td>
<td>128.1 (90.5–138.7)</td>
</tr>
<tr>
<td>Pre DBP (mmHg)</td>
<td>5</td>
<td>56</td>
<td>68.1 (44.0–76.2)</td>
<td>72.4 (55.4–81.4)</td>
</tr>
<tr>
<td>Post SBP (mmHg)</td>
<td>8</td>
<td>101</td>
<td>103.1 (64.9–116.5)</td>
<td>115.5 (81.5–129.9)</td>
</tr>
<tr>
<td>Post DBP (mmHg)</td>
<td>8</td>
<td>101</td>
<td>52.5 (32.6–66.8)</td>
<td>58.9 (50.2–72.5)</td>
</tr>
<tr>
<td>Delta SBP* (mmHg)</td>
<td>6</td>
<td>66</td>
<td>20.0 (8.1–26.3)</td>
<td>14.2 (7.4–19.3)</td>
</tr>
<tr>
<td>Delta DBP (mmHg)</td>
<td>6</td>
<td>66</td>
<td>9.5 (6.8–11.4)</td>
<td>6.9 (3.5–8.9)</td>
</tr>
<tr>
<td>Nadir SBP (mmHg)</td>
<td>6</td>
<td>79</td>
<td>91.5 (68.7–101.9)</td>
<td>104.8 (84.7–115.4)</td>
</tr>
<tr>
<td>Nadir DBP (mmHg)</td>
<td>6</td>
<td>79</td>
<td>52.5 (42.8–57.6)</td>
<td>58.4 (52.7–62.6)</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure.

*Delta = pre-dialysis minus post-dialysis measurement.

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**Table 3. Fixed effects model comparing midodrine with control**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean difference (mmHg)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post SBP</td>
<td>12.4</td>
<td>7.1–17.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Post DBP</td>
<td>7.3</td>
<td>3.7–10.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nadir SBP</td>
<td>13.3</td>
<td>8.6–18.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Nadir DBP</td>
<td>5.9</td>
<td>2.7–9.1</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure.
or both with standard therapies [10,16]. While the interventions appeared to be efficacious compared with the control period, there was no discernible difference between cool dialysate and midodrine, nor any added benefit of the combination [10]. Small sample sizes in each study would hamper the statistical power to discern what would probably be a modest effect size between these interventions. None of the remaining studies included in our analysis employed cool dialysate as a strategy during both the control and midodrine periods. It also was not clearly stated in all of the studies whether the other important co-interventions to prevent IDH such as sodium ramping and saline boluses were applied equally during the control and midodrine periods.

Another limitation was the timing of the pre-dialysis blood pressure measurement. In the studies that report the timing specifically, most reported measuring pre-dialysis blood pressures 15–30 min after the dose of midodrine was given. This may be contributing to the fact that the baseline pre-dialysis blood pressures were higher in the midodrine period compared with the control period, as is evident in Table 2. As a result, it is difficult to state with confidence that the significant differences in nadir and post-dialysis blood pressure are indeed due to the intervention, and not due to imbalances at baseline. A large randomized parallel group design, with blood pressures measured prior to administration of midodrine or placebo, would eliminate this uncertainty.

**Conclusions**

Midodrine seems to be gaining favour as a strategy to aid management of IDH. Based on the results of this systematic review, midodrine seems to be an effective and safe treatment for IDH. However, this conclusion must be viewed with caution, as most of the papers included in our analysis were not randomized, nor was it clear if patients, providers or analysts were blinded to treatment, which are factors that may have exaggerated the estimates of intervention benefit [18]. Small sample sizes would greatly impair the ability to observe rare but significant adverse effects. The authors have presented a crude estimate of the effect of midodrine on the post-dialysis and nadir systolic and diastolic blood pressures, based largely on pre-and post-intervention studies. As the role of midodrine in combination with cool dialysate remains uncertain, the authors would recommend that any future randomized trial include cooling of dialysate as a standard therapy, with which the addition of midodrine or placebo is compared. Such a large trial would confirm the utility and safety of midodrine for IDH in this highly complex patient population.
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Conflict of interest statement. None declared. Shire Pharmaceutical Development Inc. provided raw data for inclusion in this systematic review, but did not influence the analysis nor publication of these results.

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