Online Data Supplement

Chronotherapy for Hypertension in Obstructive Sleep Apnoea (CHOSA):
A Randomised, Double-blind, Placebo Controlled Crossover Trial
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Methods

Recruitment

Recruitment was stopped after 79 patients had completed the second treatment phase (96% of target) because grant funding had finished. The trial was stopped when these patients had completed the entire study.

Exclusion criteria

Additional exclusion criteria were: intolerance to Angiotensin Converting Enzyme Inhibitor (ACE-i) medications, shift workers who rotate to night shift, patients unwilling to undergo washout of ACE-i or Angiotensin Receptor Blocker (ARB) medication, poorly controlled diabetes (defined as HbA1c≥8), unstable angina, heart failure NYHA Class III and IV, recent (<6 months) revascularisation procedure or AMI, significant arrhythmia or atrial fibrillation, chronic kidney disease, more than 20% of AHI with central apneas, cognitive impairment, uncontrolled psychiatric disorders or physically unable to participate in the study.

Sleep studies

Sleep studies were performed across various centres using different polysomnography equipment but with similar scoring criteria. Patients were recruited from 2011 to 2015 which incorporates the change in recommended AASM scoring criteria in 2012.\(^1\) Throughout the
trial the oxygen desaturation index, our main PSG qualifying criteria, was based on a desaturation of $\geq 3\%$ that followed a hypopnea or an apnoea.

Run-in phase

Patients not previously on an ACE-inhibitor or ARB underwent a 4 week run-in phase (5mg perindopril for the first two weeks followed by 10mg perindopril for two weeks). Patients previously on ACE-inhibitor underwent a one week run-in phase (10mg perindopril) whilst patients on an ARB underwent a two week run-in phase (10mg perindopril). Renal function was monitored during this phase and patients with deterioration in renal function were withdrawn.

Actigraphy analysis

Patients were asked to wear an actiwatch for 24 hours, in conjunction with the 24 hour Ambulatory blood pressure monitoring (ABPM). Actiwatches were configured to collect activity and light at 15 second epochs. Actigraphy data was analysed manually using Actiware (Phillips Actiware v.6, Respironics Inc, Murrysville PA, USA). The data were analysed by one investigator using a combination of the patient’s sleep diary, reported sleep and wake times, and the data available from the actiwatch download. If these were inconsistent, a second experienced scorer was consulted for an independent analysis and consensus was obtained. Sleep onset and offset times were marked on the actogram, including naps during the day-time, and wakeful periods during the night. Hence a sleep period was not always a continuous period throughout the night. This allowed us to accurately identify sleep and wake times.

The actiware options and settings were as follows: 1. wake threshold selection was set at medium, 2. immobile minutes for sleep onset and sleep end were set at 10 minutes. However,
some patients demonstrated very frequent movements during sleep and in these patients the immobile minutes setting was reduced to zero minutes in order for the software to recognise the period as sleep. Based on the results of the analysed actogram, the investigator then assigned a status of either wake or sleep to each blood pressure recording taken over the 24 hour period.

*Measurement of blood pressure*

Office blood pressure readings were performed manually using the Mercury-Free Sphygmanomaneter UM-101 (A&D, Tokyo, Japan) and according to EHS guidelines.²

*Ambulatory blood pressure monitoring*

The machine was set to take 30 minutely readings during the day and hourly readings overnight based on anticipated sleep times according to the patient. If the proportion of successful readings was lower than 80%, the patient was asked to repeat the test. If the patient did not consent to repeat the test, the initial 24hr recording was utilised as per intention to treat. Technique was otherwise as per the EHS guidelines.³

*Medications*

Medications, both active and placebo were provided by the pharmaceutical company, Servier Laboratories (Australia). Packaging according to randomisation number and treatment arm was completed by Pharmaceutical Packaging Professionals. The medication, perindopril arginine (Coversyl) was provided in 5mg tablets. The active and placebo medications were identical in appearance and quantity.

*CPAP machines and settings*

Patients were contacted by the CPAP therapist one to two weeks after commencing CPAP to ensure that there were no issues with acclimatisation. If the CPAP therapist was concerned, the patient was reviewed face-to-face with potential change of machine and pressures to
optimise control of OSA and patient comfort. To this effect, two patients were changed from the standard fixed pressure to an auto-setting machine. At the end of the 8 week period, machines were downloaded to obtain usage and residual AHI data.

**Results**

24h-ABPM and actigraphy data quality

There were 324 24h-ABPM recordings analysed with an average of 87% successful blood pressure readings. This far exceeded the current recommendation of at least 70% of readings. There were no missing 24h blood pressure data unless the patient had withdrawn.

Of the 322 actiwatch recordings, 20 (6%) were found to be unsuccessful and self-reported sleep-wake times were used to determine sleep-wake periods for 24h ABPM.

**Weight**

There was no change in weight in patients from baseline to either morning or evening dosing. However there was a significant change in weight when CPAP was added to those on the morning active dose (-0.57kg +/- 1.6 SD, p=0.03). This contrasts with a non-significant reduction in weight in patients on an evening dose (-0.63kg +/- 1.9 SD, p=0.06), although there was no significant difference in the change in weight between the two groups (-0.07kg, p=0.90).

**Medication compliance**

Medication compliance was calculated by pill counts from returned bottles. If the bottles were not returned, the data was considered missing. This occurred for 141/1644 (8.6%) of bottles. Overall compliance was over 90% across all treatment phases and regardless of whether the medication was active or placebo. However, patients tended to be more
compliant with morning medications. In phase 1, patients took evening active tablets less than morning placebo tablets (95.8% vs 97.6%, p=0.038), and took morning active tablets more often than evening placebo tablets (97.2% vs 93.8%, p=0.002). In phase 2, patients took evening active tablets less than morning placebo tablets (90.9% vs 96%, p=0.016), but took morning active tablets equally to evening placebo tablets (96.7% vs 96.5%, p=0.92). Patients who started in phase 1 with morning active tablet dosing then had evening active tablet dosing in the phase 2 were less compliant with evening dosing in the second arm (97% vs 91%, p=0.013). There was no difference in compliance in those that started with evening active tablets in the phase 1 then had morning active tablets in phase 2 (94.5% vs 98.6%, p=0.13). In phase 3, patients were equally compliant with either morning or evening active tablets (95.3% vs 94.6% respectively, p=0.80).

**CPAP data**

CPAP compliance failed to be initially obtained from one patient’s device due to a technical issue and this patient was asked to repeat testing for a further 24 hours with CPAP and 24 hour blood pressure monitoring together. The compliance data obtained from this patient was hence from only one nights recording rather than the eight week period. Two patients did not use their machine during the entire allocated period and hence residual AHI data was unavailable.
Figure E1. Ambulatory blood pressure profiles for patients at baseline, after morning or evening dosing for six weeks, and after the addition of CPAP for eight weeks. The top panel shows systolic blood pressure (SBP) over 24 hours for the group of patients from baseline that ultimately completed the study on morning (AM) dosing and CPAP. It does not include their response to PM dosing. The bottom panel shows similar results for patients from baseline that ultimately completed the study on evening (PM) dosing and CPAP. It does not include their response to AM dosing.
Table E1. Office blood pressure results before and after treatment with morning and evening dosing of perindopril (n=80)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>AM dosing</th>
<th>PM dosing</th>
<th>Difference between groups†</th>
<th>P value for difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mmHg</td>
<td>136.1 ± 1.3</td>
<td>136.1 ± 1.2</td>
<td>-0.02 (-1.9 to 1.8)</td>
<td>0.986</td>
</tr>
<tr>
<td>Office DBP, mmHg</td>
<td>86.9 ± 1.0</td>
<td>88.8 ± 1.0</td>
<td>1.9 (0.0 to 3.7)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

*Values are means ± standard error. Analyses performed using paired samples t-test
†Refers to “PM dosing” – “AM dosing”
SBP- Systolic blood pressure, DBP – Diastolic blood pressure, AM – morning dosing; PM – evening dosing
Table E2. Office blood pressure results before and after addition of CPAP to either morning or evening dosing of perindopril*

<table>
<thead>
<tr>
<th>Variable</th>
<th>AM dosing and CPAP (n=39)</th>
<th>PM dosing and CPAP (n=38)</th>
<th>Difference between groups†</th>
<th>P value for difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mmHg</td>
<td>136.2 ± 2.2</td>
<td>137.6 ± 1.8</td>
<td>1.4 (-4.3 to 7.0)</td>
<td>0.63</td>
</tr>
<tr>
<td>Office DBP, mmHg</td>
<td>85.1 ± 1.9</td>
<td>87.0 ± 1.4</td>
<td>1.8 (-2.8 to 6.5)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Values are means ± standard error. Analyses performed using independent samples t-test
†Refers to “PM dosing and CPAP” – “AM dosing and CPAP”
SBP- Systolic blood pressure, DBP – Diastolic blood pressure, AM – morning dosing; PM – evening dosing, CPAP – Continuous positive airway pressure.
### Table E3. Sub-group analysis of non-dippers before and after treatment with morning and evening perindopril (n=21)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>AM dosing</th>
<th>Change from baseline to AM dosing (95% CI)</th>
<th>P value for change</th>
<th>PM dosing</th>
<th>Change from baseline to PM dosing (95% CI)</th>
<th>P value for change</th>
<th>Difference between groups† (95% CI)</th>
<th>P value for group comparison†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake mean SBP, mmHg</td>
<td>146.5 ± 2.7</td>
<td>135.8 ± 2.7</td>
<td>-10.7 (-12.1 to -9.2)</td>
<td>&lt;0.001</td>
<td>139.9 ± 2.7</td>
<td>-6.6 (-8.0 to -5.2)</td>
<td>&lt;0.001</td>
<td>4.1 (2.7 to 5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep mean SBP, mmHg</td>
<td>139.2 ± 2.8</td>
<td>127.0 ± 2.7</td>
<td>-12.3 (-15.3 to -9.3)</td>
<td>&lt;0.001</td>
<td>127.8 ± 2.7</td>
<td>-11.5 (-14.5 to -8.5)</td>
<td>&lt;0.001</td>
<td>0.8 (-1.9 to 3.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>24-h mean SBP, mmHg</td>
<td>145.1 ± 2.6</td>
<td>133.9 ± 2.6</td>
<td>-11.1 (-12.5 to -9.8)</td>
<td>&lt;0.001</td>
<td>137.0 ± 2.6</td>
<td>-8.1 (-9.4 to -6.7)</td>
<td>&lt;0.001</td>
<td>3.0 (1.7 to 4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wake mean DBP, mmHg</td>
<td>91.1 ± 2.0</td>
<td>84.9 ± 2.0</td>
<td>-6.2 (-7.2 to -5.2)</td>
<td>&lt;0.001</td>
<td>87.6 ± 2.0</td>
<td>-3.5 (-4.5 to -2.5)</td>
<td>&lt;0.001</td>
<td>2.7 (1.7 to 3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep mean DBP, mmHg</td>
<td>83.0 ± 1.9</td>
<td>77.9 ± 1.9</td>
<td>-5.1 (-7.3 to -2.9)</td>
<td>&lt;0.001</td>
<td>77.9 ± 1.9</td>
<td>-5.1 (-7.3 to -2.9)</td>
<td>&lt;0.001</td>
<td>0.0 (-2.0 to 2.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>24-h mean DBP, mmHg</td>
<td>89.5 ± 1.9</td>
<td>83.4 ± 1.9</td>
<td>-6.1 (-7.1 to -5.1)</td>
<td>&lt;0.001</td>
<td>85.3 ± 1.9</td>
<td>-4.2 (-5.1 to -3.2)</td>
<td>&lt;0.001</td>
<td>1.9 (1.0 to 2.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ± standard error. SBP- Systolic blood pressure, DBP – Diastolic blood pressure, AM – morning dosing; PM – evening dosing
†Refers to “Change from baseline to PM dosing” – “Change from baseline to AM dosing”
References

