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EFFECT OF EFFERVESCENT PARACETAMOL ON BLOOD PRESSURE. A CROSSOVER RANDOMIZED CLINICAL TRIAL

Short title: Effervescent paracetamol and blood pressure

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Source of Funding
The project received a research grant from the Carlos III Institute of Health, Ministry of Economy and Competitiveness (Spain), awarded in the 2011 call under Health Strategy Action 2013-2016, within the National Research Program oriented to Societal Challenges of the Technical, Scientific and Innovation Research National Plan 2008-2011 (EC10-185). The funding bodies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest
The authors report no conflicts of interest.

Word count: 4120
Number of tables: 2
Number of figures: 3
ABREVIATIONS DEFINITION LIST

BP: Blood Pressure

SBP: Systolic blood pressure

DBP: Diastolic Blood Pressure

HT: hypertension

CI: Confidence interval

ABPM: Ambulatory blood pressure monitoring

VAS: Visual analogic scale

NSAID: Non-steroidal antiinflammatory drugs

SD: standard deviation
ABSTRACT

Objective: To evaluate the effect of effervescent paracetamol on office and ambulatory blood pressure (BP) compared with non-effervescent paracetamol in hypertensive patients.

Design: This was a multicenter open crossover randomized clinical trial.

Setting: Primary care centers in Catalonia and the Basque Country.

Participants: Inclusion criteria were office BP ≤ 150/95 mmHg and daytime ambulatory BP ≤ 140/90 mmHg, stable pharmacologic or non-pharmacologic antihypertensive treatment, and concomitant chronic osteoarticular pain.

Interventions: Baseline randomized assignment to 3-week periods of effervescent paracetamol (1 g three times day) first and non-effervescent paracetamol later, or inversely, during a 7-week study period. At the start and end of each treatment period, 24-h ambulatory BP monitoring was performed.

Main outcome measures. Differences in 24-h systolic BP (SBP) between baseline and end of both treatment periods. The main analyses were performed according to the intention-to-treat principle.

Results: In intention to treat analysis, 46 patients were analysed, 21 were treated with paracetamol effervescent and non-effervescent later, and 25 followed the opposite sequence. The difference in 24h SBP between the two treatments was 3.99 mmHg (95%CI 1.35 to 6.63; p=0.004), higher in the effervescent paracetamol treatment period. Similarly, the per-protocol analysis showed a difference in 24h-SBP between the two groups of 5.04 mmHg (95%CI 1.80 to 8.28; p=0.004), higher in the effervescent paracetamol treatment period.

Self-reported pain levels did not differ between groups and did not vary by treatment period. No serious adverse events were reported in either study arm.

Conclusions: Effervescent paracetamol tablets are responsible for a significant daytime and overall increase in ambulatory 24-h SBP.
Trial registration: NCT: 02514538  EudraCT: 2010-023485-53
BACKGROUND

Given the high prevalence of hypertension (HT) especially among those aged 50 and above, it is frequently associated with other disorders, such as osteoarthritis chronic pain. Clearly, the analgesic strategy in these patients must avoid drugs that interfere with blood pressure (BP) control. The usual choice is paracetamol (1) which has various galenic formulations, including an effervescent form.

Effervescent pharmaceutical formulations contain sodium salts, mainly bicarbonate, carbonate, or citrate. A directly proportional relationship between the consumption of sodium chloride and BP has been reported (2–4), but it is not clear whether other sodium salts (citrates or carbonates, for example) also have an effect that increases BP levels. Small clinical studies, without the characteristics of usual clinical practice, have shown contradictory effects—even, in some cases, finding a reduction in BP levels associated with some sodium salts (5–8). This variability could be due to differences in study design.

Observational studies have found a risk of increased BP related to effervescent paracetamol (9,10), although confounding variables such as pain or concomitant use of other types of drugs may not have been adequately considered (9).

The lack of clinical trial results that can be applied in the majority of the population motivated the present research. The main objective was to estimate the effect on blood pressure of effervescent formulation compared to non-effervescent formulation of paracetamol in patients with hypertension.
METHODS

Study Design

This multicenter, randomized, controlled, cross-over, open, phase IV clinical trial compared the effect on BP in hypertensive patients of two different formulations of paracetamol (effervescent [A] vs. non-effervescent [B] tablets) after three weeks of treatment. The complete study design has been published (11), and no important changes to methods were made after the trial began. Given the characteristics of the condition and the effect studied, a cross-over design was chosen (Figure 1).

The primary endpoint was the change in mean values of 24-h systolic blood pressure (SBP), measured by ambulatory blood pressure monitoring (ABPM), between the start and the end of each treatment period (A and B). Secondary endpoints were the changes in mean values of 24-h diastolic blood pressure (DBP), daytime and nighttime SBP and DBP and of office SBP and DBP measurements, as well as the percentage of patients who maintained office BP levels <140/90 mmHg and 24-h values <130/80 mmHg throughout the study periods. Changes in patients’ assessment of their pain levels and adverse events were also recorded for each treatment period.

The study was carried out by doctors and nurses in 15 primary care centers in Catalonia and the Basque Country (Spain) between 2012 and 2014. The clinical trial protocol was approved by the Clinical Research Ethics Committees (IDIAP Jordi Gol and Euskadi Ethics Committee, respectively) and the Spanish Agency of Medicines and Health Products. The research followed the 2008 revision of the Helsinki Declaration, the Spanish Royal Decree 223/2004, of February 6th which regulates clinical drug trials, and the Good Clinical Practice Guideline (ICH, E6, 1996, Step 4).

Participants

Patients included in the study were older than 18 years, with hypertension, chronic osteoarticular pain, and usual need of analgesic treatment.

A mean daytime BP ≤140/90 mmHg was required for inclusion, and an office BP of ≤ 150/95 mmHg or ≤135/85 mmHg for patients with associated cardiovascular disease, or
diabetes mellitus. Other inclusion criteria were stable antihypertensive treatment, without changes in the previous month, or adequate control without antihypertensive drugs and a score between 1 and 4 on a Visual Analog Scale (VAS) indicating mild to moderate pain associated with the chronic osteoarticular disease. Patients with allergy, intolerance, or contraindication to paracetamol or tramadol were excluded, as well as those who had taken Non-Steroidal Anti-Inflammatory Drugs (NSAID) orally or parenterally in the week previous to inclusion. Other exclusion criteria were heart failure or previous cardiovascular event (coronary disease or stroke) in the last 6 months, obstructive sleep apnea, secondary hypertension, transaminases levels higher than 3 times normal values, estimated glomerular filtration rate <30 ml/min, dementia or impaired judgment, alcoholism or other addictions, pregnancy, or major changes in lifestyle (initiate or increase physical exercise, make dietary changes). Medication-related exclusions included patients treated with oral anticoagulants or subcutaneous heparin; patients for whom changes are foreseen, during the study period, in their usual dose of drugs with effects on BP (alpha blockers, tricyclic antidepressants, beta blockers in eye drops, sympathomimetic vasoconstrictors, other effervescent agents, hormonal contraceptives, NSAIDs, corticosteroids, anabolic steroids, erythropoietin, and cyclosporine). Finally, those who did not give their informed consent and those who, in the opinion of the investigator, were likely to show poor adherence or become lost to follow-up were excluded. **Intervention** The study is designed in two different treatment periods, each one lasting three weeks, both preceded by a washout period of 3 to 15 days. During both washout periods, the only analgesic allowed was tramadol. In visit 0 (figure 1), patients who met all inclusion criteria and none of the exclusion criteria were allocated through an electronic case report form (a centralized and automatic randomization procedure) to one of the treatment sequences: AB (effervescent/non-effervescent paracetamol) or BA (non-effervescent/effervescent paracetamol). Patients
were given 1 g paracetamol every 8 h during the 3 weeks of each treatment period. The soluble salt in the effervescent paracetamol was sodium citrate (545 mg sodium per dose). As recommended for second-line analgesic treatment (1), 50 mg tramadol every 8 h was permitted if pain persisted at a level >3 on the VAS.

**Assessments**

The entire randomization protocol as well as the follow-up visits was previously published (11) and the treatment sequences were shown in figure 1. In summary, after the informed consent form was signed, a screening visit was performed with a physical examination, laboratory test (if none had been done in the previous 3 months), and 24-h validated ABPM (Microlife WatchBP or Spacelabs 90207) (12,13). BP measurements were taken every 20 minutes during both waking and resting hours.

Once all the screening was made and the washout period was completed, patients who remained eligible received the medication to be used for the first treatment period (3 weeks) of their randomly assigned (AB or BA) study group. After the first 3 weeks, 24-h ABPM was performed and patients received the medication for the second study period, which ended with the fourth ABPM. Adverse events during the study were recorded in the case report form, indicating the potential relationship with study drugs; if serious adverse reactions occurred, the researcher responsible for pharmacovigilance had to be immediately notified.

The study was monitored by Clinical Research Associate (CRA) personnel.

**Statistical methods**

We estimated the sample size for a crossover trial with the aim to detect a mean difference in 24 hours SBP greater than 2 mmHg (minimum clinically relevant difference) assuming a standard deviation (SD) of 4.5 mmHg (14). With a two-sided alpha error of 5%, we estimated that 49 patients would need to be enrolled to have a statistical power of 80% considering 15% of drop-out rate.

Baseline characteristics are described by frequencies and percentages in categorical variables and by mean and SD in quantitative ones.
Main and secondary analysis was carried out on an intention-to-treat (ITT) basis with patients who fulfilled all the eligibility criteria and had a measurement of the primary outcome at the baseline visit. Only for the primary outcome, we performed a per protocol analysis with the patients who had completed the trial in the allocated arm having the final 24h SBP measurements.

To analyse the differences in BP changes between drug formulations, we fitted an ANOVA model with period, sequence and treatment as fixed factors, and subject as random factor nested within ‘sequence’. Point estimates and 95% confidence intervals of the mean differences between two formulations are provided.

For the ITT population, missing BP values were imputed using Last Observation Carried Forward (LOCF) method.

Subgroups analyses were performed according to adherence to paracetamol treatment and depending on whether the patient took any antihypertensive drugs.

All tests are two-sided significance level of 0.05 and analyses were performed using R statistical package version 3.2.5 or higher.

RESULTS

Study Population

Of the 59 patients eligible, 49 (77.6% women, n=38) were randomized: 24 initially to effervescent paracetamol and 25 to non-effervescent paracetamol tablets (Figure 2). In the ITT analyses three patients were discarded because they presented an exclusion criteria after randomization, so 46 patients were included (21 in the AB group and 25 in the BA group). The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the treatment groups.

During the study period, ten patients were lost to follow-up (5 of them due to violation of protocol for uncontrolled pain (VAS>4), unpermitted medication and non-compliance of medication) and another one withdrew consent, so 35 were included in the per-protocol analysis. Regarding the losses to follow up, they were similar between the two groups.
**Primary Endpoint**

In the intention-to-treat analysis, treatment with effervescent paracetamol was associated with an increase of 3.59 mmHg (95% CI 1.39 to 5.79; p=0.003) in 24h SBP, and non-effervescent paracetamol with a 0.33 mmHg reduction (95% CI -1.78 to -1.13; p=0.886); the difference in 24h SBP between the two treatments was 3.99 mmHg (95% CI 1.35 to 6.63; p=0.004), higher in the effervescent paracetamol treatment periods.

Similarly, the per protocol analysis showed an increase of 4.57 mmHg in 24h SBP (95% CI 2.01 to 7.13) under effervescent paracetamol treatment and a reduction of 0.21 mmHg (95% CI -2.12 to -1.71; p=0.009) at the end of non-effervescent paracetamol treatment.

The difference in 24h-SBP between the two groups was 5.04 mmHg (95% CI 1.80 to 8.28; p=0.004).

**Secondary endpoints**

**Ambulatory blood pressure**

Under effervescent paracetamol treatment, patients had higher daytime SBP, while non-effervescent tablets were associated with a reduction a significant estimated between-group difference of 5.05 mmHg (95% CI 2 to 8.10; p=0.002). Greater 24-h increases were observed in DBP and nighttime SBP but these differences did not reach statistical significance. Mean differences in ambulatory BP in the different treatment periods are shown in Figure 3.

These results were not affected by the patients’ level of pain, which remained very similar from the beginning to the end of the treatment periods in both groups (from VAS 2.8 to 2.6 for effervescent treatment, p=0.077; from VAS 2.9 to 2.6 for non-effervescent paracetamol tablets, p=0.057).

Although nonsignificant, greater increases in 24-h SBP were observed in patients who were adherent to effervescent treatment, compared to non-adherent [4.8 mmHg (95% CI 2.1 to 7.4) vs 2.2 mmHg (95% CI -6.5 to 10.9, respectively; p=0.391).

**Results stratified by antihypertensive treatment**
Among patients taking renin-angiotensin system inhibitors, the effect of effervescent paracetamol on 24h BP was significantly greater, compared to the non-effervescent formulation (4.57 mmHg, 95%CI 1.30 to 7.85 vs -1.61 mmHg, 95%CI -3.29 to -0.08; p=0.003). Differences in BP were also observed between waking and resting periods. During waking hours, the combination of effervescent paracetamol and renin-angiotensin system inhibitors was associated with a rise in SBP of 6.11 mmHg (95%CI 2.65 to 9.57).

**Variation in patients with well-controlled hypertension**

At the end of the study, 69.6% of patients had well-controlled BP (<130/80 mmHg) during 24-h ambulatory monitoring (95%CI 54.1 to 81.8) with effervescent paracetamol, and 80.4% (95%CI 65.6 to 90.1) were well controlled when taking non-effervescent tablets (p=0.131).

**Adverse effects**

Only 11 adverse events (20%) were considered to have a probable or possible relationship with the drug therapy (Table 2). No significant differences were found between the paracetamol formulations in the proportion of patients with adverse events or in the profile of study participants who did or did not experience adverse events.

**DISCUSSION**

To our knowledge, this is the first randomized controlled clinical trial to evaluate the effect on BP of effervescent paracetamol. Currently, the effect of non-effervescent paracetamol on BP is under discussion. In some cohort studies, patients taking paracetamol on a regular basis had between 1.5 and 2 times more risk of developing hypertension than those who did not take it (14,15). In a previous clinical trial with patients with coronary disease, an increase of up to 3 mmHg in the mean systolic BP and 2 mmHg in the diastolic was demonstrated with the use of paracetamol (14); however, in a case-control study (15) with hypertensive and non-hypertensive patients, but without coronary disease, this effect was not observed. In the clinical trial, paracetamol was compared with placebo, and in both studies it was used in
a non-effervescent formulation; still, paracetamol remains the recommended analgesic, on the assumption that it is less harmful than NSAIDs. The BP increase effect of the effervescent formulation salts must be added to the potential effect of paracetamol on BP.

In our clinical trial, the only difference between the two branches was the effervescent or non-effervescent formulation of paracetamol. Therefore, the potential effect of paracetamol on BP is equivalent in both arms of the study.

In our study the use of effervescent paracetamol by patients with hypertension was associated with elevated 24-h ambulatory SBP, particularly as a result of an increase during waking hours. Therefore, the increase in SBP can be attributed to the sodium salts contained in effervescent tablets. This rise in ambulatory SBP is clinically relevant and therefore may have implications for controlling the patient’s BP. We also found a greater elevation of office BP in patients with hypertension using effervescent paracetamol, but there were no significant differences. There are two possible reasons for this finding: the possibility of “white-coat hypertension” and the small number of patients included in the study sample.

In any case, the increase in ambulatory SBP was statistically significant, clinically relevant, and could have a negative impact on cardiovascular prognosis because of the more significant association of ambulatory BP, compared to office BP (16). The sample of patients included in our study was too small to permit an analysis of which patients with hypertension will experience a greater effect from effervescent tablets.

Nonetheless, it is probable that these would be patients who are more sodium-sensitive or receiving treatment with antihypertensive drugs that show a link between response to therapy and dietary salt consumption, such as angiotensin receptor blockers (17).

It is notable that effervescent paracetamol did not increase nighttime BP in our study. The explanation could be an essentially daytime use of paracetamol, totalling 3 effervescent tablets. In addition, the final tablet was taken in the evening, possibly
leading to an effect that diminished gradually during the night. On the other hand, being
stretched may increase natriuresis in some patients, partially neutralizing the effect of
the last effervescent tablet of the day on the arterial pressure.

As previously discussed, the effect seems to be attributable to the sodium salts contained
in effervescent tablets. Therefore, the effects on BP observed in the present study could
be extended to other drugs with effervescent galenic formulations, such as mucolytic
agents, cold and flu remedies, vitamin preparations, or antacids. Patients with
hypertension might also be advised against using these effervescent drugs, but this
would require additional clinical trials to verify this possibility. Our study only assessed
the paracetamol formulation containing sodium citrate.

The study had some limitations, in addition to the small sample size mentioned above.
First, it was not a blinded study. However, as the intervention was designed precisely for
the purpose of assessing the effect of the salt that gives the drug its effervescence,
blinding or masking was impossible. Other limitations were the inability to adjust for the
use of salt or other nutrients in the diet or for levels of physical activity, although
participants were asked not to make any great changes in their diet or activity level during
the 7-week study period.

From the primary care perspective, and in the conditions of usual clinical practice, there
is no easy method of determining salt consumption other than patient reporting, which is
always very subjective. The crossover clinical trial design may have compensated for the
effect of this limitation. On the other hand, the study has the added interest of being able
to eliminate an important potential confounder: the chronic pain experienced by these
patients. This variable showed little change over the course of the follow-up and was
comparable for both interventions (effervescent and non-effervescent).

As it has been previously explained, the losses to follow up were similar between the two
groups.

Our study clearly showed not only the effect of effervescent paracetamol on BP rises but
also that these increases are clinically relevant. From the clinical practice perspective,
with this new evidence it seems fully advisable not to prescribe effervescent paracetamol for patients with hypertension. This recommendation could very likely be extended to other drugs with effervescent formulations that are prescribed for other indications. This line of thinking requires further research. In addition, questions about usual use of effervescent paracetamol should be incorporated into the anamnesis of patients with hypertension before new treatment decisions are made.
CONCLUSIONS

Effervescent paracetamol produced a significant increase in 24h SBP and raised both systolic and diastolic pressure during monitoring, regardless of the level of pain reported by the patient. The use of this effervescent drug can significantly worsen control of ambulatory BP, which must be considered before deciding to intensify the therapeutic approach to poorly controlled hypertension. That is, apart from assessing the concomitant use of drugs that affect BP, routine anamnesis is advisable to clarify the consumption of any kind of effervescent drugs, but especially effervescent paracetamol.

Acknowledgments

Natalia Burgos Alonso
Ignacio López Pavón
Carlos Roca Sánchez
Rosa Maria Coma Carbó
Mariano De La Figuera Von Wichmann
Lucas Mengual Martínez
Carmen Yuste Marco
Montserrat Teixidó Colet
Josep M. Pepió i Vilambí
Riera Ciurana Tost.
Mª Antònia Vila Coll
Josep Maria Bordas Julve
Rosa Aragonès Forès
Francisco Javier Pelegrina Rodríguez
Josep Agudo Ugena
Carlos Blanco Mata
Jon de la Iglesia Berrojalbiz
Maria Cruz Gómez Fernández
BIBLIOGRAPHY


file:///C:/Users/cyran/Downloads/Sodium_bicarbonate_and_sodium_chloride__effects_10 (1).pdf


FIGURES AND TABLES

Table 1. Basal characteristics of study participants. Values are means (standard deviation) unless otherwise indicated. All comparisons are nonsignificant.

<table>
<thead>
<tr>
<th></th>
<th>Effervescent-First (n=24)</th>
<th>Noneffervescent-First (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.8 (9.6)</td>
<td>66.9 (8.9)</td>
</tr>
<tr>
<td>Women</td>
<td>18 (75%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>9.6 (5.2)</td>
<td>9.9 (6.5)</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>8 (33%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Office SBP/DBP (mmHg)</td>
<td>131.2 (10.5)/74.1 (7.7)</td>
<td>127.2 (15)/75.2 (6)</td>
</tr>
<tr>
<td>24-h SBP/DBP (mmHg)</td>
<td>122.7 (11)/69 (5.7)</td>
<td>120.1 (10.8)/70.4 (6.8)</td>
</tr>
<tr>
<td>Daytime SBP/DBP (mmHg)</td>
<td>126.2 (11)/73.5 (6.8)</td>
<td>124 (10.2)/74.9 (6.4)</td>
</tr>
<tr>
<td>Nighttime SBP/DBP (mmHg)</td>
<td>116 (12)/62.4 (5.9)</td>
<td>112.4 (14.2)/64 (7.3)</td>
</tr>
<tr>
<td>VAS (cm)</td>
<td>2.9 (1.2)</td>
<td>2.7 (1.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (8.3%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14 (58.3%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Antihypertensive treatment (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Diuretics</em></td>
<td>30</td>
<td>31.7</td>
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<tr>
<td><em>ACEI</em></td>
<td>22.5</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td>1 drug</td>
<td>2 drugs</td>
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<tr>
<td>ARB</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7.5</td>
<td></td>
</tr>
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</table>

Number of antihypertensive drugs (%)

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; VAS: Visual analog scale; ACEI: angiotensin-convertin enzyme inhibitor; ARB: angiotensin receptor blocker
Table 2: Adverse Effects.

<table>
<thead>
<tr>
<th></th>
<th>Effervescent Paracetamol</th>
<th>Paracetamol Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Migraine</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fainting/Nausea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
**Figure 1:** Visits and design of the clinical trial

V-1: 7 to 15 days before V0; V0: baseline visit; V1: week 1; V2: week 3; V3: week 4; V4: week 5; V5: week 7
Figure 2: Eligibility, Randomization, and Follow-up

59 assessed for eligibility

49 randomized

10 patients not randomized:
- 5 Patients who did not give informed consent
- 3 Diagnosis of hypertension in non-stable antihypertensive treatment (i.e., changed in the last month) or without antihypertensive drug treatment with blood pressure greater than 150 and/or 95
- 1 Patient treated with oral anticoagulants or subcutaneous heparin
- 1 Allergy, intolerance or contraindication to paracetamol or tramadol

24 Assigned to effervescent paracetamol (A), then non-effervescent (B)
- 3 excluded after randomization

25 Assigned to Non-effervescent paracetamol (B), then effervescent (A)

46 included in intention to treat analysis (21 AB/25 BA)

10 lost to follow-up
1 withdrew consent
Figure 3: Office, 24-h, daytime and nighttime mean blood pressure differences between basal and final visits

<table>
<thead>
<tr>
<th></th>
<th>ΔC</th>
<th>ΔE</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td><strong>OFFICE</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-0.11</td>
<td>0.99</td>
<td>3.10</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.26</td>
<td>0.67</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>ABPM 24h</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-0.24</td>
<td>2.69</td>
<td>2.94</td>
</tr>
<tr>
<td>DBP</td>
<td>0.25</td>
<td>2.58</td>
<td>1.94</td>
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<tr>
<td><strong>ABPM Daytime</strong></td>
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<td></td>
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<tr>
<td>SBP</td>
<td>-0.71</td>
<td>1.48</td>
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<tr>
<td>DBP</td>
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<td>1.23</td>
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<tr>
<td><strong>ABPM nighttime</strong></td>
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<tr>
<td>SBP</td>
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<td>DBP</td>
<td>0.68</td>
<td>2.03</td>
<td>0.41</td>
</tr>
</tbody>
</table>