Sodium Chloride Raises Blood Pressure in Normotensive Subjects

The Study of Sodium and Blood Pressure

Stephen Mascioli, Richard Grimm Jr., Cynthia Launer, Kenneth Svendsen, John Flack, Nelly Gonzalez, Patricia Elmer, and James Neaton

The effects of dietary sodium on blood pressure in normotensive adults is not well characterized. The Study of Sodium and Blood Pressure (SNaP) is a randomized, double-blind crossover trial using a placebo or 96 meq sodium in 4-week treatment periods separated by a 2-week washout period. Before capsule treatment periods, participants were instructed in a low sodium diet for 10 weeks to reduce urinary sodium excretion to less than 35 meq/8 hr. The low sodium diet was continued throughout the capsule treatment periods. Participants (n=48; 47 white, 1 black) were 79% male and had an average age of 52 years, a body mass index of 27.6, and a baseline blood pressure of 131/84 mm Hg. Baseline overnight urinary sodium excretion was 51 meq/8 hr and 19 meq/8 hr after the low sodium diet run-in period, before the capsule treatment periods began. Resting, seated blood pressure was measured twice at each visit in a standard fashion. Differences between sodium and placebo treatment periods were as follows: systolic blood pressure, 123.9 versus 120.3 mm Hg, respectively (p<0.001); diastolic blood pressure, 78.7 versus 76.4 mm Hg, respectively (p=0.005); and sodium excretion, 51.3 versus 30.9 meq/8 hr, respectively (p<0.001). Both systolic and diastolic blood pressures increased significant amounts in normotensive adults on a low sodium diet supplemented with 96 meq/day sodium. Long-term effects and dose-response relations need further study. (Hypertension 1991;17[suppl I]:I-21-I-26)

In recent years interest has increased in the nonpharmacological treatment of high blood pressure. This focus on nonpharmacological treatment is related to the results of large scale trials of antihypertensive drugs, which have been conducted over the past 2 decades.1-4 The results of these studies have greatly increased our understanding of the benefits of treating hypertension, but they have also raised several important questions about the safety of drug treatment for all hypertensive patients, including the possibility that specific subgroups may not benefit from drug treatment.5 Concerns have also been raised about the clinical significance of metabolic consequences of drug therapy, such as the adverse effects of thiazide diuretics on blood lipids.6 Nonpharmacological treatments that have been most commonly mentioned for lowering blood pressure are weight loss, dietary sodium reduction, and alcohol reduction. These are the modalities recommended in the most recent Joint National Committee report7 for initial nondrug therapy of "mild" diastolic hypertension. Weight loss appears well established as a means to lower pressure; however, recommendation of dietary sodium reduction has been much more controversial. This controversy is not new; in fact, the discussion of the cause-effect relation of salt or sodium to high blood pressure and the advisability of lowering dietary sodium has spanned most of this century, and the debate continues.

Several trials have been conducted that have examined the effect on blood pressure of sodium reduction alone or a combination of sodium reduction with other interventions such as weight loss or potassium supplementation. The results of these studies have been summarized in recent reviews.8,9 In some studies a low sodium diet is compared with a usual diet in a nonblinded manner; in other studies, sodium supplementation is compared with placebo in a double-blind manner. For this latter design, all patients received a low sodium diet.

Few studies have included normotensive subjects, even though the influence of sodium intake on blood pressure in normotensive subjects is highly relevant to the issue of the role of sodium reduction in the primary prevention of hypertension.
The purpose of the Study of Sodium and Pressure (SNaP) is to examine the effect of NaCl on blood pressure in normotensive subjects.

Methods

Recruitment

SNaP is a randomized, double-blind, placebo-controlled, crossover clinical trial. Participants for SNaP were recruited from lists of individuals who were ineligible for other research studies conducted by the investigators. Subjects for study were men or women aged 30–59 years with seated diastolic blood pressure of 80–89 mm Hg on entry, no treatment for or diagnosis of hypertension currently or in the past, systolic blood pressure of less than 150 mm Hg, and no serious or life-threatening illnesses.

Design

The design of the trial is shown in Figure 1. The trial was divided into two parts: 1) a low sodium diet alone and 2) a double-blind capsule crossover period combined with the low sodium diet. Participants were initially evaluated at two eligibility visits, and exclusions were made for blood pressure and other criteria. An 8-hour overnight urine collection was obtained before diet recommendations; then participants entered an 8-week period of instruction on a low sodium diet. Participants were instructed to avoid high sodium foods, substitute low sodium foods, and eliminate use of added salt. Dietary advice was given by experienced nutritionists.

After 6 weeks on the low sodium diet, adherence was assessed using five consecutive overnight urine collections. Average overnight sodium excretion was required to be 35 meq or less to be eligible for randomization to the crossover period. The dietary counseling continued throughout the entire study.

Participants meeting eligibility criteria were randomly assigned to one of two sequences of study capsules. Group 1 (n=25) received NaCl capsules (96 meq sodium/day) for 4 weeks and then entered a 2-week washout phase followed by a 4-week placebo period. Group 2 (n=23) had a 4-week placebo period first, a 2-week washout period next, and then 4 weeks of NaCl capsules. Block randomization was used to assure balance in the two treatment sequences. Participants took placebo capsules during the washout periods.

The capsules were size No. 00 interlocking gelatin capsules. The NaCl crystals (food-grade salt, 16 meq sodium/capsule) were microencapsulated with hydrogenated vegetable oil. The placebo capsules were filled with microcrystalline cellulose and were also microencapsulated (Applied Laboratories, Columbus, Ind.). To simulate as closely as possible the absorption of sodium with food, participants were instructed to take sodium capsules three times a day with meals.

Adherence to capsules was examined by capsule counts and also by analysis of overnight urine samples for sodium; samples were taken at the 4- and 10-week visits, that is, at the end of each treatment period.

Measurements

Blood pressure. Blood pressure was measured with the subject in a seated position with the cuff applied to the right arm. Two blood pressures were taken at each visit after a 5-minute rest and were assessed with a random-zero sphygmomanometer (Hawksley) and then averaged. Blood pressure technicians were certified using the technique described by Prineas.

Urine sodium. Urine was collected in a timed overnight collection for measurement of urine sodium excretion. It was divided into aliquots and measured with an ion-selective electrode.

Statistical Methods

Analysis of variance for a crossover design is used to summarize group differences for blood pressure and urine sodium excretion measurements. Before estimating pooled treatment differences, tests for residual treatment effects were performed. For blood pressure, both period 1 and 2 measurements are the average of four blood pressures (two at each visit) taken at the middle and end of treatment periods.

TABLE 1. Characteristics of Randomly Assigned Participants Before and After Dietary Counseling

<table>
<thead>
<tr>
<th></th>
<th>Before low sodium diet</th>
<th>After low sodium diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.7±5.4</td>
<td>...</td>
</tr>
<tr>
<td>Sex ( % men)</td>
<td>79.2</td>
<td>...</td>
</tr>
<tr>
<td>Race ( % white)</td>
<td>97.9</td>
<td>...</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>187.3±27.6</td>
<td>184.7±27.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.6±3.0</td>
<td>27.3±3.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.9±9.1</td>
<td>120.6±11.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>83.9±2.9</td>
<td>77.9±6.9</td>
</tr>
<tr>
<td>Overnight urine sodium excretion (meq/8 hr)</td>
<td>51.4±30.7</td>
<td>19.0±7.5</td>
</tr>
</tbody>
</table>

Values are mean±SD. Data are for 48 participants who completed the crossover portion of the study.
TABLE 2. Urinary Sodium Excretion and Systolic and Diastolic Blood Pressure Differences Between Participants Given Sodium Chloride and Placebo

<table>
<thead>
<tr>
<th>Group 1 (sodium/placebo) (n=25)</th>
<th>Period 1* (sodium)</th>
<th>Period 2* (placebo)</th>
<th>Difference† (sodium-placebo)</th>
<th>Group 2 (placebo/sodium) (n=23)</th>
<th>Period 1* (placebo)</th>
<th>Period 2* (sodium)</th>
<th>Difference† (sodium-placebo)</th>
<th>Pooled treatment differences (n=48)</th>
<th>Sodium-placebo</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urinary sodium excretion (meq/8 hr)</td>
<td>Systolic BP (mm Hg)</td>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td>Urinary sodium excretion (meq/8 hr)</td>
<td>Systolic BP (mm Hg)</td>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td>Sodium-placebo</td>
<td>95% confidence interval</td>
<td>p value</td>
</tr>
<tr>
<td>Group 1 (sodium/placebo) (n=25)</td>
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<td></td>
<td></td>
<td>Group 2 (placebo/sodium) (n=23)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 1* (sodium)</td>
<td>48.2±23.0</td>
<td>126.4±10.5</td>
<td>78.8±5.0</td>
<td>Period 1* (placebo)</td>
<td>27.7±16.0</td>
<td>118.5±10.5</td>
<td>76.6±6.5</td>
<td></td>
<td>20.2±3.6</td>
<td>(13.0, 27.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Period 2* (placebo)</td>
<td>34.1±30.8</td>
<td>122.1±9.2</td>
<td>76.1±6.0</td>
<td>Period 2* (sodium)</td>
<td>54.4±20.6</td>
<td>121.4±9.9</td>
<td>78.5±4.8</td>
<td></td>
<td>3.6±0.9</td>
<td>(1.9, 5.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>Difference† (sodium-placebo)</td>
<td>14.1±5.9</td>
<td>4.3±1.1</td>
<td>2.7±1.1</td>
<td>Difference† (sodium-placebo)</td>
<td>26.7±3.7</td>
<td>2.8±1.4</td>
<td>1.8±1.1</td>
<td></td>
<td>2.3±0.8</td>
<td>(0.8, 3.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pooled treatment differences (n=48)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sodium-placebo†</td>
<td>20.2±3.6</td>
<td>3.6±0.9</td>
<td>2.3±0.8</td>
<td>95% confidence interval</td>
<td>(13.0, 27.3)</td>
<td>(1.9, 5.3)</td>
<td>(0.8, 3.8)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>BP, blood pressure.</td>
<td>Values are mean±SD.</td>
<td>Values are mean±SEM.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Baseline Characteristics

Of the 352 persons screened for initial eligibility for the trial, 50 were randomly assigned to one of the two treatment sequences. The most common reasons for exclusion were blood pressure too low (53%) or too high (8%). Of the 66 participants who completed the 8-week dietary counseling phase, 23% were excluded for high urine sodium levels (average of five overnight collections more than 35 meq/8 hr).

Forty-eight (47 white, 1 black) individuals completed the crossover phase of the trial. Two individuals in the placebo-NaCl sequence dropped out for personal reasons (one in the placebo phase and one in the NaCl phase of treatment); their data are excluded from analysis. The characteristics of randomly assigned participants are shown in Table 1. Study participants were, on average, approximately 52 years old, predominantly male, moderately obese, with mean blood pressures of 131/84 mm Hg and mean urine sodium excretions of 51 meq/8 hr before the low sodium diet. During the diet-only phase, participants tended to lose weight, and their blood pressures fell. Urinary sodium excretion was 19 meq sodium/8 hr by the end of the diet-only phase. Group 1 (NaCl-placebo sequence) and Group 2 (placebo-NaCl sequence) did not differ in these characteristics.

FIGURE 2. Graph showing average overnight urinary sodium excretion by group.
TABLE 3. Randomized, Double-Blind, Adult Sodium Supplementation Trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Design</th>
<th>Between-group difference in sodium excretion (meq/24 hr)</th>
<th>Blood pressure difference (sodium–placebo) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacGregor et al\textsuperscript{13} (1982)</td>
<td>19</td>
<td>Crossover</td>
<td>146</td>
<td>10  5</td>
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<tr>
<td>Watt et al\textsuperscript{14}</td>
<td>18</td>
<td>Crossover</td>
<td>56</td>
<td>0.5 0.4</td>
</tr>
<tr>
<td>Australian National Committee\textsuperscript{15}</td>
<td>103</td>
<td>Parallel</td>
<td>43</td>
<td>4.8 2.8</td>
</tr>
<tr>
<td>MacGregor et al\textsuperscript{16} (1989)</td>
<td>20</td>
<td>Crossover</td>
<td>141</td>
<td>16  9</td>
</tr>
<tr>
<td>Mascioli et al\textsuperscript{17}</td>
<td>48</td>
<td>Crossover</td>
<td>59</td>
<td>8  4</td>
</tr>
</tbody>
</table>

All studies except Mascioli et al\textsuperscript{17} were done with hypertensive subjects; \(n\)=number of subjects.

**Crossover Phase**

Adherence to both placebo and NaCl capsules was excellent, averaging greater than 90% for both. Table 2 gives data on urinary sodium excretion and systolic and diastolic blood pressure during the crossover phase. There is no evidence of carryover effects in urinary sodium or in systolic or diastolic blood pressure. During the capsule treatment periods, treatment differences in sodium excretions averaged 20.2 meq/8 hr \((p<0.001)\) (Figure 2).

Systolic blood pressure averaged 3.6 mm Hg higher during the NaCl capsule treatment periods compared with the placebo period \((p<0.001)\). Sixty-five percent of study participants experienced an increase of systolic blood pressure when on NaCl capsules compared with placebo capsules (Figure 3).

Diastolic blood pressure averaged 2.3 mm Hg higher during the NaCl capsule periods compared with the placebo periods \((p<0.005)\). Sixty-nine percent of study participants experienced an increase of diastolic blood pressure on NaCl capsules compared with placebo capsules (Figure 4).

**Discussion**

These SNaP results on the effects of sodium on blood pressure are in general agreement with past studies. Sodium supplement trials may provide a better estimate of the effect of sodium on blood pressure because sodium dosage can be controlled. Because all participants are on a low sodium diet in such studies, changes in other dietary factors, such as calcium, potassium, and fat, are also comparable between treatment groups. There have been five studies (including SNaP) that have used sodium supplementation in the form of tablets or capsules as the intervention (Table 3). With the exception of the trial by Watt et al\textsuperscript{14} with nonsignificant blood pressure differences, there is a high degree of consistency among studies, suggesting that a sodium dose of 70–120 meq/day is associated with a significant in-

**Figure 3.** Graph showing changes in systolic blood pressure (SBP) from baseline by group. Blood pressures were measured at clinic visits every 2 weeks.
crease in blood pressure. An average estimate of pressure change with 100 meq/day sodium brings about a 2–4 mm Hg rise in diastolic blood pressure and a 3–6 mm Hg increase in systolic pressure. This estimate is consistent with results of the INTER-SALT Cooperative Research Group, \textsuperscript{18,19} which found a 100 meq/day sodium difference to be associated with about a 3 mm Hg difference in diastolic pressures. Therefore, it seems reasonably clear from these studies and others that dietary sodium intervention is feasible and will result in significant lowering of blood pressure. Although the estimates of the pressure effect are modest, they are significant enough to influence clinical management in many hypertensive patients, and even more importantly, if applied to the population at large, sustained reductions of pressure in this range could account for sizable reductions in mortality and morbidity attributed to blood pressure. In addition, sodium reduction could reduce the blood pressure of many mild hypertensive patients to the high-normal range, thus eliminating pharmacological therapy.

Although the relation of sodium to blood pressure is now well established and causal, there are many important questions that remain to be answered. Some of these questions are as follows: Does “sodium sensitivity” really exist in a clinically meaningful context? If so, what factors are related to sodium sensitivity, and are they intrinsic and not modifiable or extrinsic and potentially modifiable? Are there ethnic differences in responsiveness to sodium? If so, what are the factors related to differences in response by ethnic group? Is the dose relation of sodium to change in blood pressure linear or curvilinear? This question has great practical and economic significance in applying dietary sodium recommendations to the general population. What are the long-term effects, that is, over more than a few weeks or months? Are these pressure differences maintained over years? What is the relation of sodium intervention to other interventions, such as weight loss and dietary calcium and potassium, and are the effects on pressure additive? Because dietary sodium intervention tends to be individually oriented and the best results obtained when conducted by skilled nutritionists, the costs are high. More cost-effective intervention approaches need to be developed. Finally, it is important to examine the effects of non-pharmacological interventions on clinical end points, ideally cardiovascular mortality and morbidity, but also on intermediate or subclinical end points such as left ventricular mass as assessed by echocardiogram. The Hypertension Control Program \textsuperscript{20} has examined some of these questions, but in this study statistical power was marginal. The Treatment of Mild Hypertension Study \textsuperscript{21} is also examining some of these questions. It is important to continue investigation in pursuit of answers to these remaining questions.

Acknowledgments

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