Effects of a reduced-sodium added-potassium salt substitute on blood pressure in rural Indian hypertensive patients: a randomized, double-blind, controlled trial

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ABSTRACT

Background: High salt intake is a major modifiable risk factor of hypertension which is prevalent in India. It is not yet clear if salt substitutes reduce blood pressure (BP) among Indian hypertensive patients.

Objectives: Examine the acceptability, usage, and BP effects of a reduced-sodium and added-potassium salt substitute among hypertensive patients.

Methods: We enrolled 502 participants with hypertension (aged 61.6 ± 12.0 y, 58.8% women) from 7 villages in rural India. Participants were randomly assigned to receive either regular salt (100% sodium chloride) or the salt substitute (70% sodium chloride/30% potassium chloride blend), and advised to replace all home salt use. The primary outcome was the change in systolic BP (SBP) from baseline to 3 mo comparing the salt substitute and regular salt groups. Secondary outcomes included the change in diastolic BP (DBP), 24-h urinary biomarkers, and self-reported use and satisfaction with the study salt provided.

Results: A total of 494 (98%) participants completed 1 mo and 476 (95%) participants completed the 3-mo follow-up. At 3 mo, the salt substitute intervention significantly decreased the average SBP by 4.6 mmHg (95% CI: 3.0, 6.2, $P < 0.001$) and DBP by 1.1 mmHg (95% CI: 0.2, 2.1 mmHg, $P = 0.02$). There was a significant increase in 24-h urinary potassium excretion in the salt substitute group by 0.24 g/d (95% CI: 0.12, 0.35 g/d, $P < 0.001$) and a decrease in the urinary sodium to potassium ratio by 0.71 (95% CI: 0.55, 0.87, $P < 0.0001$) compared with the control group. Participants reported that they used the study salt nearly every day of the week (mean ± SD, 6.3 ± 1.8 d) and rated the taste of the study salts similarly.

Conclusion: The reduced-sodium added-potassium salt led to a substantial reduction in SBP in hypertensive patients, supporting salt substitution as an effective, low-cost intervention for BP lowering in rural India. This trial was registered at clinicaltrials.gov as NCT03909659. *Am J Clin Nutr* 2021;00:1–9.

Keywords: salt substitute, blood pressure, sodium, potassium, India

Introduction

Hypertension is a leading risk factor for cardiovascular disease (CVD) and death worldwide, afflicting low- and high-income countries alike (1). In India, the second most populous country in the world, the prevalence of hypertension is very high, with an estimated 207 million (25.3%) adults suffering from hypertension based on a recent nationally representative survey (2), and only 1 in 10 hypertensive patients achieving adequate blood pressure (BP) control (3). Such statistics highlight the importance of identifying and implementing novel, low-cost interventions to improve BP control in India.

Excess sodium intake is a causal risk factor for hypertension, and reducing sodium from dietary salt is advocated as a first-line treatment of hypertension by most national (4–6) and international hypertension societies (7–9), including in India (10). Current best estimates of usual dietary salt intake suggest adults in India consume an average of ∼10 g/d of salt (4 g/d of sodium), which is twice the WHO recommended maximum (11). In India, the majority of dietary salt is added during food preparation or dining (discretionary salt use) (12–14),

Supported by the George Institute for Global Health Seed Grant (Grant number 0141030 to JY, SRT, MT, BN, JHYW). The funders and Nutek Salt had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; RCT, randomized controlled trial; SBP, systolic blood pressure; SSiIS, Salt Substitute in India Study.

Received November 9, 2020. Accepted for publication February 10, 2021.
First published online 0, 2021; doi: https://doi.org/10.1093/ajcn/nqab054.

particularly in rural areas where there is limited access to other sources of dietary salt such as packaged and restaurant foods. Hence, strategies that reduce sodium from discretionary salt use are promising interventions for lowering population-level sodium consumption in India.

A practical method for reducing sodium from discretionary salt use is to replace regular salt (100% sodium chloride) with a "salt substitute," a product that replaces a portion of the sodium chloride in regular salt with other salts such as potassium chloride (usually 25–30%) and/or magnesium sulphate (10–14%). Meta-analyses of randomized controlled trials (RCTs) have found that compared with regular salt, use of a salt substitute significantly reduces systolic blood pressure ([SBP] –7.8 mmHg, 95% CI: –9.5, –6.2 mmHg) and diastolic blood pressure ([DBP] –4.0 mmHg, 95% CI: –5.2, –2.7 mmHg) in hypertensive patients, without serious adverse side effects (15, 16). However, it is not yet clear if salt substitutes could similarly reduce BP among Indian hypertensive patients, since none of the RCTs were conducted in Indian populations. The efficacy of salt substitutes on BP may not be entirely generalizable since uptake will depend on behaviors relating to salt use as well as the acceptability of the taste, with some reports suggesting individuals may prefer the taste of regular salt over salt substitutes (17). Thus, we designed and conducted the Salt Substitute in India Study (SSiIS) to examine the acceptability, usage, and BP effects of a reduced-sodium and added-potassium salt substitute among rural Indian individuals with a self-reported history of hypertension diagnosis.

Methods

Subjects

Eligible participants were adults aged 18 y or over with a self-reported history of hypertension diagnosed by a health professional. In addition, individuals needed to self-report eating most of their meals in their homes. Written informed consent was obtained from both the main study participants and all their household members, due to the nature of the intervention, where household members of the study participants also consumed the intervention salts during the study period. For household members aged under 18 y, informed consent was provided by a parent or guardian.

Due to concerns regarding the potential for a potassium-containing salt substitute to cause hyperkalemia (18), individuals were excluded if they or any of their household members used a potassium-sparing diuretic, potassium supplements, or had any known acute or chronic kidney disease (CKD) (19). Participants were also excluded if they or any of their household members had other reasons for any concern about the use of a salt substitute (e.g. not willing to complete the trial follow-up), were not expected to live longer than 6 mo from the date of assessment, or another member of the household was already enrolled in the study.

Participants who met the eligibility criteria were recruited from 7 villages in the Siddipet district of Telangana State in India. A study physician was included as part of the recruitment team to check the likely validity of the self-reported hypertension, and to ensure the safety of the study participants and their families, by inquiring about the presence or absence of serious kidney disease, given the concern that the use of a salt substitute may increase the risk of hyperkalemia in this patient subset.

Study design

The SSiIS was a double-blind, RCT with an intervention duration of 3 mo conducted in rural India. Recruitment began in November 2019, and follow-up was completed by April 2020. The study protocol has been published (20), and the study was approved by The George Institute for Global Health Ethics Committee (Project Number 09–2019). The study was carried out according to the Declaration of Helsinki (21). The trial was registered in the clinicaltrials.gov database (NCT03909659).

Intervention and control

The salt substitute intervention was a reduced-sodium, added-potassium salt substitute (70% sodium chloride/30% potassium chloride blend). Regular salt (100% sodium chloride) was provided to participants in the control group. Each participant was advised to replace all discretionary salt used in the household (salt added while preparing food as well as salt used to season the food while dining) with the study salt provided. Both the salt substitute and the regular salt were provided free of charge in masked, identical packaging without the manufacturer's name but with a unique identification number on each pack. The study salts also contained iodine with fortification concentrations according to Indian regulatory requirements (File No. 3/DFS/FFRC/Fortification/FSSAI-2017). As the salt substitute used in the study was not available in the Indian market, Siddharth Starch Pvt. Ltd., a company based in Maharashtra, India, was commissioned to blend and supply the product.

With an estimated salt intake of ∼10 g/d per person in India, we provided 20 g/person/d of salt substitute or regular salt to ensure a sufficient quantity to cover the households' discretionary salt use, to a maximum of 5 kg to each household for the study duration (3 mo). Directions were given to continue the use of the study salt until the end of the study.

Randomization

Participants were randomly assigned in a 1:1 ratio through a central computerized process to the salt substitute or regular salt. An independent biostatistician generated the random allocation sequence and the study team recruiting and randomly assigning patients were blinded to the randomization sequence. The study team members who performed the follow-up and evaluation of outcomes were blinded to participant treatment assignment during the study (20).

Data collection and follow-up

There were 5 face-to-face visits (20) scheduled for each participant done at the participants' homes by the study researchers. After obtaining informed consent and confirming eligibility criteria on the first visit, study staff administered a baseline questionnaire and conducted a brief physical examination including BP measurement. In addition, an appointment was

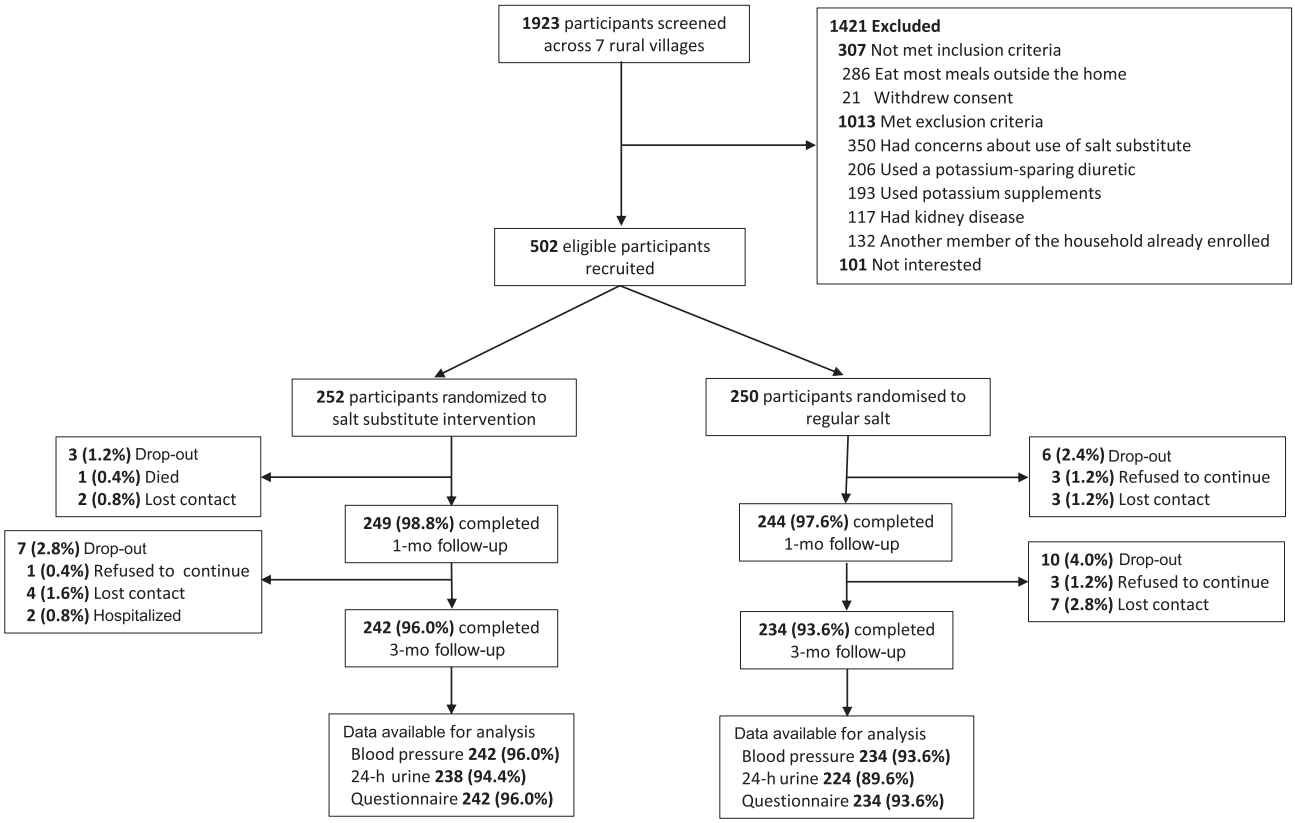

FIGURE 1 Trial flow chart.

made for the second study visit in order to obtain a complete 24-h urine specimen from each participant. After the second study visit, the participant was randomly assigned to receive the salt substitute or the regular salt for the next 3 mo. Participants were told to report any adverse events to the study team during the study. On the third visit at 1 mo and the fourth visit at 3 mo, the BP of each participant was measured and they were asked about the acceptability and usage of the study salt; 24-h urine samples were collected on the fifth (final) study visit. The fifth (final) study visit generally occurred within 5 d after the fourth study visit, i.e. on the fourth study visit (end of 3 mo) the participants had their BP measured and were asked about the acceptability and usage of the study salt. They were then asked to collect a 24-h urine sample within 5 d after the fourth visit, and to drop off the sample on the fifth study visit. If an individual was not present in the village on the day of a scheduled study visit, a follow-up visit was rescheduled for another time. All data were collected on paper forms and then inputted into a password-protected Redcap data management system server hosted by The George Institute for Global Health, India.

Primary and secondary outcomes

The primary outcome was the effect of the salt substitute on the change in SBP from baseline to 3 mo, comparing the salt substitute group with the control (regular salt) group. Secondary outcomes included the effects of the salt substitute on the change in DBP, 24-h urinary sodium and potassium excretion, and the urinary ratio of sodium to potassium from baseline to 3 mo. Finally, the acceptability and usage of the study salts, as well as salt-related knowledge, attitudes, and behaviors were assessed by surveys as exploratory outcomes.

Outcome measurements

BP was measured using automated digital BP monitors (A&D Company Limited Kitamoto-shi, UA-767 PBT) using the same protocol as published in (20) according to established standardized methods (9). Three sitting measurements were taken for each participant at each study follow-up, and the mean of the last 2 sitting measurements was used for statistical analyses.

The 24-h urine samples were collected by participants at baseline and at the end of the trial according to written and verbal instructions provided by the research team (20). Collection procedures were the same as described previously (22, 23). Total urine volumes were used to assess the completeness of the 24-h urine collection, and samples were excluded from analysis if the total 24-h urine volumes were implausible, defined as $<$500 mL or $>$6000 mL (24). Urine sodium and potassium concentrations were measured at the study site using automated electrolyte meters (Compact Water Quality Meter, LAQUAtwin-Na-11 and LAQUAtwin-K-11m, HORIBA Scientific). Estimates of sodium and potassium per 24 h (g) were derived from urine sodium and potassium concentrations (g/L) multiplied by urine volume (L). Attitudes, knowledge, and behaviors related to salt, as well as acceptability and use of the study salt substitute,

TABLE 1 Baseline characteristics of participants in the Salt Substitute in India Study[1]

	Salt substitute ($n = 252$)	Regular salt ($n = 250$)	Total ($n = 502$)
Age, years, mean ± SD	61.5 ± 11.1	61.7 ± 12.9	61.6 ± 12.0
Sex, F, no. (%)	147 (58.3)	148 (59.2)	295 (58.8)
Education, no. (%)			
Primary school or lower	220 (87.3)	217 (86.8)	437 (87.1)
High school[2]	29 (11.5)	28 (11.2)	57 (11.4)
College or higher	3 (1.2)	5 (2.0)	8 (1.6)
Current smoker, no. (%)	16 (6.3)	14 (5.6)	30 (6.0)
Past smoker, no. (%)	21 (8.3)	20 (8.0)	41 (8.2)
Alcohol consumption, current,[3] no. (%)	44 (17.5)	39 (15.6)	83 (16.5)
Alcohol consumption, past,[3] no. (%)	71 (28.2)	71 (28.4)	142 (28.3)
Medication use, no. (%)			
Antihypertensive agents	245 (97.2)	236 (94.4)	481 (95.8)
Diuretic	0 (0)	1 (0.4)	1 (0.2)
Calcium channel blockers	6 (2.4)	9 (3.6)	15 (3.0)
ACEI or ARB	70 (27.8)	80 (32.0)	150 (29.9)
β-blocker	63 (25.0)	50 (20.0)	113 (22.5)
α-blockers	107 (42.5)	97 (39.0)	204 (40.6)
Statin or other lipid-lowering drugs	1 (0.4)	1 (0.4)	2 (0.4)
BMI, kg/m^2, mean ± SD	23.1 ± 4.7	23.6 ± 4.2	23.4 ± 4.5
SBP, mmHg, mean ± SD	132.8 ± 20.3	132.1 ± 22.5	132.5 ± 21.4
DBP, mmHg, mean ± SD	83.7 ± 12.0	82.9 ± 13.1	83.3 ± 12.5
History of CVD, no. (%)	3 (1.2)	4 (1.6)	7 (1.4)
History of diabetes, no. (%)	59 (23.4)	51 (20.5)	110 (22.0)
24-h urine electrolytes concentration,[4] mean ± SD			
Sodium, g	3.80 ± 1.86	3.64 ± 1.73	3.72 ± 1.79
Potassium, g	0.82 ± 0.45	0.86 ± 0.53	0.84 ± 0.49

[1]Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[2]High school includes junior high school, senior high school, and technical secondary school.

[3]Defined as currently consuming any type of alcohol.

[4]After excluding samples that were likely incomplete, the total number of urine samples eligible for analyses was 460, including 233 in the salt substitute group and 227 in the regular salt group.

were assessed through an interviewer-administered questionnaire (17, 20).

Statistical analysis

The planned sample size was 498 participants, which would provide 80% power, with a significance level of 5% (1-sided test) to detect a 5 mmHg or greater difference in mean SBP between groups (20). Continuous data were shown as means with SDs. Categorical data were presented as numbers with corresponding percentages. Analysis of the intervention effects over the study duration was by the principle of intention-to-treat with no data imputation given the very low rate of drop-out. The between group comparisons for the primary and secondary outcomes of SBP, DBP, and urine sodium and potassium concentrations at the end of the trial were assessed by linear regression adjusted for baseline BP and recruitment site (villages). We also assessed the effects on SBP and DBP over time (baseline, 1 mo, and 3 mo), by using SAS Proc Mixed to fit mixed linear models that adjusted for baseline BP and recruitment site (village) while allowing for repeated measurements of outcomes. Differences in the acceptability and use of study salts were compared at 1 and 3 mo using unpaired t-tests and chi-squared tests as were differences in self-reported knowledge, attitudes, and behaviors related to salt measured at baseline and 3 mo. All P values were 2-tailed ($\alpha = 0.05$) and statistical analyses were carried out using SAS version 7.1 (SAS Institute Inc.).

Results

In total, 1923 participants were screened for potential inclusion in the study (**Figure 1**). A total of 1013 (53%) met exclusion criteria with a primary ineligible reason being concerns about the use of a salt substitute ($n = 350$, 18%), whereas 307 (16%) did not meet the inclusion criteria, resulting in 502 (26%) eligible participants being accepted into the study. The numbers of people who completed the 1-mo and 3-mo follow-up visits were 494 (98%) and 476 (95%), respectively. The main reasons for participants dropping out from the study were contact with participant lost ($n = 16$, 3%) and refusal to continue with the study ($n = 7$, 1%).

Baseline characteristics

Baseline demographics and medical characteristics were similar across the randomly assigned groups (**Table 1**). The mean age of participants was 62 y (SD, 12 y), greater than half were women ($n = 295$, 59%) and the majority had primary

school or lower levels of education (n = 437, 87%). Few (n = 7, 1.4%) had a history of CVD but ~1 in 5 (22.0%) had a history of diabetes mellitus. The overall mean baseline SBP and DBP values were 133 ± 21 and 83 ± 13 mmHg, respectively, and nearly all participants (n = 481, 95.8%) were using ≥1 antihypertensive medication at baseline, mostly α-blockers (40.6%). There were 4.2% participants who did not use any medication to control BP. The average 24-h urinary sodium and potassium excretion at baseline was 3.7 ± 1.8 and 0.8 ± 0.5 g, respectively.

There were no appreciable differences in baseline characteristics between participants who did and did not complete the study (**Supplementary Table 1**).

Effects of the salt substitute intervention on BP

From baseline to the end of the trial, participants in the intervention group had significantly lower SBP (mean difference, –4.58 mmHg, 95% CI: –6.20, –2.97 mmHg, P <0.001) and DBP (–1.14 mmHg, 95% CI: –2.13, –0.15, P = 0.02) than the control group (**Table 2**). The effect of the salt substitute on SBP was more prominent in men (mean difference between groups, –6.62 mmHg, 95% CI: –9.31, –3.93 mmHg) than in women (–3.12 mmHg, 95% CI: –5.13, –1.11 mmHg, $P_{interaction}$ = 0.04). The results did not differ according to age or presence of diabetes (**Supplementary Table 2**). SBP decreased from baseline to 1 mo and to 3 mo (**Figure 2**) and did not change significantly over time in the control group ($P_{linear\ mixed\ model}$ = 0.0008). Conversely, since the trend was not monotonic, there was not a significant difference in the change in DBP over time between the salt substitute and control groups ($P_{linear\ mixed\ model}$ = 0.28).

Effects of the salt substitute intervention on urinary sodium and potassium

In the salt substitute group, there was a significant decline in average 24-h urinary sodium of 0.91 g/d (95% CI: 0.78, 1.03 g/d, **Table 3**). However, a similar decline was also observed in the control group, such that by the end of the trial there was no significant difference between the intervention and control groups in urine sodium concentrations (P = 0.42). On the other hand, there was a small but significant increase in average 24-h urinary potassium excretion in the salt substitute group compared with the control group at the end of the trial, by 0.24 g/d (95% CI: 0.12, 0.35 g/d, P < 0.0001). The changes in sodium and potassium resulted in a significant decrease in the sodium to potassium (Na: K) ratio for the salt substitute group compared with the control group (mean difference in Na: K ratio, –0.71, 95% CI: –0.87, –0.55, P < 0.0001).

Self-reported acceptability and use of study salts, and knowledge and behaviors related to salt

At 1 mo and at the end of the trial, participants completed a set of survey questions related to the acceptability and use of the study salts, the results of which are shown in **Table 4**. On average, there were no significant differences between the salt substitute and control groups' responses to the questions (P ≥ 0.09 for all). Overall, the participants reported that they enjoyed the taste of

TABLE 2 Effects of salt substitute on blood pressure in the Salt Substitute in India Study[1]

	Salt substitute			Regular salt				
	Baseline (n = 252)	End of trial (n = 242)	Mean change within group[2] (95% CI)	Baseline (n = 250)	End of trial (n = 234)	Mean change within group[2] (95% CI)	Mean difference between groups[3] (95% CI)	P value for mean difference between groups[3]
SBP, mmHg, mean ± SD	132.8 ± 20.3	127.6 ± 19.6	–5.0 (–6.1, –3.9	132.1 ± 22.5	131.7 ± 21.7	–0.4 (–1.6, 0.7)	–4.58 (–6.20, –2.97)	<0.0001
DBP, mmHg, mean± SD	83.7 ± 12.0	83.0 ± 12.6	–0.6 (–1.3, 0.1)	82.9 ± 13.1	83.7 ± 13.3	0.6 (–0.1, 1.3)	–1.14 (–2.13, –0.15)	0.02

[1] Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
[2] Analyzed using paired t-test to assess mean change within group.
[3] Analyzed using linear regression assessing difference in mean blood pressure between groups, adjusted for baseline blood pressure and site of recruitment (villages).

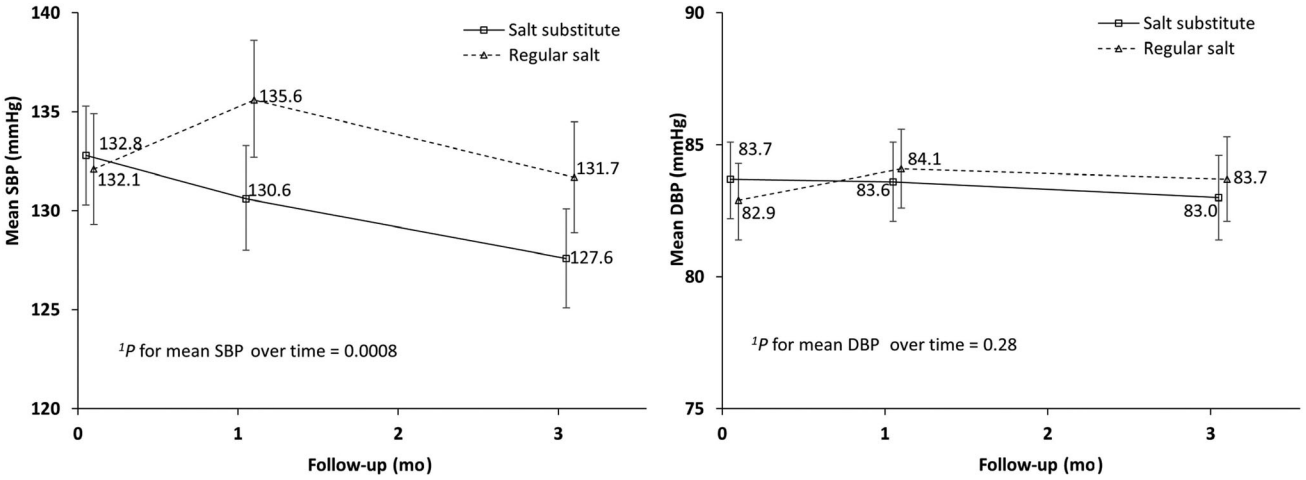

FIGURE 2 Effects of salt substitute on mean blood pressure levels over 3 mo. The values shown in the figure are mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) levels at baseline ($n = 252$ in the intervention group, $n = 250$ in the control group) and each follow-up visit by intervention group ($n = 249$ for the 1-mo visit, $n = 242$ for the 3-mo visit) and control group ($n = 244$ for the 1-mo visit, $n = 234$ for the 3-mo visit) with the symbols indicating the mean and error bars indicating the 95% CIs.[1] Differences in mean blood pressure between the 2 groups over the 3 mo were assessed using a linear mixed model that adjusted for baseline blood pressure and village and accounted for repeated measurements within the subject.

the study salts; on a scale of 1–10 (1 = disliked the taste a lot, 10 = liked the taste a lot), the mean ± SD scores for the salt substitute and regular salt were 8.6 ± 1.2 and 8.5 ± 1.1 at the end of the trial. Participants reported that they used the study salts nearly every day of the week (mean ± SD, 6.3 ± 1.8 d) and for the majority of the meals on a typical day (mean ± SD, 2.6 ± 0.6 meals). A small (~5%) and similar proportion across both groups reported that in addition to the study salts, they also used other salt.

With regards to knowledge and behaviors related to salt, again there were no significant differences between the salt substitute and control groups across any of the questions asked at baseline or follow-up ($P \geq 0.07$ for all, **Supplementary Table 3**). Notably, none of the participants had heard about reduced-sodium salt at baseline but nearly all participants considered high salt intake to be bad for health and reported trying to eat less of a food if it was very salty.

Adverse events

Two serious adverse events occurred during the study, 1 in each of the randomized study groups, and neither event was related to the study intervention (**Supplementary Table 4**).

Discussion

In the SSiIS study, provision of a reduced-sodium added-potassium salt substitute to replace regular salt for home use reduced SBP by 4.6 mmHg and DBP by 1.1 mmHg amongst hypertensive patients in rural India. The effect size compares with an average decrease in SBP/DBP of 4/2 mmHg typically achieved with the introduction of angiotensin-converting enzyme inhibitor therapy (25). Participants rated the taste of the study salt substitute favorably and our findings suggest that they readily incorporated the salt substitute into their daily cooking habits. Overall, our data suggest that the replacement of salt with a reduced-sodium added-potassium salt substitute is an acceptable and effective dietary intervention for lowering SBP in hypertensive individuals in rural India.

Despite the high prevalence of hypertension in India, there are well-recognized barriers to medical care and access to medication, particularly in rural areas, resulting in poor hypertension control (26, 27). In this context, using a salt substitute is a promising complement to therapeutic interventions. The magnitude of effect on BP is clinically meaningful with a 5 mmHg reduction in SBP anticipated to reduce the overall risk of CVD by ≥10% (28).

As expected, and consistent with prior clinical trials, our intervention did not cause adverse events, highlighting the safe profile of the salt substitute among hypertensive patients that reported no serious CKD and no use of potassium-sparing medications. This finding stands in contrast to a limited body of evidence based on case reports, that has associated the use of some salt substitutes containing proportions of potassium chloride (>40%) with nonfatal hyperkalemia in patients with CKD (29). There is a paucity of research into the dose-response relation between potassium consumption and changes in serum potassium in patients with renal disease, but a recent modeling study (29) in China (where discretionary salt use is also high) estimated that a nationwide implementation of potassium-enriched salt substitution would likely result in substantial net CVD benefit, even for individuals with CKD. Whether this would also be the case for India has not yet been estimated. Additional studies that address these questions are needed to further evaluate whether potassium-containing salt substitutes could also be safely deployed to lower BP for patients with CKD.

Our findings have policy implications. None of the participants were aware of the existence of reduced-sodium salt and our data suggest that public promotion and increased availability of salt substitutes for hypertensive patients could be an effective and scalable intervention. Screening for renal disease in the current study was by self report and a similar strategy might reasonably be used to minimize concerns and any possible

TABLE 3 Effects of salt substitute on 24-h urine electrolytes in the Salt Substitute in India Study

	Salt substitute			Regular salt				
	Baseline ($n = 233$)	End of trial[1] ($n = 207$)	Mean change within group[2] (95% CI)	Baseline ($n = 227$)	End of trial[1] ($n = 198$)	Mean change within group[2] (95% CI)	Mean differences between groups at end of trial[3] (95% CI)	*P* value for mean difference[3]
Urine sodium level, g, mean ± SD	3.80 ± 1.86)	2.90 ± 1.62	–0.91 (–1.03, –0.78)	3.64 ± 1.73	2.88 ± 1.98	–0.83 (–0.96, –0.71)	–0.07 (–0.25, 0.10)	0.42
Urine potassium level, g, mean ± SD	0.82 ± 0.45	1.42 ± 1.33	0.56 (0.48, 0.64)	0.86 ± 0.53	1.13 ± 1.06	0.32 (0.24, 0.40)	0.24 (0.12, 0.35)	<0.0001
Urinary sodium: potassium ratio, mean ± SD	5.36 ± 2.87	2.70 ± 1.58	–2.33 (–2.44, –2.22)	4.93 ± 2.13	3.47 ± 1.82	–1.62 (–1.74, –1.50)	–0.71 (–0.87, –0.55)	<0.0001

[1] After excluding samples that were likely incomplete, the total number of urine samples eligible for analyses at the end of the trial was 405, including 207 in the salt substitute group and 198 in the regular salt group.
[2] Analyzed using paired t-test to assess mean change within group.
[3] Analyzed using linear regression assessing difference in 24-h urine electrolytes between groups, adjusted for baseline measurements and sites of recruitment (villages).

risks related to hyperkalemia. Salt substitutes are low cost (e.g. 0.65AUD/kg for Tata Salt Lite, a reduced-sodium added-potassium product available in Indian supermarkets with a ∼80:20 sodium to potassium ratio) but this is about one-third more than the cost of regular salt. This could be a deterrent to widespread use, especially for lower-income populations, and a price subsidization policy might be worthwhile. Furthermore, additional studies and government investments are needed to ascertain possible supply chain issues related to potassium salt substitutes, such as how to scale-up their production and implement efficient distribution networks to enhance availability.

Our study demonstrated that since salt substitutes could be used in place of regular salt for cooking at home, they are compatible with the existing dietary habits of individuals in rural India without requiring further behavioral changes. However, it should be acknowledged that given the current high level of sodium consumption in India, further benefits could be expected with concomitant education to reduce the discretionary salt use.

The effects on BP in our trial are broadly consistent with prior RCTs conducted in other countries. A recent meta-analysis of clinical trials, most of which were conducted in China, found that use of salt substitutes reduced SBP and DBP among hypertensive patients by an average of –7.6 (95% CI: –5.6, –9.6) and –3.3 mmHg (95% CI: –1.9, –4.7), respectively (15). Meta-regression analyses in these trials did not identify gender differences in the effect of the salt substitute on BP. This suggests that our finding of effect modification by gender could be due to chance and should be interpreted cautiously.

The meta-analyses of prior RCTs suggest an overall small reduction in 24-h urine sodium excretion (0.8 g/d) but there was high heterogeneity ($I^2 = 79\%$) across studies and 6/10 trials did *not* observe a decrease in urine sodium, similar to our study (15). A possible explanation for the absence of a reduction in urinary sodium excretion is that study participants in the salt substitute group differentially used more regular salt in their cooking. This could off-set the expected reduction in sodium while leaving the rise in potassium unaffected. Our study provides some evidence to support this explanation with ∼5% of participants reporting use of additional regular salt during the trial, though this was reported for both randomized groups. We also observed an unexpected decrease in sodium intake and small increase in potassium intake in the control group. The underlying reasons are unclear, and could be due to fluctuations in background diet, perhaps due to a change in season during the study and increased availability of fresh fruits and vegetables that are key sources of dietary potassium. It is also possible that the urinary electrolyte measures were affected by chance and errors in urine collection. The reduction in SBP is consistent with reasonable adherence to the intervention and the change in the sodium: potassium ratio, which has been shown to be a stronger predictor of BP than sodium or potassium alone (30).

The strengths and limitations of our study include the randomized controlled design, the use of blinding, and the high completion rate minimizing the risks of bias. We assessed sodium and potassium intake based on 24-h urine samples, which are superior to dietary surveys and more accurate than spot-urine samples (31). The intervention duration was relatively short at 3 mo and the effect of the salt substitute on BP may vary with a longer duration of follow-up. For instance, in the China Salt Substitute and Stroke Study (SSaSS), provision of a salt

TABLE 4 Acceptability and use of study salts at 1 mo and 3 mo in the Salt Substitute in India Study

	1 mo			3 mo (end of trial)		
	Salt substitute ($n = 249$)	Regular salt ($n = 244$)	P value[1]	Salt substitute ($n = 242$)	Regular salt ($n = 234$)	P value[1]
Did you enjoy the taste of the study salts? (1 = disliked a lot; 10 = liked a lot), mean ± SD	8.4 ± 1.4	8.2 ± 1.5	0.12	8.6 ± 1.2	8.5 ± 1.1	0.41
How many days in last week did you use the study salt provided? Mean ± SD	6.5 ± 1.6	6.4 ± 1.6	0.70	6.3 (1.8)	6.3 (1.8)	0.99
For how many meals did you use the study salt during a typical day? Mean ± SD	2.7 ± 0.8	2.6 ± 0.5	0.09	2.6 (0.6)	2.5 (0.7)	0.42
How did you use the study salt? *n* (%)						
Used during cooking	242 (97.2)	238 (97.5)	0.81	236 (97.5)	224 (95.7)	0.28
Seasoning	0 (0)	0 (0)		0 (0)	0 (0)	
Did not use	7 (2.8)	6 (2.5)		6 (2.5)	10 (4.3)	
Any other salt used since the last visit, *n* (%)	14 (5.6)	12 (4.9)	0.73	13 (5.4)	16 (6.8)	0.57

[1] P value corresponds to t-test for continuous variables or chi-square test for categorical variables for comparison between the salt substitute and control group.

substitute for home cooking caused a –2.65 mmHg reduction in SBP at the 2-y follow-up (32), somewhat lower than the average reductions achieved in shorter trials. Our findings may not be generalizable to other Indian hypertensive populations, such as those living in urban centers with different dietary sources of sodium. Furthermore, we excluded hypertensive patients with kidney disease, and future studies should assess the benefit-risk profile of potassium-containing salt substitutes in this population. We did not detect clinical evidence of adverse events including risks associated with hyperkalemia, but we cannot rule out that undetected hyperkalemia was present. Another limitation is that we did not collect 24-h urine biomarkers at 1 mo due to participant burden, and thus we are unable to track the trajectory of changes in urinary sodium and potassium over time.

In conclusion, we demonstrated that replacement of regular salt with a reduced-sodium added-potassium salt for home use for 3 mo led to substantial reductions in SBP in hypertensive patients in rural India. These findings support the use of such salt substitutes for home use as a low-cost and practical intervention to reduce BP in this setting.

We thank all field investigators, the study team, and all study participants and their household members for participating in the study. We also thank Nutek Salt and Siddharth Ltd for providing the salt and the salt substitute free of charge.

The authors' contributions were as follows—BN and JY: conceived the idea of the study; BN, JY, SRT, MT, and JHYW: participated in the study design; QL: provided biostatistical support; JY: conducted the statistical analysis; JY: drafted the first version of the manuscript; and all authors: participated in the critical review of the manuscript and read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

The datasets used and analyzed during the study will be available from the corresponding author on reasonable request.

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