

The impact of short message services and personal consultation by pharmacy students on medication adherence and blood pressure control: study protocol for a cluster randomized trial

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Purpose: Hypertension prevalence is mounting at a great pace in the People's Republic of China and poses a serious threat to health care systems. Medication nonadherence is one of the key factors in controlling high blood pressure. Our study uses two-arm cluster randomized controlled trial to investigate whether personal consultation by postgraduate pharmacy students and short message services (SMS) is effective in improving medication adherence and blood pressure control.

Patients and methods: The trial will involve 384 treated patients in 8 community health care centers (CHCs). The 8 CHCs will be randomly assigned to intervention and control group in a ratio of 1:1. Patients in the intervention group will receive a personal consultation which identifies the barriers to medication adherence and SMS reminders which will be sent at 3-day intervals while patients in the control group will receive standard pharmaceutical care. Personal consultation by pharmacy students will be delivered at months 0 and 3. SMS messages will include educational information about normal blood pressure, complications of hypertension, salt intake, healthy diet, smoking cessation, regular exercise, weight control, antihypertensive medication schedule and treatment. Both groups will be followed for 6 months in order to compare their medication adherence and blood pressure at months 0, 3 and 6. The primary clinical outcome is the change in mean blood pressure and medication adherence measured at baseline, months 3 and 6. Secondary outcome is the proportion of patients reaching controlled blood pressure at months 3 and 6.

Discussion: Pharmacy students led consultation will be conducted in the process of physical examination and SMS reminders which is at low cost, may be a feasible way to address the high prevalence of hypertension in the People's Republic of China.

Keywords: medication adherence, hypertension, blood pressure, SMS reminders, personal consultation, community health care centers

Introduction

Hypertension, one of the most common non-communicable diseases, accounts for more than 26% of the world's adult population and the prevalence increases with age.¹ Globally, hypertension is also one of the leading causes of premature death, with 7.1 million people dying every year from high blood pressure-related

diseases.² For every 20 mmHg lower systolic blood pressure (SBP) or 10 mmHg lower diastolic blood pressure (DBP), the risk of a cardiovascular event is reduced by about 50%.³ Therefore, blood pressure control is the entry point for prevention and treatment of cardiovascular disease.

According to the 2017 “National Guidelines for the Prevention and Treatment of Hypertension in Primary Settings”,⁴ it is estimated that the number of hypertensive patients in the People's Republic of China has reached 270 million. Complications of hypertension, such as stroke, fundus disease, heart and kidney disease, increase the risk of disability and mortality which have posed immense financial burden on health care systems in the People's Republic of China. Adherence to a medication regimen can be defined simply as the extent to which patients take medications as prescribed by their health care providers.⁵ Hypertension, a chronic disease, requires long-term adherence to medications to reduce complications.⁶ However, approximately 20–50% of patients with chronic illnesses are reported to be non-adherent to their medications, a situation that compromises treatment effectiveness.^{7–9}

Globally, the mobile phone has become the preferred tool for communication and access to information bringing together communication.¹⁰ As of December 2018, about 1.57 billion mobile phone subscriptions had been registered in the People's Republic of China.¹¹ Short message services (SMS) has low cost, easy and wide coverage, and the potential for individualized instant delivery.¹² Furthermore, studies have confirmed the effectiveness of SMS reminders on improving medication adherence and it could be an effective tool to overcome poor medication adherence.^{13–15} SMS has been used in several diseases, such as HIV,¹⁶ diabetes mellitus¹⁷ and allergic rhinitis,¹⁸ but there are limited studies on its use in hypertensive patients. As a matter of fact, a meta-analysis evaluating the effectiveness of text messaging only included one hypertension study.¹⁹ Similarly, in the People's Republic of China, most studies focused on patients with coronary artery disease,²⁰ HIV²¹ and mental health problems.²² Studies about the effect of SMS reminders on hypertensive patients are needed to fill in the gap.

Pharmacists play a pivotal role in health care systems and have a direct impact on improving the value of medication treatment through frequent interaction with patients.^{23,24} Studies have shown that pharmacists are beneficial in improving medication adherence among patients with hypertension.^{25–29} However, health care systems are lacking in pharmacists and they are prone to sub-health

status due to work stress, overload of work and lack of sleep. The questions remain, however, as to whether pharmacists can do these interventions effectively in busy community practices.³⁰ Moreover, interventions by pharmacists cannot be widely used due to high pharmacist's cost and time constraints.³¹ The value of pharmacy students consultation has been approved in different clinical settings.^{32–34} Pharmacy students and residents conducting discharge counseling program on heart failure readmission, 89% of patients receiving the program had better understanding of medications.³² A study³³ examined the impact of 5-min counseling program led by pharmacy students among 198 participants to improve knowledge about influenza and vaccines and it showed that a targeted consultation can increase vaccination rates and change public views. American and Kenyan pharmacy students successfully provide clinical pharmacy consultations in a resource-constrained, acute-care practice setting and it suggests pharmacy students have an important role in providing improved pharmacy service, reducing medication errors and cost.³⁴ Literature showed the potential influence of student interventions on medication adherence is lacking.³⁰

The purpose of this study is to investigate whether mobile health interventions by pharmacy students are feasible in improving patient medication adherence and lowering their blood pressure in 6 months. If the intervention is effective, we can provide intervention models to government departments and help them to develop education guidelines for patients to improve their medication adherence and reduce their chances of having hypertension-related complications.

Methods

Study design

It is a 6-month, intention-to-treat, two-arm cluster randomized controlled trial to assess the effectiveness of SMS reminders and health consultation in addition to standard pharmaceutical care compared to standard pharmaceutical care only. This study used a stratified proportional sampling approach and is designed according to SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials).³⁵

According to the GDP per capita of Xi'an city, Shaanxi Province in 2017 (Statistical data from the Statistical Yearbook of Shaanxi Province in 2017), the districts in Xi'an were divided into three categories:

high, medium and low social economic development level. In each category, one district was selected randomly as the representative district, and the results selected are: Yanta district, Xincheng district and Lintong district. According to the number of permanent residents, the proportion of population in Yanta district, Xincheng district and Lintong district is about 4:2:2, so four community health care centers (CHCs) in Yanta district, two CHCs in Xincheng district and two CHCs in Lintong district were selected accordingly and they are comparable in regional characteristics. Eight CHCs will be randomized into two parallel groups in a 1:1 allocation ratio. In Yanta district, two CHCs will be selected, based on computer-generated random numbers, as intervention group and the other two will be serving as the control group. In Xincheng and Lintong districts, one CHC will be randomly selected as intervention group and the other one will be in the control group. The sampling process will ensure the generalizability of our trial results and reflect the real-world population with hypertension who are the target of our intervention, so our intervention could be used in a larger scale.

Study settings

The study will be conducted at 8 public CHCs in Xi'an, Shaanxi, the People's Republic of China. The CHCs provide a full range of primary care services. We selected CHCs within the walking distance of communities and each CHC manages approximately 2,000 patients with chronic diseases. Patients with hypertension are managed by nurses and physicians and they will be followed up four times a year by nurses through telephone, face-to-face communication or family visit. The nurses will ask patients about their medication regimen, side effects, lifestyle modifications, blood pressure and weight control. Patients who attend the CHCs for physical examination or medication treatment in the outpatient clinic will be approached for participation in the study.

Study participants

We will enroll those patients who meet the trial eligibility criteria: aged over 18 years; diagnosed with hypertension by physicians; prescribed at least one high blood pressure medication; with a SBP <220 mm Hg and a DBP <120 mm Hg at enrollment; have resident health record at CHC; signed informed consent form. Eligible patients are attending the CHCs, residing in the trial area; having access to mobile phone and can read SMS text messages.

Patients who are suffering from dementia, depression, serious heart, lung and kidney diseases; pregnant or in their lactation period; illiterate or cannot clearly express themselves or refused to participate in the study will be excluded. The inclusion and exclusion criteria will enable us to avoid selection bias and ensure the external validity of our study. All participants will be provided written informed consent to ensure their understanding of the trial.

Control group

Patients in the control group will receive standard pharmaceutical care according to "Guidelines for Good Pharmacy Practice"³⁶ (GPP). The China Non-prescription Medicines Association recommended the first edition of "Guidelines for Good Pharmacy Practice" as a standard for pharmacy practice.³⁷ According to the GPP, traditionally, the mission of pharmacy practice in the People's Republic of China is to provide medications and other health care products and services. However, in recent years the term "pharmaceutical care" has established itself as a philosophy of practice, with the patient and the community as the primary beneficiaries of the pharmacist's actions. GPP guidelines are based on the pharmaceutical care given by pharmacists. Similar to other countries, in the People's Republic of China, pharmaceutical care is a patient-centered, outcomes-oriented pharmacy practice that requires the pharmacist to work in concert with the patient and the patient's other health care providers to promote health, to prevent disease, and to assess, monitor, initiate, and modify medication use to assure that drug therapy regimens are safe and effective. The goal of pharmaceutical care is to optimize the patient's health-related quality of life, and achieve positive clinical outcomes, within realistic economic expenditures. Patients in the control group will also receive a welcome SMS at the time of recruitment to confirm their enrollment in the trial and end-of-trial message.

Intervention group

The intervention group will receive a welcome SMS, end-of-trial message and standard pharmaceutical care with additional interventions. The intervention consists of two parts: personal consultation by pharmacy students at baseline and 3 months from the baseline study and SMS reminders at 3-day intervals. According to previous study, half of the patients occasionally forgot to take their medication.³⁸ If forgetting is the primary reason for non-adherence, we will recommend patients to place their medication nearby a toothbrush or hygiene kit as a reminder. For individuals

who forget to bring their medication along when traveling, we will suggest them to place their medications in a pill container, a purse or hygiene kit.³⁹

The content of SMS is developed based on previous literature^{10,40,41} which aim to improve treatment adherence and clinical outcomes through SMS-based interventions and “National Guidelines for the Prevention and Treatment of Hypertension in Primary Settings”.⁴ SMS reminders will be developed by principal investigator, pharmacists, nurses and will be reviewed by a cardiologist in a tertiary hospital. The content of SMS includes three parts: hypertension-related knowledge, suggestions of lifestyle modifications and advice of overcoming barriers to medication adherence which is in accordance with the recommendations of our national guideline. Messages are designed to motivate medication-taking behaviors and to improve patient understanding of hypertension-related knowledge, medication regimen and medication adherence. SMS messages will include educational information about normal blood pressure, complications of hypertension, salt intake, healthy diet, smoking cessation, regular exercise, weight control, antihypertensive medication schedule and treatment. All the messages will be sent in the morning at 7 am when patients are supposed to take their medications. All SMS messages will be delivered automatically by an open access website run by a third-party company (Alibaba Cloud, Alibaba Cloud Computing Co. Ltd. Hangzhou, People's Republic of China).

Procedures

The baseline study will be conducted by pharmacy students. To reach target sample size, patients will be recruited when they are in the process of physical examination or outpatient clinic by medical staff. Informed consent will be taken from all enrolled hypertensive patients who meet the inclusion criteria. After this, Morisky Medication Adherence Scale-8 (MMAS-8) and paper-based questionnaires will be administered to patients both in the intervention group and control group. The MMAS-8 questionnaire will be done by using the Morisky Widget online (Morisky Widget, MMAS Research LLC, Las Vegas, NV, USA) on mobile tablets. The widget will give us scores and answers immediately which will allow us to identify the reasons of medication non-adherence and facilitate immediate feedback to patients. For hypertensive patients, who are unfamiliar with tablets, interviewers will read the questions to patients and type in their answers. Then, the paper-based questionnaires including patient's demographics, clinical

conditions, medication complexity, side effects, behavior and patient's knowledge will be administered to patients. The knowledge part consists of 7 statements, each requesting patients to answer with “yes”, “no”, or “not aware”. Each correct answer will be coded as 1 point, and incorrect answer or unaware of the question will be coded as zero so the maximum score is 7. The higher the score, the higher the knowledge about hypertension. The design of questionnaire was based on previous literature^{42–45} and 2017 “National Guidelines for the Prevention and Treatment of Hypertension in Primary Settings”.⁴

After that, pharmacy students who are certificated by the MMAS research group will give a personal consultation to hypertensive patients in intervention group based on their responses to the MMAS-8 questions and questionnaires. The personal consultation will last about 5 mins to identify patients' barriers to medication adherence and provide suggestions to overcome their barriers such as forgetfulness, side effects and negative beliefs. The whole process will last about 20 mins and patients will have the opportunity to ask questions during the consultation. During the intervention period, patients in the intervention group will also receive SMS reminders at 3-day intervals while patients in the control group will only receive a welcome SMS and end-of-trial SMS.

At month 3, hypertensive patients who complete baseline survey will be invited to the CHCs or will be interviewed on telephone by trained interviewers to finish the MMAS-8 in two groups. For patients in the intervention group, they will receive another personal consultation which will last for 5 mins. For patients, who are too busy to go to the CHCs or answer their phones, medical staff and pharmacy students will go to their communities to finish the follow-up study. At months 0, 3 and 6, patients will undergo assessments on medication adherence and blood pressure both in the control and intervention groups. For blood pressure measurement, patients will be measured by blinded nurses using the calibrated upper-arm electronic sphygmomanometer (OMRON HEM-7200, OMRON Corporation, Dalian). The study design is shown in Figure 1.

Outcomes

The primary outcome is change in blood pressure and medication adherence from baseline to months 3 and 6. Patients without drinking, smoking or consuming coffee or tea within 30 mins before the measurement will be measured by medical staff using certified and regularly calibrated upper-arm electronic sphygmomanometer

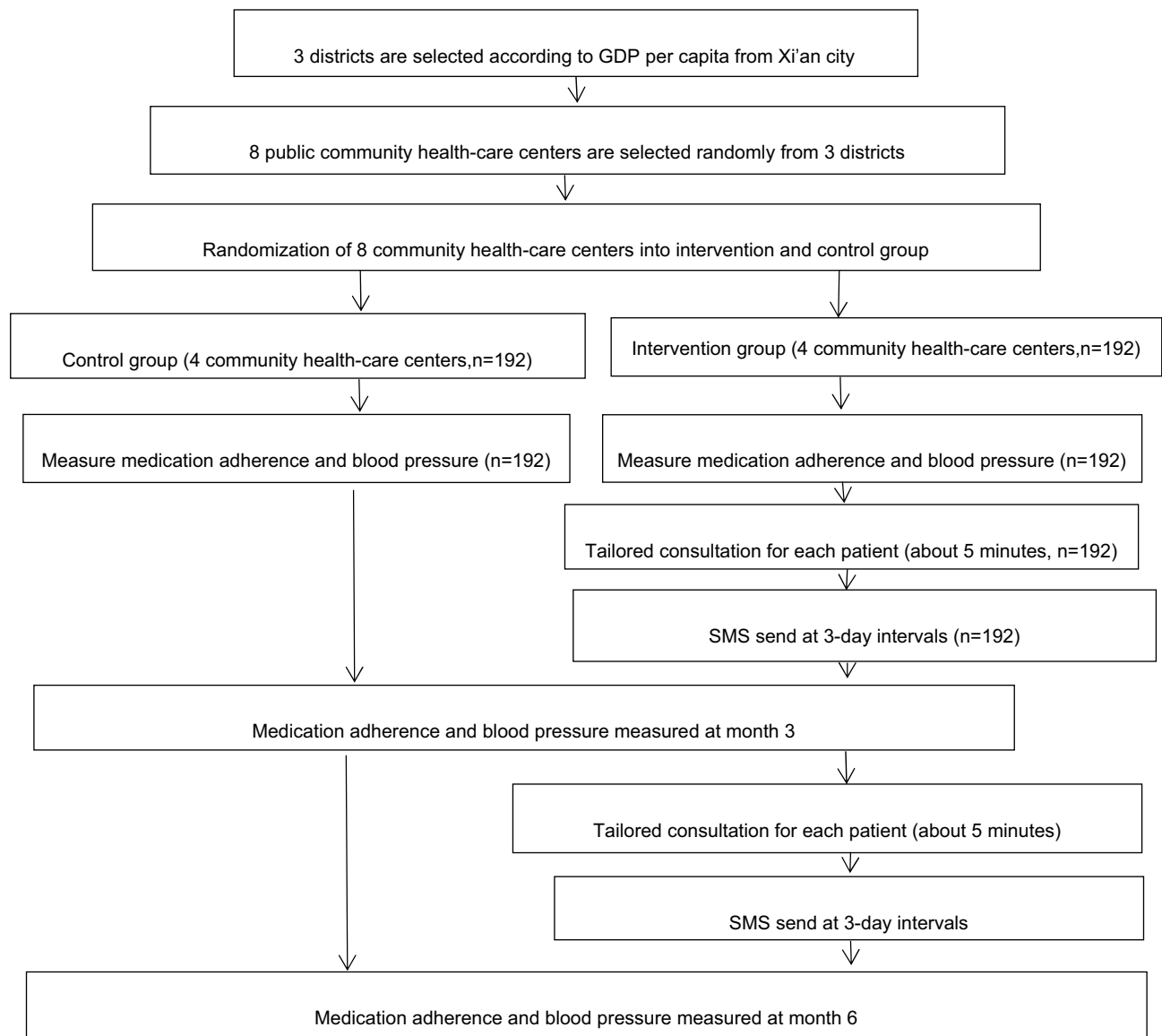


Figure 1 Study design.

according to the standard guideline. There will be two measurements taken 5 mins apart⁴⁶ and blood pressure will be the average of the two measurements.⁴ If the difference between two measurements is 5 mmHg or more, the third time measurement will be taken, and the final blood pressure will be the average of two closest measurements.⁴ Medication adherence is measured by MMAS-8 with a total score range 0–8.⁴⁷ Response answers are dichotomous (yes/no) for the first seven questions and a 5-point Likert response for the last item. Low adherence and medium adherence are defined as having <6 and 6 to <8, respectively. High adherence is defined as getting 8 in the test. It is widely used with good reliability (Cronbach's $\alpha=0.83$) and validity. The MMAS-8 demonstrated good internal

consistency (Cronbach's $\alpha = 0.77$) and test–retest reliability in Chinese population.⁴⁸

The secondary outcome is the proportion of people having controlled blood pressure at months 3 and 6. Hypertension control is defined as having a SBP <140 mmHg and a DBP <90 mmHg for hypertensive patients without diabetes or chronic kidney diseases or a SBP <150 mmHg and a DBP <90 mmHg for hypertensive patients aged over 80 years old⁴⁹ or a SBP <130 mmHg and a DBP <80 mmHg for patients with diabetes or chronic kidney disease.²⁵

Sample size

The study is based on the comparison of blood pressure between control group and intervention group at baseline

and at month 6. Based on a previous study,⁵⁰ a 5 mmHg decrease in SBP can reduce the risk of having stroke and coronary heart diseases. According to earlier study,⁵¹ we used the standard deviation of SBP (14.1 mm Hg) to calculate the sample size. The intended sample size is 384, allowing for 15% loss to follow-up, with 90% power and 5% (two-sided) level of significance.

Data analysis

At baseline study, Shapiro–Wilk test will be used to check whether the data are normally distributed. We will compare the difference between two groups on patient demographics, medication adherence, systolic and diastolic blood pressure using chi-square test or independent-samples *t*-test or Mann–Whitney test. Continuous variables will be reported as mean with standard deviation for normal data or medians with inter-quartile ranges for non-normal data. Categorical data will be presented as frequencies and percentages. Logistic regression will be performed using medication adherence and blood pressure as outcome variables to analyze the potential factors affecting them.

We will analyze the primary outcome using mix-effect model on repeated data collected at 3 and 6 months. Since repeated observations are measured within each subject, mixed models will be used to test intervention effects while taking into account within-subjects correlation. As for the secondary outcome, blood pressure control will be analyzed using mixed-effect logistic regression models. Intention-to-treat analysis will be used where all participants remain in the allocated group irrespective of their adherence with the protocol.⁴¹ After the study, data will be entered on a double-entry basis by research assistants to ensure the quality of data and then the statistician will receive anonymous data at the end of the trial.

All data analysis will be analyzed using SPSS 18.0 and $P < 0.05$ is considered to be significant.

Morisky Widget & Morisky medication adherence protocol training

The Morisky Widget & Morisky Medication Adherence Protocol Training for pharmacy students was conducted over 2 days (20–21 July 2018) by Professor Morisky and his colleagues in the MMAS research group. Professors, lecturers and pharmacy students in their master and PhD degree attended the training course. The training included 3 sessions: interactive discussion, Morisky Training Test

and Morisky Widget. On the first day, the training included demonstration and discussion on the proper use of MMAS-8 and students were asked to finish Morisky Training Evaluation test after the training. Only those students who answered 80% of questions in the evaluation correctly were qualified for the second day's training. On the second day, the qualified students observed role playing based on responses to the Morisky Widget to identify problems with medication adherence, like forgetfulness and conducted two simulated conversations with each other. The students checked the overall score, intentional and unintentional score to conduct personal consultation.

The role-playing process was evaluated by Professor Morisky. General and individual feedback was given to students after the evaluation. A total of 8 professors, lecturers and students were certificated by the MMAS research group and Professor Morisky. In total, 3 pharmacy students in their second or third years of the master curriculum were qualified by MMAS research group. To avoid inter-student variations, only one pharmacy student will deliver consultation and conduct all intervention sessions at baseline throughout the study.⁵²

Ethical statement

Ethical approval for the study was obtained from the Research Ethics Committee of Health Science Center, Xi'an Jiaotong University (No.2018531). During the investigation, the investigator will explain the purpose and related content of the survey to participants and obtain patients' informed consent. The study will be conducted in accordance with the Declaration of Helsinki. All the data will be stored in a password protected file and can only be accessed by statistician in the study.

Discussion

This study is designed to answer whether personal consultation by pharmacy students and SMS reminders in addition to standard pharmaceutical care is effective in improving patient medication adherence and blood pressure control. We will assess the efficacy and acceptability of consultation and integrating different aspects of clinical care through an open-source online platform.

Personal consultation by pharmacy students will alleviate the problem of shortage of clinical pharmacists in the People's Republic of China and SMS is widely used and at low cost which can be integrated into clinical care. According to a meta-analysis⁵³ about text message intervention, it showed that daily reminders may lead to

response fatigue and possible intrusion and showed smaller effects than interventions that messaged several times a week or weekly. In order to deliver as much as information and avoid response fatigue, we chose 3-day intervals to send messages. A feasible and preliminarily effective intervention in this study could lead to clinical trials conducted in a larger scale to benefit more patients and reduce hypertension-related morbidity and mortality.

Moreover, most of the intervention studies in the People's Republic of China focus on patient medication adherence rather than their blood pressure control. Little is known about the blood pressure control after intervention. However, in our study, we will collect data at months 0, 3 and 6 to check whether our intervention is effective to reduce patient blood pressure and we will use real-time adherence and blood pressure measurements to provide immediate feedback to patients which will help them to understand the importance of being adherent to their medication regimens. SMS reminders and pharmacy students-lead consultation are low-cost approaches and can be easily integrated into daily practice. We will send messages via a third-party website which is highly available and affordable in community settings. Through the intervention, medical staff participating in the study will realize the importance of medication adherence for addressing chronic disease management in communities.

Our study has several limitations. First of all, medication adherence is measured by patient self-report and may overestimate their medication adherence. However, MMAS-8 has high validity and reliability and is widely used in measuring medication adherence.⁴⁷ Self-reported measures could be simple, inexpensive, and straightforward and therefore can be conveniently administered in research and clinical practice settings.⁵⁴ Second, due to our time cost, response burden and fund limitation, only one city will be investigated and could not be extended to the whole province, but the sample is rather representative. Third, the study will last for 6 months; therefore, we will be unable to determine the effect of medication adherence on longer term outcomes, including hypertension-related stroke, myocardial infarction, acute coronary syndrome, heart failure, hospitalization, ER visits, morbidity and mortality. But the study is not designed to detect the effect of medication adherence and blood pressure on other clinical outcomes such as the occurrence of stroke and heart disease. Additionally, we will implement our study to a larger scale if the intervention is effective in lowering patient blood pressure to address the limitation and we will explore other intervention methods such as telephone calls and mobile phone

applications to make sure the sustainability of our study in future studies. Finally, SMS may be less effective in patients with low education level or live in the remote areas. But we exclude patients who are illiterate, and we will send messages in Chinese understood by patients with low education background and we will tell patients to read their messages sent by Xi'an Jiaotong University during the consultation. Furthermore, SMS is the most accessible and inexpensive way to remind patients to take their medicine and educate them about self-care management knowledge.

The study addresses the challenge of high prevalence of hypertension and low medication adherence to long-term treatment. SMS reminders and consultation may be an effective way to improve medication adherence and manage blood pressure in community settings.

Ethics approval and consent to participate

Ethical approval was obtained from the Research Ethics Committee of Health Science Center, Xi'an Jiaotong University. Written informed consent will be obtained from patients before enrolling in this study and patients are free to withdraw throughout the study.

Acknowledgments

The MMAS (8-item) content, name and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from Donald E. Morisky, ScD, ScM, MSPH, 14725 NE 20th St Bellevue, WA 98007, USA; dmorisky@gmail.com. We are grateful for the patients, nurses, physicians for taking part in this trial. The trial is funded by "Natural Science Foundation of China" and was approved by the Xi'an Jiaotong University's Research Ethics Committee. The authors are solely responsible for the study design, field study, data analysis and draft the manuscript and the final protocol.

Author contributions

This is a collaborative research, each of the listed people provided important intellectual contribution to study design. PPZ drafted the protocol. PPZ, QL, AHG and KH drafted the final manuscript while DEM and YF revised the final protocol. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Morisky is the developer/owner of the copyrighted and trademarked protected Morisky Medication Adherence Scale and sells MMAS licenses and consulting services through MMAS Research LLC, 14725 NE 20th St., Bellevue, Washington 98007. Dr Morisky also reports personal fees from MMAS Research LLC, during the conduct of the study; receives personal fees from MMAS Research, LLC, outside the submitted work. The authors report no other conflicts of interest in this work.

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