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Notification of international normalized ratio test in atrial fibrillation patients treated with warfarin via short message service: Study protocol for a randomized controlled trial

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Abstract

Background: Atrial Fibrillation (AF) is the most common abnormal heart rhythm. AF patients usually use warfarin therapy. Safety and efficacy of warfarin are dependent on maintaining the International Normalized Ratio (INR) within the therapeutic range.

Objective: We will use a Short Message Service (SMS) to evaluate the effect of a reminder on carrying out the INR laboratory test in a timely manner.

Methods: This study (a Randomized Controlled Trial) will be done in Loghman hospital Tehran, Iran. Convenience sampling will be done and 400 AF patients that have inclusion criteria will be randomized equally to an intervention or control group. Patients in the intervention group will receive an SMS that will remind them of the INR test date. The SMS will be sent at 6 PM on the day before and 8 AM on the scheduled date but the patients of the control group will receive usual care without any SMS reminders. We will evaluate the effect of reminders on carrying out the INR test in a timely manner and maintaining the INR in the therapeutic range. Patients' follow-up will be done via telephone conversation to identify thromboembolic events, bleeding and mortality. The data will be analyzed by IBM SPSS version 24. We will use independent samples t-test or Mann–Whitney and Chi-square tests for the analyses of outcomes.

Discussion: This protocol describes the randomized control trial to study the effects of the SMS reminder system on adherence to the timing of INR test in AF patients treated with warfarin. The research will also form the basis for future decision support systems for monitoring of patients who receive oral anticoagulants.

Trial registration: Iranian Registry of Clinical Trials (http://www.irct.ir) was used to register the trial and IRCT ID was IRCT2016052528070N1.

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Keywords: Stroke, Atrial fibrillation, Warfarin, Hemorrhage, Short Message Service, International Normalized Ratio, Mortality

1. Introduction

AF is the most common heart arrhythmia, and causes blood stasis within the left atrium and increases the risk of thrombus formation (1). The most important complication of AF is stroke. Warfarin is a vitamin k antagonist that inhibits the coagulation cascade and reduces the risk of thrombus formation (2). On the other hand, warfarin therapy increases the risk of bleeding, especially in the first three months of treatment and is more seen in elderly patients with AF (3). INR is a blood test used to monitor the effects of warfarin and measure the clotting time. The risk of bleeding increases significantly when the INR is higher than the therapeutic INR range. When the INR is less than the therapeutic INR range, warfarin does not produce desirable protection against stroke. Therapeutic INR range for AF patients is 2.0-3.0 (4). Fluctuations in INR levels are related to many drug-food and drug-drug interactions and concurrent diseases (5). A systematic review showed that patients who were receiving long-term warfarin, spent

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55% of their time in the therapeutic INR range (6). The relationship between the increase in time out of the therapeutic range and an increased risk of mortality, stroke and other thromboembolic events has been identified (7). So, regular testing of the INR is necessary due to the changes in INR levels for all people who take warfarin to ensure the effectiveness of treatment and patient safety (8). Between the known factors, Noncompliance (41.8%) was the most important factor affecting fluctuations of the INR (9). Reminders that have been used for improvement in patient compliance were useful in reducing delays in monitoring (10). Furthermore, forgetting and confusion about the date of the appointment were mentioned as the main reasons for nonattendance (11). Nonattendance at outpatient appointments wastes time and resources, and is a major burden on health systems (12). Phone calls, emails or text messages can be used as pre-appointment reminders. Pre-appointment reminders are defined as actions to remind patients to attend appointments (13). Since the effectiveness of these methods have been shown to increase the attendance rate at outpatient clinics (14, 15), we believe that these will be effective in carrying out on-time INR tests. SMS reminders were used and recommended for diagnosis and treatment in tuberculosis clinic appointments and primary care (13, 16). The most common reasons for widespread use of SMS are: The pervasiveness of mobile usage in different countries (17, 18), convenience, immediacy and confidentiality (19). SMS messages can be sent automatically in bulk so costs are reduced compared to phone or postal reminders, while SMS and phone reminders had the same effectiveness (20). So, SMS will be used in this study. No study has yet assessed the effects of SMS on the INR test in patients taking warfarin. The hypothesis of this research is that the intervention group that receive SMS reminders will do the INR test in more appropriate time rather than the control group and therefore their INR will be maintained in the therapeutic range more than the control group. So, we expect the reductions in thromboembolic events, and bleeding and mortality in the intervention group. The primary aim of this study is to evaluate the effect of SMS reminders on carrying out the INR test in a timely manner. Finally, we would like to determine the long-term effectiveness of SMS on maintaining the INR in the therapeutic range, reductions of thromboembolic events, bleeding and mortality.

2. Material and Methods

2.1. Trial design

This study will be a Randomized Control Trial (RCT). The study will be started in June 2016 and continued for nine months. Randomization will be done at the patient level. Convenience sampling will be done and 400 patients will be recruited and allocated to the intervention group that will receive SMS reminders for INR test (two hundred patients) or the control group that will not receive any reminder for the INR test (two hundred patients).

2.2. Participants

The study will be done in Loghman hospital in Tehran, Iran's capital. It is an educational hospital and affiliated to Shahid Beheshti University of Medical Sciences. It is a 420-bed hospital and high ranking in the list of evaluated hospitals. One of the authors (MS) will conduct the study in the hospital. The research populations are the AF patients who will be referred to the cardiology department of this hospital.

2.3. Selection criteria

Newly diagnosed AF patients who must take warfarin with outpatient follow-up will be included. AF will be diagnosed by ECG. CHA2DS2-VASc was used for predicting stroke in AF patients (21). AF patients with CHA2DS2-VASc score ≥2 will take Oral anticoagulant (OAC) such as warfarin (22, 23). Exclusion criteria are:

- AF Patients with cognitive impairment and consumption of non-compliance to treatment with warfarin
- When AF Patients or their carers do not have mobile phones for sending SMS.

2.4. Intervention

We have developed a web based program which has a user interface for data entry. Patient characteristics such as age, sex, congestive heart failure, hypertension, diabetes mellitus, history of stroke/transient ischemic attack/thromboembolic, vascular disease, start date warfarin and mobile number of patient (or mobile number of carer) are entered at the first visit by the secretarial assistant of the clinic under the supervision of the cardiologist. The date when the INR test must be done is determined by the cardiologist. This data must be maintained in the database of patients and INR note book. In the next visit, the date of INR test, the INR result and the next test date are determined and entered in the database of patients and INR note book by a cardiologist, using an SMS panel (http://www.payam-resan.com). The required data will be sent to the SMS panel for sending an SMS to the patients at the appropriate time. Patients in the intervention group will receive an SMS that reminds them of the INR test date. The SMS will be sent at 6 PM on the day before and 8 AM on the scheduled date but the patients of the control group will not receive these reminders and will use an INR note book. For example, if the following INR test date is

3/14/2017, this SMS text will be sent: "This is a reminder of the INR test on 3/14/2017, please make an appointment with your cardiologist after getting your test result". Follow-up will be done nine months later and data such as bleeding, thromboembolic events and mortality will be collected in both groups.

2.5. Outcomes

The primary outcome is carrying out the INR test in a timely manner. Carrying out the INR test in a timely manner means that the INR test must be done in the time specified by the cardiologist. The number of days between scheduled date and actual date will be calculated. The secondary outcomes are: percentage of measurements in therapeutic INR range, thromboembolic events, bleeding and mortality. Percentage of measurements in therapeutic INR range is calculated by dividing the number of visits that had INR results in therapeutic range by the total number of visits. Patients' follow-up will be done via telephone conversation with them or their carers. If the patient is hospitalized during follow up, the documents will be checked, and bleeding and thromboembolic events will be collected.

2.6. Sample size

A power analysis showed that 183 patients for the intervention group and 183 patients for the control group are needed for a power of 0.8 when assuming patients who receive long-time warfarin spent on average 50% of their measurements in the therapeutic INR range, and at least 15 percent improvement for the intervention group, with an alpha of 0.05. We assume percentages of patients lost to follow-up will be 9% so the required sample size is almost 400 patients.

2.7. Randomization

Randomization plan generator (http://www.randomization.com) will be used and implemented in the web based program. For simple randomization of patients (24) our program randomly assigned patients to the SMS group and the control group. Allocation concealment will be ensured by the use of unpredictable sequence numbers. Four hundred patients will be randomized into two equally sized groups. Patients cannot be blinded to the SMS because patients in the control group do not receive SMS but cardiologists and outcome assessors will be blinded from knowing which patient is in the intervention group.

2.8. Data analysis

The intention to treat principle will be used and outcomes will be analyzed according to the original allocation of patients, regardless of whether they actually received SMS or not. Demographics and baseline characteristics of patients in each group will be presented and will be analyzed for differences in the two groups by independent samples t-test or Mann–Whitney for numerical data, and chi-square for categorical data. Differences between primary and secondary outcomes in groups will be tested by independent samples t-test. Where assumptions for parametric analysis have not been fulfilled, non-parametric analysis will be replaced to make these comparisons. The data will be analyzed by IBM SPSS version 24.

2.9. Ethical considerations

This study is a part of a proposal approved by the Medical Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1394.524). The research assistant of Loghman hospital has approved the study. The intervention is an SMS reminder, a non-invasive intervention that will not interfere with the patient's treatment. Moreover, we will use non-identifiable patient data for analysis, and data will be only accessed by authorized persons. According to the above, just a verbal consent will be obtained to participate in this study. This RCT is registered with the Iranian Registry of Clinical Trials and registration ID is IRCT2016052528070N1.

3. Discussion

This paper will specify a protocol for investigating an SMS system to remind AF patients of their forthcoming INR test. We will design a web site and use an SMS panel to send text messages to mobile phones. The aim of this proposed randomized controlled trial protocol is to provide valuable information about using SMS for oral anticoagulation management. Anticoagulation clinics are special clinics to help patients who are taking warfarin. If our system that reminds upcoming appointments for INR test is successful in improving anticoagulation control, it can be used in these anticoagulation clinics. The relevant and objective outcomes that provide a complete assessment of the SMS system are one of the strengths. Clinical outcomes such as thromboembolic events, bleeding and mortality caused by them will also be considered. According to our knowledge this is the first study that will use SMS to remind the patients of the INR test. This research will also form the basis for future decision support

systems for monitoring of patients who receive oral anticoagulants. Studies showed that computerized decision support systems are effective for oral anticoagulation management (25, 26). CONSORT statements (27) will be used to improve the reporting of RCT. We will conduct the research in a single center and include only newly diagnosed AF patients that must take warfarin so that we have limitation in patient selection. For future work, for one appointment an SMS reminder can be sent not only to the patient but also to the patient's carer. We think percentage of INR measurements in the therapeutic range can be improved. Instead of using intention to treat principle, the patient or the patient's carer can reply 'yes' to confirm that they have read the SMS and per-protocol analysis can be done.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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