Increasing cardiovascular medication adherence

A Medical Research Council complex mHealth intervention mixed-methods feasibility study to inform global practice

ABSTRACT

Aims to evaluate a mHealth intervention to increase medication adherence among Iranian coronary heart disease patients.

Design Quantitative-dominant mixed-methods study

Data Source Iranian coronary heart disease patients' responses and most recent clinical documents as well as responses from Iranian cardiac nurses who participated in this study.

Methods The study was conducted between September 2015 and April 2016 drawing upon the Medical Research Council's Framework. Phase one comprised of a patients' survey and focus groups with cardiac nurses. The automated short message service reminder was piloted in phase two. We recruited 78 patients and randomised to receive either 12-week daily reminders or usual care. The primary outcome was the effect on medication adherence; secondary outcomes were self-efficacy, ejection fraction, functional capacity, readmission rate and quality of life.

Results Feasibility was evidenced by high ownership of mobile phones and high interest in receiving reminders. Participants in the intervention group showed significantly higher medication adherence compared to the control group.

Conclusion The mHealth intervention was well accepted and feasible with early evidence of effectiveness that needs to be confirmed in a fully powered future randomised clinical trial.

IMPACT

Problem?

- Poor medication adherence has been identified as a barrier to effective treatment of coronary heart disease.
- Acceptability and feasibility of a theory-based mHealth intervention to improve medication adherence for Iranian coronary heart disease patients is not known.

Findings?

- The mHealth intervention was well-accepted and feasible by Iranian coronary heart disease patients.

- The mHealth intervention has the potential to increase cardiovascular medication adherence; a definitive Randomised Control Trial is required to confirm the effectiveness.

Impact?

- Healthcare providers' perceptions and patients' preferences need to be understood when designing interventions.
- The findings can inform the translation and scale-up of text-messaging to improve medication taking and reduce evidence practice gaps.

KEYWORDS

Coronary Heart Disease; Secondary Prevention; Medication Adherence; mHealth; Text Messaging; Nurses; Iran.

1. INTRODUCTION

Cardiovascular Disease (CVD) is the main reason for mortality worldwide, accounting for more than 17 million deaths each year (World Health Organisation, 2019). In particular, mortality rates caused by CVD are increasing in low- and middle-income countries (World Health Organisation, 2019). Reducing the prevalence, morbidity and mortality of CVD, as the leading cause of the wider burden of non-communicable disease, is a major world health priority (World Health Organisation, 2019). In Iran, Coronary Heart Disease (CHD) - the most important type of CVD - accounts for nearly 50% of all deaths per year. Approximately 20% of Iranian adults aged 30 years and over in Tehran, the capital city, have symptoms or signs of CHD (Hadaegh, Harati, Ghanbarian, & Azizi, 2009). According to a 10-year population-based cohort study conducted in Iran, the crude CHD incidence rate in men was about twice that in women (11.9 vs. 6.5 per 1000 person-years) (Khalili et al., 2014). Given the high prevalence of and a predicted large rise in CHD over the coming decades, the Ministry of Health and Education of Iran has given priority to research exploring strategies to reduce cardiovascular mortality by 25% in the next 10 years (Mansoori et al., 2018).

1.1 Background

CHD patients could benefit from treatment to reduce the risk of recurrent cardiovascular events and mortality; this is known as secondary prevention that includes Cardiac Rehabilitation (CR), lifestyle changes and pharmacological treatment (Anderson et al., 2016) Research has shown that consistent use of medications and participating in CR can improve risk factors and decrease mortality and hospital readmission (Anderson et al., 2016; Kabboul et al., 2018). Despite the importance of secondary prevention, Medication Adherence (MA) is suboptimal among survivors of cardiovascular events; only a range from 13-60% of patients are fully adherent to anti-platelet, statins, Beta Blockers and the combination of all three (Garavalia, Garavalia, Spertus, & Decker, 2009; Kyanko, Franklin, & Angell, 2013; Rodriguez et al., 2013). According to a systematic review of 76 studies conducted in developing countries including Iran, pooled cardiovascular MA was found to be unsatisfying (only 57.5%) (Bowry, Shrank, Lee, Stedman, & Choudhry, 2011).

Poor adherence to medications can be attributed to both intentional (i.e. patient decides not to follow the treatment) and/or non-intentional (i.e. due to uncontrolled barriers such as forgetfulness) reasons(Brown et al., 2016). Almost half of the medication non-adherence is unintentional or due to forgetfulness, complexity of the treatment regimen, problems of accessibility, cost and competing life demands (Brown et al., 2016; Gadkari & McHorney, 2012).

There is growing evidence that mHealth interventions are an effective and acceptable means of improving both intentional and non-intentional adherence (Hamine, Gerth-Guyette, Faulx, Green, & Ginsburg, 2015; Thakkar et al., 2016). Mobile phones can deliver interventions via Short Messaging Service (SMS), Smart phone applications (apps), video messaging, "push" notifications, or via mobile websites (Kay, Santos, & Takane, 2011). In a recent systematic review of ten studies of varying designs, 607 patients from five countries were included (Coorey, Neubeck, Mulley, & Redfern, 2018). Interventions targeted hypertension, heart failure, stroke and CR populations. According to the authors, MA, rehospitalisation rate and quality of life were among the factors that were enhanced among mHealth users. The International Telecommunication Union (2018), reported that there were over 87 million mobile phone subscriptions (108.2 per 100 inhabitants) in Iran. Iranian main operators communicated more than 40 million SMS each day (Goodarzi, Ebrahimzadeh, Rabi, Saedipoor, & Jafarabadi, 2012), allowing extensive reach, utilisation and potential effectiveness of mHealth solutions. To date and our knowledge, there have been limited studies on the use of mobile phone to improve MA exclusively for patients with CHD in the setting of CR in Iran.

2. THE STUDY

2.1 Aim

This study aimed to refine and pilot a pre-developed theory-based mHealth intervention (BLINDED FOR PEER REVIEW) using the Medical Research Council (MRC) framework (2018) to improve cardiovascular MA in Iranian adult, male and female CR outpatients. Specifically, the focus of this study was on the preclinical, re/modelling and feasibility phases of the MRC framework.

2.2 Design

In accordance with the MRC framework (2018), the multi-stage mixed-methods study consisted of the first two consecutive phases of development and feasibility of the intervention in preparation for a full Randomised Controlled Trial (RCT) (Registration number: ISRCTN10549665). A text-messaging mHealth intervention had been developed and piloted previously among ACS patients in Malaysia that showed significant improvements in MA and heart functional status (BLINDED FOR PEER REVIEW). This time we tested the same intervention for Iranian CHD patients after undertaking the stages mapped in the MRC framework to ensure the intervention would be appropriate to the Iranian context. In the first phase, the theoretical basis of the intervention was refined; in the modelling phase, exploring Iranian nurses' and patients' views allowed an understanding of required modifications to the intervention. In the second phase, the feasibility of the intervention was tested.

2.2.1 Phase 1: Intervention (re)Modelling

The theoretical basis of the intervention

We identified and reviewed the relevant theoretical literature, Behaviour Change Techniques (BCTs) and published evidence base concerning cardiovascular medication non-adherence. The electronic databases CINAHL (Cumulative Index of Nursing and Allied Health Literature), Cochrane, Campbell Collaboration, Medline, Embase, GlobalHealth and PsycINFO to June 2017 were searched using the following keywords: Cardiovascular diseases/ or heart diseases/ or coronary disease AND text messaging/ or reminder systems/ or telephone or mobile applications AND patient compliance/ or MA. The research team identified key findings regarding mHealth interventions and information deemed suitable to the study setting.

Iterative decisions about search strategy, data extraction and analysis were discussed in meetings attended by all authors and documented in a study log. Based on the study focus, the following were set as the inclusion criteria:

-Review or trial mHealth as the main study focus;

-Study utilised mHealth by adults (>18 years) of both gender;

-Published in English language;

Duplicates were removed and articles were excluded if they exhibited one or more of the following characteristics:

-The patient was not the study target population (i.e., provider-focused);
-Described a study protocol;
-Involved children and/or people younger than 18 as the target population;
-Used mHealth for acute conditions;
-Used mHealth for assessment, monitoring or measurement;
-Proposed or developed a model or device.

Publications were initially screened for potential inclusion based on the review of title and abstract by two independent reviewers (BLINDED FOR PEER REVIEW). Information including objectives, types of mHealth intervention used, setting, study sample characteristics, outcomes measured, and results reported were extracted using Microsoft Excel. Usability, feasibility, and acceptability of the applied mHealth intervention, the theoretical basis and the effect on patient's outcome (ie. cardiovascular medication adherence), and any disease-specific clinical outcomes of the intervention were reviewed. A descriptive review of the studies was performed and the findings from these research studies summarised, with emphasis on results reported in trials. Methodological quality was assessed for all full text manuscripts included in the review. Selected studies were evaluated for their quality using the Consolidated Standards of Reporting Trials (CONSORT) guidelines for Randomised Controlled Trials. Any disagreement in interpretation of data and inclusion of studies between reviewers was resolved by consensus (BLINDED FOR PEER REVIEW).

Patients' Perception Survey

A self-completion survey conducted among a convenience sample of male and female CHD (i.e. Myocardial Infarction, angina or revascularisation) patients, aged 18 and over presented at CR clinic in a hospital affiliated to Tehran University of Medical Sciences (TUMS). Specifically, the survey aimed at identifying:

- the pattern of ownership, utilisation of mobile phones in Iranian CHD patients (Objective 1); and
- a preferable design for the study intervention based on CHD patients' opinions in Iran (Objective 2).

Given that the CR clinic at the study setting had on average 120 admissions per month for a 24-session exercise programme, then the required sample size was n=92 with a 95% confidence level, 5% margin of error. Estimating a 70%

participation rate, 132 eligible CHD patients attending the CR program were asked to participate over a period of three weeks in September 2015. Of 132 subjects, 123 (93.18%) consented and agreed to complete the questionnaire. All patients completed sociodemographic information along with the survey questionnaire, self-reported MA and Health-Related Quality of Life (HRQoL) during a face-to-face visit.

Survey Instruments

Electronic Supplementary Material adapted for use from a similar study (Shet et al., 2010) and consisting of 21 items that covered two main domains of enquiry (1) what is the pattern of ownership and use of mobile phones among CHD patients and; (2) what might a patient-preferred design for a mobile phone-based intervention to influence MA look like was utilised.

The Persian-version of the Morisky Self-Reported MA Scale (MMAS-8) was used after receiving a signed license contract and copyright agreement from the owner. It is one of the most reliable and widely used scales to determine adherence to cardiovascular medications. The internal consistency of the MMAS-8 (Cronbach's alpha reliability) is 0.83 with good concurrent and predictive validity. This measure has been also found to positively correlate with pharmacy fills rates (≥75%; r=0.46; P<0.001) (Morisky, Ang, Krousel-Wood, & Ward, 2008). The instrument measures non-adherence to medications for reasons such as forgetfulness, carelessness, feeling better, or feeling worse (AlGhurair, Hughes, Simpson, & Guirguis, 2012).

HRQoL was evaluated using the validated Persian translation of the Short Form Health Survey Version 2.0 (SF-12v2). The SF-12v2 is a multi-purpose Short Form (SF) generic measure of health status that uses a Likert scale format with high internal consistency, test-retest reliability, construct validity, and criterion validity (Fleishman, Selim, & Kazis, 2010; Ware et al., 2009). The reliability of the Iranian version of SF-12v2 for both physical and mental summary measures exceeded the 0.70 level for Cronbach's alpha indicating satisfactory results (0.87 and 0.82, respectively) (Montazeri et al., 2011). We used the standard four-week recall period version in this study.

Focus Groups

Principal Nurse Supervisors/ Matrons in three hospitals affiliated to TUMS were gatekeepers of the study. They were asked to verbally invite cardiac nurses from CR

clinics, provide a brief explanation of the study and arrange a date and venue for the Focus Group Discussions (FGDs). A purposive sample of 23 male and female nurse staff with at least six months clinical experience were recruited. The FGDs were conducted and facilitated by (BLINDED FOR PEER REVIEW) on three different days in November 2015, as part of her PhD studies (which contained qualitative methods training), mentored by (BLINDED FOR PEER REVIEW), a professor in nursing and an experienced qualitative researcher. Before the start of the FGDs, (BLINDED FOR PEER REVIEW) explained the study and the ground rules and importance of maintaining confidentiality. Then she asked all participants to sign the consent forms. The FGDs were conducted in the native language of participants, which was typically Farsi. An interview guide was developed to structure FGDs. Interview questions were pilot tested with colleagues at TUMS to assess timing and ensure validity. All responses were open-ended and the discussions were flexible allowing pursuit of issues raised by the participants that were not in the original FGDs' protocol. FGDs specific objectives were to explore:

- Iranian cardiac nurses' perspectives about the potential effect of a mHealth intervention among Iranian CHD patients (Objective 3); and

- Potential barriers and facilitators to implementation of the mHealth intervention through which such interventions may affect cardiovascular MA in the Iranian context (Objective 4).

Specifically, participants were asked to reflect on (1) their experience with applying mHealth (2) positive and negative aspects of mHealth (3) challenges of using mHealth for patients and healthcare providers (4) strategies for best implementing a mHealth-based intervention to improve cardiovascular MA. All FGDs were audio-recorded with permission from participants and transcribed verbatim after each session. The average FGD time was fifty minutes. As a validity check, the researcher asked participants to verify a verbal summary of the key points (Krueger, 2014).

A thematic coding and categorising were used to interpret the data adapted from approaches to qualitative content analysis discussed by Graneheim and Lundman (2004). Following steps have been taken:

The transcript was read and brief notes were taken in the margin when interesting or relevant information was found. After that, the notes made in the margins were

reviewed and the different types of information were listed. The next step was to read the list and categorise each item in order to establish a framework of thematic ideas. It was then identified whether or not the categories could be linked in any way and they were listed as major or minor themes. At this stage, the various major and minor categories were compared and contrasted. Finally, all of the categories were reviewed and it was ascertained whether some categories can be merged or if some need to then be sub-categorised. All original transcripts were reviewed and all steps were taken several times to ensure that all the information that needs to be categorised has been so.

(BLINDED FOR PEER REVIEW) identified themes that emerged from the data. Data coding was discussed with (BLINDED FOR PEER REVIEW) and (BLINDED FOR PEER REVIEW), allowing comparison of data interpretation and subsequent coding refinement. The results were compared and discussed with other authors to reach agreement.

2.2.2 Phase 2: Feasibility Study

The second phase was conducted between February and April 2016 and included a 12-week feasibility RCT (pre-test, post-test parallel group design) to:

- evaluate the effect of a 12-week mHealth intervention on the primary outcome: MA of Iranian male and female CHD patients participating in CR (Objective 5);
- evaluate the effect of a 12-week mHealth intervention on the secondary outcomes: MA Self-Efficacy (MASE); cardiac Ejection Fraction (EF); cardiac Functional Capacity (FC); CHD-related readmission/mortality rate and HR-QOL of Iranian male and female CHD patients participating in CR (Objective 6);
- explore the association between socio-demographic factors of the subjects and MA in both intervention and control groups (Objective 7);
- explore the perception of participants in the intervention group towards the received mHealth intervention at the end of the study (Objective 8); and
- identify the recruitment and retention rate and inform the sample size required for a future definitive RCT (Objective 9).

Sample and Setting

According to Lancaster et al. (2004) for sample size estimation in a feasibility study, a general rule of thumb is to take 30 patients or greater to estimate a parameter. The gatekeepers provided a brief explanation of the study to the CHD patients who were newly admitted to the CR clinic of the same hospital in which the survey and one of the FGDs were conducted. (BLINDED FOR PEER REVIEW) recruited the patients (n=78) who agreed to take part in the study and gained their written consent.

Random Allocation

Block randomisation was used with a block size of four. The blocks were chosen using the random number list generated in Microsoft Excel. Allocation was concealed using a sealed non-transparent envelope. (BLINDED FOR PEER REVIEW) generated the random allocation sequence, enrolled participants at the CR clinic, and assigned participants to interventions.

Control

The control group were not exposed to the study intervention. For the purposes of this study, usual care was defined as the CR care that was currently provided for CHD patients 4 to 6 weeks after discharge from hospitals in Iran that involved 24-sessions of supervised exercise training in combination with educational and psychological support.

Intervention

The intervention group received automated timely medication reminders for 12 weeks based on a predefined template every morning (This pattern was defined according to the phase I study findings). The 12 weeks of the intervention was selected as it takes approximately 10 weeks (based on daily repetition) for participants to adopt new behaviours (eg. medication taking) (Gardner, Lally, & Wardle, 2012).

A detailed description of the study intervention is presented elsewhere (BLINDED FOR PEER REVIEW). In short, the software consisted of various parts that were responsible for gathering and managing the information related to the patients and their medications, storing data, scheduling, sending text messages and recording

delivery reports automatically. Table 1 presents some examples of the text messages based on the principles of the study theoretical frameworks.

Blinding

Due to the nature of the intervention, it was impossible to blind either the participants or the researcher to the study group assignment.

Data Collection

Demographic information were collected at baseline. All participants were assessed face-to-face by (BLINDED FOR PEER REVIEW) in the study site two times: at baseline (pre-test: T1) and at the endpoint of the study (post-test, after 12 weeks: T2). At each point in time, all study outcomes were recorded. At the endpoint of the study, patients who received the intervention were asked to complete a survey on their satisfaction with the intervention. Feasibility were assessed by records of recrutiment and participation, reasons for drop-out, and web-analytics to determine text messages' delivery.

Measurment Instruments

The primary outcome of interest was the proportion of participants adhering to a complete cardiac medication regimen at 12 weeks measured using the MMAS-8. Secondary outcomes were:

- MASE using the 26-item and patient-derived scale (Ogedegbe, Mancuso, Allegrante, & Charlson, 2003);
- FC using the New York Heart Association (NYHA) classification, LVEF (based on the exercise test and echocardiography reports by cardiologists who were unaware of the study group assignment);
- CHD-related readmission/mortality rate (based on the most recent patients' documents)
- HRQoL (using two SF-12v2 questionnaires, one pre-test, one post-test completed by all participants); and
- patients' perception about the applied intervention using a self-administered survey adopted from the previous study (BLINDED FOR PEER REVIEW).

Ethical considerations

Ethical approval obtained from the Research Ethics Committee of the University of Edinburgh and the Hospitals in which the study took place (Ethics Approval Code: NURS006 and 92-04-28-28802-145738, respectively).

Data Analysis

All data were analysed using the computer program Statistical Packages for Social Sciences (SPSS) version 21. The significance level in this study was $\alpha=0.05$. The primary outcome from the MMAS-8 provided categorical data including high adherence (score of 8), medium adherence (score of 6 to <8) and low adherence (scores of <6). All secondary outcomes results were provided in categorical data including FC (Class I: no symptoms, II: mild symptoms, III: marked limitation and IV: severe limitations), as well as death and hospital readmission rates except the scores of perceived MASE, EF, and HRQoL. Exploratory statistical analysis was performed to generate preliminary data and assess within and between-group differences in primary and secondary outcomes. All statistical tests upon which each p-value is based have been provided in a footnote to Table 4. Statistical tests were chosen based on the type of variable (e.g. categorical or continuous) and on whether the comparison groups were paired or independent. In particular, for the primary outcome analysis, a Chi-squared test was performed. The outcome of patients' MA level (low, medium and high) was cross-tabulated against the study groups (intervention and control). Since two categories had low number of counts (2 and 3), we confirmed the primary outcome result by merging the medium and low adherence categories into a single category called non-adherence, and then applying a Fisher's Exact test. The Relative Risk (RR) with 95% confidence interval was also calculated based on the risk of non-adherence ("low/medium" adherence) at 12 weeks. The absolute difference in the percentages of patients with non-adherence at 12 weeks was also calculated (with 95% CI calculated using the exact method in Altman et al. 2013).

The Multiple Logistic Regression was used to assess any association between socio-demographic variables (ie. age, sex, education, marital status, employment, living arrangement, monthly income, family size, diagnosis, diagnosis time, co-morbid, hospital stay) and medication adherence.

Credibility/rigour

There were crucial steps undertaken to ensure the scientific rigour of this study:

(1) the controlled study design with participants randomly allocated to both study groups;

(2) carefully re-designed and tailored the mHealth intervention to the Iranian context through undertaking the stages mapped in the MRC framework and understanding nurses' perceptions and CHD patients' preferences;

(3) applying a reliable and validated quantitative measures for primary and secondary outcomes assessment at baseline and endpoint of the study.

(4) issues of trustworthiness for qualitative phase of the study were carefully followed by criteria mentioned by Graneheim and Lundman (2004). To achieve credibility, the participants were selected to have different years of experience, age, and education level. To address dependability and transferability, the authors provided a clear description of the context, participants, data collection and process of analysis and findings followed by some suggestions on how our findings may be transferred to other contexts.

3. RESULTS

3.1 Phase 1 – Intervention (re)Modelling

3.1.1 The theoretical basis of the intervention

The theoretical basis of the study intervention was based on the principles of self-efficacy within the Social Cognitive Theory (SCT) (Bandura, 2012). Bandura's SCT is one of the most relevant theoretical perspectives used in MA reasoning. SCT was chosen because it concerns perceived self-efficacy and individual goals that influence the attainment of a new behaviour (eg. taking medications) or the changing of an existing behaviour (eg. medication non-adherence) over time (Bandura, 2012). The intervention also benefited from the application of the principles of the WHO Adherence Model (2003) in which both intra- and interpersonal factors have been identified as important dimensions that influence MA. According to this model, the mHealth intervention was designed to improve cardiovascular MA through addressing the most common barriers to adherence such as patient-related factors

(eg. forgetfulness and low self-efficacy in taking medications) and healthcare system-related factors (eg. lack of patient-provider interaction).

The Dixon and Johnston's Health Behaviour Change Competency Framework (HBCC) maps each BCT to one or more of three identified routes to behaviour change, namely: Motivation development to promote skills that help that motivation to be transformed into Action; and Prompted or cued routes to behaviour (MAP) (Dixon & Johnston, 2010). The mHealth intervention targeted the third route of the MAP (i.e. the prompted or cued route) that supports behaviour (i.e. medication taking) without the need for the constant cognitive attempt required by the other routes.

3.1.2 Patients' Perception Survey

The results of the Iranian CHD patients' survey confirmed the acceptability of using mHealth interventions using text messaging to improve MA for this group of patients. Mobile phone ownership (n=118/123) and the use of text messages (n=84/123) were relatively high among the respondents of the survey. This finding indicated that using automated medication reminders delivered by text messaging might be the most acceptable mHealth intervention in this particular context. Table 2 summarises the remodelling of the intervention based on the findings from both patients' survey and nurses' FGDs following the stages of the MRC framework.

3.1.3 Qualitative Focus Groups

The mean and Standard Deviation (SD) of nurse participants' age was 36.64 (6.69) years, predominantly female (19/23, 82.6%), with an average of 12.06 (SD: 6.51) years' work experience.

The data from the FGDs confirmed that Iranian cardiac nurses perceived the mHealth intervention useful for patients who are at risk of medication non-adherence mostly due to unintentional reasons (e.g. forgetfulness and carelessness) during the early phase of discharge from hospital. These illustrative quotes support this assertion:

> *"It can really work especially for those patients who are forgetful. Some of them are so busy; but this intervention sends them reminders so that they'll remember…now, it's time for taking medications"* (Participant 10, FG 2).

"The most high risk time is when patients discharge from the hospital. I mean...when they are at home and they may forget when and how to take their drugs'' (Participant 11, FG 2).

Post-discharge follow-up and interaction between patients and healthcare providers play an important role in the statements expressed by all the FGDs; for example, one of the more experienced nurses identified that there is no interaction and follow-up with patients after hospital discharge:

"Unfortunately, most of our patients are missed after going home and are no longer in contact with us. That is because our hospitals are inefficient regarding patients' post-discharge follow-up and I can say this kind of intervention is absolutely one of the essentials" (Participant 3, FG 1).

During the nurses' discussions, a key issue identified was the lack of electronic health system to provide a connection between hospital and home. The example below demonstrates that patient-provider connection after inpatient stay can be established through a remote follow-up using mHealth interventions.

"There is no interconnected electronic health system or mHealth in our hospitals. How we can provide follow-up for our discharged patients? You know…just a few of them may call me if they have questions about their health care needs and medications. Patients really need this kind of intervention as a means of follow-up and support from their healthcare providers." (Participant 9, FG 2).

The nurses also expressed their opinions and recommendations about the refinement of the study mHealth intervention. The majority of participants suggested surveying patients and conducting a pilot study to have a better understanding of feasibility and acceptability of the intervention. They also provided suggestions about following-up with patients using other mediums along with text messages as well as pragmatic considerations in developing text message reminders (e.g. less frequent text messages to prevent patients' dependency and fatigue over time). More information can be found in Table 2.

3.2 Phase 2: Feasibility Study

The final mHealth intervention was piloted after refinement as shown in Table 2. During the recruitment period (February 2016), of 98 CR patients admitted to the outpatient CR clinic, 78 (76.4%) eligible patients consented to participate in the study and were randomly assigned to control (n=39) and intervention groups (n=39). Figure 1 presents the flow diagram of the study based on the CONSORT guideline (Schultz, 2010).

Characteristics of all 78 participants are shown in Table 3. All variables were similar between study groups.

According to the findings from the second phase, the mHealth intervention improved the primary outcome of the study with a highly significant difference in self-reported MA levels between the control and intervention groups, χ^2 (2) = 23.4; P<0.001. The RR indicated that it was 2.19 times more likely for the control group to be less adherent to their medications than the intervention group (RR = 2.19; 95% CI 1.5 - 3.19). The absolute difference between the proportions of non-adherence was estimated to be 51% (95% CI 35% to 64%).

Among secondary outcomes, the mHealth intervention was significantly associated with improved MASE scores (U=505; P=0.035) and cardiac FC (χ^2 (1) =9.7, P=0.002) compared with control group.

All secondary outcomes except FC improved significantly in the intervention group at the end of the study. However, these outcomes showed significant negative changes in the control group over time. Table 4 illustrates the baseline and follow-up data obtained from Phase 2 of the study. The study of the association between participants' characteristics and MA indicated that socio-demographic data had no statistically significant relationship with MA.

Findings to Inform Future Definitive Large-scale RCT

In this study, the results showed the majority of the participants (n=28/39, 71.8%) in the intervention group who received SMS reminders to take their cardiovascular medications perceived the mHealth intervention positively. The recruitment approach via CR clinic seemed to work well and indicated feasibility of recruitment. No financial incentives were offered to the patients. The overal attrition rate was only 3.8% (n=3/78) with the reason for loss to follow-up readmission for surgery. No harms, unintended consequences or effects were reported.The results of the feasibility trial helped to inform the sample size needed for a future definitive RCT. A sample size of 130 patients per group (260 in total) is required to have 90% power to detect a realistic true difference of 20% or greater for the between-group percentage of patients with high adherence to their medication in a future study, assuming a (two-sided) 5% significance level.

4. DISCUSSION

The results showed positive feedback for the acceptability and feasibility of mHealth intervention to improve cardiocascular MA in an Iranian CR setting. Exploratory analysis also revealed a significant improvement in the primary and secondary outcomes of the study. The findings of patients' perception survey indicated that there is a high ownership of mobile phones and utilisation of SMS among Iranian CHD patients and the mHealth intervention perceived helpful by this group of patients in taking cardiovascular medications. The survey results also confirmed the importance of obtaining patients' preferences (shared decision making) about the timing, frequency and content of text message intervention before they were implemented. This is consistent with the findings from a systematic review which identified that mHealth interventions must be flexible as well as culturally and socially appropriate to the wishes and needs of the patients (Gandapur et al., 2016).

In addition to the patients' survey results, the intervention was informed by qualitative findings in which cardiac nurse professionals expressed potential effects of the mHealth interventions, its associated challenges in the context of Iran and pragmatic suggestions to enhance the intervention design. This study revealed that Iranian cardiac nurses were open to the introduction of the mHealth intervention to improve cardiovascular MA and provided suggestions for optimising the design and evaluation of the study intervention. In fact, nurses believed that the use of mHealth intervention would be necessary as it has the potential to improve medication taking and patients' link to healthcare providers after discharge. The results are in line with the findings of a previous study, in which Iranian healthcare professionals have emphasised the necessity of applying eHealth (i.e. an overarching term that includes mHealth and teleHealth) in practice (Ayatollahi, Sarabi, & Langarizadeh, 2015).

During the second phase the remodelled intervention was piloted among Iranian CHD patients to evaluate the acceptability and feasibility in practice. It also provided the opportunity to determine sample size, the potential effect (effect size), recruitment and attrition rate. Patients in this study had inadequate MA before the intervention. The mHealth intervention used in this study improved all primary and secondary outcomes at the end of the study. These findings are in line with the work of other researchers that examined the effect of SMS reminders on MA in a variety of

medical conditions including asthma (Strandbygaard, Thomsen, & Backer, 2010), cardiovascular (Fang & Li, 2016; Pfaeffli Dale et al., 2015), diabetic , stroke (Arora, Peters, Burner, Lam, & Menchine, 2014; Kamal et al., 2015) and hypertensive patients (Bobrow et al., 2016).

4.1 Implications

Nonadherence to cardiac medications may result in increased morbidity and mortality, thus mHealth interventions may enhance adherence and health outcomes. This study has established feasibility and high satisfaction with a text messaging intervention among patients with CHD. Text message reminders improved adherence in cardiovascular medications, which are critical in preventing progression of the negative outcomes, and the disease-related complications during the vulnerable time following a cardiac event.

In developing countries including Iran, the health care resources are concentrated in urban areas and health system performance is constrained by limited infrastructure, inequality and shortages of healthcare providers (Chavehpour, Rashidian, Woldemichael, & Takian, 2019; Seddighi & Mousavi, 2019). However, according to the present study findings, automated text-messaging as a type of mHealth intervention has the potential to help by removing physical barriers to care and service delivery and by improving poor patient-provider communication. This could also help nurses, as the primary providers of healthcare, to achieve the Sustainable Development Goals (SDGs) and support dimensions of Universal Health Coverage (UHC). Unlike complicated interventions and time-consuming face-to-face approaches, SMS reminders are transmitted automatically to patients beyond a specific location with limited efforts from health care professionals. Although there is a potential for low-cost scalability and reproducibility of mHealth, evidence for the effectiveness of mHealth use in improving health-related quality measures, such as disability-adjusted life-years remains limited, especially for the developing world.

Finally, economic outcomes are considerable. The effectiveness of mHealth interventions to improve secondary prevention of cardiovascular disease has important implications from financial perspective, as well. This is particularly of importance when considering that medication nonadherence was found to be the leading cause of CHD-related rehospitalisations in Iran, increasing the economic

burden of this disease (Heydarpour, Saeidi, Ezzati, Soroush, & Komasi, 2015). Improved cardiovascular health outcomes and eliminated health care expenses for both patients and health system, could justify mHealth solutions. Further research is needed to economically evaluate the mHealth interventions, their costs, and their intended clinical outcomes and potential adverse effects.

4.2 Limitations

There are some limitations to the present study that should also be noted. Because the sample size was small and only included CHD patients who presented at an outpatient CR clinic, they might not represent the wider Iranian CHD population. In addition, the intervention was refined and tailored to the Iranian settings which may limit the generalisability of the study findings to wider country settings. However, linking the components of the intervention to the theory or conceptual framework may be an effective way to address the generalisability issue of the study findings and provide a sound theoretical basis for further studies in other country settings.

Another study limitation is the patients' self-completion bias, although the self-report questionnaire is simple, cost-efficient and the most common method of data collection (Basu, Garg, Sharma, & Singh, 2019; Jimmy & Jose, 2011). It may be affected by recall bias and socially desirable responding (Basu et al., 2019; Berben et al., 2011); however, a comparison of other studies demonstrated that there was an association between a patient's self-report of medication intake and blood drug levels (Grover, Oberoi, Rehan, Gupta, & Yadav, 2019; Ho, Bryson, & Rumsfeld, 2009). According to the literature, there is no "gold standard" to measure MA behaviour (Basu et al., 2019; Jimmy & Jose, 2011). Direct methods such as the detection of a metabolite or marker in patients' blood are often impractical, costly and invasive (Stewart, Mc Namara, & George, 2014). Moreover, to the researcher's knowledge, electronic monitoring devices for medication taking were not available in Iran during the study time. There was no electronic pharmacy claim data in this country to monitor the prescription refill or measuring adherence using Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC). Pill counts may not be a reliable method because patients can appear adherent by changing medications between bottles or throwing them out before a follow-up visit (Basu et al., 2019; Jimmy & Jose, 2011). To address the issue of subjectivity of self-reporting,

we used results of electrocardiograms, stress tests and echocardiograms of the patients to assess the NYHA, FC and LVEF.

Our results may also have been subject to the bias inherent in the application of the randomisation, intervention and data collection by the same researcher. Careful efforts were made to prevent any influence on the data collection and analysis during or after the trial. All stages of the study had a clear plan and supervised by two professors and one doctor in nursing who had expertise both in the field of quantitative and qualitative research methods. Having several meetings with all authors and statistician helped to minimise the bias that the pre-assumptions might cause.

5. CONCLUSIONS

Qualitative and quantitative data collected in this study suggested that the mHealth intervention had the desired effect on cardiovascular MA among Iranian CHD patients. The study findings also confirmed that the recruitment and data collection strategies used were feasible for implementation in a larger RCT. According to the MRC framework, the next step will be to assess the intervention cost-effectiveness and to validate the present study results by conducting a definitive RCT. As the major contribution to global practice, the findings inform the translation and scale-up of the text-messaging technology to improve CHD patients' self-efficacy in medication taking and reduce evidence practice gaps.

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