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Assessment of medication adherence and the costs associated with a calendar blister pack intervention among hypertensive patients in Malaysia: A randomized controlled trial

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Abstract

Objectives: To assess the efficacy and costs of a calendar blister packaging intervention used to improve medication adherence.

Method: A parallel randomized controlled trial was conducted with 73 hypertensive patients (intervention group = 35, control group = 38) at Hospital Kulim, Malaysia, for 7 months.

Results: The intervention group demonstrated a significant improvement in medication possession ratio ($p < 0.05$) and percentage of on-time refills ($p < 0.01$) compared to control group. In addition, there was significantly lower blood pressure ($p < 0.05$) in intervention group. From the provider perspective, the average annual treatment cost per patient in the intervention group was MYR 2178.66 (~USD 526.95) (95% confidence interval = 1786.39–2570.94) compared to MYR 2693.09 (~USD 651.37) (95% confidence interval = 1903.23–3482.95) in the control group.

Conclusion: This study provides evidence that calendar blister packaging has a positive impact on medication adherence, blood pressure and also has the potential for considerable cost savings.

Keywords

Medication packaging, medication adherence, hypertension

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Introduction

According to Keehan et al.,[1] more than 2.7 trillion dollars are spent annually on health care in the United States, 213 billion of which are avoidable. In addition, approximately 68% of the preventable costs were due to medication non-adherence and delayed implementation of evidence-based treatment.[2] Medication non-adherence is a complex and multidimensional healthcare problem. In general, medication adherence rates are lower in chronic disease patients than in those with acute disease.[3] Patients with chronic disease require a lifelong commitment to medication to achieve adequate control and to prevent progression of their disease. However, the adherence rate for those with chronic illness, especially hypertension, is low and drops dramatically after the first 6 months of treatment.[4]

Of the chronic diseases, hypertension is one that is associated with high avoidable costs and low adherence rates.[2] In Malaysia, the National Health and Morbidity Survey in 2015 reported that the overall prevalence of hypertension for adults aged 18 years and above was 30.3%.[5] A study conducted in Malaysia by Ramli et al.[6] in 2012 reported that

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only 53.4% of the hypertensive patients in Malaysia were adherent to their antihypertensive medication. The public healthcare system in Malaysia provided cheap and affordable health services to all Malaysian citizens, whereby primary healthcare cost is only MYR 1 for outpatient treatment and MYR 5 for specialist care. In addition, senior citizen aged 60 years and above is entitled for free health care.[7] Even though the Malaysia population is with this good and easy accessibility to effective antihypertensive medical therapy under public healthcare system, only 35% of Malaysian hypertensive patients have achieved optimal blood-pressure control.[8]

Low adherence to antihypertensive medication is associated with poor blood-pressure control and results in high healthcare costs, poor treatment outcomes, an increased risk of cardiovascular illness and poor quality of life.[4,9] There are many reasons for the low adherence, including doubts about treatment efficacy, financial issues, low health literacy, individual beliefs and perceptions about the disease, as well as ethnicity, age group and income level.[10,11]

Various interventions aiming to improve medication adherence in hypertension have been studied.[12–14] Interventions to improve adherence can be classified into different categories including technical (e.g. dosage simplification and special packaging), behavioural (e.g. reminders and patient diaries), educational (e.g. providing knowledge and information related to the disease), social support (e.g. buddy system) and structural interventions (e.g. disease management program).[15] However, interventions that are designed for long-term care generally require active involvement of healthcare resources and thus are usually costly and labour-intensive. Passive technical interventions such as calendar blister packs (CBPs) have recently been receiving increased interest, as they could improve adherence with minimal involvement of healthcare resources. CBPs are an innovative unit-of-use packaging system in which each tablet's blister is labelled with a day or date feature that is designed to provide a visual record of when the patient last took the medicine.[16]

However, CBP interventions have not been widely studied in the Asian setting when compared to education or counselling interventions to improve adherence rates among hypertensive patients.[17] Thus, the objective of this study was to investigate the effect of a CBP intervention on medication adherence, blood pressure and associated costs among hypertensive patients in a Malaysian setting.

Methods

Study design and setting

This was a randomized controlled trial with two parallel groups (CBP and normal blister pack). This study was conducted in the Outpatient Pharmacy Department in a district hospital (12 wards with 314 beds) at Kedah, Malaysia. Recruitment occurred between January 2015 and March 2015.

Sample size

The primary outcome variable in this study was medication adherence rate. According to a previous published study, of the 30 million people in the Malaysia population, 30.3% of those aged 18 years and above had hypertension, and the medication adherence rate in Malaysia was 53.4%.[5,6] The sample size was calculated to detect the mean difference in medication adherence between the intervention and control groups at the end of the intervention period. An odds ratio of 1.7 was used, as this value has previously been reported in a quantitative review on the effect of CBP on medication adherence among hypertension patients.[18] Assuming a type-I error of 5% ($\alpha = 0.05$) and power of 80%, a sample size of 26 patients per arm was required for the analysis. Based on reported literature and considering a 30% possible post-randomization exclusion, loss to follow-up and drop-out,[19] a minimum sample size of 68 patients was needed in this study, with 34 patients in each arm.

Selection criteria

A consecutive sample of hypertensive patients was targeted for this study. Potential patients were identified through prescription screening and were recruited by a research assistant and study pharmacist at the outpatients' pharmacy department. The inclusion criteria were as follows: patients aged 18–75 years who had filled a prescription of amlodipine for the treatment of hypertension for at least 3 months; had been diagnosed with hypertension for at least 6 months; and agreed to follow-ups for the 7-month study period. The doses of amlodipine could be changed during the study period, and other antihypertensive agents could be added or discontinued. The exclusion criteria for the study were as follows: patients who exhibited cognitive impairment, visual impairment, moderate-severe valvular heart disease, pericarditis or myocarditis; had a recent ($\leqslant$ 3 months) history of stroke, abnormal thyroid function, haemochromatosis or alcohol abuse or were hepatitis B, hepatitis C, HIV or cancer patients; were pregnant or planned to be pregnant during the study; had known secondary arterial hypertension or end-stage renal failure or were receiving dialysis; and were illiterate in both Malay and English. Finally, patients who used an organized pill box or required special or third-party assistance to take their medications were excluded from this study. Patients were considered drop-outs or lost to follow-up if they did not refill their prescription at least once after signing the informed consent form or did not visit the outpatient pharmacy for refills during the entire 7-month study period. Patients were required to refill their prescription at least once after signing the informed consent form for the investigator to compute the adherence rate. The end points of the study included death, completion of the 7-month study period, lack of need for amlodipine as part of hypertension treatment, discharge to a health clinic and discontinuation of follow-up at Hospital Kulim.

Figure 1. Calendar-packaged and normal-packaged medications.

Study protocol

Prior to consent, eligible patients were screened verbally for their ability to either read or write in English or Malay. After patients signed the informed consent form, the baseline assessment was administered by a research assistant. The baseline assessment included self-reported demographic questions, education level, household income, medical history and blood-pressure measurement. After the baseline assessment, the patients were randomly allocated (1:1) into the intervention or control group using block randomization with 10 patients per block, reported according to the CONSORT statement. Randomization was conducted using computer pre-generated randomized number lists generated by the investigator using Random Allocation Software Version 1.0.[20] CBPs containing amlodipine with seven tablets per strip, labelled with the day feature on the back of the blister pack, were dispensed to the patients in the intervention group, whereas patients in the control group were given amlodipine in a normal blister pack, which had seven tablets in a strip without the day feature on the back (Figure 1).

Due to the packaging of the medicine, patients, study pharmacist and investigators were not blinded to the study assignment. The dosage of amlodipine was determined by the prescribing physician. The physicians who provided care to the patients and the research assistant who had direct contact with the patients were blinded to the assignment, and patients were advised not to discuss study allocation with them in order to reduce performance bias.[21] The medication was then dispensed by study pharmacist using a colour-coded labelling system. Two different colour codes were used to label the medication box and the patient's prescription to indicate the intervention (yellow) and control group (blue). Pharmacy assistants prepared the amlodipine according to the colour code on the prescription and recorded the patient's study ID and the date on the stock card for each refill. The medications were then labelled and counter-checked by study pharmacist before being dispensed to the patients according to the study guidelines. For patients in the intervention group, the pharmacist advised them to take the medicine once a day according to the days of the week or number sequence stated on the blister pack, and the patients were advised to self-monitor their medication consumption as recommended to complete a strip of medicine each week. For patients in the control group, study pharmacists dispensed the medications according to the hospital's standard drug counselling protocol.

After study assignment, the patients were scheduled to visit the study pharmacist to refill their prescription every 28 days from the first day of enrolment during the 7-month follow-up period. All patients who receive long-term care in Malaysia Ministry of Health facilities are required to refill their prescription every 28 days as part of the ministry's effort to reduce medication wastage. The current study applied the same protocol to avoid patient confusion.[22] Blood-pressure measurements were recorded by a research assistant at baseline and at 3 and 6 months after enrolment. On each occasion, blood pressure was measured in exactly the same way, with three measurements taken 5 minutes apart; patients were at rest for 5 minutes in a seated position with back support, and blood pressure was measured using an automated measurement device (OMROM Healthcare, HEM-7322). The mean of the three measurements was used as the blood-pressure level at the visit. The date of every medication refilled by the patients was recorded by a study pharmacist or pharmacy assistant. Any occurrences of cardiovascular morbidity including angina, myocardial infarction, and stroke and use of medical services including hospitalization and emergency department visits in the prior 3 months were recorded from the patients' medical records.

Outcomes

The primary outcome in this study was medication adherence, and the secondary outcomes were blood pressure and cost.

Patient adherence was assessed using percentage of on-time refills and medication possession ratio (MPR). The assumptions in this study were that the patients would only refill their prescription when they had finished their medications. Moreover, the investigator assumed that the patients were not holding their medications if they refilled their prescription.

The percentage of on-time refills was defined by patients refilling their medication within 5 days before or after the appointment date.[23] MPR was calculated as the total day's supply for amlodipine received during the study (except for the last refill) divided by the number of days between the dates of the first and last dispensing of prescriptions.[24]

Costs

All cost data were collected individually for each patient according to the study protocol and were obtained from patient medical records over a period of 12 months. Costs per outpatient visit, inpatient visit, imaging and procedures were based on the government specialist hospitals' treatment charges for foreigners from the Ministry of Health, Malaysia,[25]

and were supplemented by primary data from the intervention. Costs of drugs were based on the total drugs supplied per patient multiplied by the actual acquisition price of the hospital. Costs of laboratory tests were determined by the average fee for foreigners in the Ministry of Health facility multiplied by the number of tests for each patient. Expert opinions and assumptions were used to estimate the cost of treating a clinical event when the unit costs were unavailable.

Statistical analysis

Data were analysed according to the per protocol principle. Data were examined using Pearson's chi-square analysis for categorical variables. For continuous variables, Shapiro–Wilk statistical test was used to examine the distribution of the data. Significance in this test indicates that the continuous variable was not normally distributed. To examine the differences between the groups, nonparametric Mann–Whitney's U test were used for non-normally distributed variables and t-test for independent samples was performed for normally distributed variables. Wilcoxon signed-rank test was performed to examine the difference within group at baseline and at the end of the study. Multiple linear regression models were conducted to determine independent correlates of medication adherence and blood pressure; percentage of on-time refill, MPR, systolic and diastolic blood pressure was modelled separately. A p-value<0.05 was considered statistically significant at one-tailed. Statistical analyses were performed using SPSS Statistics software, version 22 (IBM, SPSS, Armonk, NY) and Microsoft Excel 2010.

Ethical approval

Ethical approval was obtained from the Medical Research and Ethical Committee of the Malaysian Ministry of Health (NMRR-14-765-21178) on 7 October 2014, and written informed consent was obtained from each patient either in English or Malay prior to their enrolment in this study.

Results

Patient enrolment and characteristics

Overall, a total of 520 patients receiving amlodipine as part of their antihypertensive treatment were assessed for eligibility. Of these patients, 260 (50%) were excluded as they did not meet the study criteria. A further, 113 (21.73%) patients were also excluded because the patients did not refill their medication personally (their medications were collected by family members on their behalf). In this study, patients were required to attend the refills in person to have their blood pressure measured during the patient visit at the pharmacy (Figure 2).

A total of 83 patients were recruited into this study, 30 (36%) were females and 53 (64%) were males. In total, 41 patients were randomized into the intervention group and 42 patients into the control group. However, four patients in the intervention group and four patients in the control group dropped out of the study in the first month, and physicians stopped prescribing amlodipine for two patients in the intervention group at the third and fifth month. The mean age of the patients in the intervention group was 55.85 years (standard deviation (SD) = 10.25) at baseline and was 56.55 years (SD = 10.42) for the control group. The baseline characteristics did not differ significantly between the two groups (Table 1).

Outcomes

Table 2 showed the comparison of medication adherence and blood pressure between the intervention and control groups. The MPR for the control group decreased significantly from 0.9940 at baseline to 0.9787 at the end of this study ($p < 0.01$). However, the MPR for the intervention group remained unchanged throughout the study ($p > 0.05$). Overall, the MPR was 0.9910 and 0.9787 for the intervention and control groups, respectively, at the end of this study. The overall MPR was significantly higher ($p < 0.05$) for intervention group than the control group, although the absolute difference was small (1.2%). In multiple linear regression analysis, intervention group showed a higher MPR than control group ($\beta = 0.007$, 95% confidence interval (CI) 0.002–0.011, $p < 0.01$) after controlling the study duration and patient age.

The percentage of on-time refills was significantly higher for intervention group compared to the control group ($p < 0.05$). After adjusted the study duration and patient age in multiple linear regression, there was a significant different in percentage of on-time refill between the groups, with intervention group ($\beta = 0.061$, 95% CI = 0.034–0.088, $p < 0.001$) higher in percentage of on-time refill than the control group.

The blood pressure in each group decreases significantly from baseline to the end of this study ($p < 0.05$), and there were no significant differences in blood pressure between the intervention and control groups at baseline and at the third month of the study ($p > 0.05$). However at the sixth month assessment, the intervention group showed a significantly lower systolic blood pressure ($p < 0.01$) and diastolic blood pressure ($p < 0.05$) than the control group. In multiple linear regressions, intervention group was significantly associated with lower systolic blood pressure compared to the control group ($\beta = -4.355$, 95% CI = −8.419 to – 0.291, $p < 0.05$) after controlling the patient age and study duration. However, there was no significant improvement in diastolic blood pressure ($\beta = -2.475$, 95% CI = −5.215 to 0.265, $p = 0.076$).

Cost analysis

The cost analysis of 73 patients showed that the total cost of treatment for patients in the control and intervention groups

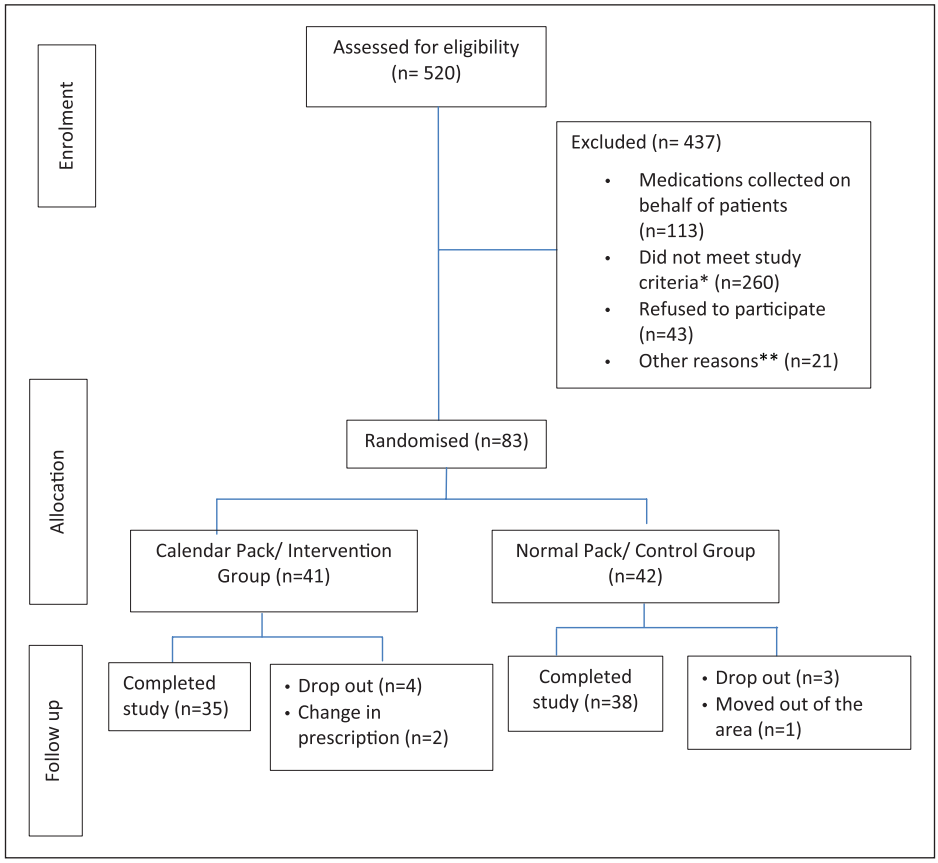

Figure 2. CONSORT diagram displaying the flow of participants through the study.
*Patients are below 18 years and above 75 years of age, with amlodipine treatment for hypertension less than 3 months, diagnosed with hypertension for less than 6 months and met the exclusion criteria in this study.
**Patients who are not able to commit for 7-month study; patients who are currently on 2.5-mg amlodipine; patients who have concern about the changes of drug manufacturer will affect drug performance; patients who are on wheelchair.

was MYR 102,337.39 and MYR 76,253.23, respectively. The treatment cost was dominated by the cost of laboratory tests (MYR 38,779 in the control group and MYR 35,295 in the intervention group) and the cost of outpatient visits (MYR 19,080 and MYR 17,040 for the control and intervention groups, respectively). Patients in the intervention group had fewer inpatient visits and consumed less cardiovascular-related drugs than the control group (Table 3).

The mean cost of treatment for the control group was MYR 2693.09 per patient and was MYR 2178.66 per patient for the intervention group. The mean cost difference between the two groups was MYR 514.43. For each of the treatment costs, patients in the intervention group showed a lower mean cost than the control group. However, there was no statistically significant difference between the groups in terms of the treatment cost of each item (Table 4).

Discussion

Improvements in medication adherence, treatment outcomes and cost were demonstrated in this randomized controlled trial study that compared the use of CBP for daily doses against normal blister packs among hypertensive patients. The CBP for daily medication dosage used in this study is unique and different from the packaging studied by Simmons et al.[26] and Valenstein et al.[27] The CBP used in the Simmons et al. and Valenstein et al. studies contained 7 days of therapies arranged on a strip prepared by pharmacists that were labelled with medication-specific instructions and the times of day (morning, noon, evening and night) at which the doses had to be taken. In contrast, the CBP used in our study was four individual strips of medicine (amlodipine) packed in a single box by the drug manufacturer, each of which contained four rows of seven single tablets and incorporated the number of days in a week that the dose had to be taken. This provided an ongoing visual record of the doses that needed to be taken each day. Moreover, it may also have allowed the patient to track the doses missed each week, and third parties such as family members were also able to monitor the patients' medication consumption based on the packaging. Thus, the CBP packaging design may have guided the patients towards taking their medication on time and thus slowly developing the habit of adherence to their medication.[23,28]

Table 1. Patients' characteristics at baseline.

Characteristics	Intervention group (n = 41)	Control group (n = 42)	p-value
Age (years), mean (SD)	55.85 (10.25)	56.55 (10.42)	0.761[a]
Gender, n (%)			
Male	23 (56.10)	30 (71.43)	0.146[b]
Female	18 (43.90)	12 (28.57)	
Ethnicity, n (%)			
Malay	26 (63.41)	26 (61.9)	0.368[b]
Chinese	7 (17.07)	5 (11.90)	
Indian	8 (19.51)	9 (21.43)	
Other	0 (0)	2 (4.76)	
Education level, n (%)			
⩽ Secondary education	36 (87.80)	32 (76.19)	0.169[b]
⩾ College/university	5 (12.20)	10 (23.81)	
Household income, n (%)			
<MYR 1500	23 (56.10)	20 (47.62)	0.629[b]
MYR 1501–MYR 4500	13 (31.71)	14 (33.33)	
>MYR 4501	5 (12.20)	8 (19.05)	
Years of hypertension, median (IQR)	5.00 (1.50–10.00)	4.50 (1.00–11.50)	0.575[a]
Number of drugs			
1, n (%)	12 (29.27)	12 (28.57)	0.695[b]
2, n (%)	16 (39.02)	13 (30.95)	
3, n (%)	11 (26.83)	16 (38.10)	
4, n (%)	1 (2.44)	1 (2.38)	
5, n (%)	1 (2.44)	0 (0)	
Blood pressure			
Systolic, mean (SD)	138.37 (19.81)	139.48 (14.67)	0.773[a]
Diastolic, mean (SD)	85.45 (12.24)	86.16 (10.89)	0.780[a]
Weight (kg), mean (SD)	73.44 (13.38)	72.60 (10.90)	0.756[a]
Height (m), mean (SD)	1.61 (0.09)	1.62 (0.08)	0.954[a]
BMI (kg/m^2), mean (SD)	28.16 (4.62)	27.78 (3.36)	0.665[a]

SD: standard deviation; IQR: interquartile range; MYR: Malaysian Ringgit.
[a]p-value from t-test for independent samples.
[b]p-value from Pearson's chi-square test.

In addition to the improvement in medication adherence, this study also demonstrated a significant improvement in both systolic and diastolic blood pressure between the intervention and control groups. This simple and labour-saving calendar packaging design can assist patients in identifying the correct medication and in taking medications more reliably. This packaging design has also been found to be useful for elderly patients and patients with memory deficits to monitor their medication consumption and thus improve their adherence to medications, ultimately leading to better treatment outcomes.[23]

To our knowledge, this is the first study in Southeast Asia to evaluate the cost of a CBP intervention to improve medication adherence among hypertensive patients. Previous studies have been conducted to evaluate the effects of various interventions including medication counselling and family member-based supervision on medication adherence among hypertensive patients in Asian countries.[29,30] The cost analysis in this study showed that there was a difference of MYR 26,084.16 in total healthcare costs per year between the two groups. This finding showed that improved medication adherence was associated with lower total healthcare expenditures. This was consistent with a study by Iuga and McGuire[31] that showed that improved medication adherence among patients with chronic diseases substantially reduced overall medical costs and use of emergency and inpatient services. These services are key drivers in the overall reduction of healthcare costs.[31]

However, there was a numerical but not significant difference between the groups in the treatment costs per patient. Over a 12-month period, the mean cost of treatment for intervention patients was lower than the control group. As CBP medication improved patients' medication adherence, it could lead to better blood-pressure control and avoid progression of the disease.[32] There were fewer patients in the intervention group who required additional procedures, imaging services, and hospital admissions compared to the control group in this study. However, the

Table 2. Comparison of medication adherence and blood pressure between the two groups.

	Control group	Intervention group	p-value
MPR[a]			
Observation 1 (n = 38, n = 37)	0.994 (0.020)	0.992 (0.021)	0.249
Observation 2 (n = 38, n = 37)	0.988 (0.027)	0.993 (0.015)	0.357
Observation 3 (n = 38, n = 37)	0.989 (0.022)	0.993 (0.014)	0.136
Observation 4 (n = 38, n = 36)	0.989 (0.019)	0.993 (0.012)	0.183
Observation 5 (n = 38, n = 35)	0.985 (0.033)	0.994 (0.011)	0.069
Observation 6 (n = 38, n = 35)	0.979 (0.048)	0.990 (0.026)	0.035
Overall MPR (n = 38, n = 35)	0.979 (0.043)	0.991 (0.023)	0.012*
% Patients who refilled their prescriptions on time	0.929 (0.119)	0.992 (0.006)	0.001**
Systolic blood pressure, mmHg			
Baseline (n = 42, n = 41)	139.484 (14.668)	138.374 (19.814)	0.272
Third month (n = 38, n = 37)	131.386 (10.370)	130.784 (18.585)	0.108
Sixth month (n = 38, n = 35)	129.728 (13.535)	123.590 (17.376)	0.005**
Diastolic blood pressure, mmHg			
Baseline (n = 42, n = 41)	86.160 (10.892)	85.448 (12.244)	0.293
Third month (n = 38, n = 37)	82.711 (9.289)	82.037 (11.778)	0.295
Sixth month (n = 38, n = 35)	81.360 (9.999)	78.057 (12.393)	0.043*

MPR: medication possession ratio;
[a]Results are presented as the mean (standard deviation).
*$p < 0.05$, statistically significant at one-tailed;
**$p < 0.001$, statistically significant at one-tailed.

Table 3. Comparison of total treatment costs per year between the two groups.

Total cost	Control group (%), n = 38	Intervention group (%), n = 35	Difference
Outpatient, MYR (SD)	19,080.00 (18.64)	17,040.00 (22.35)	2040.00
Inpatient, MYR (SD)	18,137.30 (17.72)	4315.21 (5.66)	13,822.09
Laboratory test, MYR (SD)	38,779.00 (37.89)	35,295.00 (46.29)	3484.00
Procedures and imaging, MYR (SD)	6741.00 (6.59)	2180.00 (2.86)	4561.00
Drugs, MYR (SD)			
Cardiovascular	7,670.37 (7.50)	6,672.53 (8.75)	997.84
Non-cardiovascular	11,929.71 (11.66)	10,750.49 (14.10)	1,179.22
Total cost, MYR	102,337.39	76,253.23	26,084.16

MYR: Malaysian Ringgit; SD: standard deviation.

Table 4. Mean cost of treatment per patient between the control and intervention group.

	Control group[a]	Intervention group[a]	95% CI for mean
Outpatient, n = 38, n = 35	502.11 (100.03)	486.86 (148.24)	465.67–523.91
Inpatient, n = 2, n = 1	9068.65 (4984.89)	4315.21 (0)	−3613.09 to 18,581.43
Laboratory test, n = 38, n = 35	1020.5 (390.01)	1008.43 (535.63)	906.86–1122.57
Procedure and imaging, n = 13, n = 9	518.54 (549.40)	242.22 (150.06)	207.02–603.98
Drugs			
Cardiovascular-related drugs, n = 38, n = 35	201.85 (169.76)	190.64 (210.55)	152.35–240.61
Non-cardiovascular-related drugs, n = 32, n = 33	372.80 (439.06)	325.77 (147.88)	249.27–448.58
Total, mean	2693.0891 (2403.05)	2178.66 (1141.94)	2000.68–2892.22

[a]Malaysian Ringgit (standard deviation).

sample size was not large enough to demonstrate a statically significant difference in the treatment cost between the groups.

In randomized controlled trials, analyses commonly use the intent-to-treat principle, in which all randomized patients are analysed according to their randomized group. However, deviations from this approach are common, especially in analyses of incomplete and missing data, which may result in a more adherent cohort, bias estimates, and possible invalid inferences.[33] As the MPR could not be computed without at least one refill by the patients, thus the per protocol principle was used for the analysis in this study. Although the sample size was reduced due to this exclusion, with this approach, the adherence and blood-pressure outcomes were more reliable and specially linked to aspects of the intervention.

Finally, the MPR was high in this study, as MPR was defined as the total number of medications supply to patients over the refill interval. Thus, patients who routinely refill their medications early would have an inflated MPR as the numerator (total medications supply) would be larger than the denominator (refill interval). For chronic diseases, patients who were on long-term medications, it is common for them to refill their medications before running out. Apart from this, the public healthcare system in Malaysia provided cheap, affordable health services and free-of-charges prescription refills to Malaysian citizens if patients refill their medication on time.[7] Thus, these would lead to high MPR among chronic disease patients in Malaysia.

Limitations

There were several limitations to this study. This study was limited by a small sample size, and the time frame of the intervention was short, which might have affected the long-term study outcomes. Longer intervention periods may provide a better reflection of the intervention's effects on patient medication adherence, blood pressure and costs. Moreover, the findings may not be generalizable internationally as the study was based in Malaysia and was limited to elderly patients who were currently on multiple prescribed medications including amlodipine as part of their hypertensive treatment. The results might not be applicable to elderly patients in assisted living or those with cognitive and mental impairment. This study excluded a large number of patients due to their inability to personally refill their prescription. Although this could mean that the study might be more applicable to our subgroup of patients, our sample closely resembled the characteristics of outpatients in public facilities that allow family members to collect medications on behalf of the patient.[34] In addition, similar response could be expected from the excluded patients given the close proximity of the baseline adherence rate with other local study.[35] Finally, due to the study and packaging design, both the patients and pharmacists were not blinded, and the Hawthorne effect could have occurred in the intervention group.

Conclusion

This study combined a wide range of adherence measurements. The MPR and percentage of on-time refills favoured the use of CBP over the control condition for medication adherence, indicating the robustness and reliability of the findings. Moreover, CBP also improved the blood pressure among the study patients. As this packaging does not require special technical skills, it is therefore suitable for patients of all ages, especially elderly patients. The cost of treatment per patient in the CBP group was numerically lower than that of patients receiving the normal blister pack. From the provider perspective, this finding is encouraging because CBP could likely lead to long-term substantial cost savings from avoidable direct healthcare expenditures. Thus, future studies should conduct more detailed cost-effective analyses with a larger sample size and a longer intervention period.

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Declaration of conflicting interests

The authors declare a potential conflict of interest from research funding provided by Kotra Pharma (M) Sdn Bhd.

Ethical approval

This randomized controlled trial was registered under Malaysia National Medical Research Register: NMRR-14-765-21178. Written informed consent was obtained from all subjects before the study.

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