Can Medication Packaging Improve Glycemic Control and Blood Pressure in Type 2 Diabetes?

Results from a randomized controlled trial

D. SIMMONS, FRACP, MD
M. UPJOHN, RN
G.D. GAMBLE, MSC

OBJECTIVE — To assess the impact of calendar blister pack (CBP) use on glycemic and blood pressure control.

RESEARCH DESIGN AND METHODS — We conducted an 8-month randomized controlled double-blind study among diabetic patients with poor glucose control (HbA_{1c} >9.0%) in an urban area of South Auckland, New Zealand, with a high proportion of Maori and Pacific Islands people. Subjects included 68 consecutive patients, of whom 50% were prescribed three or more medications per day.

RESULTS — HbA_{1c} was reduced by 0.95 ± 0.22% in the CBP group and 0.15 ± 0.25% in the control group (P = 0.026). Diastolic blood pressure decreased 5.8 ± 1.5 mmHg in the CBP group and increased 0.1 ± 1.9 mmHg in the control group (P = 0.0041). Systolic blood pressure did not change significantly.

CONCLUSIONS — CBPs should be considered among diabetic patients with poor glycemic control receiving multiple medications.

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Good glucose and blood pressure control are essential for the prevention of diabetic complications (1–3). Besides ongoing self-care and clinical monitoring, appropriate medication is pivotal in achieving these metabolic targets. Such medication for patients with type 2 diabetes, along with those for other comorbidities (e.g., ischemic heart disease), may require a complex regimen involving 10–15 tablets taken each day. It has previously been shown that complexity of medication regimen is inversely proportional to adherence (4). Among diabetic patients on oral antidiabetic agents, adherence ranges from 79% among those on a once-daily dose to 38% among those on a three-times-a-day dose (5). Assessing adherence has its own difficulties. In one study, adherence to sulfonylurea therapy was 53% when assessed by electronic medication event monitoring systems but 69–71% using other assessment methods (6).

The introduction of special packaging for medications has been associated with improved adherence in some studies, particularly in the elderly (7). However, few outcomes-focused randomized trials have been undertaken, with most concentrating on measures of adherence. None has investigated the impact of such packaging on metabolic control among diabetic patients, in spite of the high level of complexity of their medication needs and their lack of symptomatic cues.

In view of this, we have undertaken a double-blind randomized controlled trial comparing the impact on glycemic and blood pressure control of patients who received calendar blister packs (CBPs) (Fig. 1) contained within a "medication box" with patients who received the same medication box without the CBPs.

RESEARCH DESIGN AND METHODS

The study was an 8-month randomized controlled double-blind study among diabetic patients cared for by general practitioners in Otara, a suburb of Auckland, New Zealand, with a low socioeconomic level. General practitioners invited consecutive patients into the study if they had an HbA_{1c} of >9%. The general practitioners concerned were known to care for >400 diabetic patients between them. Most of the patients in the area were either Maori or of Pacific Islands origin. Once patients had agreed to participate in the study, a research nurse with a research assistant able to speak the same language as the subject visited the patient at home and completed a brief questionnaire, measured seated blood pressure using a standard sphygmomanometer, and recorded weight and height. A blood sample was taken for HbA_{1c}. Questionnaires, blood pressure, weight, and sample for HbA_{1c} were also taken 4 and 8 months after patients entered the study. Patients were instructed to keep the general practitioner, research nurse, and assistants blinded as to which packaging they were using. HbA_{1c} was measured using cation exchange high-performance liquid chromatography (Diamat; Bio-Rad, Richmond, CA; upper limit of reference range 6.2%) and comparable with that used in the Diabetes Control and Complications Trial.

From the Department of Rural Health (D.S.), University of Melbourne, Shepparton, Victoria, Australia; and the Diabetes Projects Trust (M.U., G.G.), Middlemore Hospital, Otahuhu, Auckland, New Zealand.

Address correspondence and reprint requests to D. Simmons, Department of Rural Health, Faculty Medicine Dentistry and Health Sciences, University of Melbourne, P.O. Box 6500, Shepparton VIC 3630, Australia. E-mail: d.simmons@medicine.unimelb.edu.au.

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Abbreviations: CBP, calendar blister pack; dBP, diastolic blood pressure; sBP, systolic blood pressure; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

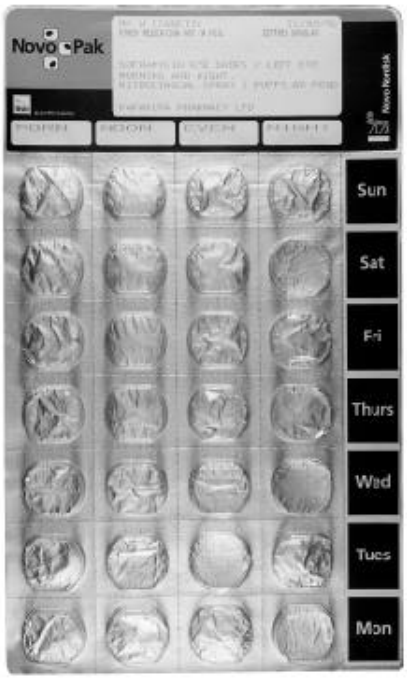

Figure 1—*Example of a calendar blister pack.*

Patients were randomized using a random number sheet by a third party. Those living in the same house were randomized to the same packaging. The intervention group received a special kit including the medication within a CBP in a labeled box and instructions on how to take the medication. The control group received the same packaging but with the medication contained within the usual containers. The medication boxes were all prepared at one pharmacy and delivered to the study participants at home. General practitioners delivered their care independently of the study. The study was approved by the North Health Ethics Committee.

Statistical analysis

The study had 80% power at the 5% significance level to detect an absolute difference in HbA_{1c} of 0.8% (observed SD = 1.5%). Analyses were conducted on an intention-to-treat basis. Statistics were analyzed using SPSS (version 7.5) (SPSS, Chicago). All tests were two-tailed, and $P < 0.05$ was taken as significant. Comparisons between the two groups were made using χ^2 test for discrete variables and Student's *t* test for continuous variables. The effect of treatment of all continuous outcome variables was tested using the MIXED procedures of SAS to estimate main and interaction effects of repeated observations over time (8). A maximum likelihood approach was used to impute missing-at-random data within the mixed model. Post hoc tests of significant main and interaction effects were performed using the methods of Tukey. To remove between-subject differences at baseline, the dependent variables entered in the model were the change from baseline to 4 months and the change from baseline to 8 months. Results are presented as marginal adjusted means.

RESULTS

The two groups were well matched for age, sex, ethnicity, and benefit status as shown in Table 1. Given that there was random allocation to each treatment, comparisons are inappropriate because differences can only be a result of chance, although control subjects had better baseline HbA_{1c} and diastolic blood pressure (dBP). Patients were prescribed up to 20 tablets each day (median 5, interquartile range 3–8), 50% received antihypertensive medication, and 96% oral antidiabetic medication. The clinical purpose was known by patients for 96 ± 12% of personal medications.

All but one subject (who withdrew) remained in the study at 4 months, although one subject (CBP group) missed an assessment at that time. However, by 8 months, two control subjects had moved and we were not able to contact them, and one control subject withdrew from the study. One control subject and two in the CBP group were commenced on insulin. The total number of tablets received increased by 2% in the CBP group and 4% in the control group. There was no change in knowledge of medication between the groups. The new packaging was found to be useful by 26 (77%) of those with CBPs and 7 (27%) of the control group ($P < 0.001$). Very few subjects were aware of other packaging methods (9% with CBPs vs. 12% control subjects). Table 2 shows the change in HbA_{1c}, dBP, and systolic blood pressure (sBP) over the 8-month period. HbA_{1c} and dBP were reduced significantly, but no significant change in sBP or measures of body habitus occurred.

Table 1—*Baseline characteristics of study groups*

	CBP group	Control group
n	36	32
Age (years)	55 ± 11	53 ± 11
Male	11 (31)	9 (28)
Pacific Islands origin	26 (74)	25 (78)
Age at diagnosis (years)	48 ± 12	45 ± 11
Beneficiary	26 (72)	22 (69)
Insulin treated	2 (6)	5 (16)
On >3 medications/day	17 (47)	17 (53)
HbA_{1c} (%)	9.9 ± 2.2	9.5 ± 1.7
sBP (mmHg)	141 ± 16	142 ± 18
dBP (mmHg)	84 ± 10	80 ± 9
Weight (kg)	100.4 ± 24.3	104.1 ± 26.6
Waist (cm)	107 ± 16	110 ± 14
Height (cm)	163.7 ± 7.9	164.7 ± 7.7
BMI (kg/m^2)	37.3 ± 8.0	38.5 ± 10.2

Data are *n*, means ± SD, or *n* (%).

Table 2—*Change in HbA_{1c} and blood pressure during the study*

	4 months	8 months	*P* (CBP vs. control)
HbA_{1c} (%)			0.026
CBP group	−0.85 ± 0.22	−0.95 ± 0.22	
Control group	−0.45 ± 0.26	−0.15 ± 0.25	
sBP (mmHg)			0.89
CBP group	−0.7 ± 2.4	−3.6 ± 2.3	
Control group	−2.5 ± 2.6	−2.6 ± 2.8	
dBP (mmHg)			0.0041
CBP group	−3.9 ± 1.5	−5.8 ± 1.5	
Control group	1.4 ± 1.8	0.1 ± 1.9	

Data are means ± SD.

CONCLUSIONS — This study has shown that the use of CBPs in a group with poor glucose control was associated with a reduction in HbA_{1c} over an 8-month period equivalent to that required to achieve a clinically meaningful reduction in risk of complications as shown in the U.K. Prospective Diabetes Study (UKPDS) (1). The reduction in dBP was also statistically and clinically significant (2). There were no other changes in care identified and, in particular, no significant difference in medications prescribed or medication knowledge. The blinding process appeared to be effective, with few subjects being aware whether they were part of the intervention or control group. Whether this was a "double-blind" trial is open to debate, since 10% of patients had knowledge of other types of packaging. The data from this study would support the use of CBPs among patients with poor blood glucose control.

Although the use of CBPs is not new, few studies report their impact on patient outcomes. They have been shown to improve compliance in some elderly patients (7,9–11) but not others (12) and in glaucoma patients (13). They have shown no benefit in leprosy patients (14), and failed to have an impact on blood pressure among hypertensive patients in a randomized trial (15). Only one group, using unit-of-use packs, has demonstrated a reduction in total, hospital, laboratory, and physician costs in patients with hypertension (16) and newly diagnosed diabetes (17) and only when used in combination with mailed prescription-refill reminders. In New Zealand, use of such packs is limited, and a subsidy for their use was removed in 1991 (18).

A cost-effectiveness analysis is required to balance the cost of the packaging (NZ$3/week [~U.S.$1.50]) with the predicted reductions in hospitalizations associated with the improved metabolic control. However, in our study, few clinical events and few medication or management changes occurred, and little time off work for subject or caregiver was required. A longer trial would therefore be needed for a realistic economic assessment. The cost of delivering the pharmaceutical agents to the subjects was designed to ensure the feasibility of the study. The need was substantiated by the increasing numbers defaulting on payment through the study (from 16% initially to 21 and 25% at the second and third pickups, respectively). This aspect of the study was introduced from the knowledge that personal costs of diabetes are substantial among patients in South Auckland, particularly those of Pacific Islands origin (19). Indeed, in the study above, 47% of Pacific Islands patients reported that the costs of medication reduced their ability to self medicate.

In addition to the results, this study was notable for its ability to attract general practitioners not usually involved with trials and patients who predominantly spoke English as a second language (20). As patients with poor glucose control, they were clearly not the more accommodating patients usually associated with randomized trials. How much this was the result of the presence of an ongoing diabetes control program in the area (commencing with a household survey) (21) is unclear. Only 35% had been interviewed by the household survey, which had occurred ~6 years earlier.

The reason behind the failure to reduce sBP to the same extent as dBP is unclear. In the UKPDS, both sBP and dBP were reduced, and the sBP appeared to be of greater importance in relation to vascular outcomes (2). Although dyslipidemia would also potentially be of importance, in New Zealand, access to lipid-lowering medications was severely restricted at the time and only four patients were receiving lipid-lowering therapy. Thus the study did not assess this aspect of metabolic control. Areas of self-care unrelated to pharmaceutical treatment were also not investigated, although they are likely to be of importance (22). The impact of the marginal differences in HbA_{1c} and dBP, as well as the small number of subjects aware of other kinds of packaging, is unlikely to be major but highlights the importance of more studies using CBPs.

In summary, we have shown that in diabetic patients with poor metabolic control, CBPs may play a role in improving metabolic control. Whether this is additional to other improvements in care was not investigated.

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