Study investigating the impact of pharmacist involvement on the outcomes of diabetes medication therapy adherence program Malaysia

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Abstract: Involvement of pharmacists in improving medication adherence among diabetic patients is recognized globally. In Malaysian healthcare system, pharmacists are also operating health services i.e. Diabetes Medication Therapy Adherence Clinic (DMTAC). This study aimed to assess the clinical outcomes of patients managed by pharmacists (DMTAC), in a Malaysian hospital setting. This was an open labelled randomised study. Type 2 diabetes patients with HbA1c ≥8% were recruited and arbitrarily divided into the intervention group (usual care plus DMTAC) and the non-intervention group (usual care only). Those enrolled in the intervention group were scheduled for follow-up for eight consecutive visits. Improvements in lab results were compared longitudinally (pre and post analysis) between the groups. Data analysis was done using PASW 18® version. A total of 76 patients were enrolled, with 39 patients in the intervention group and 37 patients in the non-intervention group. Mean HbA1c (-0.90% vs. -0.08%, p=0.011) and fasting blood glucose levels (-3.45mmol.l vs. +0.79mmol/l, p=0.002) reduced significantly between the intervention group vs. non-intervention group. Total cholesterol and low-density lipoprotein cholesterol (LDL-C) were also significantly reduced in the intervention group (TC -0.34mmol/l, p=0.018) (LDL -0.45mmol/l, p=0.001). In conclusion, pharmacists managed DMTAC significantly improved glycaemic control and lipid profile of diabetic patients.

Keywords: Adherence, pharmacists manage clinic, glycaemic control, type 2 diabetes, Malaysia.

INTRODUCTION

For decades, diabetes mellitus has remained a global challenge. In recent years, the prevalence of type 2 diabetes is increasing at an alarming rate worldwide (Wild *et al.*, 2004). In developing countries like Malaysia, people aged 30 years and above are at a high risk of developing type 2 diabetes. In 1996, the incidence of type 2 diabetes was 8.3%. That fig. jumped up to 14.9% in 2006 (Mafauzy 2006; Letchuman *et al.*, 2010). Therefore, the overall risk for the macro- and micro-vascular complications due to type 2 diabetes may have doubled as well. Adherence to therapy and intensive glycemic control are considered as the two cornerstones to reduce complications caused by type 2 diabetes (Stratton *et al.*, 2000). Apart from that, adopting a multiple disciplinary team approach is crucial to ensure the effective management of the disease and can improve outcomes (Renders *et al.*, 2001). Several studies have shown that team-based approaches between physicians, nurses and pharmacists have increased the therapeutic outcomes and overall improvement in glycaemic control (Leal *et al.*, 2004; Coast-Senior *et al.*, 1998).

Since 2006, pharmacists from a public hospital in Malaysia (Hospital Pulau Pinang) have involved in Diabetes Medication Therapy Adherence Clinic (DMTAC). The main aim of this service was to assign additional interventions for patients with poor glycaemic control (glycosylated hemoglobin, HbA1c ≥ 8%). Patients enrolled in this program will receive additional counseling from the pharmacist, on top of the usual physician's consultation. Ironically, there are no concrete studies to date that measures the real impact of additional counseling by pharmacists on patients' clinical outcomes. The closest one will be a retrospective study that used the patients as their own control, therefore lacking randomization (Lim and Lim, 2010). Thus, it is hard to ascertain the contributing factors for glycaemic control. The purposes of this study were to evaluate the effectiveness of the DMTAC program and determine the benefit of extra pharmacist service added to the usual care for a multiethnic population in a non-specialty clinic located in the Outpatient Department.

METHODOLOGY

This study was conducted at the Outpatient Clinic of Hospital Pulau Pinang, Malaysia. The conduct of the study was approved by Medical Research Ethics Committee, Ministry of Health, Malaysia. Patients with type 2 diabetes were enrolled between February 2009 and May 2009 and the study ended in May 2010.

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Inclusion and exclusion criteria

The inclusion criteria were patients under the care of the diabetic clinic at the Outpatient Department with glycosylated haemoglobin (HbA1c) ≥8%. Diabetes patients who had been followed-up by other hospital departments such as Endocrine and Cardiology Department were excluded.

Study design and sample size calculation

This was a prospective randomized open-labeled study. The patients were referred by the doctors or were identified by the pharmacists during their routine clinical follow-up. The selected patients were then randomly divided into two arms, intervention and non-intervention groups, according to their most recent HbA1c.

Sample size was calculated using the previous data from Choe *et al*, (2005) to compare the mean of HbA1c between the intervention and control group. A total of 42 patients in each study group was needed to detect the difference of 1.3% (8.0% versus 9.3%) with 80% certainty (power) and using an alpha level of 0.05 (Power and Sample Size Calculations, Dupont and Plummer, Version 3.0.12, 2009). With anticipation of 20% drop out rate, a total of 50 patients was selected in each study group.

Non-intervention group

Patients in the non-intervention group were instructed to receive routine clinical follow-up with the doctors every 3 to 4 months. No education was provided to the patients in this arm.

Intervention group

Patients in the intervention group received DMTAC program on top of their routine clinical follow-up. Initially, patients were interviewed by DMTAC pharmacists to get detailed medical, family and social histories, diet and exercise patterns. A booklet to guide them regarding their medications, antidiabetic medicines and targets for diabetes, lipid and blood pressure was given to each patient.

During the routine clinical follow-up, the patient's medication history was reviewed by DMTAC pharmacists and counseling on any inappropriate drug use was provided. At the same time, interventions involving adding and adjusting medications and ordering indicated lab tests were made after discussed and approved by the doctors. After the clinical session ended, medications were dispensed to the patients and education related to diabetes was instigated.

In addition, schedule meetings were given to the patients at 2-weeks to 2-month intervals that coincided with the drug refills or clinical follow-up date. The patients met the pharmacists for a total of eight visits. During each visits, structured individualized education on medications, diabetes treatment and complications as well as healthy lifestyle advice was given. Besides, blood glucose monitoring was performed by the pharmacists. The pharmacists had the approval from the doctors to adjust the insulin doses within 4 units of the prescribed dose at a time according to the patient's blood glucose levels when necessary. Patients' knowledge on medications and compliance were also assessed. Patients' adherence was measured using Modified Morisky Medication Adherence Scale (MMMAS) with total score of 11 and it was classified to low adherence (score<6), medium adherence (score 6 to <8) and high adherence (score ≥8) (Morisky *et al*., 2008). Patients who defaulted routine clinical follow-up or lost to follow-up with pharmacists (failed to attend 3 or more scheduled pharmacy visits) were withdrawn from the study.

Data collection

The primary outcome was the changes of HbA1c by comparing pre-intervention values (before seeing the pharmacist) with post-intervention values within the period under pharmacist management. Other outcomes included body mass index (BMI), blood pressure, fasting blood glucose (FBG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglyceride (TG). Patients' diabetes medication regimens were observed and evaluation of new insulin cases were included. In addition, patients' adherence was also measured.

STATISTICAL ANALYSIS

Data were analyzed using PASW© version 18 (Formerly known as SPSS). Mann-Whitney and Wilcoxon-signed rank were used to compare the difference between and within groups. Differences in the demographic characteristics and medication regimen between the groups were examined using the chi-square test for categorical variables. The results were significant if the p value was <0.05.

RESULTS

A total of 120 patients consented to participate in this randomized control study (fig. 1). Of the 120 patients, 20 patients were excluded. In the intervention group, 39 patients completed the eight visits with the pharmacists. On the other hand, 37 patients in the non-intervention group completed this study. The baseline characteristics and diabetes medication regimes of the selected patients were shown in table 1.

The study observed the changes of glycaemic control, body mass index (BMI) and blood pressure within and between groups. The changes of lipid profile and adherence were only analyzed in intervention group as

there was not sufficient data in non-intervention group. There were no differences of baseline HbA1c and FBG between groups. The changes in glycaemic control, blood pressure and body mass index were shown in table 2. The changes of lipid profiles for the intervention arm were shown in table 3.

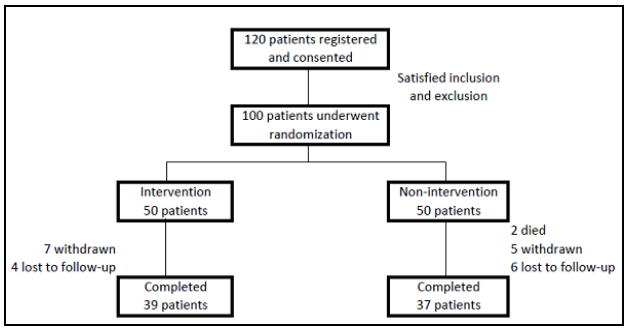

Fig. 1: Enrollment, randomization and follow-up of subjects.

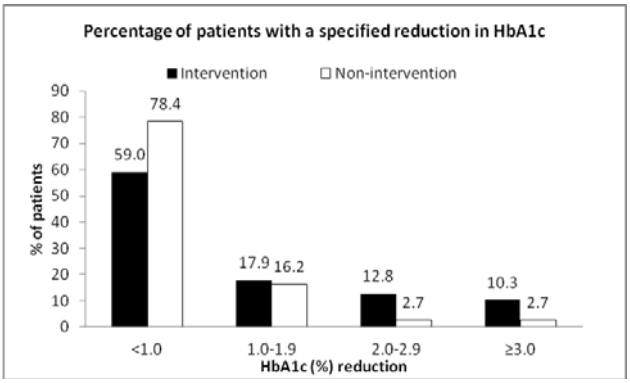

Fig. 2: Percentage of patients with a specified reduction in HbA1c.

The mean HbA1c in the intervention group decreased significantly from 10.11% to 9.21% (p=0.001). However, the reduction of mean HbA1c in the non-intervention group was not significant (p=0.491). The mean HbA1c reduction of 0.90% in the intervention group was significantly different than the reduction in the non-intervention group (p=0.011). Sixteen patients (41%) had significantly achieved at least 1% drop in HbA1c in the intervention group as compared to eight patients (21.6%) in the non-intervention group (fig. 2).

In addition, the FBG was significantly improved in the intervention group with a reduction of 3.45mmol/l (p=0.002) and there was significant difference of mean FBG between the intervention and non-intervention groups. The difference of systolic blood pressure was significant between groups (p=0.026) with the reduction of mean systolic blood pressure in the intervention group but elevated systolic blood pressure in non-intervention group. Both groups had improvement in diastolic blood pressure but the results were not significant within and between groups (p=0.320). The body mass index reduction was not significant in the intervention group but increased insignificantly in the non-intervention group and the difference between the groups was not significant.

There was a significant reduction of 0.34mmol/l (p=0.018) in mean total cholesterol in intervention group. Mean LDL cholesterol also reduced significantly by 0.45mmol/l (p=0.001). However, there were no significant changes in the TG and HDL cholesterol. New insulin cases were significantly higher in the intervention group as compared to the non-intervention group (table 4). Majority of the patients had addition of basal insulin. Furthermore, adherence of medications among patients in the intervention group improved significantly as the mean MMMAS score improved from 6.31 (medium adherence) to 10.62 (high adherence), p<0.001.

DISCUSSION

This randomized prospective study was the first of its kind to be conducted in Malaysia. We found that the addition of pharmacists managed Diabetes Medication Therapy Adherence Clinic (DMTAC) program had improved glycaemic control, lipid parameters and adherence significantly in type 2 diabetes patients. The mean HbA1c lowered by 0.9% significantly from baseline in the intervention group whereas the reduction of HbA1c in the non-intervention group was not significant. The result was similar to a randomized prospective study by Davidson *et al.*, (2000), where the reduction of mean HbA1c (0.8%) in the intervention group (n=50) was significant within and between groups. Even though in another randomized study conducted in Southern Thailand among Muslim diabetic patients, the HbA1c reduced significantly by 0.8% in the intervention group, the reduction was not significant between intervention and usual care groups as HbA1c reduced by 0.6% in the usual care group (Phumipamorn *et al.*, 2008). Besides, study by Odegard *et al.,* (2005) also proved that mean HbA1c reduced significantly within groups but not between groups (p=0.61).

The UKPDS study has proved that every 1% reduction of mean HbA1c is associated with 21% risk reduction for any endpoint related to diabetes and 37% risk reduction for micro vascular complications (Stratton *et al.*, 2000). Patients with extra DMTAC program had a mean HbA1c reduction of 0.9% that is indirectly associated with 19% risk reduction for any endpoint related to diabetes and 33% risk reduction for micro vascular complications like retinopathy and nephropathy. As the result, this has indirectly improved the quality of life of patients. The fasting blood glucose (FBG) reduced by 3.45mmol/l significantly in the intervention group and increased by 0.79mmol/l in the non-intervention group. The reduction of FBG in the intervention group was greater compared to randomized prospective study among rural patients in

Table 1: Baseline characteristics of intervention and non-intervention groups

Variables	Intervention Group, n=39 (%)	Non-intervention Group, n=37 (%)	p-value
Age (y) Mean (SD) Min Max	57.00±1.56 32 years 80 years	55.62±1.49 34 years 77 years	0.286
Gender Male Female	 18 (46.2) 21 (53.8)	 17 (45.9) 20 (54.1)	0.584
Ethnicity Malay Chinese Indian	 11 (28.2) 18 (46.2) 10 (25.6)	 12 (32.4) 13 (35.2) 12 (32.4)	0.613
HbA1c (%)	10.11±0.26	9.71±0.34	0.647
FBG (mmol/l)	11.35±1.00	9.33±0.64	0.097
BMI (kg/m^2)	27.86±0.97	26.92±0.84	0.350
Blood pressure Systolic BP (mmHg) Diastolic BP (mmHg)	135.81±2.49 83.87±1.65	133.64±2.17 83.64±1.14	0.533 0.930
Diabetes Therapy Single OHA* SU† + Metformin SU† + Metformin (Max dose‡) Basal insulin + OHAs§ Insulin + Metformin Insulin alone	 3 (7.7) 8 (20.5) 18 (46.2) 7 (17.9) 2 (5.1) 1 (2.6)	 1 (2.7) 12 (32.7) 14 (37.8) 10 (27.0) 0 (0) 0 (0)	0.328

*OHA= oral hypoglycaemic agent, †SU= sulphonylurea, ‡Max dose= gliclazide 320mg/day or glibenclamide 20mg/day + Metformin 2g/day, §OHAs= sulphonylureas (gliclazide or glibenclamide) and metformin.

Table 2: Differences in outcomes among the intervention and non-intervention group

Outcome measures	Baseline	Intervention Group (n=39)		p-value	Baseline	Non-intervention Group (n=37)		p-value	Between group
		End of study	Mean difference			End of study	Mean difference		p-value
HbA1c (%)	10.11± 0.26	9.21± 0.27	-0.90	0.001*	9.71± 0.34	9.63± 0.29	-0.08	0.491	0.011*
FBG (mmol/l)	11.35 ±1.00	7.90± 0.64	-3.45	0.002*	9.33± 0.64	10.11 ±0.828	+0.79	0.338	0.002*
BMI (kg/m^2)	27.86± 0.97	27.57 ±0.99	-0.29	0.145	26.92 ±0.84	27.01 ±0.87	+0.09	0.360	0.237
Systolic BP (mmHg)	135.81± 2.49	132.26 ±2.21	-3.55	0.153	133.64 ±2.17	139.39 ±2.75	+5.75	0.073	0.026*
Diastolic BP (mmHg)	83.87 ±1.65	81.29 ±1.45	-2.58	0.078	83.64 ±1.14	83.64 ±1.22	0.00	0.983	0.320

India that reported a significant reduction of capillary blood glucose by 25mg/dl (1.39mmol/l) in the intervention group but increased of blood glucose in the control (Arun *et al.*, 2008).

The patients with extra DMTAC program were treated more aggressively compared to usual care groups. This can be seen by the number of new insulin cases in the intervention group. The increased use of insulin may be a possible reason of better glycaemic control in the intervention group. Study has proved that primary care clinicians and patients were reluctant to initiate insulin therapy (Del Prato *et al.*, 2005). The 3rd National Health and Morbidity survey conducted in Malaysia had reported that a very small number of type 2 diabetes patients were on insulin (3.1% on insulin alone and 4.1% on insulin and oral agents combination) as compared to patients treated solely on oral hypoglycaemic agents (77.1%) (Letchuman *et al.*, 2010). Besides, patient-related barriers such as fear of needles, lack of knowledge on diabetes and the requirement of insulin, inconvenient treatment regimes and concerns of hypoglycaemia induced by insulin have

Table 3: Changes in lipid profiles in the intervention group

Outcome measures	Baseline	End of study	Mean difference	P-value
TC (mmol/l)	5.27±0.14	4.93±0.19	-0.34	0.018*
LDL-C (mmol/l)	3.23±0.12	2.78±0.13	-0.45	0.001*
TG (mmol/l)	1.98±0.18	1.91±0.23	-0.07	0.276
HDL-C (mmol/l)	1.17±0.05	1.22±0.05	+0.05	0.092

*Data are mean ±SD. TC=total cholesterol, TG=triglyceride

Table 4: New insulin cases in intervention and non-intervention groups

	Intervention group n=39 (%)	Non-intervention group n=37 (%)	P-value
Additional basal insulin	15 (38.5)	5 (13.5)	0.01*
Basal insulin to full insulin	4 (10.3)	1 (2.7)	

further declined the initiation of insulin therapy (Del Prato *et al*., 2005; Meece, 2006; Korytkowski, 2002). Therefore, pharmacists play a significant role in educating and helping patients to understand diabetes and the need of insulin to overcome their unfound fear of insulin therapy.

Besides, improvement in patients' adherence towards their medication regimen may be the reason for better glycaemic control in the intervention group. Patients in the intervention group had high adherence significantly with mean MMMAS score of 10.6 after DMTAC program. This was similar to retrospective study that was conducted in the specialty clinic that reported improvement from medium adherence to high adherence (Lim and Lim, 2010). Hence, pharmacists played important role in educating patients to understand their disease and medication regimens so that the adherence could improve.

Systolic blood pressure reduced in the pharmacist-managed group significantly as compared to non-intervention group where the systolic blood pressure increased. Diastolic blood pressure reduced in both groups but the decrease was not significant. Patients in the intervention group achieved a mean blood pressure of 132/81mmHg, which is almost at the target blood pressure for diabetics (≤130/80mmHg), according to the Malaysian Clinical Practice Guidelines for the management of type 2 diabetes (Ministry of Health Malaysia 2009). The Fremantle Diabetes Study showed that 92 subjects of pharmaceutical care patients had significant drops in systolic and diastolic blood pressure, twice the amount reduced in 88 patients in the usual care (Clifford *et al*., 2005). New data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has proven that there is no extra benefit in cardiovascular events to lower systolic blood pressure intensively to a goal of <120mmHg compared to standard care that aim for <140mmHg (Cushman *et al*., 2010). However, evidence from landmark study, UKPDS proved that every 10mmHg drop in systolic blood pressure was associated with 11% risk reduction for myocardial infarction (Adler *et al*., 2000). The 3.5mmHg reduction of mean systolic blood pressure in the intervention group indirectly achieved about 4% risk reduction for myocardial infarction.

As for the lipid parameters, total cholesterol and low-density lipoprotein cholesterol (LDL) reduced significantly in the intervention group. A prospective study by Leal *et al*. showed a significant reduction in total cholesterol and LDL cholesterol in indigent Spanish speaking patients with diabetes mellitus (Leal *et al*., 2004). This study showed a significant 14% drop of LDL cholesterol in patients with extra pharmacist-managed group compared to the Diabetes Initiative Program that showed a significant drop of 7.8% in LDL cholesterol (Ramser *et al*., 2008). LDL cholesterol reduction is linear to relative risk reduction of major coronary heart disease (Grundy *et al*., 2004). Therefore, patients in the intervention group indirectly managed to achieve 14% relative risk reduction of major coronary heart disease in this study. The present study also found that the HDL cholesterol of patients in the intervention group improved and this finding is similar to other related studies reported (Kiel and McCord, 2005; Cioffi, 2004). However, mean HDL cholesterol of 1.22mmol/l had achieved that target of ≥1.1mmol/l as set by the Malaysian Clinical Practice Guidelines (Ministry of Health Malaysia, 2009). Although weight reduction is the primary goal of treating diabetes, the difference in body mass index that indirectly related to weight was not significant within and between groups. Body mass index reduced slightly in the intervention group but contrast in the usual care group. This suggests that we should emphasize more on education about diet and exercise to further improve the cardiovascular outcomes.

Finally, limitations exist in this study. Although the subjects were randomly divided, this is an open labeled study and the physicians were aware of this study. Thus, overall care may be improved during the duration of the study. Bias may occur as the data were analyzed by the

same pharmacists who actually involved in the intervention group. Besides, the populations were small and unable to represent the entire diabetes population. Duration of this study was short; therefore long term efficacy of DMTAC program was unknown. Moreover, we could not determine impact of pharmacists in reducing lipid parameters compare to usual care as data of lipid parameters was not sufficient in the non-intervention group. However, the intention of this study was to determine if extra pharmacists counseling could further improved the outcomes and not to evaluate the physician care. This study acts as preliminary data on the effectiveness of DMTAC program in Malaysia.

CONCLUSION

Additional pharmacists managed DMTAC program had significantly improved HbA1c, fasting blood glucose, total cholesterol and LDL cholesterol as well as adherence to medication regimens in multi-ethnic type 2 diabetes patients in the Outpatient Clinic, Hospital Pulau Pinang. These findings provide evidence of the effectiveness of pharmaceutical care in diabetes and suggest that pharmacists shall expand their service especially to patients with uncontrolled diabetes.

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