ORIGINAL ARTICLE

The effectiveness of diabetes medication therapy adherence clinic to improve glycaemic control among patients with type 2 diabetes mellitus: a randomised controlled trial

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ABSTRACT

Introduction: In Malaysia, Diabetes Medication Therapy Adherence Clinic (DMTAC) in hospital settings significantly improved patients' glycaemic control and cardiovascular risk. Until now no randomised controlled trial of DMTAC has been done in a primary care setting where the access to subspecialist services (endocrinologists, expensive medication, etc.) is limited. The objective of this research is to compare the glycaemic control among diabetes mellitus (DM) patients between those received additional DMTAC service and those received normal clinic service in primary care settings.

Materials and Method: This was a parallel, randomised controlled study. The selected participants were patients aged 18 to 70 years with type 2 DM on diabetic medication who were being treated in Kota Samarahan Health Clinic with HbA1c above 8% and who never attended any education of DM prior to the study. The control group received normal clinic visits with consultations by a medical officer. The intervention group received four or more DMTAC visits in addition to normal clinic visits. The primary outcomes were HbA1c while the secondary outcomes were the occurrence of severe hypoglycaemia, weight gain and medication compliance of patients. The subjects were randomised by numbered envelope opened chronologically by the investigator during the initial assessment. All health care professionals (nurse, lab staff and medical officer) except DMTAC pharmacist managing the subjects were blinded as there were no markings on the patients notes indicating that they were in this study. The demographic data was collected during screening while health data including glycated haemoglobin (HbA1c) levels were collected at baseline, sixth month and one year.

Results: In all, 100 patients were randomised into control and intervention groups (n=50 per arm). The change of HbA1c in the intervention group (mean=-1.58) was significantly more than the control group (mean=-0.48) at 12 months with a mean difference of -1.10% (p=0.005, Cohen's *d*=0.627). Both study groups had similar significant changes of subjects from non-compliance to compliance (control group, n=11 vs. intervention group, n=10). The changes of BMI after 12 months between control group (0.24 kg/m^2) and intervention group (0.24 kg/m^2) was not significant (p=0.910). There were no episodes of severe hypoglycaemia detected in both groups.

Conclusion: The addition of DMTAC service in primary care can improve glycaemic control among patients.

The study was registered in the National Medical Research Register (Malaysia): NMRR-13-1449-18955

FUNDING: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All blood test was done in our setting.

KEY WORDS:
Pharmacist intervention, diabetes mellitus, glycaemic control, HbA1c, ambulatory

INTRODUCTION

The International Diabetes Federation reported that the prevalence of diabetes among Malaysian adults (20-79 years old) in 2013 was only 10.1% (estimated 1,913,240 with 1,035,060 undiagnosed cases) but it rose to 16.9% (estimated 3,492,600 with 1,766,800 undiagnosed cases) in 2017.[1] The prevalence of Diabetes reported for Malaysia (16.9%) has risen faster and nearly doubled from global prevalence as reported by the World Health Organization (8.5%).[2]

Previous studies have indicated that for 1.0% reduction in HbA1c, there is a 21% reduction in death related to diabetes, 14% reduction in the incidence of myocardial infarction and 37% reduction in the incidence of microvascular complications.[3] There was also a continuous lower risk of diabetes-related complications among patients with better glycaemic control initially.[4] United Kingdom health economics estimated that the cost reduction from avoided complications due to 1% HbA1c reduction over 25 years based on unit cost inflated to 2014 was ranged from £1280 per person for people with HbA1c ≤ 7.5%, to £2223 for people with HbA1c > 8.0% to 9.0%.[5]

This article was accepted: 4 March 2020
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However, as reported in 2012 in Malaysia, only 37.9% of known diabetes achieved a HbA1c of below 7.0%.[6] Medication Therapy Adherence Clinic (a pharmacist-managed or assisted clinic adapted from ambulatory care pharmacy practice in America) has been operating in Malaysia since 2004 and the Diabetes Medication Therapy Adherence Clinic (DMTAC) was established in 2006. Pharmacists collaborate with endocrine specialists, medical officers and diabetes nurses in DMTAC to maximize the benefits of medication and reduce complications through the most suitable treatment options and patient education. DMTAC aims to improve on the quality, safety, and cost effectiveness of patient care.[7]

To date, there is no randomised controlled trial done in primary care settings in a town environment with limited access to diabetes support team such as endocrine specialist, dietician, physiotherapist. The uncontrolled diabetes patients are from education level of secondary school or less. Due to the difference in the demographic of patients and healthcare support, the response to pharmacist intervention might also differ, thus the importance to conduct a DMTAC intervention study.

Most of the previous studies (pertaining to pharmacy) diabetes intervention, the common side effects of better glycaemic control such as weight gain and the occurrence hypoglycaemia was not investigated. Only one study blinded all healthcare staff except for the pharmacists.[8] Studies had shown that adherence and compliance to medication can independently contribute to lower the HbA1c up to 1.12 %.[9,10] Limited data was available on DMTAC effect on medication compliance and the link of contribution of medication compliance to HbA1c changes in DMTAC patient.

The objective of this research was to compare the glycaemic control among the uncontrolled diabetes mellitus (DM) patients among those who received additional DMTAC service and those received normal clinic service in a primary care setting. The primary outcome considered was the HbA1c level. The secondary outcomes were weight gain, the occurrence of severe hypoglycaemia and medication compliance.

MATERIALS AND METHODS

This was a parallel, randomised controlled study. Based on the sample size calculation, one hundred eligible type 2 diabetes patients (50 patients each for control and intervention groups) attending the Kota Samarahan Health clinic during the study period were recruited from March 2015 until April 2016, and the period of 12 months commenced upon recruitment. The intervention period advanced simultaneously with the recruitment of new subjects and ended in April 2017 (Figure 1).

Patient recruitment

The investigator, a DMTAC pharmacist selected patients from convenient screening of patients during dispensing and referrals from other clinical staff (pharmacists, doctors, diabetic nurses and medical assistants) for diabetes counselling.

The inclusion criteria were patients aged 18 to 70 years' old with type 2 DM, on at least one medication for diabetes, follow up for at least 6 months at our health clinic, HbA1c of more than 8.00% (Malaysia DMTAC guidelines) and those who never attended DMTAC or other diabetic educator follow-up. The exclusion criteria were (1) subjects themselves or close relatives were involved or previously involved in diabetic research, (2) limited literacy level compromising those in counting numbers and recognising numbers as self-care was required (most patient come alone without caretakers), and (3) those unlikely to complete the study including patients with plans to move, terminally ill, unable to commit to clinic visits judged by the investigator based on patient's comment, plan to become pregnant or pregnant and on dialysis or scheduled for elective surgery within the duration of the study.

Our team consists of family medicine specialists, medical officers, pharmacists, nutritionists, visiting dieticians, physiotherapists, occupational therapists and diabetic educator nurses. The health clinic routinely offers DMTAC service. The health clinic treats patients from rural and urban areas and has ISO 9001/2015.

Intervention

All patients in both the intervention and control groups were managed similarly with other regular DMTAC and non-DMTAC patients. The intervention was a 12-month follow-up of at least four DMTAC visits within 9 months in addition to the usual care by medical officers. On the DMTAC and clinic visit day, the intervention group subject was first assessed by a nurse. After the DMTAC visit, the patient had their normal clinic visit. The investigator would not interfere with the number of clinic visits required by the patient. After the clinical visit, the patient was required to revisit the investigator for the following DMTAC visits appointment.

In this study, the pharmacist incorporated the MTAC Diabetes Protocols in managing the medication and disease of the patients. Each DMTAC's visit took about 30 to 60 minutes and each patient was required to attend at least four DMTAC visits. The pharmacist reviewed the DMTAC missions and anticipated patient's benefits. The pharmacist formulated individualized medication and disease management plan (patient-centric goal setting and education, pharmaceutical intervention, and behavioural change encouragement to increase medication adherence and healthy living) according to the comprehensive needs of the patients. The pharmacist also formulated a long-term plan to maintain the behaviour and clinical outcomes of patients after their glycaemic control was stabilised and were was discharged.

In addition to that, a pharmaceutical review including identifying drug-related problems, solving drug-related problems and drug therapy monitoring was done by the pharmacist at the earliest opportunity available and whenever required. The pharmacist would adopt an individualised HbA1c goal and pharmacotherapy (patients with risk of severe hypoglycaemia, limited life expectancy or extensive co-morbidity less stringent glycaemic target.[11,12]

The workflow for the control group was the same as the DMTAC intervention group excluding the visit to the DMTAC which is normal medical officer consultation. A friendly reminder was given at least one week before each appointment, blood test or assessment session. The appointment dates would be rescheduled up to 3 times due to defaulted follow-up before any patient was considered as a drop out.

Outcome measure

The demographic data collected from the patients included date of birth, gender, race, height, weight, occupation, education level, smoking and alcohol intake history. The medical history, on the other hand, included the duration of diabetes of patients since the diagnosis, co-morbidities, other illness, current medication, current vital signs and laboratory parameters.

Blood tests (HbA1c) was measured using D-10™ Haemoglobin Testing System and were done at baseline, sixth month and twelfth month. Blood glucose test was done using Freestyle Optium Neo H (Abbott) every time the selected patients come for clinic visits. Other laboratory tests (blood urea, serum electrolytes, creatinine, and cholesterol) were conducted on baseline and at the end of study.

The secondary outcome weight and height used for BMI calculation was measured using a monthly calibrated medical mechanical weighing scale Detecto 2491. Severe hypoglycaemia was collected by referring to patient's medical record and patient's recall of any hypoglycaemia unresolved with sugar intake treatment and with severe symptoms (confusion, abnormal behaviour or both, seizures, or loss of consciousness) requiring third-party assistance followed by a health clinic or hospital visit. Incidence of other types of hypoglycaemias was difficult to be determined as some patients did not own a glucometer and no proper blood glucose monitoring was done at home.

Compliance to medication by self-report was done twice, at baseline and at the end of the study. Good medication compliance is defined as taking 80% to 120% of the medication prescribed. Patients who missed more than 20% of the medication was considered as non-compliant.[13]

Changes to outcome

Fasting blood glucose was excluded as the outcome of this study midway. Upon questioning, more than 50% of the patients had incorrect fasting routine of taking antidiabetic medication of more than one hour before fasting blood glucose (FBG) was taken. There were also a few missing fasting blood glucose test readings because the subjects did not have any previous fasting results during the research recruitment process. Fasting glucose concentrations can also vary considerably in a single person from day to day.[14,15,16,17] Therefore, fasting blood glucose reading was excluded as an endpoint for this study.

Sample size calculation

The sample size calculation was powered to detect changes in HbA1c. $p < 0.05$ with the power of 80% accepted as significant using a one-tailed test based on Lim's study.[18] The baseline HbA1c was set to be 8%, with a standard deviation of 0.3 and effect size of 0.3 was estimated. By using the PS sample size calculation, the sample size was 17 per group. With an estimated calculation of 50% drop-out rate, approximately 100 patients were required (50 per arm). Thus, the investigator would recruit 50 subjects for each group from Kota Samarahan Health Clinic.

Patient randomisation

The process of randomisation was carried out using computer generated random allocation numbers (www.random.org). Randomly allocated intervention group was concealed in an envelope prior to the recruitment process by another pharmacist not involved in other parts of the study. During the patient recruitment process, each numbered envelope was opened chronologically by the investigator during the initial assessment after the patient had signed the informed consent form.

Blinding process

The medical officer treating the subject was blinded on the participating patients in this study. There was no indication in the outpatient record card and blood test assessment form. The blood test assessment was pre-signed by the medical officer and hand out to the subjects at the correct time frame by the investigator. The exact time frame of patient recruitment was not informed to the other healthcare staff. As such, the identification of the subject was not possible.

The investigator (DMTAC pharmacist) was not blinded because she was in charge of the recruitment process, running of DMTAC and data collection. The selection bias in the recruitment process was minimised by recruiting all referred patient fulfilling the inclusion criteria and willing to participate in the research. The demographic and outcome was all collected via patient medical record card with no additional intervention by the investigator. Different individual for these processes was not possible as there was only one DMTAC pharmacist who was also the main investigator.

Statistical analysis

There was a modified intention to treat analysis which included non-compliance and protocol deviations but excluded dropout such as subject self-withdrawn from the study, transferred to other clinic for follow-up where data collection was deemed impossible. Extra care was taken to minimise drop-out and to continue to follow up those who withdrew from the study. The last observation carried forward was also not used in this research because the data collected was only done in the 6th month for HbA1c and in the 12th month for all health related outcomes including HbA1c.

The subject demographic information, medical history and other variables which might had an effect in the HbA1c outcome was collected. Gender, smoking status, alcohol dependence status was collected as dichotomous variables. Race, occupation status, education status, and medication compliance was collected as nominal variable. Pearson's Chi-Square test was used to compare the dichotomous and nominal variables. Data pertaining to age, body mass index, duration of diabetes, fasting blood glucose, and HbA1c at

baseline were collected as continuous variables. Independent T-test was subsequently used to compare the control group and intervention groups for continuous variables and fulfilling all assumption (no significant outliers, dependent variable approximately normally distributed, and homogeneity of variance). If the assumption was not met, a Mann Whitney test would be used.

Outcomes in terms of HbA1c in sixth month and twelfth month were compared with baseline for each research group using a paired T-test if all the assumption was met (no significant outliers and the dependent variable between the two groups was approximately normally distributed). The result can be used to check if there was any significant difference between baseline sixth month and twelfth month for each group. If the assumption was not met a Wilcoxon Signed Ranks test would be used instead.

Independent T-test was used to compare the difference in the changes of between the HbA1c baseline with the post six months and post 12 months if all test assumption was met (no significant outliers, dependent variable approximately normally distributed, homogeneity of variance).

A linear regression was done to check the variables that had potential to influence the difference between HbA1c baseline and HbA1c post 12 months' outcome. All assumptions were checked prior to running the linear regression. The linear regression was run both in stepwise and enter methods. The assumption was only checked via stepwise method. The linear regression was first run in the enter methods to check the relationship of taking in all the confounding factors into consideration. Stepwise regression was then run to check the best combination of confounding variables would influence the HbA1c outcome variable. The variables that did not significantly contribute to the outcome were excluded.

Ethical consideration

There were no modifications in the scope of work of the healthcare professionals (nurses, medical officers, and pharmacists) and services (DMTAC and normal clinic visits) received. All subjects received normal counselling by a pharmacist if referred for education. The patients in the control group were allowed to withdraw from the study at any time during the study period and join the DMTAC at any point of time but these cases were considered as dropout during the analysis stage. This research was approved by Malaysia National Medical Research and Ethnic Committee.

RESULTS

Participant flow

The numbers of participants that were randomly assigned, received intended treatment, and analysed for the outcome were summarised in Figure 1.

Dropouts

Five subjects dropped out from the control group, three subjects were transferred, one subject defaulted test because of insufficient HbA1c test reagent and one subject could not be contacted. There were nine subjects defaulted in the intervention group. Four subjects were transferred, two subjects were withdrawn from the study, one subject defaulted test because of insufficient HbA1c test reagent and two subjects were hospitalised (Stroke and pneumonia not due to DMTAC) and did their follow-up in other clinics. Hence, there were 86 subjects who completed the research. The dropout was completely random and the deletion method was used for analysis of endpoint outcome.

Baseline assessment

A total of 102 patients were screened for the eligibility for this study but only 100 were recruited. Two patients were excluded (one control group subject and one intervention group subject) because their HbA1c was lower than 8%. All patients were assessed over 12 months. Table I shows the baseline characteristics of all recruited patients.

There was no significant difference in the baseline characteristics of control group and intervention group except for occupation ($p = 0.009$).

Outcome

There was a significant difference of HbA1c at the endpoint 12 months' result of the between the control group (n= 45, 9.56%) and intervention group (n=41, 8.69%) $p = 0.017$ (Table II).

Both control and intervention groups had a reduction of HbA1c at 12th month as compared to baseline but only the intervention group showed significant HbA1c change with a difference of -1.58 ± 1.79 %, $t(40) = -6.57$, $p < 0.001$. HbA1c changes in 12 months were also significantly more in the intervention group (-1.58 %) compared to the control group (-0.48 %) $p = 0.005$ (Table III).

There was no significant difference in the BMI of both groups at 12th month (BMI control group=29.15 kg/m^2, n=45 vs intervention group =28.62 kg/m^2, n=41, p=0.559). The difference in the increase of BMI between the control group (0.24 kg/m^2) and intervention group (0.24 kg/m2) was not statistically significant (p=0.910).

There was no incidence of severe hypoglycaemia reported in both control and intervention groups.

Medication compliance

There was no significant difference in patient compliances at the end of study between the study groups as both groups had 38 patients compliant to medication, p=0.234. A total of 11 subjects showed improvement in medication compliance in the control group and 10 subjects improved in medication compliance in the intervention group. There was a significant improvement in compliance for both groups ($p<0.001$) tested using Cochran's Q test. However, the difference in the change of medication compliance between study groups was not statistically significant, p=0.995.

Controlling the variables

A multiple-linear regression was run to predict the change of HbA1c in a one-year period from all baseline possible confounding factors such as subject baseline HbA1c, research group, gender, employment status, education level, ethnic, baseline diabetes treatment plan, BMI group, compliance group, duration of diabetes and age. All linear regression assumption was checked. Using the stepwise method, it was

Table I: Baseline characteristics of recruited patients by group (n = 100)

Variable		Samarahan's Diabetes Register %	Total Subject	Control (n=50)	Intervention (n=50)	P value
Age (years), mean (SD)			100	52.38 (11.39)	52.66 (9.35)	0.893[a]
Gender	Male	40.56	38	17	21	0.410[b]
	Female	59.44	62	33	29	
Race	Malay	56.26	47	26	21	0.604[b]
	Chinese	6.56	13	6	7	
	Sarawak Bumi	36.58	40	18	22	
	Other	0.60	0	0	0	
Occupation	Working	N/A	54	20	34	0.009[b]
	Unemployed/ Housewife	N/A	14	11	3	
	Retired	N/A	32	19	13	
Education	No formal education	N/A	21	11	10	0.258[b]
	Primary	N/A	31	19	12	
	Secondary	N/A	40	18	22	
	Tertiary	N/A	8	2	6	
Smoking	Non-Smoker	N/A	5	2	3	0.646[b]
	Smoker	N/A	95	48	47	
Alcohol	Non-Alcoholic	N/A	3	1	2	0.558[b]
	Alcoholic	N/A	98	49	48	
Baseline Treatment Plan	Diet only	4.37	0	0	0	
	OHA (1)	75.95	49	20	29	0.056[b]
	OHA + Basal insulin (2)	18.09	51	21	10	
	Basal bolus insulin (3)			9	11	
Baseline HbA1c (%), mean (SD)		6.9	100	10.04 (1.29)	10.46 (1.64)	0.162[a]
Baseline FBG (mmol/L), mean (SD)		6.4	84	10.21 (3.50)	10.12 (3.51)	0.905[a]
Baseline BMI (kg/m^2), mean (SD)		27.7	100	28.83 (4.62)	27.96 (5.43)	0.368[c]
Compliance	Yes	N/A	63	29	34	0.300[b]
	No		36	21	16	
Duration of diabetes (year), mean (SD)		N/A	100	7.30 (5.27)	7.07 (4.60)	0.928[c]

SD = Standard deviation
OHA = Oral anti-diabetic medication
FBG = Fasting blood glucose
BMI = Body mass index
a = Independent T-test
b = Pearson Chi-Square Test
c = Mann-Whitney U Test

Table II: Comparison of haemoglobin A1c and body mass index between intervention and control group at 6 and 12 months after intervention

Variable	Control group, mean (SD)		Intervention group, mean (SD)		P value (control vs intervention)	
	6th month	12th month	6th month	12th month	6th month	12th month
HbA1c (%)	9.55 (1.70)	9.56 (1.65)	8.94 (1.68)	8.69 (1.79)	0.086[a]	0.017[a]
BMI (kg/m^2)	NA	29.15 (4.95)	NA	28.62 (5.77)	NA	0.559[b]

a = Independent T-test
b = Mann-Whitney U Test

Table III: Comparison of changes in haemoglobin A1c and body mass index between intervention and control group at 12 months after intervention

P value	Control group, mean (SD)		Intervention group, mean (SD)		P value (control group vs intervention group	Cohen's d (control group vs intervention group)
	Change in 12 months (SD)	P value	Change in 12 months (SD)	P value		
HbA1c (%)	-0.48 (1.72)	0.069[a]	-1.58 (1.79)	<0.001[a]	0.005[c]	0.627
BMI (kg/m^2)	0.24 (1.20)	0.310[b]	0.27 (1.79)	0.421[b]	0.910[d]	0.020

a = Paired T-test
b = Wilcoxon Signed Ranks test
c = Independent T-test
d = Mann-Whitney U test

Table IV: Summary of multiple linear regression analysis for changes of HbA1c in 12 months

Model	Unstandardized Coefficients		Standardized Coefficient	t	Sig
	B	Std. Error	Beta		
(Constant)	4.580	1.191		3.846	<0.001
Baseline HbA1c	-0.608	0.109	-0.470	-5.593	<0.001
Treatment = 1: Oral Medication 2: Basal Insulin + Oral 3: Basal + Bolus Insulin	1.017	0.202	0.427	5.046	<0.001
Research Group 1: Control Group 2. Intervention group	-0.762	0.306	-0.209	-2.488	0.015

Dependent Variable: Change of HbA1c in 12 months' period
R^2 = 0.435 (adjusted R^2 = 0.414)
Regression equation: HbA1c change in 12 months
= 4.580 – 0.608 (Baseline hbA1c) + 1.017 (Treatment) – 0.762 (Group)
Variable checked using stepwise analysis: research group, gender, employment status, education level, ethnic, baseline diabetes treatment plan, BMI weight group, and compliance group as categorical variable; baseline HbA1c, duration of diabetes, age as continuous variable.
G power = 0.9999, effect size f^2 = 0.7699

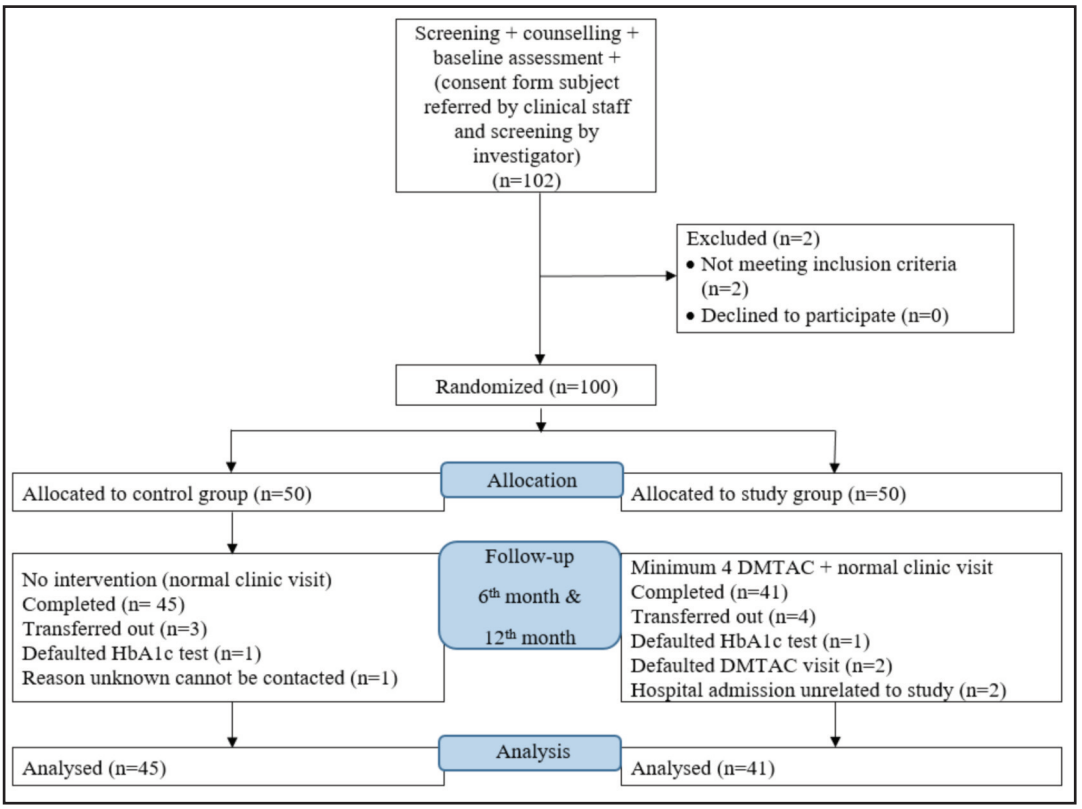

Fig. 1: Enrolment flow diagram.

found that baseline HbA1c (p <0.001), research group (p=0.015), and baseline diabetes treatment plan (p<0.001) statistically significantly predicted the change of HbA1c in 12 months' period, F (3, 82) = 21.04, p<0.001, R^2 = 0.435 (Table IV). All three variables were statistically significant to the prediction, p < 0.05. Running the pos-hoc power analysis using G power, total sample size of 100, effect size f^2 = 0.7699 and 11 factors, the g power of the regression is 0.9999.

DISCUSSION

Outcomes interpretation and generalisability

Diabetes patients tend to have an HbA1c increase of 0.47% every year on average with most therapies without intervention.[19] However, in this study, the control group (no intervention) managed to delay the diabetes progression with a slight non-significant improvement of HbA1c and the intervention group significantly improve patients' glycaemic control. Both patients in the control group and intervention group had additional blood tests and pharmacist counselling during baseline, blood test reminder at 6th month and study endpoint. Patients were aware that their glycaemic control was being monitored more closely during the study period. All these factors would have contributed slightly to the patient HbA1c improvement in both groups. This was further supported by several randomised controlled trials of intervention versus placebo as a slight improvement in HbA1c of around 0.4% was also seen in the placebo group (no intervention but increased frequency of clinic visits and blood tests).[20,21]

There was a significant effect of baseline HbA1c, treatment plan and the study group on HbA1c changed in 12 months (Table IV). The baseline HbA1c had the highest negative correlation with the changes in HbA1c over a one-year period according to results from the linear regression done. Each increase of baseline HbA1c caused a further reduction of 0.608 in the HbA1c changes in 12 months' period. This was because patients starting with high HbA1c had a bigger room for HbA1c improvement. This fact was further supported by studies that recruited patients with HbA1c starting from 7%. [22,23,24] and they proved it was challenging to achieve a significant difference in HbA1c improvement with a small sample size.

In terms of treatment plan, the patients who had more complicated insulin treatment plan at baseline had reduced HbA1c improvement. According to the results from linear regression, baseline treatment group (step one versus step two versus step three) has an overall effect on changes of HbA1c in 12 months' time, regardless of other confounding factors (Table IV). Each increase of treatment plan step produced a further increase of 1.02 in the HbA1c changes in 12 months' period (p = 0.001). A prevalence study in Malaysia showed that patients on oral anti diabetic medication (OHA) alone had better glycaemic control compared to patient on combination of OHA and insulin. These might be due to the fact that patients with less diabetes complication and severity had a simpler treatment plan to begin with, thus improvement in glycaemic control was easier to achieve.

There was no significant difference in the HbA1c baseline and treatment regime between the control and intervention groups (p=0.056). The intervention group caused a further reduction of 0.76 in the HbA1c changes in 12 months' period after controlling for the other confounding factors (baseline HbA1c and treatment plan).

In the 12-month study period, the changes of HbA1c between the control group (-0.48±1.71%) and the intervention group (-1.58±1.79%) showed a mean difference of -1.13% [95% CI=-1.87, -0.39]. As compared to a meta-analysis done by Linda with a mean improvement HbA1c of 0.71% (P<0.001), a better reduction of HbA1c was obtained in this study.[25] Therefore, it can be concluded that the DMTAC service provided was comparable to pharmacist intervention worldwide. However, there are still improvements that can be done as the average HbA1c achieved was 8.70 ± 1.80% which was higher than the individualised HbA1c target set for diabetes patients. DMTAC should be encouraged in all facility and recommended for all uncontrolled diabetes patient. In clinical setting with limited resources, DMTAC should be initially prioritised for diabetes patient with higher HbA1c and simpler treatment plan to maximise the improvement in patient glycaemic control.

A study of 2176 diabetic patients from 12 countries showed that there was a mean weight gain of 1.78kg in the first year of starting insulin.[26] The United Kingdom Prospective Diabetes Study showed that there was a weight gain over the 10 years with the highest increase of mean 4.0kg in diabetes patients on insulin.[27] The most common given diabetic medication treatment in Kota Samarahan Health clinic are metformin, gliclazide and insulin which often result in hyperinsulinaemia, an increase in hypoglycaemia and weight gain.[28] In this study, no significant BMI changes between the study groups were observed and this might be due to the effective diet and lifestyle modification of the patients via education. This shows that DMTAC was able to improve glycaemic control without contributing to significant weight gain in the first year.

In the ACCORD trial, annual hypoglycaemia rates were higher in the intensive treatment group (target HbA1c below 6.5%) as compared to the control group (target HbA1c below 7.5%) with a ratio of 3.3% vs. 1.1% with a significant increase in mortality (257 vs 203) and no significant reduction in major cardiovascular events in 3.5 years.[29] ACCORD trial and ADVANCE trial showed a possible relationship between treatment assigned, increased severe hypoglycaemia, and increased mortality risk.[30] Good intervention should have improved glycaemic control without significant increase in hypoglycaemia risk. There was no severe hypoglycaemia report in patients from both groups on this study.

Although this study indicated that patient with good medication compliance had better improvement in HbA1c, the compliance group was not a confounding variable for HbA1c changes (linear regression). Both study groups had similar improvement in medication compliance suggest that there are other factors which might contribute the improved glycaemic control such as health education, lifestyle and diet changes.

Limitations of the study

The main investigator for this research was the DMTAC pharmacist. There was some conflict of interest which might result in more attention given in the research subject compared to real life scenario. This research was only done in one facility and a different facility would have slightly different healthcare and DMTAC setting. The majority of the subjects cannot afford to do home blood glucose monitoring frequently. Careful monitoring will also reduce the risk of undetected hypoglycaemia and enabling insulin intensification near normoglycaemia safely.[31] Home blood glucose may be one of the factors influencing the HbA1c changes but it was not looked into in this study. It is preferable to blind the DMTAC pharmacist and the DMTAC pharmacist should not be involved in this research to prevent overtreatment in pharmacist interventions. Patient compliance to medication was known as a confounding factor and several studies suggest that subjects in the intervention group who showed improvement in glycaemic control was largely due improved medication adherence.[32] The exact scoring of medication adherence improvement was not reported because of licensing issue.

CONCLUSION

In this 12-month study period, the changes of HbA1c between the control group (-0.48 ± 1.72%) and the intervention group (-1.58± 1.79%) show a weight mean difference of -1.13% [95% CI = -1.87, -0.39]. Results from the regression analysis (dependent variable - change of HbA1c in one year and independent variable – all other baseline variable) found that the baseline HbA1c, baseline treatment plan and research group had significant influence on the outcome. The

improvement of compliance had a significant effect on the changes on HbA1c in 12 month's period but the change in treatment plan for the patient did not. This indicates that the improvement in glycaemic control is not solely due to the improvement of medication adherence or change of medication but the combination of different factors including diet and lifestyle. There was no adverse reaction reported from the DMTAC service provided. Besides that, there were no significant changes in BMI in the intervention group (increased 0.27kg) as compared to the control group (increased 0.24kg). There were no episodes of severe hypoglycaemia detected in both control and intervention groups. Therefore, it can be concluded that DMTAC service combined with regular clinic visits can successfully improve patient glycaemic control without incurring any significant weight gain or hypoglycaemia.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial with a National Medical Research identification number of 13-1449-18955 had received approval from National Institute of Health (Ministry of Health Malaysia) and Medical Research and Ethics Committee (Ministry of Health Malaysia).

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for permission to publish this article. Our utmost gratitude to staff of Ministry of Health Malaysia especially Dr. Nur Fatihah Oh Abdullah (Pejabat Kesihatan Bahagian Samarahan) and all the staff from Kota Samarahan Health Clinic. My appreciation goes to the Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak for the support in this research.

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