IMPROVING GLYCAEMIC CONTROL IN MALAYSIAN PATIENTS WITH TYPE 2 DIABETES WITH INSULIN PUMP THERAPY- ANALYSIS FROM A SINGLE TERTIARY CENTRE

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Introduction

- Type 2 diabetes is a progressive disease, characterized by ongoing decline in beta cell function. In advanced disease, many patients develop worsening diabetes control, and ultimately require insulin.
- In addition, a growing number of insulin-treated patients require high doses of insulin.
- Opt2mise study demonstrated the efficacy of insulin pump therapy in long standing poorly controlled type 2 diabetes on multiple daily injections.[1]
- In Malaysia, approximately 30% of insulin users were on premixed insulin regimen due to the cost and presumed convenience.[2] Those patients who fail premixed insulin are usually intensified with multiple daily injections of insulin.

Aim

- To evaluate the comparative efficacy of insulin pump therapy versus multiple daily injections in insulin resistant type 2 DM patients who are sub-optimally controlled with premixed insulin regimen.

Methodology

Study design (Figure 1)

- 12 – months randomized, parallel-group, open-label trial with a single-arm cross-over in the continuation phase
- Participants were recruited from the Endocrine clinics and General Medical outpatient clinics, Putrajaya Hospital since January 2016.
- The participants were insulin-taking patients who were sub optimally controlled on premixed insulin regimen twice or three times daily(defined as having an HbA1c > 8%).
- The participants entered an 8-week dose optimisation run-in period and at the end of the run-in period, insulin dosage was at minimum 1.0U/kg/day and at maximum 1.7 U/kg/day, or a maximum of 200 U/day.
- This was followed by randomisation into two interventional arms which were CSII and MDI. After 6 months, the participants on the MDI arm crossed over to CSII for another 6 months. Neither patients nor investigators were masked to treatment allocation.


Figure 1. Study design.
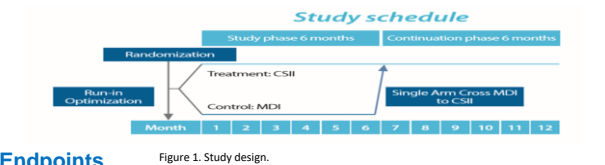
Endpoints

- Primary endpoint : change in mean glycated haemoglobin between baseline and 6 months
- Secondary endpoints : safety, metabolic profiles, total insulin dosage, within group difference in HbA1c from 6 months to 12 months and the number of self-monitoring blood glucose(SMBG)/day.
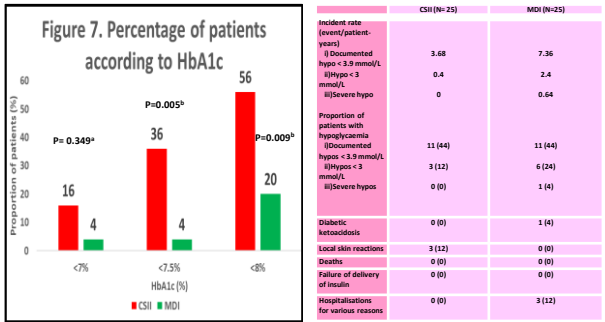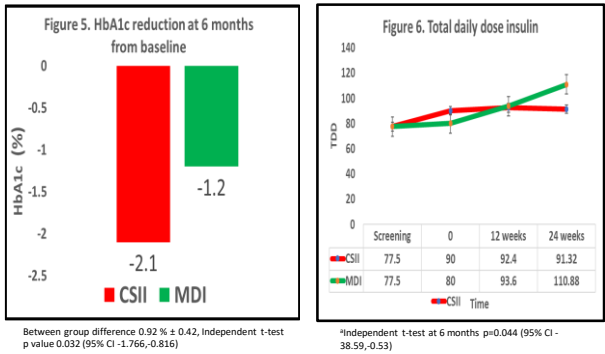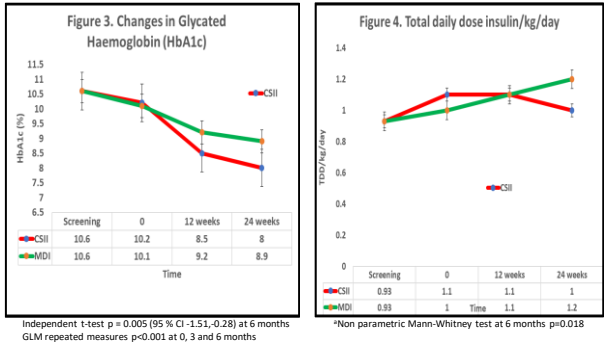
Results

- These results were the analysis for the first 6 months.

Figure 2. Flowchart of the recruitment process.
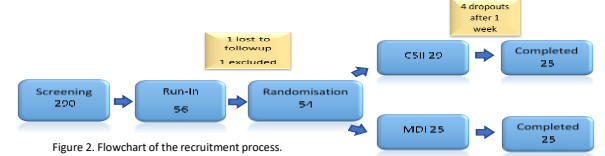
	CSII (N=25)	MDI (N=25)	P values
Age (years)*	52.0 ± 14.50	56.0 ± 16.50	0.854
Gender			
Male	16 (64)	14 (56)	0.564
Female	9 (36)	11 (44)	
Ethnicity			
Malay	19 (76)	20 (80)	
Chinese	3 (12)	0 (0)	0.309
Indian	3 (12)	4 (16)	
Others	0 (0)	1 (4)	
Duration of diabetes (years)	13.8 ± 7.00	13.7 ± 6.93	0.950
HbA1c (%)	10.2 ± 1.51	10.1 ± 1.79	0.953
FBS (mmol/L)	9.6 ± 3.00	8.1 ± 3.07	0.083
Smoker	1 (4)	4 (16)	0.349
Non smoker	24 (96)	21 (84)	
Use of metformin	24 (96)	24 (96)	1.000
Dose of metformin (mg)*	2.0 ± 0.50	2.0 ± 0.00	0.296
Type of insulin			
Human insulin	17 (68)	18 (72)	0.754
Insulin analogues	8 (32)	7 (28)	
Systolic BP (mm/Hg)	132.0 ± 15.66	131.2 ± 9.24	0.827
Diastolic BP (mm/Hg)	79.6 ± 6.61	76.4 ± 7.56	0.113
Weight (kg)*	79.9 ± 20.10	80.0 ± 32.10	0.691
BMI (kg/m²)	30.3 ± 5.03	30.1 ± 6.60	0.909
Total daily dose of insulin*	90.0 ± 32.50	80.0 ± 40.00	0.064
Total daily dose/kg/day*	1.1 ± 0.48	1.0 ± 0.19	0.063
Total cholesterol (mmol/L)*	4.3 ± 1.50	4.6 ± 1.30	0.938
LDL (mmol/L)*	2.4 ± 1.00	2.6 ± 1.20	0.573
HDL (mmol/L)	1.0 ± 0.18	1.1 ± 0.33	0.229
TG (mmol/L)*	1.7 ± 1.20	1.2 ± 1.00	0.062
Cardiovascular disease	2 (8)	7 (28)	0.138
Cerebrovascular disease	1 (4)	1 (4)	1.00
Peripheral vascular disease	0 (0)	0 (0)	NA
Nephropathy	21 (84)	15 (60)	0.059
Retinopathy	15 (60)	13 (52)	0.569
Neuropathy	18 (72)	18 (72)	1.00
Hypertension	23 (92)	21 (84)	0.384
Dyslipidaemia	25 (100)	25 (100)	NA

Table 1. Demographic data and patients' characteristics at the baseline
Data are presented as mean ± SD and frequency (%) unless otherwise stated. * Data in median ± IQR. Categorical variables comparison with Pearson Chi Square and Fisher Exact. Numerical variables comparison with independent t-tests(mean) and non-parametric Mann-Whitney tests(median).

Figure 3. Changes in Glycated Haemoglobin (HbA1c)

	Screening	0	12 weeks	24 weeks
CSII	10.6	10.2	8.5	8
MDI	10.6	10.1	9.2	8.9

Independent t-test p = 0.005 (95 % CI -1.51,-0.28) at 6 months
GLM repeated measures p<0.001 at 0, 3 and 6 months

Figure 4. Total daily dose insulin/kg/day

	Screening	0	12 weeks	24 weeks
CSII	0.93	1.1	1.1	1
MDI	0.93	1	1.1	1.2

[a]Non parametric Mann-Whitney test at 6 months p=0.018

Figure 5. HbA1c reduction at 6 months from baseline

Between group difference 0.92 % ± 0.42, Independent t-test p value 0.032 (95% CI -1.766,-0.816)

Figure 6. Total daily dose insulin

	Screening	0	12 weeks	24 weeks
CSII	77.5	90	92.4	91.32
MDI	77.5	80	93.6	110.88

[a]Independent t-test at 6 months p=0.044 (95% CI -38.59,-0.53)

Figure 7. Percentage of patients according to HbA1c

P= 0.349[a] P=0.005[b] P=0.009[b]

[a] Fisher's Exact Test   [b] Chi-Square Test

	CSII (n=25)	MDI (n=25)	P values
Weight change at 6 months (kg)	2.1 ± 3.00	2.9 ± 3.65	0.260[a]
SMBG/day	1.2 ± 0.72	0.96 ± 0.67	0.187[a]
Systolic BP (mmHg)	132.1 ± 9.33	136.4 ± 15.03	0.237[a]
Diastolic BP (mmHg)	79.2 ± 6.84	77.7 ± 8.78	0.509[a]
Total cholesterol (mmol/L)	4.0 ± 1.60	4.3 ± 1.20	0.683[b]
LDL (mmol/L)	2.3 ± 1.20	2.4 ± 1.00	0.579[b]
HDL (mmol/L)	1.1 ± 0.22	1.1 ± 0.50	0.144[a]
TG (mmol/L)	1.7 ± 1.00	1.2 ± 0.90	0.080[b]

Table 3. Metabolic parameters at 6 months.
[a] Independent t-tests [b] non-parametric Mann-Whitney

	CSII (N=25)	MDI (N=25)
Incident rate (event/patient-years)		
i) Documented hypo < 3.9 mmol/L	3.68	7.36
ii)Hypo < 3 mmol/L	0.4	2.4
iii)Severe hypo	0	0.64
Proportion of patients with hypoglycaemia		
i)Documented hypos < 3.9 mmol/L	11 (44)	11 (44)
ii)Hypos < 3 mmol/L	3 (12)	6 (24)
iii)Severe hypos	0 (0)	1 (4)
Diabetic ketoacidosis	0 (0)	1 (4)
Local skin reactions	3 (12)	0 (0)
Deaths	0 (0)	0 (0)
Failure of delivery of insulin	0 (0)	0 (0)
Hospitalisations for various reasons	0 (0)	3 (12)

Table 2. Hypoglycaemia rates and adverse effects

		CSII (n=25)	P values
HbA1c at randomisation < 9% [b]		-0.9 ± 0.50	0.001 [d]
HbA1c at randomisation > 9%		-2.2 ± 1.48	
BMI < 30 kg/m2 [a]		-2.0 ± 0.96	0.640 [c]
BMI > 30 kg/m2		-2.2 ± 1.40	
Wizard use for correction	Use	19 (76)	0.106 [c]
	Not Use	6 (24)	
Carbohydrate counting	Yes	10 (40)	0.300 [c]
	No	15 (60)	

Table 4. Subanalysis of HbA1c reduction and the effect of variables in CSII group
[a]mean(SD) [b]median(IQR) [c]Independent t-test [d]Mann-Whitney

Discussion

- Improvements in HbA1c were achieved in both groups, but with greater improvement observed with pump therapy.
- Potential explanations include:
1)a more physiological method of delivery
2)Improved absorption of smaller subcutaneous insulin depots with continuous insulin infusion
3)Prevention of the hyperglycaemia of the dawn phenomenon
4)Prevention of hypoglycaemia that becomes a barrier to insulin intensification
5)improved adherence to insulin dosing
- The improvement in HbA1c was observed with significantly reduced insulin requirement and less hypoglycaemia events.
- Pump therapy in type 2 diabetes can be successful without requiring use of a bolus calculator and without the need for carbohydrate ratio determination at each meal.

Conclusion

- Insulin pump therapy is effective and safe for insulin resistant type 2 DM patients who have been on intensified premixed insulin and remained far from achieving target glycaemic control.

References
1. Reznik Y, Cohen O, Aronson R, Conget I, Runzis S, Castaneda J, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. The Lancet. 2014; 384 (9950): 1265–1272
2. Mafauzy Mohamed, Zanariah Hussein, Avideh Nazeri, Siew Pheng Chan. DiabCare 2013: A cross-sectional study of hospital based diabetes care delivery and prevention of diabetes related complications in Malaysia. Med J Malaysia. 2016; 71(4):177-185