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COMPARATIVE STUDY TO MONITOR THE EFFICACY AND THE SAFETY OF BIPHASIC HUMAN INSULIN (INSULIN H MIX-RECOMBINANT DNA, 30/70)

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ABSTRACT
The study to confirm efficacy and safety of biphasic H-Mix insulin manufactured by SEDICO from raw material of Wockhardt & Biocon compared to the reference insulin (Mixtard insulin) with regards to the dose of insulin and local reaction to injection. 212 diabetic patients were grouped into 4 groups as follows: Group 1A (Type 1 DM, Insulin H-Mix), Group 1B (Type 1 DM, Mixtard Insulin), Group 2A (Type 2 DM, Insulin H-Mix), and Group 2B (Type 2 DM, Mixtard Insulin). All enrolled subjects underwent medical evaluation at three months intervals with patient blinded, comparative controlled study. Fasting blood Glucose (FBG) decreased 14.7% and 6.8% between V1 & V3 in group 1A and 1B respectively. There was decrease of 2.4% and 4.2% between V1 & V3 in group 2A and 2B respectively. Glycosylated hemoglobin (HbA1c) decreased 5.9% between visit 3 & 1 in group 1A and increased by 1.1% in group 1B. HbA1c increased 0.2% and decreased 5.2% in groups 2A & 2B respectively, with no statistical significant difference between the 2 groups. An increase of 0.2% and decrease of 4.6% in total daily insulin dose/kg/day between V1 & V3 in groups 1A & 1B respectively. There was an increase of 23% and 14.8% in total daily dose/kg/day between V1 & V3 in groups 2A & 2B respectively, with no statistical significant difference between the 2 groups. No local reaction to insulin injection occurred in group 1A between V1 and V3, while 2% in group 1B, 14% in group 2A & 9% in group 2B had local reactions. Insulin H-Mix of SEDICO from raw material of Wockhardt & Biocon is effective in lowering fasting blood glucose and HbA1c and safe as well as the reference insulin (Mixtard insulin) in the treatment of diabetes mellitus type 1 and type 2.

KEYWORDS: Safety, Efficacy, Biphasic Insulin, diabetes, SEDICO, Biocon, Wockhardt.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both, as described by WHO in 1999. Diabetes mellitus has various effects that may include long term damage or dysfunctions to a variety of organs, such as progression of retinopathy with possible blindness, nephropathy, and/or neuropathy which may lead to foot ulcers and amputation. Moreover, people with diabetes are at a higher risk of cardiovascular, cerebrovascular and peripheral vascular diseases [1]. Insulin deficiency or the resistance to insulin action is due to the pathogenesis of the beta cells destruction in the pancreas. Due to the insufficient action of insulin on it target tissue this leads to abnormalities in protein, fat and carbohydrate metabolism. The clinical diagnosis of diabetes is often presented with symptoms such as increased thirst and urine volume, recurrent infections, and high levels of glycosuria are often present [2]. Diabetes is progressively becoming a major chronic disease burden all over the world[3]. Diabetes prevalence is approximately 20.0% in urban Egypt[4]. Due to diabetes; the prevalence of retinopathy is 41.5% and albuminuria 21% in Egypt. Also, nephropathy prevalence is 6.7% in hospital outpatient clinics to 46.3% in hospital inpatients in Egypt. Moreover, the prevalence of diabetic neuropathy ranged from 21.9% in hospital outpatient clinics to 60% in hospital inpatient clinics in Egypt[5,6]. Diabetes is managed through either oral medication or insulin injections. The majority of previous studies compare different treatments regimens. However, in this study two biphasic human insulins are compared to each other; Insulin locally manufactured by Sedico from raw materials Biocon & Wockhardt compared to insulin Mixtard.

MATERIALS & METHODS

This is a patient blinded and controlled study based in Egypt as insulin vials were removed from their carton packs and covered by a label with the randomization code. it has been designed to monitor the efficacy and safety of Biphasic Insulin (H Mix- Recombinant DNA, 30/70 of SEDICO from raw material of Wockhardt & Biocon compared to others than of SEDICO) 1-2 injections a day, in type 1 and 2 diabetes mellitus, who have inadequate glycemic control on their existing anti diabetic treatment in daily clinical practice. This study is a clinical trial that has 2 treatment groups. Subjects who were enrolled in this study agreed to the release of information and to provide answers to questions about their treatment with insulin H Mix, which reflect the care they receive under routine clinical circumstances. Subjects participating in this study were prescribed Biphasic insulin, as part of routine clinical practice in the National Institute of Diabetes and

Endocrinology disease (NIDE). All enrolled subjects who received Biphasic insulin 30/70 underwent medical evaluation at intervals of approximately Month 0, Month 3 and Month 6. At each visit; blood analysis (FBG and HbA1c) and BMI were done for the patients. The recruitment period was approximately 6 months. Patients were grouped into 4 groups as follows: 48 patients in group 1A (Type 1 DM, received Insulin H-Mix), 45 patients in group 1B (Type 1 DM, received Mixtard Insulin), 57 patients in group 2A (Type 2 DM, received Insulin H-Mix), and 57 patients in group 2B (Type 2 DM, received Mixtard Insulin).

STUDY POPULATION

Inclusion Criteria

•Patients (men and women aged ≥12) with diabetes mellitus type 1 or type 2, who were not controlled on other anti-diabetic treatment.
•Signed Informed consent by subjects, witness and/or legal representative (aged between 12-21years) at enrolment into the study.
•Able and willing to perform self-monitoring blood glucose tests
•HbA1c: over 7.0 %

Exclusion Criteria

•Patient were not fulfilling the inclusion criteria
•Patient who were participating in other study.
•Patient who were hospitalized.
•Pregnant or lactating females.
•Patients receiving corticosteroid.
•Metabolic disorder.

Statistical analysis

Statistical analysis was conducted using SPSS version 21. The sample will be described for demographic and background variables. Frequency tables (number & per cent) were done for safety/tolerability analysis and chi-square test for detecting significant change over study visits. Descriptive analysis and t-test or Chi-Squire were used to test significant change/reduction in comparison to baseline as regards FBG, HbA1c, average dosage of given insulin and body weight. Mann Whitney U test was used to compare median of number of hypoglycemic attacks and Blood Glucose level at time of attack.

As this is a comparative study for patients received biphasic H-Mix insulin manufactured by SEDICO from raw material of Wockhardt & Biocon compared to the reference insulin, Mixtard insulin. We estimated the percent decrease of Hba1c in both groups as 5% and 5.5%, so, a sample size of 200 patients would give a power of 92.7% (Margin of Error = 5%) at 95% confidence level.

Demography

The mean age for each group of patients was; 35.5±15.6, 31.4 ±14.8, 53.4 ±7.9 and 52.4±9.3 years, for groups 1A, 1B, 2A, & 2B respectively with no statistical significant difference between patients in group 1A & 1B and group 2A & 2B. Regarding gender; females were more than males. Group 1A; 20 (42%) males & 28 (58%) females and Group 1B: 16 (36%) males & 29 (64%) females with no statistical significant difference between the 2 groups (*p*- value = 0.545). Group 2A: 15 (26%) males & 46 (74%) females and Group 2B: 12 (21%) males & 45 (79%) females with no statistical significant difference between the 2 groups (*p*- value = 0.509). Also, duration since diagnosis as diabetic shows no significant difference between 1A & 1B and 2A & 2B, as seen in table 1 below.

TABLE 1: Demography

		1A	% to 1A	1B	% to 1B	2A	% to 2A	2B	% to 2B
Age (yrs.)	Count	48		45		57		57	
	Mean± SD	35.5±15.6		31.4±14.8		53.4±7.9		52.4±7.9	
	Min	14.3		14.5		34.6		29	
	Max	62		66.9		69.3		75.8	
	p-value		0.203	NS			0.577	NS	
Gender	Male	20	42%	16	36%	15	26%	12	21%
	Female	28	58%	29	64%	42	74%	45	79%
	p-value		0.545	NS			0.509	NS	
Duration Since DM Diagnosis (Years)	Count	48		45		57		57	
	Mean± SD	12.7±7.7		13.5±8.1		14.8±7.1		14.5±5.9	
	Min	1		1		4		4	
	Max	31		31		36		34	
	p-value		0.607	NS			0.763	NS	
	< 2 Yrs.	3	6%	4	9%	0	0%	0	0%
	2 to 10 Yrs.	19	40%	13	29%	13	23%	14	25%
	10 to 20 Yrs.	18	38%	20	44%	34	60%	34	60%
	> 20 Yrs.	8	17%	8	18%	9	16%	9	16%

RESULTS

The study enrolled 212 patients, out of them 207 were evaluable for efficacy as they completed their visit V3 (6 months from base line visit). Five subjects stopped the study drug (2 patients were withdrawn due to SAE (both group 1A), one patient was lost to follow up (group 2A), one patient due to unsatisfactory therapeutic effect (group 2B) and one patient withdrew consent (group 2A). There was no statistical significant difference between fasting blood glucose and HbA1c at base line in groups 1A & 1B and 2A & 2B, see table 2 and 4.

TABLE 2: FBG at Baseline

FBG at baseline (mg/dl)	1A	1B	2A	2B
Count	48	45	57	57
Mean± SD	302±125.3	252±120.5	227±81.9	230±91.8
Range	73-689	64-570	49-444	78-437
P-Value	0.051	NS	0.864	NS

As for the FBG; the four groups showed a percentage decrease between visit 3 & visit 1. There was a decrease of 44.21mg/dl with 14.7% decrease and 17.16 mg/dl with 6.8% decrease between V1 & V3 in group 1A and 1B respectively, with no statistically significant difference in FBG between group 1A and 1B after treatment (*p*-value = 0.344). There was decrease of 5.54 mg/dl with 2.4% decrease and 9.58 mg/dl with 4.2% decrease between V1 & V3 in group 2A and 2B respectively, with no statistically significant difference in FBG between Group 2A and 2B after treatment (*p*-value = 0.805) as shown in table 3.

TABLE 3: FBG (mg/dl)

FBG (mg/dl)	1A		1B		2A		2B	
	V1	V3	V1	V3	V1	V3	V1	V3
Count	47	47	44	44	52	52	53	53
Mean	301	257	253	236	227	221	229	219
SD	126	105	122	90	82	75	94	77
Min	73	89	64	60	49	80	78	84
Max	689	575	570	482	444	439	437	434
Mean Differ	-44.21		-17.16		-5.54		-9.58	
Percent Chan	-14.7%		-6.8%		-2.4%		-4.2%	
P-value	0.344 NS				0.805 NS			

TABLE 4: HbA1c At Baseline

HbA1c at baseline (%)	1A	1B	2A	2B
Count	48	45	57	57
Mean± SD	10.5±1.7	9.9±1.5	9.6±1.6	9.9±1.7
Range	7.1-13.9	7.8-13.6	7.1-13.8	7.0-13.9
P-Value	0.059 NS		0.303 NS	

HbA1c showed a decrease of 5.9% between visit 3 & 1 in group 1A and increase of 1.1% in group 1B. There was a statistically significant difference in HbA1c between group 1A and 1B after treatment (*p*-value = 0.021). HbA1c showed increase of 0.2% and decrease of 5.2% in group 2A & 2B respectively. However there was no statistically significant difference in HbA1c between group 2A and 2B after treatment. (*p-value* = 0.064), as shown in table 5.

TABLE 5: HbA1c (%)

HbA1c (%)	1A		1B		2A		2B	
	V1	V3	V1	V3	V1	V3	V1	V3
Count	48	48	45	45	57	57	57	57
Mean	10.5	9.9	9.9	10.0	9.6	9.6	9.9	9.4
SD	1.7	1.6	1.5	1.8	1.6	1.8	1.7	1.7
Min	7.1	7.2	7.8	6.1	7.1	6.7	7.0	6.7
Max	13.9	13.0	13.6	13.9	13.8	13.4	13.9	13.7
Mean Dince	-0.62		0.10		0.02		-0.52	
Percent Cha	-5.9%		1.1%		0.2%		-5.2%	
P-value	0.021 *				0.064 NS			

HbA1c Percent Change

There was an increase of 0.2% and decrease of 4.6% in total daily insulin dose/kg/day between V1 & V3 in group 1A & 1B respectively, however there was no statistically significant difference in total daily insulin dose/kg/day between V1 & V3 in group 1A and 1B (*p*-value = 0.146).

There was an increase of 15.9% and 7.8% in total daily dose/kg/day between V1 & V3 in group 2A & 2B respectively, however there was no statistically significant difference in total daily insulin dose/kg/day between V1 & V3 in groups 2A and 2B (*p*-value = 0.085), as shown in table 6.

TABLE 6: Total Daily Dose of insulin (dose/kg/day)

Total Daily Dose of Insulin	1A		1B		2A		2B	
(dose/kg/day)	V1	V3	V1	V3	V1	V3	V1	V3
Count	48	48	44	44	57	57	57	57
Mean	1.6	1.6	1.8	1.7	1.5	1.7	1.5	1.6
SD	0.6	0.6	0.6	0.6	0.4	0.5	0.3	0.4
Min	0.3	0.6	0.6	0.6	0.8	0.8	0.9	0.5
Max	3.3	3.2	3.8	4.0	2.5	3.1	2.2	2.7
Mean Difference	0.00		-0.8		0.23		0.12	
Percent Change	0.2%		-4.6%		15.9%		7.8%	
P-value	0.146 NS				0.085 NS			

Systolic blood pressure (SBP) showed an increase between V1 & V3 in groups 1A and 1B of 0.4% and 0.8% respectively, with no statistical significant difference between the 2 groups (*p*-value = 0.831). SBP showed decrease between V1 &V3 in groups 2A and 2B of 2.5% and 3.1% respectively, however there was no statistically significant difference in SBP between the 2 groups (*p*-value = 0.839). Diastolic blood pressure (DBP) showed decrease in DBP between V1 & V3 in group 1A of 0.8% and increase in group 1B of 2.3%, however there was no statistically significant difference in DBP between the 2 groups (*p*-value = 0.103). DBP showed decrease between V1 & V3 in group 2A of 1.7% and no change in group 2B, with no statistically significant difference in DBP between the 2 groups (*p*-value = 0.489). Regarding BMI there was an increase between V1 &V3 in groups 1A and 1B of 1.5% and 1.2%, respectively, however there was no statistically significant difference between the 2 groups (*p*-value = 0.720). Also, BMI showed an increase between V1 & V3 in groups 2A and 2B of 6.3%, with no statistically significant difference between the 2 groups (*p*-value = 0.883). All patients had Normal Physical Examination in V1, V2 and V3 in the four groups with no statistical significant difference between group 1A & 1B and group 2A & 2B, as shown in table 7.

TABLE 7: BMI

BMI	1A		1B		2A		2B	
	V1	V3	V1	V3	V1	V3	V1	V3
Count	48	48	44	44	57	57	57	57
Mean	28.6	29.0	28.6	29.0	32.0	33.9	32.2	34.2
SD	7.0	6.8	7.7	7.8	4.9	5.4	5.4	5.9
Min	18.7	18.8	16.7	17.0	20.8	21.9	23.3	24.3
Max	52.5	50.8	48.9	50.6	50.1	50.1	47.8	54.8
Me	0.43		0.35		1.95		2.02	
Per	1.5%		1.2%		6.1%		6.3%	
P-value	0.720 NS				0.883 NS			

Ten percent of patients in group 1A had hypoglycemic attacks between V1 and V3, while 2% of the patients in group 1B had hypoglycemic attacks, with no statistically significant difference between group 1A and 1B (*p*-value = 0.108). 19% of patients in group 2A and 2B had hypoglycemic attacks with no statistical significant difference. It was due to increased exercise, increase in insulin intake and decreased food intake, as shown in table 8.

TABLE 8: Hypoglycemia Attacks

		1A	%	1B	%	2A	%	2B	%
Hypoglycemia	Yes	5	10%	1	2%	11	19%	11	19%
	None	43	90%	44	98%	46	81%	46	81%
If yes, number of attacks	Count	5		1		11		11	
	Median	2		2		3		3	
	Min	1		2		1		1	
	Max	7		2		8		7	
Blood Glucose at time of attack	Count	5		1		10		11	
	Median	47		42		68		58	
	Min	41		42		38		41	
	Max	62		42		80		71	
Reasons of Hypoglycemia	Increased exercise	2	40%	0	0%	5	45%	1	9%
	Decreased food intake	4	80%	1	100%	9	82%	6	55%
	Increased Insulin Intake	0	0%	0	0%	1	9%	5	45%

No local reaction to insulin Injection in group 1A between V1 and V3, while 2% of patients in group 1B had local reactions with no statistically significant difference between group 1A and 1B (*p*-value = 0.752, Mann Whitney U test), 14% of the patients in group 2A & 9% in group 2B had local reaction with no statistically significant difference between group 2A and 2B (*p*-value = 0.346, Mann Whitney U test), as shown in table 9.

TABLE 9: Local Reactions

		1A	%	1B	%	2A	%	2B	%
Local reaction	Yes	0	0%	1	2%	8	14%	5	9%
	None	48	100%	44	98%	49	86%	52	91%
p-value	0.299						0.377		
	NS						NS		
If yes, please describe	Swelling	0	0%	0	0%	2	4%	2	4%
	Bluish discoloration	0	0%	0	0%	3	5%	0	0%
	Redness and Itching	0	0%	1	2%	0	0%	1	2%
	Redness	0	0%	0	0%	2	4%	0	0%
	Itching	0	0%	0	0%	1	2%	1	2%
	Burning sensation	0	0%	0	0%	0	0%	1	2%

AE were found in all 4 groups; 6%, 6.7%, 13.6%, 20.7% of 1A, 1B, 2A, and 2B patients respectively, however there was no statistically significant difference between group 1A and 1B (*p*-value = 0.552, Mann Whitney U test) and no statistically significant difference between group 2A and 2B (*p*-value = 0.358, Mann Whitney U test), as shown in table 10.

TABLE 10: Adverse Events

Adverse Events		1A	%	1B	%	2A	%	2B	%
Serious/Non Serious	Not Serious	1	2.0%	3	6.7%	8	13.6%	12	20.7%
	Serious	2	4.0%	0	0.0%	0	0.0%	0	0.0%
Severity	Mild	1	2.0%	1	2.2%	4	6.8%	4	6.9%
	Moderate	2	4.0%	2	4.4%	1	1.7%	8	13.8%
	Severe	0	0.0%	0	0.0%	3	5.1%	0	0.0%
Relationship to study drug	Not suspected	3	6.0%	3	6.7%	8	13.6%	11	19.0%
	Suspected	0	0.0%	0	0.0%	0	0.0%	1	1.7%
Ongoing	Yes	1	2.0%	1	2.2%	6	10.2%	7	12.1%
	No	2	4.0%	2	4.4%	2	3.4%	5	8.6%
Action Taken	Concomitant medication taken	0	0.0%	2	4.4%	5	8.5%	7	12.1%
	Study drug permanently discontinued due to AE	1	2.0%	0	0.0%	1	1.7%	1	1.7%
	No action taken	1	2.0%	0	0.0%	1	1.7%	1	1.7%
	Concomitant medication taken, and non-drug therapy given	0	0.0%	1	2.2%	5	8.5%	7	12.1%
	Non-drug therapy given	0	0.0%	0	0.0%	1	1.7%	3	5.2%
	Hospitalization/prolonged hospitalization	1	2.0%	0	0.0%	0	0.0%	0	0.0%

Two serious adverse events occurred during the study. The first one was a patient in group 1A; who had Ketosis (dehydration, vomiting and Polyuria). SAE was not related to the study drug intake but due to decrease food intake (Ramadan fasting; starvation) and the PI decided to discontinue his participation in the study. The second SAE was a group 1A patient who suffered from moderate ketosis (polyuria & polydipsia), SAE was not related to the study drug intake, and she was admitted to the hospital and released in the same day. However, she was withdrawn from the study as per the investigator opinion.

DISCUSSION

Similar glycemic control is shown when insulin mixtures are administered twice daily such as multiple daily injections intense course, in type 2 diabetic patients [7]. On the other hand, self-mixed split of insulin are characterized by its error risk, although it is effective in achieving glycemic control. This is due to the inaccuracy that the patients can encounter through mixing the insulin themselves, since the dose must be correct during the mixing technique in order to reach the full potential of the short-acting insulin effect. Therefore, giving an advantage to pre-mixed insulin, mixed suspension human insulin 70/30 (70% NPH insulin and 30% regular insulin), since it is a more convenient single vial reducing dosing errors and improving accuracy[8,9]. Moreover, in a randomized 12-week, open-label trial in 294 patients with type 1 or type 2 diabetes, the premixed 70/30 aspart mixture was compared with premixed 70/30 human insulin administered twice daily[10]. The results showed that there was no difference between the groups regarding hypoglycemia incidence, there was no significance with either insulin mixture regarding weight gain, and although after treatment with the aspart mixture the mean blood glucose level was significantly lower (about 1.0 mmol/L, $P < 0.05$) after breakfast, before lunch, after dinner, and at bedtime, compared with blood glucose levels after treatment with the human insulin mixture at each time point, there was no significant difference between the groups in HbA1c concentration[10]. The development of premixed insulin has been made to lessen the injections in order to reach basal and prandial insulin requirements. However, this requires mealtime adherence and limits dose adjusting. The disadvantage is that mixtures don't allow separate alterations for high blood sugar. Since NPH is the only long-acting insulin that is used, so when the doses in a mixture are increased or decreased, the amount of both

the short acting insulin and long-acting insulin changes, which increases the risk of both high and low blood sugars. Pre-mixing can't be done with glargine (Lantus®) and detemir (Levemir®), since they can't be mixed with insulin in the same syringe [11]. Both basal and prandial insulin exogenous delivery is needed for physiological insulin replacement, [12] which is usually done by basal-bolus regime (3 bolus and 1-2 basal injections)[13]. This regimen is not convenient for frequent injections patients; however, it has a 'physiological' advantage[13]. Basal-bolus regimes are more necessary in type 1 patients than in type 2, since type 2 patients may be able to prevent ketosis and severe hyperglycemia due to the secretion of some amount of residual insulin[14]. The 'Initiate Plus Trial' has proved that over 40% of subjects achieved target HbA1c through the help of primary care settings, minimal dietary therapy, and self-titration of aspart premixed[15]. The 1-2-3 study illustrated the efficacy and safety, where target was achieved in 41%, 70% and 77% subjects, respectively, when using premixed aspart insulin in once daily, twice daily and thrice daily doses. So if the initiation regime of once or twice daily injections is to achieve target, premixed insulin can be used for therapy amplification[16]. The basal bolus regime for type 1 diabetes is considered the most physiological subcutaneous insulin replacement. However, while creating an insulin preparation several psycho sociocultural factors should be considered[17]. Some patients are prescribed with premixed insulin for many practical reasons, such as adolescents or children who are unable to take 4 or 5 injections per day, however the regime limitations are well explained to them. Since rapid acting insulin can be administered at lunch time in combination with the twice daily insulin to attain better control with only 3 injections, unlike the basal-bolus regime requiring 4 to 5 injections[17].

The 2-8 week treat-to-target INITAITE study published the dosed aspart 70/30 twice daily in a 1:1 ratio and compared results to dosing of insulin glargine alone at bedtime. It was shown that aspart 70/30 was more effective than daily glargine in achieving an HbA1c target of <6.5% (42% vs. 28%, respectively, achieved HbA1c ≤ 6.5%) and an HbA1c target of < 7% (66% vs. 40%, respectively, achieved HbA1c 7%). Episodes of minor hypoglycemia were more frequent in the aspart 70/30 group compared to the glargine group (3.4 episodes /year compared with 0.7 episodes /year, respectively)[18]. However, another study reported a lower proportion than the 66% reported in the clinical trial conducted by Raskin *et al*. where 31% of patients were able to achieve target HbA1c of ≤ 7% [19]. Our study compares two pre-mixed insulin preparations to ensure the efficacy, safety and non-inferiority of Sedico's H-Mix Insulin prepared by raw materials from Biocon & Wockhardt, compared to Insulin Mixtard. Our study's result shows that, there was no statistical difference between groups 1A and 1B, and between groups 2A and 2B after 6 months of using the insulin from the baseline regarding; FBG, HbA1c, daily insulin dose and hypoglycemic attacks. There was a decrease in FBG in both groups receiving Insulin H-Mix and Mixtard insulin. However, HbA1c decreased in groups 1A and 2B (type 1 Diabetics receiving Insulin H-Mix, and type 2 Diabetics receiving Mixtard) and increased in groups 1B and 2A (type 1 diabetics receiving Mixtard and type 2 diabetics receiving Insulin H-Mix). This shows that Insulin H-Mix efficacy is higher in lowering HbA1c in type 1 diabetes, than in type 2, but we cannot depend on that as this is a non-inferiority study. So we conclude that insulin Sedico is not inferior than that of the comparable insulin as regarding to the control of blood glucose. Regarding the total daily insulin dose, it was increased in groups 1A, 2A, and 2B, but decreased with group 1B (diabetics receiving Mixtard). The BMI increased in all the four groups by the end of the study, showing no significant statistical difference between the diabetic patients' type 1 & 2 and which insulin they were receiving. Concerning blood pressure; SBP showed an increase between V1 & V3 in groups 1A and 1B, DBP showed decreased between V1 & V3 in group 1A. Moreover, SBP showed a decrease between V1 & V3 and DBP showed decrease between V1 &V3. This illustrates that treatment with insulin is effective in lowering BP for type 2 diabetic patients.

As for the safety of the insulin, there were hypoglycemic attacks in all four groups, although the percentages were different, however this shows that the safety of the 2 types of used insulin were similar in action. Although the percentages of hypoglycemic attacks in patient groups treated with Insulin H-Mix cannot be undermined (10% and 19%), their frequency can be traced to poor patient compliance. The fact that a very high statistical difference exists between hypoglycemic incidences in type 2 diabetic patients treated with Insulin H-Mix (19%) can be accounted for by poor sedentary lifestyle and lack of modification in eating habits, but lastly there was no statistical significant difference between all groups as regarding to hypoglycemic attacks. There were local reactions towards the insulin injection in groups 1B, 2A, and 2B; however, no local reactions occurred in group 1A (diabetics type 1 receiving Insulin H-Mix). Adverse events were found in all four groups, however only one was suspected to the study drug. The two serious adverse events occurred in patients from group 1A, however, they weren't suspected to the study drug. The points discussed above show the efficacy and safety of Insulin H-Mix of SEDICO.

CONCLUSION

Insulin H-Mix of SEDICO manufactured from raw material of Wockhardt & Biocon is effective in lowering fasting blood glucose and HbA1c and safe as well as the reference insulin (Mixtard insulin) in the treatment of diabetes mellitus type 1 and type 2.

RECOMMENDATION

Nevertheless the results reveal equivalence of both measured products & the capability of an Egyptian Pharmaceutical company to manufacture a bio-similar, comparable in efficacy and safety to the international standards. Still diabetes management is a multi-factorial process requires other components rather than insulin, to situate patients upon appropriate guidelines averages (*e.g.* life style modifications, nutrition adjustment, weight control, exercise supervision & above all continuous Physician and Patient Education). This drags attention towards the necessity of initiating and conducting well-

structured programs for Unifying International Guidelines for Physicians Practice, and Raising Awareness for patients & their families; to be applied upon nationwide, especially to cover rural areas.

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