INTERNATIONAL JOURNAL OF UNANI AND INTEGRATIVE MEDICINE

E-ISSN: 2616-4558
P-ISSN: 2616-454X
IJUIM 2019; 3(4): 98-102
Received: 11-08-2019
Accepted: 15-09-2019

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Efficacy of a unani formulation and BGR-34 in ziabetus shakri (Type-2 DM): A comparative clinical trial

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Abstract
Background and objectives: The number of people with diabetes is growing rapidly worldwide. Long term hyperglycaemia leads to macro and microvascular complications, resistance to the conventional treatment and increase in complications communicates to have alternative treatment for controlling hyperglycaemia and reducing complications of Diabetes mellitus. Hence a clinical trial conducted to evaluate the efficacy of Unani Formulation in comparison with BGR 34 in Type 2 Diabetes Mellitus.
Methods: This study was conducted as single blind, randomized, controlled clinical trial on 45 patients of diabetes test (n=25) and control (n=20) for 56 days. Test group received Unani formulation and control group BGR-34® twice a day before meal.
Efficacy of both groups was assessed as subjective parameters weekly and objective parameters FBS, PPBS fortnightly and HbA1c before and after treatment.
Results: Subjective parameters polyuria, polyphagia, nocturia, polydypsia, tiredness, weight loss and blurring of vision were found to be highly significant in both the groups, by using Dunn Friedman Test with post test with $P<0.0001$. Inter group comparison was done using Kruskall-Wallis test and $P<0.0001$ was observed in polyuria at 56th day from baseline whereas, objective parameters using repeated ANOVA for intra group analysis and Mann Whitney U test inter group analysis for FBS was found suggestive significant in control group (p=0.0496) in comparison with test group (p=0.082), and PPBS, HbA1c were found insignificant clinically with p >0.05 in both the group.
Interpretation & Conclusion: This comparative analyses of test versus control drugs was not found significant objectively, but clinically significant in subjective parameters. But throughout the study there will be no significant adverse effect observed.

Keywords: Type 2 diabetes; unani formulation; BGR-34®

Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria; is mainly due to lack of insulin secretion from beta cells of pancreas and desensitization of insulin receptors for insulin characterized by polyuria, nocturia, polyphagia, polydipsia, increased appetite, blurring of vision, gradual loss of Weight [1, 2]
According to IDF Atlas 8th edition 2017 worldwide prevalence of Diabetes is 525 millions and it is expected to be 629 million by the year 2045 [3], and one in every two adults with diabetes are undiagnosed. In India 4.2 million peoples are undiagnosed diabetes between the age group of 20-79 years. Presently 327 million peoples are in the age group of 20-64 years and 123 million over 65 years of age undiagnosed.
The prevalence of type 2 DM is becoming more common among the adults age between 45 and 64 years [4] and the incidence varies from one geographical region to the other as a result of environmental changes and lifestyle risk factors [5]. The symptoms of type 2 diabetes are increased thirst, frequent urination, tiredness, slow- healing wounds, loss of weight, recurrent infections, blurring of vision and tingling or numbness in hands and feet [3].
Untreatable diabetes leads to micro vascular (diabetic retinopathy, nephropathy and neuropath) and macro vascular (ischemic heart disease, peripheral vascular diseases and cerebrovascular disease) complications with risk of diabetic foot ulcer and amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction and dryness of vagina in females Primary aim of using drugs is to save life and prevent long term complications [6, 7, 8].
The only main stay for patients with type 1 DM is insulin replacement therapy while diet and lifestyle modifications are more responsible for managing type 2 DM [9].

Numerous oral hypoglycemic drugs are available such as biguanides and sulfonylureas but the main disadvantage of currently available medicines is they have to take throughout the life. Owing to dreadful complications of Diabetes mellitus and to find out relatively safe and effective drug for its management, search for safe and effective therapeutic agent becomes a thrust area for research, in the field of medical science.

As far as the Unani system of medicine is concerned, Diabetes mellitus is treated since Greco- Arab period.

In Unani literature enough evidence available with reference to the effective use of various drugs in the management of diabetes mellitus.

Out of such enlisted drugs a formulation is selected from the Akseer Azam which Consisting of Kishneez Kushk (*Coriandum sativum*), Gule Surkh (Rosa *damascena*), Tabasheer (*Bambusa arundinacea*), Tukhme kahu (*Lactuca sativa*), Tukhme karafs (*Apium graveolens*), Gile Armani (*Armenian bole*), Gulnar (*Punica granatum*), Samagh e arabi (*Acacia arabica*), Kafoor (*Cinnamomum camphora*) [9] is being evaluated for its efficacy in DM type 2.Therefore, a study contemplated to comparatively evaluate the efficacy of test drug scientifically with the marketed drug, as a comparative clinical trail and carried at the Department of Moalajat, National Institute of Unani Medicine (NIUM), Bengaluru between March 2017 to February 2018 after the approval of the Institutional Ethical Committee for Biomedical Research of NIUM vide No (NIUM/2015-16/007/Moal/07) dated 25/08/2016.The eligible patients enrolled into the study based on the inclusion criterion, after taking written consent. In this study 45 patients selected with the help of computer randomization table and randomly allocated into test (n=25) and control (n=20) groups, test group was treated with Unani Formulation (Qurs) twice a day, whereas control group was given BGR-34®, 2 tablets twice a day before meal, both the groups were treated for 8 weeks. The efficacy of both groups was evaluated weekly on the basis of subjective parameters like Kasrate Boul (Polyuria), Kasratat Boul Asnal-lail (Nocturia), Kasrate Atash (Polydipsia), Naham (Polyphagia), Faqdaanul wazan (Weight loss), Fatigue (Taab, Takan), Blurring of Vision and objective parameters such as FBS, PPBS were assessed every fortnightly and HbA_1c in Baseline and 56th day.

Criterion for the Selection subjects

Inclusion criteria

- Both gender
- Patients between 35-60 years of age
- Known cases of DM with < 3yrs of disease history, with or without drug (single or multi) therapy
- Fasting blood sugar (FBS) >126mg/dl - <126mg/dl.
- Post Prandial blood sugar (PPBS) - >140mg/dl – 250mg/dl.
- bA1c - >6.5 - <10%

Exclusion Criteria

- Known cases of Type 2 Diabetes Mellitus with complications.
- Patients with a history of more than 3yrs of the disease.
- Fasting Blood Sugar <126mg/dl and >200mg/dl
- Post prandial blood sugar <140mg/dl and >250mg/dl
- HbA1c<6.5 - >10%
- Pregnant & lactating mothers.
- History of any systemic illnesses, and hypertension
- History of any other disorders of metabolism.

Investigations: Certain investigations were carried out with the aim to exclude the patients with pathological conditions mentioned under exclusion criteria and to assess the efficacy of treatment group and to establish the safety of the test drug.

Following investigations were done in each and every case before and after the treatment to comparatively evaluate the efficacies of a Unani Formulation and BGR-34® in Diabetes Mellitus (Type-2 Diabetes Mellitus).

- Hemogram with ESR
- FBS and PPBS
- HbA1c
- LFT (ALT, AST and ALK Phosphatase)
- KFT (Blood Urea and Serum Creatinine)
- Urine routine, microscopy (Albumin and sugar)

Method of collection of data

Through clinical study of patients visiting Moalajat OPD, NIUM Bangalore.

Method of preparation, dosage and mode of administration of test drug

Test formulation is procured from market in the form of raw materials and makes fine powder for Qurs preparation in NIUM pharmacy, as per NFU medicine with GMP. Each patient in test group was given test drug at the dose of 4 tablets (500 mg each) twice a day in before meal for the 8 weeks.

Administration of standard control drug

The control drug BGR-34® was supplied by AIMIL Pharmaceuticals given at a dose of 2 tablets (500 mg each) was given orally twice a day before meal for 8 weeks.

Statistical analysis: Analytical tests were carried out using Instat Graph Pad. Repeated measure ANOVA is used for intra group comparison. Between group, Mann Whitney U test for baseline and Unpaired T test for post treatment analysis.

Results

A total of 180 patients were screened, out of which 45 eligible patients were enrolled.

The demographic data of the two groups are shown in Table-1.

Table 1: Demographic Data

Age in years	Test group	Control group	Total
30-40	4 (16%)	5 (25%)	9 (20%)
41-50	13 (52%)	9 (45%)	22 (48.88%)
51-60	8 (32%)	6 (30%)	15 (33.33%)
Total	25 (100%)	20 (100%)	45 (100%)

Duration of illness			
1-3months	4(16%)	7(35%)	11 (24.44%)
4-6months	2(8%)	3(15%)	5(11.11%)
7-12months	6(24%)	4(20%)	10(22.22%)
1-2yrs	2(8%)	2(10%)	4(8.88%)
Newly Diagnosed	11(44%)	4(20%)	15(33.33%)
Total	25(100%)	20 (100%)	45(100%)

Family history

Present	13(52%)	7(35%)	20(44.44%)
Absent	12(48%)	13(65%)	25(55.55%)
Total	25(100%)	20(100%)	45(100%)

Dietary habits

Mixed	23(92%)	18(90%)	41(91.11%)
Vegetarian	2(8%)	2(10%)	4(8.88%)
Total	25(100%)	20(100%)	45(100%)

Table 2: Effect of study on FBS and PPBS among the groups

FBS	0th day	14th day	28th day	42th day	56 th day	P
						value
Test	141.24±33.83	167.88±51.20	157.24±51.19	152.2±43.36	14 7.88±36.70	0.082
Group						
Control	138.4±25.56	178.45±48.83	177.3±58.42	176.3±59.77	17 2.15±60.45	0.0496
Group						
P value	0.98				0.10	

PPBS	0th day	14th day	28th day	42th day	56th day	P value
Test	227.04±41.36	237.8±69.55	228.6±63.41	211±49.0 9	219±50.15	0.344
group						
Control	229.5±46.98	262.95±72.44	258.95±72.89	257.52±64.53	252.05±79.56	0.249
group						
P value	0.92				0.15	

Table 3: Effects of study on HbA1camong the groups

FBS	Before Treatment	After treatment	Pvalue
Test group	7.68±1.04	7.85±1.11	0.32
Control group	7.28±0.77	8±1.26	
Total	0.18		

Results and Discussion

As depicted in Table 1 that maximum number of patients 23 (51.1%) were recruited in age group of 41-50 yrs, and only 9 (20%) were <40yrs.According to IDF Diabetes Atlas 6th edition,382million people with diabetes are aged between 40 and 59 yrs. This study coincides with the IDF finding as more number of patients are aged between 41-50yrs followed by 51-60yrs [3]. Highest incidence 23 (51.1%) was observed in male patients while 22 (48.9%) are female patients. This study observation claim made by Kaytzky-Willer A [10] and Valadares ALR [11] that the prevalence of diabetes is more among females than males. The duration of illness was between 1-10months in 33 (73.3%) patients, 11-20months in 9 (20%), 21-30 months in 3 (6.7%). This observation indicates that patients with early history of patients. Dietary habit was mixed in 41 (91.11%) patients and only 4 (8.88%) patients was pure vegetarian. Many clinical study-based data are available to suggest the relationship of diet with disease as observed by Jitendra *et al* [12] and Rowena *et al* [13]. Among 45 patients 26(57.8%) had positive family history of DM and 19 (42.2%) reported with no positive family history. This study has association between family history and diabetes accordance with the finding by Das M *et al* [14].

Effect on subjective parameters

Test and control groups were assessed for subjective parameters on the arbitrary rating scale of nil, mild, moderate and severe. It was found that test group showed 100% reduction in polyuria compared to 85% prediction in control group in both the groups, the reduction in polyuria was significant statistically (P<0.0001). Reduction of polyuria in test group may be attributed due to ingredients due to ingredients like Kishneez Khusk, Tabasheer, Gile Armani, Samage Arabi, Gulnar present in test formulation performance *Qabiz* (astringent) and Muqavvi-e-Gurdah properties which enhance the Quwat-e-Maseka and decrease Quwate Dafeah of Kidney [15, 18]. In nocturia 100% improvement in test group compared to 95% in control group This improvement may be attributed due to ingredients like Kishneez Khusk, Tabasheer, Gile Armani, Samage Arabi, Gulnar present in test formulation performance *Qabiz* (astringent) and Muqavvi-e-Gurdah properties which enhance the Quwat-e-Maseka and decrease Quwate Dafeah of Kidney[15-18]. In polydipsia, 88% improvement in test group from base line to 56th day compared to 65% in control which is statistically significant (P<0.001**) using Chi-Square/paired proportion Test. The effect may be due to *Mubarrid, Musakkin Atash, Qabiz* [15-18]. In polyphagia, 100% improvement in test group from base line to 56th day compared to 80% in control group which is statistically significant (P<0.001**) The effect may be due to Mubarrid, Musakkin (Kahu, Kishneez, Gule surkh) and Mujaffif (Tabasheer, and gile Armani), Qabiz described by Ibn Baitar, Hakim Nazmul Ghani, Allama Kabiruddin [15, 19, 21]. It was found that test group showed 76% reduction in weight compared to control group of 25% reduction which is statistically significant (P<0.001**) reduction of weight loss in test group may be due to Har Yabis mizaj of some ingredient of test formulation [17, 22, 23]. Tiredness showed 100% reduction in test group compared to control group of 85% of reduction which is statistically significant (P<0.001**) some ingredients of test formulation, like Kishneez Khusk, Gule Surkh, Tabasheer, Tukhme Kahu, Samage Arabi are possess antioxidant, immunomodulator, analgesic and anti-inflamtory activity which prevent the formation of lactic acids in muscles due to presence of alkaloids, flavonoids, glycosides accordance with the finding of Mohammadi *et al* [24], Goyal AK [25], Damerum A [26], Kooti W [27]. In blurring of vision, it was found that test group showed 16% of reduction compared to control group of 5% reduction.

Effect on objective parameters

The Mean±SEM score for FBS in test group on 0th day and 56th day was 141.24±33.83 and 147.88±36.70 Respectively, with a difference of 4.32+6.66 with p value <0.082 using repeated measure of ANOVA for intragroup analysis. The

Mean+SEM score in control group were 138.4±25.56 and 172.15±60.459 respectively with p value <0.0496 by using repeated measure ANOVA for intragroup analysis which statistically significant but clinically insignificant. Intergroup comparison using Mann Whitney U test P value at base line is 0.86 and at 4th follow up is 0.99 which statistically insignificant. A number of pre-clinical studies have claimed the hypoglycaemic effects of ingredients present in both test and control drug *and* the same has been observed are mentioned above. But such effects were not observed in our study and the influencing factors might be many.

The Mean±SEM score for PPBS in test group was PPBS 227.04+41.36 and 219+50.15 with difference as 8+1.06 with p value < 0.344 using repeated measure of ANOVA for intragroup analysis. Where as in control group The Mean ± SEM score of PPBS at baseline to 4th follow up was found to be 229.5±46.98 and 252.05±79.56 respectively with P value <0.249 by using repeated measure ANOVA for intra group analysis which is statistically insignificant Inter group comparision using Mann Whitney U test p value at baseline is 0.92 and at 4th follow up is 0.15 which is statistically insignificant. Test formulation ingredients have reported for antidiabetic activity viz; Coriandum sativum, Rosa damascena, Bambusa arundinacea, Lactuca sativa, Apium graveolens, Ammonium bole and Punica granatum, Acacia nilotica [24, 25, 28, 30].

The Mean ± SEM score for HbA1c in test group was on 0th day and 56th day as 7.68±1.04 and 7.85±1.11 respectively, with a difference 0.17±0.07 using Dunn Friedman test with *P*<0.56 suggestive significant. The Mean ± SEM score for control group is 7.28±0.77 and 8. ±1.26 on 0th day and 56th day respectively, with a difference of 0.72±0.49 with moderately significant *P*<0.039. When Mean ± SEM score of HbA1c in both groups, Test and Control, were compared statistically by using Kruskal-Wallis Test was found suggestive insignificant p value <0.18.

The effect of the study on safety parameters was assessed with reference to the findings of pre and post study clinically, haematologically and biochemically. The clinical findings like unusual effects or reaction were not observed. Similarly haematological and biochemical parameter were found within the normal range, and all safety parameters were found statistically insignificant.

Therefore, these study methods were found free from any adverse effects, hence, concluded safe and they may be used in the management of type 2 DM.

Conclusion

The present study evidences that the test formulation is effective in subjective parameters in terms of reducing polyuria, nocturia, polyphagia, polydipsia, tiredness, blurring of vision, weight loss, whereas effect in objective parameters such as FBS found suggestive significant in control group, whereas PPBS and HbA1c found insignificant in both groups without demonstrating adverse effect. Thus it can be concluded that the BGR 34 is effective in Ziabetes shakri in comparision of test drug i.e., unani formulation consist of Kishneez khushk, Gule surkh, Tabasheer, Gulnar, Tukhme kahu, Tukhme karafs, Samagh-e-arabi, Gile Armani and Kafoor. The limitation of this study was the small sample size and shorter duration of trail. As diverse mechanisms are involved in development and management of Ziabetes shakri, Hence elaborate studies are recommended to ascertain pharmacological actions of research drug. Therfore, studies should be designed for longer duration and on larger sample size with modified methodology.

Acknowledgement
Thanks

Funding: Institutionally funding study
Conflict of Interest: Nil

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