RESEARCH ARTICLE

A comparative study of niacinamide and vildagliptin and their co-administration with metformin on fasting blood glucose levels in streptozotocin induced Diabetic rats

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Background: This study was focused to determine efficacy of primarily dietary supplement like niacinamide when used alone in high or optimum doses or in co-administration with newer gliptins like vildagliptin and to compare with empirical noble antidiabetic drug; metformin.

Methods: Healthy male wistar rats weighing 150-250 grams were divided into seven groups, six animals in each group. These groups were normal control, diabetic control (placebo treated), metformin treated, vildagliptin treated, niacinamide (optimum and high doses) treated and vildagliptin and optimum dose of niacinamide (co-administered) treated groups of diabetic rats. Diabetes was induced by freshly prepared streptozotocin (65 mg/kg), 15-20 minutes pretreated with niacinamide (230 mg/kg), both by single intraperitoneal injection. The fasting blood samples were determined by glucose oxidase method. Simple line and bar graph were used to depict trends of FBS of different groups on day 0,7,14,21,28,35 and 42. One way ANOVA post-hoc (Tukey's HSD) test was used to compare the effect of drugs on different group.

Results: FBS of Group A remained static throughout study. Increasing trend of FBS mean were noticed finally in group B and group F with 28.93% and 8.97% elevation respectively from initial reading. Maximum reduction in mean FBS values were noted in group C (52.58%) followed by group G (46.36%) and group D (42.94%) whereas small reduction of 10.85% was noted in group E. Group F showed initial reduction followed by progressive rise in FBS. Inter group comparison results of day 42 showed p-value ≥ 0.05 among metformin (group C), vildagliptin (group D) and co-administration of vildagliptin with optimum dose of niacinamide (group G). Rest of treatment groups were compared to each other to demonstrate p-value ≤ 0.001 or highly significant changes in mean FBS value on day 42.

Conclusion: Vildagliptin and its co-administration with optimum dose of niacinamide had more lowering of FBS as compared to vildagliptin alone. Optimum dose of niacinamide treatment caused lowering in blood sugar but high dose paradoxically raised FBS level of streptozotocin induced diabetic rats.

Key Words: *Metformin; Vildagliptin; Niacinamide; Streptozotocin; Co-administration; Tukey's HSD test*

INTRODUCTION

Diabetes is an established ailment prevalent since past many eras and it continues as global threat with increasing trend over last few decades [1]. According to "The International Diabetes Federation", the worldwide cases of Diabetes trend about 463 million adults (20-79 year) till year 2019 and 374 million people are at increased risk of developing type 2 diabetes so that estimated rise of worldwide diabetic cases about 578 million people by 2030 and 700 million by 2045. Approximately 79% of adults with diabetes belong to low and middle income countries. It has caused ~4.2 million deaths so far alone in year 2019. About 10% of global health expenditure ($ 760 million) is spent on diabetic management every year [2]. Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease where synthesis, utilization of the insulin of both are impaired leading to hyperglycemia. Clinicians are in search of complete cure of the disease so the quest for developing newer antidiabetic agents is pursued rigorously by continuous trial globally. To fight against diabetes currently we have many established drugs like insulin and oral hypoglycaemic agents e.g. sulfonylurea, biguanides and thiazolidinediones that play major role in the control and management of this disease. In this series, development of newer drugs and other add on therapy with lesser side effects need to be focussed to prevent Diabetes and their complications.

Metformin is very popular and widely used as first line empirical therapy and regarded as noble antidiabetic agent known to treat T2DM. But, it should be avoided in patients with renal and hepatic impairment. The use of metformin is contraindicated in patients with a serum creatinine 1.5 mg/dl or higher in male patients or 1.4 mg/dl or higher in female patients also should not be used in patient with hypotensive states, cardiovascular, respiratory diseases [3,4].

Vildagliptin, a dipeptidyl peptidase-1(DPP-4) inhibitor, decreases the inactivation of Glucagon like Peptide-1(GLP-1) thereby increasing its secretion, accompanied with a decrease in that of glucagon. Important vildagliptin induced beneficial effects in Type 2 Diabetes Mellitus (T2DM) include significant reduction in HB1Ac (0.8-1.0%) along with a reduction in fasting as well as postprandial plasma glucose [5,6]. It showed improved efficacy over time (may be due to GLP-1-induced increase in beta-cell number and mass) without weight gain and hypoglycemia which are common side effects of insulin and other oral hypoglycemic agents [7,8]. These observations, made during several clinical trials, suggest that vildagliptin and other DPP-4 inhibitors may play an important role in the management and preservation of T2DM, particularly being valuable in preventing the development and progression of the disease, which has not been possible till now with any other antidiabetic agent [9].

Oral therapy for type 2 diabetes, when used appropriately, should safely assist patients to achieve glycemic target with desired effectiveness and tolerability. Therefore, the progressive nature of type 2 diabetes usually requires a combination of two or more oral agents in long term. Like gliptins, niacinamide may be appressed in prevention and possible cure of diabetes. It is a form of vitamin B3 found in plant and animal sources, mostly used as dietary supplement. Oral niacinamide is primarily indicated as medication for preventing vitamin B3 deficiency and pellagra and many neuromuscular disorders. [10]. Additionally, niacinamide has likely preventive role in treating type II diabetes but its prime role as regular treatment is yet to establish. Few previous studies have been carried out in past to support its relevance. Yamada have shown disappearance of glycosuria and an improvement in glucose tolerance during niacinamide therapy in insulin-dependent diabetes mellitus (IDDM) induced mice [11]. Niacinamide alters beta function and blood sugar level in the dose and time dependent manner. It was found helpful in preserving beta cell function of pancreas [12]. Since

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niacinamide indication in diabetes is mostly limited to its few complications and associated comorbities if any. So, it should be planned to grow it as mainstream therapy along with newer antihyperglycemic agents to ensure better control of diabetes mellitus and associated neuropathy. Unique role of niacinamide in protecting β cells of pancreas also found useful in preparing diabetic rat experimental model along with streptozotocin which destroys β cells unconditionally [13,14].

A very few supported literature on this study. Herein, purpose of our study is to compare the antihyperglycemic effect among niacinamide and vildagliptin, their co-administration and metformin.

METHODOLOGY

Preparation of animals

Healthy male wistar rats weighing between 150-250 grams were taken for the present study. The animals were kept in clean and dry cages placed in animal house with 12 h: 12 h light-dark cycle at room temperature and humidity. The cages were floored with a layer of saw dust for absorption of urine of rats as there would be excess of urination of diabetic rats. They were allowed to acclimatize there for a period of one month and were fed with standard laboratory diet consisting of germinated black gram; commercial feeds and water were given ad libitum. Experiment was carried out with ethical norms approved by Institutional Animal Ethics Committee (IAEC) Guidelines. Only the healthy and active rats having fasting blood glucose of 140-200 mg/dl were included in this study and sick or inactive rats with undesired fasting blood sugar level were excluded from the study.

Grouping of animals

Total 60 male wistar rats found suitable for study. Out of which 6 rats were grouped as normal control (Group A). Rest 54 rats were prepared for induction of diabetes. 18 rats were disposed of, as two rats died and rest of them found unsuitable for the study or failed to justify the inclusion criteria. Finally, 36 rats were divided in six groups (B, C, D, E, F and G) other than group A with six animals in each group.

Preparation of 0.1 M citrate buffer

0.1 M citrate buffer is required for preparing physiochemically stable STZ solution. For this, 31.5 ml of citric acid was mixed with 18.5 ml of sodium citrate and deionized water was further added to adjust final volume to 100 ml. The pH of citrate buffer solution was found to be 4.21 measured by a sensitive pH meter, which was within required pH range of citrate buffer.

Our study required preparation of type 2 diabetic model with moderate hyperglycemia (140-200 mg/dl) to demonstrate reversal of blood glucose level after giving test doses of proposed and established antidiabetic drugs. We followed most widely accepted and popular Pellegrino Masiello model of pre treatment with nicotinamide (230 mg/kg) before administering streptozotocin (65 mg/kg) both intraperitoneally needed for successful induction of type 2 diabetes in wistar rats [13].

Preparation of streptozotocin (STZ)

Pure streptozotocin has alkaline pH approx. 7.4 itself. STZ was freshly prepared because it is unstable in both water and saline, though freely soluble. It was stabilized in 0.1 M citrate buffer to achieve required pH (ranges between 4.0 - 4.5). Stability of streptozotocin brings about increase in its half-life which is pre-requisite for successful induction of diabetes. It was administered in strength of dose 65 mg/kg body weight [13]. For this, 520 mg of STZ powder was dissolved in 40 ml of freshly prepared ice cold 0.1 M citrate buffer, so that 1 ml contained 13 mg of STZ required for 200 gram of rat. Required dose was further delivered to each rat intraperitoneally according to their weight using 1 ml disposable syringe with 26 gauge needle.

Preparation of niacinamide for induction

Niacinamide was administered in single dose of 230 mg/kg body weight before STZ injection to make desired type 2 diabetic model. For this, 4.6 gram of nicotinamide powder was measured using vacuum digital weighing machine and dissolved in 100 ml of deionized water, so that 1 ml contained 46 mg of nicotinamide, required for 200 gram weight of rat. Doses titrations were done according to weight of each rat using 1 ml disposable syringe with 26 gauge needle.

Induction of diabetes type 2 Diabetes was induced according to Masiello model by administering freshly prepared nicotinamide followed by streptozotocin by single intraperitoneal injection. For this, animals were deprived of food overnight and only were allowed access to water. By next day, firstly, each animal of group B, C, D, E, F and G were administered nicotinamide 230 mg/kg. After 15-20 minutes streptozotocin 65 mg/kg was given to each animal of these groups [13]. Animals were held with its ventrum exposed and head pointed downward. This caused upward movement of abdominal viscera towards the animal's diaphragm to avoid accidental puncture of organs. Then, 1 ml disposable syringe with 26 gauge needle was gently inserted into the abdominal cavity in the lower right quadrant. The needle was directed towards the animal's head at 15-20 degrees angle and inserted approximately 5 mm to avoid any possible injury to the caecum and urinary bladder. After induction, the rats were given to drink 5% dextrose normal saline overnight to overcome the drug induced hypoglycemia.

After 72 hours of streptozotocin injection, fasting blood glucose level was determined and induction of diabetes was confirmed. The diabetic rats were allowed access to tap water and normal laboratory diet freely, and were maintained at room temperature in their cages for next 7 days for stabilization of diabetes and acclimatization under these circumstances. The rats having fasting blood glucose levels 140-200 mg/dl were used for the study.

Drugs

The information related to drugs and chemicals are as follows:

Niacinamide, 100 gram powder

Streptozotocin (sterile powder) 1 gm vial

Metformin, 500 mg tablets

Vildagliptin 50 mg tablets

Preparation of niacinamide for treatment

Daily optimum dose of niacinamide was considered 1 g/kg to produce sugar lowering effects on diabetic rats [12]. It was 18 mg (1000 mg x 0.018) for 200 g of rat in two divided doses. 180 mg of niacinamide powder was measured and dissolved in 20 ml of 1% gum acacia to prepare uniform suspension. 1 ml containing 9 mg per dose was required for 200 g of rat. Now according to weight of each rat of this test group E, drug was titrated and administered twice daily using gavage tube. Only freshly prepared suspension were used each day.

Daily high dose of niacinamide was considered 1-4 g/kg to produce detrimental effects on diabetic rats [12]. On an average 63 mg (3500 mg x 0.018) for 200 g of rat in two divided doses was taken as high dose treatment. 630 mg of niacinamide powder was measured and dissolved in 20 ml of 1% gum acacia to prepare uniform suspension. 1 ml containing 31.5 mg per dose was required for 200 g of rat. Now according to weight of each rat of this test group F, drug was titrated and administered twice daily using gavage tube. Only freshly prepared suspension were used each day

Preparation of the other drugs

The tablet metformin was triturated and a uniform suspension was made using 1% gum acacia. This was prepared by 500 mg of tablet dissolving in 50 ml of gum acacia suspension. 18 ml (~ 180 mg of drug) of this suspension was diluted with addition 2 ml of deionized water to make 20 ml of suspension, so that 1 ml contained 9 mg (500 mg multiplied by 0.018) of desired amount of drug for 200 g of rat. Now according to weight of each rat of this test group C, drug was titrated and administered using gavage tube. Only freshly prepared suspensions were used each day.

The tablet vildagliptin was powdered and a uniform suspension was made using 1% gum acacia. Daily dose was 1.8 mg (100 mg x 0.018) for 200 g of rat in two divided doses. It was prepared by 50 mg of tablet dissolving in 50 ml of gum acacia suspension. 18 ml (approx. 18 mg of drug) of this suspension was diluted with addition 2 ml of deionized water to make 20 ml of suspension, so that 1 ml contained 0.9 mg (50 mg multiplied by 0.018) of desired dose of drug twice daily for 200 g of rat. Now, according to weight of each rat of this test group D, drug was titrated and administered twice daily using gavage tube. Only freshly prepared suspensions were used each day.

Co-administration of vildagliptin and niacinamide

0.9 mg/ml of vildagliptin and 9 mg/ml of niacinamide as prepared above

were co-administered twice daily to group E rats. Drugs were delivered according to weight of each rat using gavage tube.

Drug administration to animals: All the seven groups (A, B, C, D, E, F and G) animals were labeled separately and color coded with the help of permanent marker. They were kept in different labeled cages enlisted with their corresponding drug treatment category according to the Table 1 below:

After allowing 10 days for the induction and stabilization of diabetes, drugs were administered from 10th day and this was considered as day 0 for the treatment of group B, C, D, E and F. The doses of the drugs were calculated on the basis of body surface area. Before starting treatment, fasting blood glucose levels for day 0 were estimated for all groups including group A. All the treatments were carried out for a period of 42 days. The fasting blood samples were collected from all the groups on further days 0, 7, 14, 21, 28, 35 and 42. Blood glucose levels were determined by glucose oxidase method as described below.

Estimation of blood glucose

Fasting blood glucose was estimated on day 0, 7, 14, 21, 28, 35 and 42 by glucose oxidase method using Acu-check active glucometer. For this, the rats were kept deprived of food overnight but allowed free access to water. Blood samples were collected from the tail end of rats. The tail was cleaned by sterile cotton with spirit and was cut 0.5 mm just enough to ooze out one drop of blood. This was allowed on the proper reaction zone of the strip. Then fasting blood sugar level was recorded and noted down in the master chart. After taking the blood sample tail end of each rat was applied with povidone iodine ointment using fresh cotton piece to prevent any sepsis.

RESULTS

The mean value of Fasting blood sugar of different groups group (A, B, C, D, E, F and G) were calculated every weekend (on day 0,7, 14,21,28,35 and 42) which were compiled in Table 2 as below:

mg/dl on 42 days. Fasting blood glucose in metformin treated (group C) and vildagliptin treated (group D) in first week were 171.17 ± 18.433 mg/dl and 167.67 ± 18.425 mg/dl and it had a decreasing tendency to reach normal blood sugar level with FBS value 81.17 ± 2.994 mg/dl and 95.67 ± 2.251 mg/dl respectively. However more decline was seen with group C as compared to group D. Optimum dose of niacinamide treated group E showed little decline in FBS mean value to 149.17 ± 11.197 mg/dl on day 42 from FBS reading 167.5 ± 17.614 mg/dl on Day 0. However high dose niacinamide treated group F showed little increase in FBS mean value to 178.17 ± .279 mg/dl on day 42 from FBS reading 163.5 ± 18.141 mg/dl on Day 0. Vildagliptin and niacinamide co-administered group G comparatively demonstrated better control of blood sugar in 6 weeks treatment (with FBS mean value to 89.67± 3.615 mg/dl on Day 42) than vildagliptin alone of group D. Trends of blood sugar level on weekly reading from day 0 to Day 42 were depicted through in Figure 1.

FBS of Group A remained static throughout study with negligible changes in mean FBS reading. Increasing trend of FBS mean were noticed in group B and group F with 28.93% and 8.97% elevation respectively from initial reading. Maximum reduction in mean FBS was noted in group C (52.58%) followed by group G (46.36%) and group D (42.94%) whereas decline of 10.85% was noted in group E (Figure 2).

One-way ANOVA post-hoc analysis (Tukey's HSD Test) found intergroup p-values insignificant for group G with respect to group C ($p=0.594$) and to group D ($p=0.878$). P-value was closely insignificant for group C vs group D ($p=0.071$) on last reading taken on day 42. Otherwise all diabetic rat groups under treatment showed highly significant p-value ($p \leq 0.001$) when compared to each other. Optimum dose niacinamide treated group E also showed decreasing trends in FBS with $p \leq 0.05$ when compared with high dose niacinamide treated group F which had elevated last FBS reading (Table 3).

TABLE 1

FBS value (Mean ± Standard deviation) in mg/dl of different animal groups (A to G) under study on day (0,7,14,21,28,35 and 42)

Group	No. of rats	Drugs	Dose/day (Per oral)
A (normal control)	6	Vehicle (Gum acacia 1%)	10 ml/kg body weight
B (Diabetic control)	6	Vehicle (Gum acacia 1%)	10 ml/kg body weight
C (metformin)	6	Metformin	500 mg/70 kg body weight [(500 mg × 0.018)/ml] OD
D (vildagliptin)	6	Vildagliptin	100 mg/70 kg body weight [(100 mg × 0.018)/ml] in two divided doses BD
E (Optimum dose Niacinamide)	6	Optimum dose Niacinamide	1000 mg/70 kg body weight [(1000 mg × 0.018)/ml] in two divided doses BD
F (High dose Niacinamide)	6	High dose Niacinamide	3500 mg/70 kg body weight [(3500 mg × 0.018)/ml] in two divided doses BD
G (Vildagliptin+Optimum dose Niacinamide)	6	Vildagliptin+Optimum dose Niacinamide	100 mg/70 kg body weight+1000 mg/70 kg body weight [(100 mg × 0.018)/ml+(1000 mg × 0.018)/ml] in two divided doses BD

TABLE 2

FBS value (Mean ± Standard deviation) in mg/dl of different animal groups (A to G) under study on day (0,7,14,21,28,35 and 42)

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Group A	85.67 ± 1.751	86.83 ± 1.722	86.5 ± 1.643	85.17 ± 1.329	84.83 ± 1.602	84.17 ± 2.041	84.33 ± 1.751
Group B	168.83 ± 16.952	179.5 ± 10.015	187.5 ± 15.136	199.83 ± 14.999	206.83 ± 10.381	212.33 ± 7.501	217.67 ± 6.772
Group C	171.17 ± 18.433	114.3 3 ± 8.238	100.67 ± 3.933	91.67 ± 4.633	86.17 ± 2.927	83.83 ± 3.125	81.17 ± 2.994
Group D	167.67 ± 18.425	134.33 ± 9.522	125.33 ± 6.743	110.17 ± 8.727	98.67 ± 3.266	96.83 ± 2.994	95.67 ± 2.251
Group E	167.33 ± 17.614	63.67 ± 17.072	160.5 ± 16.477	158.33 ± 15.253	155.17 ± 12.156	152.17 ± 11.911	149.17 ± 11.197
Group F	163.5 ± 18.141	159.17 ± 18.968	158.33 ± 18.041	160.67 ± 18.019	163.33 ± 17.580	170.33 ± 16.488	178.17 ± 17.279
Group G	167.17 ± 17.826	128.83 ± 11.566	116.33 ± 9.026	103.33 ± 5.785	91.83 ± 3.710	90.17 ± 3.488	89.67 ± 3.615

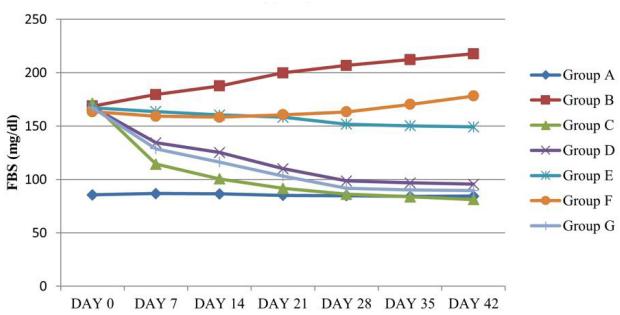

Figure 1) *Trends of FBS measured in all groups on day 0,7,14,21,28,35 and 42..*

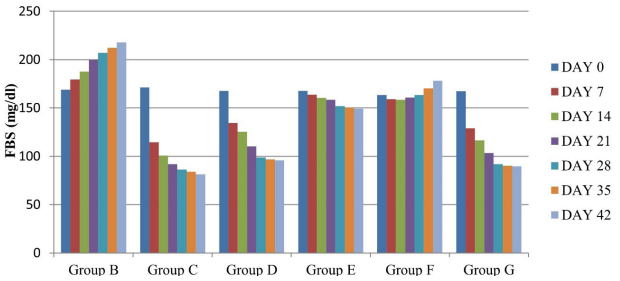

Figure 2) *Groupwise FBS changes in different treatment groups of streptozotocin induced diabetic rats under study.*

TABLE 3

Inter group comparison of Fasting Blood sugar mean values on day 42 using One-way ANOVA post-hoc analysis (Tukey's HSD Test)

S. No.	Group to Group comparison	95% C. I.		Mean difference	S. E.	p- value
		Lower bound	Upper bound			
1	Group B to group C	121.25	151.75	136.5	4.879	0
2	Group B to group D	106.75	137.25	122	4.879	0
3	Group B to group E	53.25	83.75	68.5	4.879	0
4	Group B to group F	24.25	54.75	39.5	4.879	0
5	Group B to group G	112.75	143.25	128	4.879	0
6	Group D to group C	-75	29.75	14.5	4.879	0.071
7	Group D to group G	-9.25	21.25	6	4.879	0.878
8	Group E to group C	52.75	83.25	68	4.879	0
9	Group E to group D	38.25	68.75	53.5	4.879	0
10	Group E to group G	44.25	74.75	59.5	4.879	0
11	Group F to group C	81.75	112.25	97	4.879	0
12	Group F to group D	67.25	97.75	82.5	4.879	0
13	Group F to group E	13.75	44.25	29	4.879	0
14	Group F to group G	73.25	103.75	88.5	4.879	0
15	Group G to group C	-6.75	23.75	8.5	4.879	0.594

DISCUSSION

In the prospect of present study it was demonstrated that induction of diabetes and moderate hyperglycemia was key to proceed with our experimental module. Pellegrino Masiello. Administered streptozotocin preinjected with niacinamide both single intra peritoneal injection in dose dependent manner to produces diabetic rats with different blood sugar level [13]. Streptozotocin induces DNA damage and protein glycosylation. Damaged DNA induces activation of poly ADP ribosylation, which in turn causes apoptosis selectively and β cells destruction [14-16]. Nicotinamide is a direct precursor of NAD as well as an inhibitor of poly (ADP-ribose) synthetase. Therefore, it increases NAD+ concentration in β cells by down regulation of this NAD consuming enzyme. On the other hand, poly (ADP-ribose) synthetase is activated by STZ which causes depletion of NAD. Furthermore, pancreatic islets exhibited increased nitric oxide (NO) production enhancing β cells injury. The nicotinamide protection of beta-cells is facilitated by inhibiting both nitric oxide generation and apoptosis. It is suggested that the combined administration of STZ with suitable dosages of nicotinamide to adult rats leads to the development of an interesting novel diabetic syndrome, characterized by moderate and stable hyperglycemia and preserves approximately 40% of normal pancreatic insulin storage. Attenuated death of pancreatic β-cells in animals upon NAM administration is proposed to be driven by PARP inhibition-mediated cell protection, enhanced mitochondrial integrity, and reduced ROS generation. It is being proven that pre administration of nicotinamide may up regulate and increase the NAD store and prevent excessive damage to β cells, so that ideal type 2 diabetes mellitus model with moderate hyperglycemia get produced [17-19].

Despite of pharmacological and therapeutic supremacy of metformin and gliptins, dose titrated niacinamide emerged as better option for treatment and control of diabetes and its neural complications on long run. One of the noble antidiabetic drug metformin had maximum lowering of fasting blood glucose level in our study. Though metformin stood best among oral hypoglycemic agents but cases of diabetes associated with chronic kidney disease and fear of lactic acidosis serve shifting to other pharmacotherapy as described by Lalau and Arnouts [20]. Gliptins like vildagliptin managed stable FBS in our study when administered alone and in co-administration too. Its insulin tropic and beta cell mass nourishing property were possible reasons for consistent normoglycemia [5,21,22]. It is well established antihyperglycemic drug with minimal drug interactions and side effects. Williams described its cardiovascular safety and rare incidences of causing pancreatitis but causal association was not found significant in clinical settings [23,24].

Optimum dose pattern of niacinamide when used alone, demonstrated reduction of FBS up to considerable extent. On the other hand, high dose of niacinamide showed slight initial reduction followed by progressive elevation in FBS level of diabetic rats.

Shi Sheng Zhou. Suggested that nicotinamide overload played a role in type II diabetes, which induced an increase in plasma N -methylnicotinamide, associated with oxidative stress and insulin resistance [25]. Hwang and Song. in their animal study concluded that treatment with 1 or 4 g/kg oral niacinamide for 8 weeks led to oxidative DNA damage in hepatic and renal tissues, impaired glucose tolerance and insulin sensitivity and dose more higher >4.5 g/kg showed lethal toxicity in experimental animals [12]. Niacinamide doses had differential effect on blood glucose but optimum dose can be investigated to establish among prime pharmacotherapy in treating T2DM and related complications.

Vildagliptin when co administered with niacinamide (in optimum doses) showed improved results towards normoglycemic stabilization of blood sugar levels in our study. Consistency in antihyperglycemic effect and attaining glycemic control within 42 days of treatment confirmed their efficacy equivalent to established antidiabetic agents Both co-administered drugs preserves beta cell mass and function as suggested by few other studies. Rapid recovery and absence of any mortality confirmed their likely synergistic effectiveness with no visible side effect during study period. But, their long term efficacy, safety and tolerance have to be set up through clinical trials ahead. In the context of their prospective benefits, the possible fixed dose combination might to be established as boon to existing pharmacotherapy.

CONCLUSION

Treatment group under study concluded differential changes in fasting blood sugar level. Streptozotocin induced diabetic rat model produced possible type 2 diabetes in wistar rats with moderate level hyperglycemia as suggested by Masiello. This facilitated recordable changes with minimal morbidity and mortality in experimental animals. Single intra peritoneal dose niacinamide and further optimum oral dose niacinamide lowered FBS up to considerable extent. But high dose paradoxically raised FBS level of streptozotocin induced diabetic rats. Metformin showed maximum and fastest decline in FBS reading which suggested its hypoglycemic efficiency as well. Vildagliptin and its co-administration with optimum dose of niacinamide had more lowering of FBS as compared to vildagliptin alone. This finding finally concluded that likely additive or synergistic activity was present in co-administered drug for effective lowering in fasting blood sugar level.

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CONFLICT OF INTERESET

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee (Memo No. 11, IAEC/IEC RIMS Ranchi, Dated 21/03/2016)

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REFERENCES

1. Shaw JE, Sicree RA, Zimmet PZ, et al. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87:4-14.
2. Diabetes facts and figures. IDF Diabetes Atlas Ninth edition 2019.
3. Bailey CJ. Metformin: effects on micro and macrovascular complications in type 2 diabetes. Cardiovasc Drugs Ther. 2008;22(3):215-24.
4. Bodmer M, Meier C, Krähenbühl S, et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes care. 2008 1;31(11):2086-91.
5. Mari A, Sallas WM, He YL, Watson C, et al. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed β-cell function in patients with type 2 diabetes. J. Clin. Endocrinol. Metab. J CLIN ENDOCR METAB 2005 1;90(8):4888-94.
6. Ahren B, Landin-Olsson M, Jansson P, et al. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab. 2004; 89:2078-84
7. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet. 2006;368(9548):1696-705.
8. Laurence LB, Bruce AC, Bjorn KC. Goodman and Gillman the Pharmacological Basis of Therapeutics: Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. GLP-1 Based Agents.2012; 43:1261-64.
9. Winkler G. Incretin enhancers, incretin mimetics–from therapeutic concept to clinical application. Orvosi hetilap. 2007;148(13):579-87.
10. Niacin: Health benefits, uses, side effects, dosage.
11. Yamada K, Nonaka K, Hanafusa T, et al. Preventive and Therapeutic Effects of Large-Dose Niacinamide Injections on Diabetes Associated with Insulitis: An Observation in Non-obese Diabetic (NOD) Mice. ADA 1982; 31(9): 749-753

12. Hwang ES, Song SB. Possible Adverse Effects of High-Dose Nicotinamide: Mechanisms and Safety Assessment. Biomolecules 2020;10:687-98
13. Pellegrino Masiello, Christophe Broca, Rene Gross, et al. Experimental NIDDM: Development of a New Model in Adult Rats Administered Streptozotocin and Nicotinamide. J Diabetes.1998; 47:224-9
14. Yamamoto H, Uchigata Y, Okamoto H. DNA strand breaks in pancreatic islets by invivo administration of alloxan or streptozotocin. Biochem Biophys Res Commun. 1981;103(3):1014-20.
15. Gandhi GR, Sasikumar P. Antidiabetic effect of merremia emarginata burm F. in streptozotocin induced diabetic rats. Asian Pac J Trop Biomed. 2012; 2(4):281-6.
16. West E, Simon OR, Morrison EY. Streptozotocin alters pancreatic beta-cell responsiveness to glucose within six hours of injection into rats. West Indian Med J. 1996 ;45(2):60-2.
17. Masiello P, Bergamini E. Nicotinamide and streptozotocin diabetes in the rat. Factors influencing the effectiveness of the protection. Experientia. 1977; 33(9):1246-7.
18. Masiello P, Wollheim CB, Gori Z, et al. Streptozotocin-induced functioning islet cell tumor in the rat: high frequency of induction and biological properties of the tumor cells. Toxicol. Pathol. 1984;12(3):274-80
19. Nayak Y, Hillemane V, Daroji VK, et al. Antidiabetic activity of benzopyrone analogues in nicotinamide-streptozotocin induced type 2 diabetes in rats. Science World Journal. 2014.
20. Lalau JD, Arnouts P, Sharif A, De Broe ME. Metformin and other antidiabetic agents in renal failure patients. Kidney Int 2015 1;87(2):308-22.
21. Gallwitz B. Glucagon-like peptide-1 as a treatment option for type 2 diabetes and its role in restoring beta-cell mass. Diabetes Technol Ther 2005 1;7(4):651-7.
22. Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action. Diabetes care. 20071;30(6):1335-43.
23. Williams R, de Vries F, Kothny W, et al. Cardiovascular safety of vildagliptin in patients with type 2 diabetes: a European multi-database, non-interventional post-authorization safety study. Diabetes Obes Metab. 2017;19(10):1473-8.
24. Williams R, Kothny W, Serban C, et al. Pancreatic safety of vildagliptin in patients with type 2 diabetes mellitus: A European, noninterventional, postauthorization safety study. Endocrinol Diab Metab. 2019;2(2):e00052.
25. Zhou SS, Da Li WP, Guo M, Lun YZ, Zhou YM, Xiao FC, Jing LX, Sun SX, Zhang LB, Luo N, Bian FN. Nicotinamide overload may play a role in the development of type 2 diabetes. World J Gastroenterol. 2009;15(45):5674.