JITDC-Journal of Innovative Therapeutics and Drug Care
Volume 1, Issue 2 | September -2025
e-ISSN: 3068-8728 Print ISSN: 3068-8701

Combination of Niclosamide and Metformin for Glycemic Management of Type 2 Diabetes: A Pilot Study

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Received: 12-07-2025; Revised: 29-07-2025; Accepted: 18-08-2025; Published: 06-09-2025

Abstract:

The aim of this randomized open-label pilot study is to study the effectiveness of the combination of niclosamide, a repurposed anthelmintic, and metformin to treat glycemic control in adults having poorly controlled Type 2 Diabetes Mellitus (T2DM). Forty patients were recruited arbitrarily into 2 arms; one arm was used with 1000 mg BID metformin and the other arm with 1000 mg BID metformin coupled with 500 mg BID niclosamide taken 12 weeks each. The major outcomes such as HbA1c, fasting plasma glucose (FPG), insulin resistance (HOMA-IR) were improved significantly in the combination therapy group than in the metformin group. The combination group showed an average decrease in HbA1c of -1.6% compared to metformin group of -0.9 ($p < 0.05$). There were cases of mild gastrointestinal discomfort in 20 percent of participants. Such observations justify the prospect of niclosamide repurposing in the management of T2DM, especially in low-resource contexts.

Keywords: ***Type 2 Dabetes Mellitus, Niclosamide, Metformin, Glycemic Control, DRUP, HbA1c, Insulin Resistance, Randomised Pilot Study.***

1. Introduction

1.1 The Big Picture of Type 2 Diabetes Mellitus (T2DM) and the Problem of Its Management

Type 2 Diabetes Mellitus (T2DM) is a metabolic disease that is long-standing due to insulin resistance and the inability to produce this compound, thus increasing the level of glucose in the blood. It is a condition that impacts more than 400 million individuals around the world and the prevalence of more than 10-15 percent increases rapidly, as obesity, physical inactivity, and unhealthy eating habits are on the rise. T2DM is another factor of morbidity and mortality, and it leads to cardiovascular disease, nephropathy, neuropathy, and retinopathy. Effective control of T2DM necessitates optimal levels of blood glucose so as to curtail the occurrence of such complications.

Lifestyle intervention (diet and physical exercise) and pharmacotherapy make up the major way of T2DM management. Nevertheless, it is well known that a number of patients cannot sustain glycemic control because of the interplay of multiple changes including non adherence to medications, progressive 8-cell dysfunction, and the multi-drug requirement that optimizes each of the multiple pathophysiological pathways of the disease.

The problem is that, despite the current range of treatment options, the glycemic control level of a large percentage of T2DM patients is suboptimal. This points to the critical necessity of developing efficient and cost-effective new treatment methods that can lead to the improved management of diabetes particularly in resource-poor languages.(1)

1.2 The First-Line Treatment with Metformin and Its Impossibility

Biguanide, metformin, is the basis of the pharmacologic treatment of T2DM and has been proposed as the initial therapeutic intervention in most clinical guidelines. The principle of its action is mainly the decrease in hepatic production of glucose, enhancing the sensitivity of insulin, and raising the consumption of glucose by peripheral tissues. Moreover, metformin has a positive effect on lipid profiles, weight control, and even a cardioprotective effect. These qualities give metformin widespread application and a fairly well-tolerated nature when it comes to dealing with T2DM.

Nonetheless, metformin possesses limitations, although it appears to be relatively effective. Gastrointestinal side effects (nausea, diarrhea etc.) can affect compliance in some patients, whereas in other patients, it can be insulin resistance or 8-cell burnout, resulting in successively deteriorating glycemic control over time. Moreover, it is possible that metformin alone will not be enough to provide glycemic control over a long period of time which

will require the use of other drugs such as sulfonylureas, DPP-4 inhibitor or GLP-1 agonist. Consequently, there continues to be the requirement of adjunct therapies which could enhance the efficacy of metformin, and decrease polypharmacy burden.

1.3 Endocrine pharmacotherapy repurposing of drugs

Drug repurposing (drug repositioning) can be a very attractive approach especially in the field of endocrine pharmacotherapy where new avenues are sought to treat diseases that are not being addressed effectively by the existing ones. This is done by discovering new uses of old drugs thus it can be more cost effective and much quicker than a conventional drug development protocol. Repurposing of previously tested drugs with the same safety profile albeit they were used as therapeutic option in other clinical contexts can be conducted to provide a faster path to market, lower risks as a drug with a previously established track record of safety, and greater capacity to access treatment, particularly in resource-constrained environments.

In this perception, repositioning repurposed drugs has the possibility of meeting the unmet need regarding the challenge of glycemic control, insulin resistance, 2-cell dysfunction in relation to T2DM. One example of such a drug is niclosamide which is a repurposing drug with a traditional indication of anthelmintic administration to treat parasitic diseases; it displays new metabolic regulatory effects in another disease model.

1.4 The Newer Metabolic Properties of Niclosamide

In recent times, it has been discovered that niclosamide is a drug originally used to treat parasitic conditions having interesting metabolic effects that may make it helpful in the treatment of T2DM. Niclosamide has been found to exert its action by a variety of actions, including the uncoupling of mitochondria, a phenomenon potentially activating the cellular metabolism process. It is also thought to stimulate the energy-sensing AMP-activated protein kinase (AMPK) pathway which is the major regulator of energy homeostasis and insulin sensitivity.

Niclosamide can ameliorate insulin resistance, decrease hepatic glucose synthesis, and increase peripheral glucose extraction, which is of paramount importance in the treatment of T2DM. Notably, its mitochondrial modulatory effect could have a fat metabolism benefit, as well (which should help with weight and optimize lipid levels).

1.5 To achieve the objective to combine niclosamide with metformin, optimal dose determination was needed in relation to ocular distribution and estimated dosing regimens.

Considering the similarities in the mechanism of action of both medicines, niclosamide and metformin, combining the two drugs has great potential of promoting glycemic control in patients with T2DM. Although metformin is mainly effective in insulin resistance and hepatic glucose production, the effects of uncoupling mitochondrion and activation of AMPK in niclosamide can lead to an even better cellular energy balance and insulin sensitivity. The rationale to mix niclosamide with metformin is to investigate the possibility of the synergetic effects of these two drugs to have a better glycemic control, lessen treatment with other drugs, and have better long-term patient outcomes in cases of poorly controlled T2DM.(2)

The combination treatment would be especially useful in regions where treatment with medications is a challenge due to resource constraints and cost-effectiveness is a crucial factor. Besides, the combination can give a new approach to the management of progressive nature of T2DM, and as a supplement to this prevalent and troublesome disorder.

2. Pharmacological Background

2.1 The Mechanisms of Action Metformin and Niclosamide

The principal trend of metformin treatment consists of lowering hepatic glucose production. It also prevents the production of glucose by the liver through gluconeogenesis thus, reducing the supply of glucose into the blood. Metformin is also a peripheral insulin sensitivity-enhancing agent inside tissues like skeletal muscle tissues and adipocytes that result in enhancing of glucose uptake and use. Further, the metformin enhances the AMPK (AMP-activated protein kinase) which is the central regulator of energy balance. The stimulation of AMPK enhances energy efficiency in cells and contributes to the decrease in executive lipids which is useful in the management of insulin resistance- a characteristic of T2DM. The positive effects of metformin are not limited to regulating glucose, and there are studies showing it has potential cardioprotective effects and can also improve lipid levels, thus lowering the chances of having cardiovascular incidents, which are widespread in T2DM.

Niclosamide is a metabolism regulator drug whose initial use was in treating parasitic diseases as an anthelmintic. Niclosamide exerts its main activity via mitochondrial uncoupling leading to proton gradient across the inner membrane of the mitochondria to increase in energy expenditure and cellular metabolism. This mechanism can

contribute to the improvement of the overall tissue insulin sensitivity. Moreover, another drug known as niclosamide was demonstrated to exert similar effects on AMPK activation like metformin and regulates important metabolic pathways in glucose regulation and fat metabolism. Niclosamide can enhance fatty acid oxidation and glucose uptake, as well as increase insulin signaling, via AMPK activation. Such mechanisms indicate that niclosamide may facilitate the effects of metformin on treating insulin resistance and blood glucose levels in T2DM.

2.2 Amplification of AMPK and Mitochondrial Uncoupling of Glycemic Control

The AMPK pathway regulates the energy balance in cells. Under diabetes condition, the stimulation of AMPK plays a very important role in enhancing insulin sensitivity and in lipid deposition decrease in the insulin-resistant tissues, like liver and muscle. Metformin is an activator of AMPK, whereas niclosamide does the same but via different molecular mechanisms. Metformin increases AMPK activity through inhibition of the mitochondrial complex I resulting in an elevation of AMP and thus activation of AMPK. This has a cascading effect such as inhibition of gluconeogenesis, augmentation of glucose uptake, and metabolism of lipids.(3)

In contrast, the mechanism of action in the case of niclosamide is the uncoupling of the mitochondrion, which depresses the efficiency of the mitochondrial electron transport chain and invariably causes an expenditure of energy. When uncoupling occurs, it leads to elevated energy requirement in cells triggering AMPK in order to restore the state of energy. This process of activating AMPK can enhance insulin sensitivity and induce glucose uptake in the skeletal muscle and adipose tissue. Also, fat oxidation can be enhanced by mitochondrial uncoupling at a time when obesity, one of the main comorbidities in T2DM patients, needs to be alleviated.

The synergy of the concerted actions of AMPK activator with mitochondrial uncouplers may deliver even higher therapeutic outcomes, thereby linking together metformin and niclosamide would have synergistic anti-glycemic effects in a synergistic manner.

2.3 Preclinical and Early-Phase Research on Niclosamide Metabolic Disease

Niclosamide has been effective in tissue culture and early preclinical and clinical trials in the treatment of the metabolic syndrome of obesity, insulin resistance, and non-alcoholic fatty liver disease (NAFLD). Niclosamide was depicted to cut down weight, hepatic triglycerides, and blood glucose in rodent models of obesity-induced insulin resistance. The research implied that niclosamide can be used in the enhancement of insulin sensitivity and metabolic potentials. Further, in vitro analysis demonstrated that niclosamide could stimulate AMPK and uncoupling proteins in the mitochondrial, noting that the drug would produce a beneficial impact on glucose homeostasis through its ability to influence energy metabolism.

Small-scale human data, albeit inadequate, have proposed that niclosamide can be effectively tolerated and have the beneficial outcome of improving glucose metabolism and insulin sensitivity. These findings are a good justification of a more clinical study on the effects of niclosamide as a supplement to the modern T2DM treatment, including metformin.

2.4 Justifications Therapeutic Repurposing T2DM

Re-purposing Therapeutic repurposing researches as to how existing drugs may be taken up in new indications. Some of the advantages of this approach are that development timelines are accelerated, the cost reduces and that it has the benefit of prior safety data. The repurposing interest in niclosamide to treat diabetes type 2 is linked to the new-generation metabolic properties attributed to this drug, such as activation of the AMPK enzyme and stimulation of mitochondrial uncoupling which can also assist in addressing the major factors of insulin resistance and glucose intolerance.

As it is already known that metformin remains one of the pillars in T2DM management, the mixture of metformin and niclosamide may introduce an effective glycemic control approach in patients with T2DM who are not responding well to metformin monotherapeutic approach. Niclosamide repurposing provides a new form of dual-mechanism-of-action (activating AMPK to reduce insulin resistance and uncoupling to address mitochondrial dysfunction) adjunctive treatment generating a very appealing possibility as a combination treatment in T2DM management. Moreover, the relatively low cost of niclosamide combined with the fact that it is a generic drug render it interesting in resource poor locations where affordability of medicines to treat diabetes will be a central issue.(4)

3. Methodology

3.1 Study Design: Pilot Open-label Randomized Trial

This pilot clinical trial was a randomized, open-label and pilot study aimed at determining the efficiency and safety of the combination of niclosamide and metformin in the treatment of patients with less than optimal control of Type 2 Diabetes Mellitus (T2DM). The open-label design enabled both the participants and researchers to know the treatments that were applied, and only a pilot study was possible in terms of effectiveness, but there is the likelihood of bias to present itself, as far as subjective variables such as side effects and general satisfaction with treatment are concerned.

Each subject was randomized to enter one of the two treatment arms so that the probability of being allocated to metformin-only arm or combination therapy arm of the trial was equal. The main aim was to determine the effects of niclosamide combo with metformin on glycemic control by adopting HbA1c/fasting plasma glucose (FPG)/insulin resistance (Homa-IR) as key end points. It was also possible in this design to make an exploratory investigation of the safety profile of the combination therapy.

3.2 Inclusion/Exclusion Lebensrichtlinie Criteria

The investigation of the inclusion and exclusion criteria was developed to make sure that the study population was relevant and the findings could be applied to the target population that was the patients with poorly controlled T2DM.

Inclusion Criteria:

- Age: The age of the participants will be between 18 and 75.
- T2DM Diagnosis: People that were clinically diagnosed with Type 2 Diabetes Mellitus and met the language of diagnosis, i.e. HbA1c equal to or above 7.5 percent or FPG equal to or above 126 mg/dL.
- Poorly controlled diabetes: Patients who are not well-controlled on metformin 1000 mg bid, or HbA1c 7.5 or higher in spite of oral diabetes therapy.
- Constant drug timetables: Patients, who had been taking metformin constantly at least 3 months prior to the research.
- Readiness to abide with the protocol of the study and give an informed consent.

Exclusion Criteria:

- Severe complications: The participants with severe complications such as cardiovascular disease or severe diabetic neuropathy or end-stage renal disease.
- Pregnancy or breastfeeding: Women in the course of pregnancy or breastfeeding.
- Metformin and (or) niclosamide contraindications: Individuals with known allergy or adverse effects of metformin or niclosamide.
- History of alcohol or drug abuse: The individuals who have a history of alcohol or drug abuse which could affect the outcome of the study later.
- Severe gastrointestinal diseases: Gastrointestinal discomfort has been noted as a side effect of both the chosen pharmaceutical agents, metformin and niclosamide, therefore, to limit confounding factors, people with severe gastrointestinal diseases were excluded.

3.3 Allocation to group,Treatment regimens

After recruiting the patients and screening them to establish their eligibility, they were randomly assigned to either of the two treatment groups namely:

Metformin only group: In this group, metformin was taken with normal dose 1000 mg two times a day. Depending on tolerability and adherence, a dose adjustment was provided when needed with the principal focus being the assessment of the impact of metformin monotherapy.

Combination therapy group It was the combination therapy group that was treated with a combination of niclosamide (500 mg bid) and metformin (1000 mg bid). Niclosamide was chosen because of its new potential in boosting metabolic homeostasis and doing this in a beneficial manner through its activation of AMPK and mitochondrial uncoupling (both known to be helpful in the management of diabetes type 2).

Both therapies lasted 12 weeks and the patients were advised to consume the drugs with food to reduce the incidences of indigestion. In the course of the study, it was not allowed to make any corrections of dose beyond exceptional circumstances prompted by the adverse events or medical necessity. The two groups were monitored throughout the study duration and side effects of the two groups and their compliance to the treatment and the test of any potential hypoglycemia or occurrence of any adverse events were observed.(5)

3.4 Duration of the research and follow up of the patients

The duration of the study was one month, which was considered sufficiently long to determine the short-term glycemic factor and short enough to determine the short side effects and how tolerable the combination therapy was. A follow-up procedure was followed where issues like progress of the patient and its safety feelings were addressed during the study.

At the most important moments during the time span, patients were evaluated to be as follows:

Screening visit Preliminary eligibility estimate and baseline blood (preliminary test HbA1c, FPG, HOMA-IR).

Week 4: Intermediate visit to check the adherence of the treatment, safety and preliminary comments on the changes in the glycemic control. Replicated HbA1c, FPG blood testing, and inquiring patients regarding any side effects, in particular intestinal complaints, were conducted.

Week 8: Additional checkup and follow-up on the progress of the treatment, side effects and other blood levels.

Week 12 (final visit): Visit to determine the overall efficiency of the treatment (including HbA1c, FPG, and HOMA-IR), adverse events, and obtain the feedback concerning the experience the patient had in taking the medications. At this stage, blood tests and clinical assessments were done.

In the case of any adverse events (AEs) that may have been experienced in tenure of undertaking the study, it was duly noted and followed up during the follow up period. In case any participant subjected to severe adverse response, he/she was given correct measures and in cases he/she had to be removed out of the test to avoid safety of the participant. Patients were also advised to continue with the treatment in the usual care at the end of the study.

This well-rounded study endeavor was intended to have a proper interpretation on the expected advantages and the safety of using niclosamide in permutation with metformin in treating poorly controlled T2DM.

4. Safety and the Outcome Measures

4.1 HbA1c, FPG, HOMA-IR Primary Outcomes:

The main outcomes of the study were selected in order to determine whether or not the combination therapy of niclosamide and metformin increases glycemic control in patients with poorly controlled Type 2 diabetes mellitus (T2DM). These are the most commonly accepted and confirmed indicators of both long-term and short-term control of glucose:

HbA1c (Glycated Hemoglobin): HbA1C is a test that also indicates a general view of average levels of glucose in the two to three previous months. It is the typical indicator of measuring the general control of glycemia and relates directly to a likelihood of having diabetes-related complications. Decreasing HbA1c represents enhanced control of blood sugar on a long-term basis.

Fasting Plasma Glucose (FPG): FPG is a test that determines the amount of glucose in the blood that someone takes after spending the night without food. It is a significant predictor of insulin resistance and glucose control, which tells how a patient would control his blood glucose levels when he is not subjected to an oral nutrient load. A decline in FPG implies some subsequent enhancements in the insulin sensitivity and pancreatic functions.

HOMA-IR (Homeostasis Model Assessment of Insulin Resistance): HOMA-IR is a mathematical formula that determines the amount of insulin resistance, relative to the fasting level of insulin and glucose. Insulin resistance is one of the characteristics of T2DM and it plays a key role in explaining the pathophysiology of the disease. Decrease of HOMA-IR means that the insulin sensitivity of the patient is becoming better, which is a significant therapeutic target in diabetes management.

These major outcomes have been chosen to address overall impact of the combination therapy on the key metabolic deficits related to T2DM, i.e. glycemic control and insulin resistance, and gain insight into the prospects of niclosamide in combination with metformin as adjuvant therapy.(6)

4.2 Data Collection and the Timelines and Procedures

To determine the effectiveness of the treatment and its safety, data were collected at some of the important points during the study. The data gathering is made in the following way:

Screening Visit: The basic demographic information was taken and medical history along with HbA1c, FPG, HOMA-IR at the baseline were also recorded. All the pre-treatment values of the primary endpoints were due to this baseline data.

Week 4: Here, the level of HbA1c and FPG was re-evaluated in a midpoint visit in order to track the possible changes on the glycemic control early in the visit. Also, the HOMA-IR was used to measure the progression of

improvements in the insulin resistance. The respondents were also required to indicate their symptom burden and negative events they have experienced so far.

Week 8: The second follow-up exam was performed, and HbA1c, FPG, HOMA-IR were measured one more time and the further adherence to treatment of the participants was taken into account. All side effects were recorded and the safety profile was also followed up at this stage.

Week 12 (Exit Study): The last data collection was made with additional data of HbA1c, FPG and HOMA-IR. There was a complete assessment of any new developments with regard to these key endpoints in order to determine the efficacy of the combination therapy. Besides, follow-up assessments were to be undertaken after the treatment, in order to ascertain that any untoward effects were documented accordingly.

All of these measurements were performed as per set clinical guidelines and all the results were recorded in the data management system of the study to be analyzed.

4.3 Safety-Monitoring, and Adverse Events Documentation

The study paid great attention to the issue of safety of niclosamide and metformin. The participants were asked to report adverse events (AEs) and these were recorded during every visit. Adverse events were defined as mild, moderate and severe since it was based on the effect it had on the health and daily activities of the patient.

Monitoring of safety was:

Vital signs (e.g., blood pressure, heart rate) baseline and follow up measurements.

Blood tests (e.g. liver functioning, kidney functioning) to ascertain the safety of the drug.

Gastrointestinal monitoring: The gastrointestinal side effect of metformin is one of the most well-documented effects; since niclosamide is known to have gastrointestinal side effects as well, questions regarding nausea, vomiting, and diarrhea were specifically asked of participants.

In case of any significant adverse events (SAEs) those were reported and patients got proper medical treatment. All of the adverse incidents were also typed using the Common Terminology Criteria Adverse Events (CTCAE).

4.4 Patient compliance and Tolerability Assessment

On each follow-up visit, patient adherence was evaluated through self-reports and through the counting of pills. This method gave an indication of the extent to which patients did an excellent job of complying with their own prescribed treatment regime and it enabled the study team to determine whether adherence was having an effect on treatment response.

The critical point was also on tolerability. The patients were requested, on a regular basis (every 3 weeks), to note the occurrence of any of the side effects including the effects that concerned the gastrointestinal system (which was a common problem with both metformin and niclosamide) These side effects have been evaluated on the scales of how severe they occur and measures were taken in order to amend them where possible i.e. supportive care provided or dieting advice to alleviate discomfort.

The tolerability of the treatment was to be assessed through the readiness of the patient to remain in the study and all instances of discontinuation and dose changes were to be captured in detail. Subjects would be advised to speak up and be allowed to drop out in case of intolerances and severe side effects that are concerning with regard to safety.(7)

In general, the research was conducted to assess not only the efficacy of niclosamide which was combined with metformin but also to make sure that the treatment was well-tolerated and safe to the participants of the research who had T2DM.

5. Results

5.1 Change in HbA1c (The Two Groups)

Change in HbA1c was the primary endpoint of the study which is a significant indicator of long-term glycemic control in the patient population with Type 2 Diabetes Mellitus (T2DM). The mean HbA1c concentration at baseline was comparable in both groups of treatment and it was equal to 8.2 %. The combination group (metformin + niclosamide) demonstrated a marked decrease in HbA1c 12 weeks into the treatment, the overall modifications were -1.6 and -0.9 percent. The metformin monotherapy group, on the other hand, showed a mean fall of -0.9 per cent ($p < 0.05$).

This difference shows that the supplement of niclosamide to metformin treatment enhanced the long-term glycemic control more than the combination therapy thereby lending credit to the hypothesis that combination therapy of metformin and niclosamide has a synergism effect on glycemic regulation.

5.2 A lowering of Fasting Plasma Glucose

The second main outcome measure of the study was the change in Fasting plasma glucose (FPG) that gives real-time picture of the instantaneous glycemic state of the patient. The level of FPG was close in both the groups during baseline with a mean value of 158 mg/dL. At the end of 12 weeks, the combination therapy group had a means of reduction of -23 mg/dL ($p < 0.05$), the metformin only group recorded a decline of -13 mg/dL ($p = 0.12$). Even though the decrease in FPG was only significant in the combination group, there was a trend of improvement in fasting glucose in both treatments. The fact that the combination group has a greater decrease indicates that the factor that can further contribute to the glucose-lowering effect of metformin are factors like higher insulin sensitivity and glucose uptake, which may be increased thanks to niclosamide.

5.3 Insulin Resistance (HOMA-IR)

Improvement of insulin resistance was the third major endpoint, which was quantified with the aid of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The baseline HOMA-IR levels were equally distributed in both groups with 4.5 as the mean value. At the end of the 12 weeks of treatment, the combination therapy group had a mean improvement of -1.3 and metformin-only group had average decrease of -0.7 ($p < 0.05$).

This means that addition of a dosage of niclosamide to metformin will result in greater enhancement of insulin sensitivity than when use of metformin alone. As evidence of HOMA-IR improving, the combination therapy can improve insulin sensitivity by lowering insulin resistance more efficiently, and this tendency is a major mechanism of T2DM treatment.

5.4 Number and Character of Side Effects

The safety played an essential role in the study, and adverse events (AEs) were carefully checked in individuals. The rate of side effects was in general favourable, slight gastrointestinal discomfort being the most frequently reported adverse effect. The individuals in the combination group showed 20 percent of gastrointestinal side effects, including nausea and diarrhea, which were aligned with the recognized side effects of the two drugs, metformin and niclosamide. The corresponding figure was 15% in the metformin-only category of participants who had identical symptoms.

No serious adverse events (SAEs) were noted in either arm study and all the adverse events were self-limiting and did not require use of additional dose or termination of the medication. No apparent difference in the vital signs or lab values (liver or kidney functioning) was observed between the groups, indicating that the two therapies were well tolerated generally.(8)

5.5 Comparative Critique of Treatment Results of Combination and Monotherapy

The comparison that was done on the combination therapy group (metformin + niclosamide) and monotherapy group (metformin only) indicated clearly that the combination therapy was better as regards to glycemic control and insulin resistance. Combination therapy also resulted in more pronounced decreases in HbA1c (-1.6% vs. -0.9%) and FPG (-23 mg/dL vs. -13 mg/dL) and significant improvement in insulin sensitivity demonstrated by more pronounced decrease in HOMA-IR (-1.3 vs. -0.7).

Both groups were similar as far as their safety profiles were concerned and gastrointestinal discomfort was a most prevalent adverse event, but mild and transient. Impressively, the group that received the combination therapy had a slight elevation in terms of experiencing gastrointestinal side effects (20%) as compared to the group that received metformin alone (15 percent), but there were no serious complications or side effects severity that necessitated the discontinuation of the combination therapy treatment.(9)

Generally, the niclosamide and metformin combination was of great help compared to metformin in terms of attaining Glycemic control and insulin sensitivity. The findings are considered to indicate the potential of niclosamide as an adjunct treatment of T2DM especially individuals that need extra assistance in regulating their glycemic levels or those with intolerance towards any other treatment method. Nonetheless, these conclusions should be expanded by bigger studies in order to ensure them and consider the safety and efficacy of this combination therapy in the long run.(10)

Table :1 Efficacy Data Summary

Group	HbA1c Change (%)	FPG Change (mg/dL)	HOMA-IR Change
Combination (Metformin + Niclosamide)	-1.6	-23	-1.3
Monotherapy (Metformin)	-0.9	-13	-0.7

Table :2 Adverse Events Summary

Adverse Event	Combination (Metformin + Niclosamide)	Monotherapy (Metformin)
Gastrointestinal Discomfort (Nausea, Diarrhea)	20	15
Fatigue	5	4
Headache	5	3

6. Conclusion

6.1 Outcomes of Efficacy

This is a randomized, open-label pilot study that proves that the combination of the niclosamide and metformin group results in a significant improvement in glycemic control and insulin sensitivity in adults with poorly controlled Type 2 Diabetes mellitus (T2DM). To be more exact, average decrease in HbA1c in combination group was -1.6%, and in metformin-only group it was -0.9% which is statistically significant ($p < 0.05$). Moreover, the combination therapy resulted in a stronger decline in fasting plasma glucose (FPG) and insulin resistance (HOMA-IR), and this finding strengthens the notion of niclosamide to augment effects of metformin on metabolism. Combination therapy had a greater impact on the levels of HbA1c and FPG, meaning it had better glycemic control when compared to metformin monotherapy. Based on these findings, it can be stated that niclosamide may provide an interesting alternative when it comes to the management of insulin resistance and hyperglycemia in patients with T2DM.

6.2 Tolerability and Safety Niclosamide-Metformin Combination

The combination niclosamide and metformin were, in general, well tolerated by the participants in terms of safety and tolerability. The most significantly occurring adverse events were mild gastrointestinal type effects such as nausea and diarrhea in line with the existing side effects of the two drugs. In the combination group, such gastrointestinal symptoms were observed in about 20 percent of study participants, and 15 percent of all the participants in the metformin-only group reported such adverse effects. Notably, there were no serious adverse events (SAEs), and the adverse effects were self-limiting in the study, being resolved and stopping dosage adjustments or therapy discontinuation. Also, there were no major alterations in the vital signs and laboratory markers (e.g. liver or renal functions) which indicates that the combination therapy posed no new safety issues. In general, the niclosamide-metformin combination presented a favorable safety profile that could be compared to the one of metformin monotherapy and all side effects were minor and temporary.

6.3 Applications Implications

Its considerable efficacy and good safety profile that have been shown by the combination of niclosamide and metformin have significant implications in terms of low-resource and cost-sensitive environments. As a generic drug that was not developed as a delta-opioid antagonist but rather an anthelminthic, niclosamide is widely accessible, at a low cost as well. The repurposing as a glycemic control agent in T2DM may present a low cost adjunct treatment option in the region where better diabetes management options are not accessible. Niclosamide, in this kind of an environment, where newer branded medicines are not readily available, could possibly do the job of seizing a vital niche in the diabetes management armamentarium. Metformin (an already used and affordable first-line agent with a long history of use) and niclosamide are low-cost treatment combinations that may provide an effective and cost-effective way of achieving improved glycemic control and insulin sensitivity and alleviation of the burden of diabetes-related complications in resource-limiting countries.

6.4 Bigger, Controlled Trials to Ascertain Results are Fair

As encouraging as were the final results of this pilot study, they depend on the rather limited sample size and short-term treatment course. Therefore, additional bigger and controlled clinical trials should be carried out to establish the effectiveness and safety of the niclosamide-metformin combination in the treatment of Type 2 Diabetes Mellitus. Potential future research should focus on the wider range of participants and populations and it will also need to evaluate the long-term positive effects of the combination therapy as well as its side-effects. Also, placebo-controlled studies would be useful to better test the individual improvement of glycemic control attributed to niclosamide. Multicenter trials may also serve to give a better idea regarding the overall applicability

of the findings in different care treatment options, so that the advantages of combination therapeutic approach are identical in the broader spectrum of clinical trial.

Overall, the niclosamide-metformin combination may be an effective adjuvant of poorly controlled T2DM, especially in low-resource infrastructures. Nevertheless, these findings still have to be corroborated by further studies and identify what groups of patients and what sort of time of treatment would grant the best outcomes.

Acknowledgement: Nil

Conflicts of interest

The authors have no conflicts of interest to declare

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