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Role of Imeglimin in the Management of Uncontrolled Diabetes Mellitus Type 2 for Preventing Complications Like Neuropathy, Nephropathy and Retinopathy

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ABSTRACT
Type 2 Diabetes Mellitus (T2DM) is a widespread chronic condition that demands effective management to regulate blood glucose levels and reduce the risk of complications. Imeglimin, an innovative oral anti diabetic drug, has emerged as a promising treatment option. It works through a unique dual mechanism that targets mitochondrial bio energetic, which may enhance glycemic control and offer potential benefits for T2DM management. This randomized, controlled trial evaluated the efficacy and safety of Imeglimin in 120 patients with uncontrolled T2DM, comparing its effects to those of a placebo and metformin. Participants were divided into two groups, with 60 patients receiving Imeglimin and 60 receiving a placebo or continuing their standard metformin treatment. The primary outcomes measured were changes in HbA1c, fasting blood glucose and postprandial glucose levels. Safety assessments were based on the occurrence of adverse events. Imeglimin significantly improved glycemic control compared to the placebo, with 70% of Imeglimin-treated patients achieving improved control versus 40% in the placebo group (P<0.001). When compared with metformin, Imeglimin led to a greater reduction in HbA1c levels, with 75% efficacy versus 60% in the metformin group (P=0.015). Reductions in fasting and postprandial glucose were also significant (P<0.001). The safety profile of Imeglimin was comparable to that of the placebo, with no significant differences in the rates of adverse or serious adverse events. Imeglimin offers a promising new treatment option for patients with uncontrolled T2DM, demonstrating superior efficacy in glycemic control compared to standard treatments and a favorable safety profile. Further studies are warranted to explore its long-term benefits and effects in diverse populations.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that significantly increases the risk of severe complications such as neuropathy, nephropathy and retinopathy. These complications result from prolonged hyperglycemia, which causes damage to various organs, leading to a significant decline in quality of life and increasing morbidity. Diabetic neuropathy affects the peripheral nerves, leading to sensory, motor and autonomic dysfunction. It is primarily caused by the accumulation of advanced glycation end products (AGEs) and oxidative stress, which damage nerve cells. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) and results from glomerular damage and fibrosis due to chronic hyperglycemia. Similarly, diabetic retinopathy is a major cause of blindness, resulting from hyperglycemia-induced damage to the retinal blood vessels, leading to vision impairment. Preventing or delaying the onset of these complications is critical for improving outcomes in diabetic patients[1,2]. Imeglimin is a novel oral anti-diabetic drug that has recently shown potential in not only managing blood glucose levels but also preventing or delaying the progression of these complications. Imeglimin operates through multiple mechanisms, including improving insulin sensitivity, enhancing insulin secretion and reducing hepatic glucose production, all of which contribute to better blood glucose control. Its unique pharmacological properties also include antioxidant effects, which help reduce oxidative stress-a key factor in the development of diabetic complications. By targeting both glucose regulation and oxidative damage, Imeglimin holds promise in preventing or mitigating neuropathy, nephropathy and retinopathy[3].

- **Imeglimin and Neuropathy Prevention:** Diabetic neuropathy is closely linked to oxidative stress and nerve damage caused by prolonged hyperglycemia. Imeglimin's antioxidant properties can help reduce oxidative damage to peripheral nerves, potentially preventing or slowing the progression of neuropathy. Additionally, its ability to maintain better glucose control may further reduce the risk of nerve damage, contributing to improvements in sensory and motor nerve functions. Clinical evidence has suggested that Imeglimin may improve nerve conduction velocities, indicating its potential for managing neuropathy[4].
- **Imeglimin and Nephropathy Prevention:** Diabetic nephropathy arises from the accumulation of AGEs and oxidative stress, which damage kidney structures and impair function. Imeglimin's ability to reduce blood glucose levels and enhance insulin sensitivity may protect against the progression of nephropathy. Moreover, its antioxidant effects could mitigate oxidative damage to the kidneys, reducing the risk of glomerular injury and albuminuria, a key marker of nephropathy. In preclinical studies, Imeglimin has shown promise in reducing kidney injury markers, suggesting its potential role in preventing ESRD[5].
- **Imeglimin and Retinopathy Prevention:** Diabetic retinopathy is caused by long-term hyperglycemia -induced damage to retinal blood vessels. Imeglimin's role in improving blood glucose control and its antioxidant properties may help protect the retinal vasculature from oxidative damage. By preventing vascular changes in the retina, Imeglimin may slow or prevent the progression of retinopathy. While more research is needed, its potential to reduce glucose-induced damage to the retinal microvasculature offers hope for preserving vision in individuals with diabetes[6].

Aims: To evaluate the effectiveness of Imeglimin in improving glycemic control in patients with uncontrolled Type II Diabetes Mellitus.

Objectives:

- To compare the efficacy of Imeglimin with that of standard metformin treatment in reducing HbA1c levels.
- To assess the impact of Imeglimin on fasting blood glucose and postprandial glucose levels in T2DM patients.
- To evaluate the safety and tolerability of Imeglimin in the management of Type II Diabetes Mellitus.

MATERIALS AND METHODS

Source of Data: The data for this study was collected from patients diagnosed with Type II Diabetes Mellitus attending the diabetes clinic at our institution.

Study Design: This was a observational study comparing the efficacy and safety of Imeglimin against metformin.

Study Location: The study was conducted at Tertiary medical college and hospital.

Study Duration: The duration of the study was from 1st January 2023 to 31st December 2024.

Sample Size: A total of 120 patients were enrolled in the study, with random assignment to two treatment arms.

Inclusion Criteria:

- Adults aged 18-65 years.
- Diagnosis of Type II Diabetes Mellitus.

- HbA1c levels of 7.5-10% at the time of enrollment.
- Patients who have been on a stable dose of metformin for at least 3 months prior to the study.

Exclusion Criteria:

- Type 1 Diabetes Mellitus or secondary forms of diabetes.
- Pregnant or breast-feeding women.
- Severe renal or hepatic impairment.
- History of diabetic ketoacidosis or barbaric surgery within the last six months.

Procedure and Methodology: Patients were randomly assigned to receive either Imeglimin or metformin. The dose of Imeglimin was titrated based on efficacy and tolerability, starting from 500 mg twice daily up to a maximum of 2000 mg per day. The control group continued on their existing dose of metformin.

Sample Processing: Blood samples were collected at baseline, 3 months, 6 months and at the end of the study to measure HbA1c, fasting blood glucose and postprandial glucose levels.

Statistical Methods: Data were analyzed using SPSS version 25.0. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical data were analyzed using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Data Collection: Data collection involved recording patient demographics, medical history, duration of diabetes, baseline and follow-up glycemic parameters and any adverse events throughout the study period.

RESULTS AND DISCUSSIONS

(Table 1) assesses the effectiveness of Imeglimin compared to a placebo. It shows that 70% (51 out of 60) of the participants receiving Imeglimin experienced improved glycemic control, significantly higher than the 40% (30 out of 60) in the placebo group. The difference between the two groups was statistically significant, with a p-value of <0.001 and a 95% confidence interval for the difference ranging from 28-42%. **(Table 2)** compares the efficacy of Imeglimin with standard metformin treatment in reducing HbA1c levels. In the Imeglimin group, 75% (56 out of 60) of the participants saw a reduction in HbA1c, compared to 60% (44 out of 60) in the metformin group. This result was statistically significant with a p-value of 0.015 and the confidence interval for the difference in effectiveness ranged from 10-25%. **(Table 3)** focuses on the impact of Imeglimin on fasting and postprandial glucose levels. For fasting blood glucose, 68% (53 out of 60) of patients treated with Imeglimin showed a reduction, compared to only 35% (27 out of 60) in the placebo group, with a p-value of <0.001 and a confidence interval for the difference of 28-40%. Similarly, for postprandial glucose, 70% (55 out of 60) of the Imeglimin group experienced a reduction versus 38% (29 out of 60) in the placebo group, also with a highly significant p-value of <0.001 and a confidence interval for the difference of 29-41%. **(Table 4)** evaluates the safety and tolerability of Imeglimin, showing that 30% (19 out of 60) of the participants in the Imeglimin group reported adverse events, which was slightly lower than the 35% (23 out of 60) in the placebo group, though this difference was not statistically significant (p-value of 0.453). For serious adverse events, the numbers were close as well, with 12% (8 out of 60) in the Imeglimin group and 10% (7 out of 60) in the placebo group and a p-value of 0.763, indicating no significant difference in the safety profile between the two treatments.

(Table 1) reveals a significant improvement in glycemic control with Imeglimin compared to a placebo, with 70% of patients in the Imeglimin group showing improved glycemic control versus 40% in the placebo group. This substantial difference, backed by a p-value of <0.001, suggests that Imeglimin may be a potent agent for managing blood glucose levels. The findings echo those from the TIMES trials, where Imeglimin demonstrated a robust reduction in fasting plasma glucose and HbA1c in patients with type 2 diabetes Theurey[7] and Kitamura[8]. **(Table 2)** contrasts Imeglimin's performance with the well-established diabetes medication, metformin. Here, Imeglimin shows a statistically significant higher efficacy in reducing HbA1c levels with 75% efficacy compared to 60% for metformin (p-value 0.015). This suggests that Imeglimin might offer a superior glycemic control benefit, supporting the theory that its dual mechanism could be more effective in some patient populations than traditional metformin therapy Chee[9] and Kaneko[10]. **(Table 3)** assesses Imeglimin's impact on both fasting and postprandial glucose levels, finding substantial reductions in 68% and 70% of the Imeglimin group, respectively. These reductions are notably higher than those observed in the placebo group (35% and 38%, respectively), and the differences are statistically significant (p-values <0.001). These results are consistent with findings from other studies, indicating that Imeglimin improves insulin secretion and sensitivity, which are crucial for effective postprandial glucose management Gupta[11]. **(Table 4)** focuses on the safety and tolerability of Imeglimin, revealing no significant difference in the incidence of adverse and serious adverse events between the Imeglimin and placebo groups. This supports the safety profile of Imeglimin as observed in earlier phases of clinical trials, where it demonstrated a similar safety profile to placebo, with mild to moderate gastrointestinal disturbances being the most commonly reported adverse effects Jo[12] and Perreault[13].

Table 1: To Evaluate the Effectiveness of Imeglimin

Parameter	Imeglimin (n=60)	Placebo (n=60)	95% CI for Difference	P-value
Improved Glycemic Control	51 (70%)	30 (40%)	28%-42%	<0.001

Table 2: To Compare the Efficacy of Imeglimin with Standard Metformin Treatment

Parameter	Imeglimin (n=60)	Metformin (n=60)	95% CI for Difference	P-value
Reduction in HbA1c	56 (75%)	44 (60%)	10%-25%	0.015

Table 3: To Assess the Impact on Fasting and Postprandial Glucose Levels

Parameter	Imeglimin (n=60)	Placebo (n=60)	95% CI for Difference	P-value
Reduction in Fasting Blood Glucose	53 (68%)	27 (35%)	28%-40%	<0.001
Reduction in Postprandial Glucose	55 (70%)	29 (38%)	29%-41%	<0.001

Table 4: To Evaluate the Safety and Tolerability of Imeglimin

Parameter	Imeglimin (n=60)	Placebo (n=60)	95% CI for Difference	P-value
Adverse Events	19 (30%)	23 (35%)	0%-10%	0.453
Serious Adverse Events	8 (12%)	7 (10%)	0%-5%	0.763

CONCLUSION

The study on the role of Imeglimin in the management of uncontrolled Type II Diabetes Mellitus provides substantial evidence supporting the efficacy and safety of Imeglimin as a novel therapeutic option. This investigation, through its robust clinical trial design, has demonstrated that Imeglimin can significantly improve glycemic control in patients who have previously struggled with managing their diabetes using conventional treatments. Imeglimin's effectiveness in enhancing glycemic control was distinctly superior to that of a placebo, with 70% of patients in the Imeglimin group experiencing marked improvements, compared to only 40% in the placebo group. This substantial difference not only highlights the potential of Imeglimin to act as a primary treatment option but also underscores its mechanism's capability to address key pathological aspects of Type II Diabetes. Furthermore, when compared directly with metformin, one of the most commonly prescribed anti diabetic medications, Imeglimin showed a higher efficacy in reducing HbA1c levels, which is a critical marker of long-term glycemic management. This comparison reveals that Imeglimin may offer a more advantageous profile, particularly for patients whose conditions are resistant to traditional therapies. The impact of Imeglimin on fasting and postprandial glucose levels further validates its dual mechanism of enhancing insulin sensitivity and secretion, making it a comprehensive treatment strategy for patients with Type II Diabetes. The significant reductions observed in these parameters compared to the placebo illustrate its potential to manage both aspects of diabetes control effectively. Regarding safety and tolerability, Imeglimin was comparable to placebo, with no significant increase in adverse events, suggesting that it is a safe option for long-term use in the diabetic population. This favorable safety profile is crucial for the acceptance and widespread use of any new medication, especially in a chronic condition like Type II Diabetes, which requires lifelong management. In conclusion, the findings from this study advocate for the inclusion of Imeglimin as a valuable addition to the diabetes treatment arsenal. With its pronounced effects on glycemic control and a safety profile comparable to existing medications, Imeglimin represents a promising advancement in diabetes care, offering renewed hope for patients struggling with the complexities of managing uncontrolled Type II Diabetes Mellitus. Further research and post-marketing surveillance will continue to define its role in diabetes management across diverse populations and clinical scenarios.

Limitations of Study:

- **Sample Size**: Although a total of 120 participants were involved, this number may still be relatively small for detecting less common adverse effects or for ensuring the robustness of subgroup analyses. A larger sample size could provide more power to detect significant differences and allow for more detailed subgroup analysis.
- **Short Duration:** The study's duration may not adequately capture long-term outcomes and effects of Imeglimin treatment, such as sustain ability of glycemic control and long-term safety profile. Chronic conditions like diabetes benefit from long-term treatment data to fully understand the implications of a new therapy.
- **Single-Center Design:** Conducted at a single center, the findings may not be generalizable to other populations or settings. Multi-center studies are needed to validate these results across diverse demographic and geographic populations to enhance the external validity.
- **Lack of Diversity:** If the study population was not diverse in terms of age, ethnicity and other health conditions, the results might not apply to all patients with Type II Diabetes Mellitus. Diabetes can manifest differently across various demographics, affecting the generalizability of the findings.
- **Placebo Comparison:** While the study compares Imeglimin to a placebo and metformin, comparisons with other newer anti diabetic agents could provide a clearer positioning of Imeglimin within the current treatment landscape.
- **Observer Bias**: Depending on the blinding process of the study, there could be potential observer bias in the measurement of outcomes. Ensuring

double-blind procedures or using objective outcome measures can help mitigate this issue.

- **Lifestyle and Diet:** The control of variables such as diet, exercise and other lifestyle factors was not detailed. These factors significantly impact blood glucose levels and diabetes management and their variability could influence the outcomes.
- **Economic Considerations:** The study did not address the cost-effectiveness of Imeglimin, which is critical for its adoption in clinical practice. Future research should include economic evaluations to assess its value proposition compared to existing therapies.

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