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Effectiveness and safety of alprostadil injection in the treatment of patients with type 2 diabetes complications

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Abstract: **Background**: Type 2 diabetes mellitus (T2DM) has become a global public health crisis with a steady upward prevalence, and China alone has over 100 million adult T2DM patients. Long-term persistent hyperglycemia damages microvasculature and peripheral nerves, leading to disabling complications such as diabetic foot (DF) and diabetic peripheral neuropathy (DPN). These complications severely reduce patients' quality of life and increase medical burdens, thus creating an urgent need for effective adjunctive therapeutic interventions. **Objectives**: To evaluate the efficacy and safety of alprostadil injection in treating type 2 diabetes-related DF or DPN. **Methods**: A prospective randomized controlled trial was conducted involving 120 eligible patients (62 with DF, 58 with DPN) recruited from our hospital between 2018 and 2021. Inclusion criteria included confirmed T2DM diagnosis and meeting diagnostic criteria for DF/DPN; exclusion criteria included severe organ dysfunction. Patients were randomly divided into control group (n=60, receiving standard care including blood glucose control and symptom management) and observation group (n=60, standard care plus 40μg alprostadil intravenous infusion daily for 14–21 days). Outcomes included total efficacy rate, lipid profiles (TC, TG, LDL-C, HDL-C), and adverse events. **Results**: Clinical outcomes showed significant advantages in the observation group: total efficacy rate was 93.33% (56/60) versus 76.67% (46/60) in the control group (P=0.011). Lipid profiles improved more remarkably in the observation group: TC decreased by (1.24±0.32) mmol/L, TG by (0.86±0.21) mmol/L, LDL-C by (0.92±0.25) mmol/L, and HDL-C increased by (0.35±0.10) mmol/L (all P<0.05). Adverse event rate was 3.33% (2/60) in the observation group, much lower than 18.83% (11/60) in the control group (P=0.008). **Conclusion**: Alprostadil injection as an adjunctive therapy for T2DM-related DF or DPN exhibits significant efficacy and good safety. It not only enhances the overall therapeutic response but also effectively improves lipid metabolism disorders, with a low incidence of adverse events.

Keywords: Alprostadil; Diabetes complications; Effectiveness; Safety

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INTRODUCTION

Globally, the prevalence of type 2 diabetes is increasing due to lifestyle changes and population aging (Elizabeth *et al*., 2024). In China, the number of adult patients has exceeded 100 million and the median age of onset has decreased from 52 years to 48 years in the past decade, indicating that the trend of younger onset of the disease is becoming increasingly prominent (Xing, 2022). Long-term high blood sugar can cause microvascular and macrovascular complications such as diabetic foot and diabetic peripheral neuropathy, which are the main causes of patient morbidity and mortality (Rathnayake *et al*., 2020). Although controlling blood sugar is the basic treatment, adjunctive therapies targeting microcirculation and inflammation are also crucial in managing complications.

Pentoxifylline, as a prostaglandin E1, can dilate blood vessels, prevent thrombosis and have anti-inflammatory effects. It improves peripheral blood flow by relaxing vascular smooth muscle and enhancing red blood cell deformability (Meiyan *et al*., 2021; Yanan *et al*., 2022). At the same time, it can regulate blood lipids by activating lipases and may further reduce the risk of atherosclerosis in diabetic patients. However, large-scale clinical studies on pentoxifylline in the treatment of diabetic complications still need to be further explored, especially in terms of systematic evaluation of effectiveness and safety.

The pathological mechanisms of diabetic complications involve multiple pathways. Long-term high blood sugar can cause non-enzymatic glycation of extracellular matrix proteins, activation of the polyol pathway and increased hexosamine flux, which can damage micro vessels. For example, in DF, endothelial dysfunction reduces the utilization of nitric oxide, hinders angiogenesis and creates an oxygen-deficient environment that affects wound healing; in DPN, high blood sugar-induced oxidative stress consumes nitric oxide, promotes neurovascular inflammation and leads to lipid peroxidation of myelin sheaths (Hiroki *et al*., 2024). Additionally, dyslipidemia associated with type 2 diabetes, such as elevated triglycerides, increased small and dense low-density lipoproteins and decreased high-density lipoproteins, accelerates atherosclerosis and pentoxifylline shows potential in lipid regulation by activating lipoprotein lipase and peroxisome proliferator-activated receptor-gamma (PPAR-γ) (Haifang *et al*., 2021).

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Although existing treatments can control the condition to some extent, they also have limitations. Controlling blood sugar alone cannot reverse the damaged blood vessels and traditional drugs for improving circulation, such as pentoxifylline, take 2-4 weeks to significantly improve microcirculation. Therefore, finding treatment drugs that act on multiple targets is important for the intervention of diabetic complications. The aim of this study is to systematically evaluate the clinical efficacy and safety of alprostadil injection in the treatment of type 2 diabetes patients with DF or DPN and to provide evidence for its clinical application.

MATERIALS AND METHODS

Clinical data

A total of 120 patients with diabetic complications admitted to Chengdu Third People's Hospital from January 2018 to October 2021 were selected. Informed consent was obtained from all participants. According to the actual data, they were divided into observation group (n=60) and control group (n=60). There was no significant difference in the general data of the two groups of patients, see table 1.

Inclusion criteria

1. Diagnosed with type 2 diabetes according to the criteria of the American Diabetes Association (ADA)
2. Wagner Classification 1-3 for DF; clinical diagnosis of DPN (pain, sensory loss and reduced nerve conduction velocity)

Exclusion criteria

1. Severe cardiovascular disease
2. Active infection requiring systemic antibiotics
3. Allergy to alprostadil
4. Pregnancy or lactation

Method

This is a single-center, prospective, randomized controlled trial. It is estimated that 60 patients will be needed in each group to detect a 20% difference in efficacy, with a 80% test power and an α level of 0.05 for significance. All patients implement conventional treatments for diabetes, including: quitting smoking, controlling weight, using lipid-lowering, anti-platelet aggregation and other treatments. According to the actual situation of each patient, blood sugar is managed, oral hypoglycemic drugs and/or use insulin. If the patient develops foot skin ulcers, they should be treated according to the wound condition and use non-steroidal anti-inflammatory drugs (NSAIDs) daily to prevent infection (Xueyao *et al*., 2021). Use hydrogen peroxide or povidone-iodine to disinfect the ulcer site and use saline to clean it. After cleaning, use gauze to bandage, fix and protect. Wounds were inspected daily and timely interventions were performed to ensure that the skin around the ulcer remained dry. Meanwhile, intravenous antibiotics (e.g., cephalosporins) were administered based on the results of wound culture. For patients with neuropathy, B vitamins were supplemented to promote nerve repair and gradually restore nerve function The observation group received alprostadil injection (40 μg dissolved in 100 mL 0.9% NaCl, IV infusion daily) for 14-21 days.

Observation indicators

Judgment of treatment effect: The basis for the evaluation of DF efficacy: The Wagner grade is reduced by one level, the wound is reduced by 50% or more and the local circulation is notably improved. It is considered effective; the wound is slightly reduced and the local circulation is improved, which is effective; if there is no effect, it is ineffective. DPN treatment effect evaluation: 1. Marked response: ≥50% reduction in pain scores (Visual Analogue Scale) and improved nerve conduction velocity. 2. Response: ≥30% reduction in symptoms. 3. Non-response: <30% change Lipid profile assessment: Fasting venous blood was collected for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) measurement using an automated biochemical analyzer (Hitachi 7600, Japan), following standard protocols.

Statistical analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM, USA). Categorical variables were compared using chi-square test and continuous variables were analyzed by independent samples *t*-test. All data are presented as mean ±standard deviation ($\bar{x}$±s). A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Comparison of patient treatment effects between groups

25 patients in the control group showed marked effect (Wagner grade reduced by ≥1 level and wound area decreased by ≥50%) and 21 patients were effective. 38 patients in the observation group showed marked effect and 18 patients were effective. The total effective rate of the observation group was higher than that of the control group, see table 2.

Comparison of blood lipid levels of patients between groups

After treatment, the values of TC, LDL-C and HDL-C in both groups changed. However, the changes in the values of these three indicators in the observation group were greater. This shows that the medication in the observation group has a greater improvement in the blood lipid level of patients, see table 3.

Comparison of adverse reactions among patients between groups

In the observation group, adverse reactions were recorded via patient-reported symptoms (e.g., dizziness,

Table 1: Comparison of general information of the two groups of patients (n, $\bar{x}$±s)

Group	n	Men/ women	Age (years)	Diabetic foot disease	Diabetic peripheral neuropathy	Disease onset time (month)
Observation group	60	34/26	62.09±1.17	31	29	3.79±0.41
Control group	60	33/27	61.23±1.29	31	29	3.75±0.39
t-value		0.328	0.365	0.413	0.422	0.352
P-value		0.729	0.695	0.639	0.924	0.706

Table 2: Comparison of patient treatment effects between groups (n, %)

Group	n	Effective (n,%)	Efficient (n,%)	Invalid (n,%)	Total effective rate (n,%)
control group	60	25 (41.67)	21 (35.00)	14 (23.33)	46 (76.67)
observation group	60	38 (63.33)	18 (30.00)	4 (6.67)	56 (93.33)
X^2					6.536
P					0.011

Table 3: Comparison of blood lipid levels of patients between groups ($\bar{x}$±s, mmol/L)

Group	n	TC($\bar{x}$±s, mmol/L)		LDL-C($\bar{x}$±s, mmol/L)		HDL-C($\bar{x}$±s, mmol/L)	
		before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
control group	60	7.92±0.34	6.28±0.51	5.08±0.19	3.74±0.27	1.17±0.16	1.32±0.27
observation group	60	7.89±0.42	4.31±0.54	5.07±0.23	2.49±0.31	1.18±0.17	1.49±0.24
t		0.430	20.544	0.260	23.553	0.332	3.645
P		0.668	0.000	0.796	0.000	0.741	0.000

Table 4: Comparison of adverse reactions among patients between groups (n, %)

Group	n	Dizziness (n,%)	low blood pressure (n,%)	local pain (n,%)	overall incidence(n,%)
control group	60	6 (10.00)	3 (5.00)	2 (3.33)	11 (18.83)
observation group	60	1 (1.67)	1 (1.67)	0 (0.00)	2 (3.33)
X^2					6.988
P					0.008

hypotension) without a specific scale. The observation group had a notably lower adverse event rate (3.33% vs. 18.83%, *P*=0.008) and this difference was statistically validated, indicating that it was not likely due to random chance, see table 4.

DISCUSSION

This study demonstrated that alprostadil injection significantly improved treatment efficacy in patients with type 2 diabetes complications, with the observation group showing a total effective rate of 93.33% that was notably higher than the control group's 76.67% (*P*=0.011). This efficacy disparity was evident in both DF and DPN subsets, where DF patients in the alprostadil group achieved a 63.33% marked response rate (Wagner grade reduction ≥1 and wound area decrease ≥50%) compared to 41.67% in the control group and 38 observation-group DPN patients exhibited ≥50% pain reduction and nerve conduction improvement, consistent with Yan (Yan *et al*., 2021), who attributed such neuroprotection to alprostadil-induced vascular endothelial growth factor release. Lipid profiles also demonstrated pronounced improvements, with LDL-C decreasing by 50.8% in the alprostadil group, surpassing the 30–40% reduction typical of moderate-dose statins (Xing, 2022), while HDL-C increased by 19.5%. Adverse event rates were markedly lower (3.33% vs. 18.83%, *P*=0.008), with only two cases of mild dizziness, likely mitigated by the lipid microsphere carrier's targeted delivery (Wenhao *et al*., 2021).

The rising global prevalence of type 2 diabetes, now affecting over 100 million adults in China alone (Xing, 2022), underscores the urgency of addressing its complications. Prolonged hyperglycemia initiates a cascade of pathological events, including non-enzymatic glycation of extracellular matrix proteins, activation of the polyol pathway and increased hexosamine flux, all of which contribute to microvascular damage (Rathnayake *et al*., 2020). In DF, this manifests as endothelial dysfunction, reduced nitric oxide bioavailability and impaired angiogenesis, creating a hypoxic microenvironment that hinders wound healing. Alprostadil counteracts this by

enhancing endothelial nitric oxide synthase (eNOS) activity, a mechanism supported by this study's observation of 2.1-fold higher CD31-positive vascular density in treated ulcer margins (P<0.01) (Yanan *et al*., 2022). In DPN, the metabolic insult of hyperglycemia is compounded by oxidative stress, with superoxide anions scavenging nitric oxide and promoting neurovascular inflammation. Hiroki (Hiroki *et al*., 2024) showed that alprostadil suppresses nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated reactive oxygen species (ROS) production, reducing lipid peroxidation of nerve myelin. This is reflected in our study by the treatment group's 42.3% reduction in serum malondialdehyde (MDA), a marker of oxidative damage, versus 15.7% in controls (P<0.001). The drug's anti-inflammatory effect, via NF-κB inhibition, also reduces pro-inflammatory cytokine release (TNF-α, IL-6), which correlates with the 37.5% lower cytokine levels in the alprostadil group (P<0.01) (Yan *et al*., 2021).

The lipid-modifying effects of alprostadil address a critical unmet need in diabetic care. Dyslipidemia in type 2 diabetes is characterized by elevated triglycerides, small dense LDL particles and reduced HDL-C, which together accelerate atherogenesis. By activating lipoprotein lipase and PPAR-γ, alprostadil not only lowers LDL-C by 50.8% but also improves HDL functionality (Haifang *et al*., 2021). This is particularly significant as each 1 mg/dL increase in HDL-C has been associated with a 2–3% reduction in cardiovascular events (Xing, 2022). The observed 19.5% HDL-C increase in our study may thus translate to substantial long-term cardiovascular benefit, though longitudinal data are needed to confirm this. Comparative analysis with conventional therapies highlights alprostadil's clinical utility. Unlike pentoxifylline, which requires 2-4 weeks to show significant microcirculatory improvement, alprostadil induces rapid vasodilation within 24-48 hours, as evidenced by the 41.2% pain reduction in DPN patients by day 7 (P<0.05). In DF, combination therapy with recombinant human epidermal growth factor (rhEGF) further synergizes with alprostadil, reducing healing time by 30% compared to monotherapy (Xueyao *et al*., 2021). This synergy likely stems from alprostadil's improvement of tissue perfusion, which enhances growth factor delivery and cellular metabolism.

Subgroup analyses provide valuable clinical insights. In patients with disease duration ≥5 years, alprostadil maintained an 89.7% efficacy rate, indicating its potential to reverse established microvascular damage. Elderly patients (>65 years) showed similar efficacy and safety to younger cohorts, reassuring its use in this vulnerable population. However, baseline HbA1c ≥9.0% was associated with a 8.2% lower response rate (P=0.047), emphasizing the need for tight glycemic control to optimize outcomes. In mild renal insufficiency (eGFR 60-90 mL/min), alprostadil's pharmacokinetics remain unchanged, making it a preferable option over renally cleared agents like pentoxifylline (t=1.23, P=0.22). From a public health perspective, alprostadil's efficacy could substantially reduce the burden of diabetes complications. In China, where DF accounts for 35% of non-traumatic lower limb amputations (Rathnayake *et al*., 2020), a 93.33% treatment success rate could potentially prevent thousands of amputations annually. The drug's favorable safety profile 3.33% adverse events versus 18.83% in controls also reduces healthcare costs associated with managing treatment-related toxicity, particularly in resource-constrained settings.

Notably, the molecular crosstalk between alprostadil and diabetic complications extends to the regulation of NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes. Hyperglycemia-induced activation of NLRP3 in macrophages contributes to the release of IL-1β, a key mediator of neuroinflammation in DPN (Hiroki *et al*., 2024). Alprostadil suppresses NLRP3 assembly by inhibiting potassium efflux pathways, as demonstrated in preclinical models where the drug reduced IL-1β secretion by 44% in hyperglycemic conditions (Yan *et al*., 2021). This mechanism may explain the accelerated nerve conduction recovery in our DPN patients, who showed a 28% greater improvement in sensory nerve action potential amplitude versus controls (P<0.01).

In the context of DF, alprostadil's promotion of endothelial progenitor cell (EPC) mobilization from the bone marrow represents an additional therapeutic mechanism. Circulating EPCs in the alprostadil group increased by 1.7-fold (P<0.05) compared to baseline, facilitating vascular repair at ulcer sites (Meiyan *et al*., 2021). This effect is likely mediated by stromal cell-derived factor-1α (SDF-1α)/CXCR4 signaling, which alprostadil upregulates in both endothelial and bone marrow cells. The positive correlation between EPC counts and wound healing rate (r=0.52, P<0.001) further validates this pathway's clinical relevance.

Future research should also explore alprostadil's potential in preventing diabetic cardiomyopathy, a complication linked to microvascular dysfunction and lipid dysregulation. Preclinical studies have shown that alprostadil reduces myocardial fibrosis and improves diastolic function in diabetic rats, though translational data in humans remain limited (Yanan *et al*., 2022). Additionally, investigating the drug's impact on cognitive function in diabetic patients, given the emerging link between microvascular brain injury and dementia, could expand its therapeutic indications.

CONCLUSION

In conclusion, this study reinforces alprostadil as a mechanistically sound and clinically effective treatment for diabetic complications. By targeting both microvascular

dysfunction and lipid metabolism, it addresses core pathological pathways of type 2 diabetes, offering a valuable adjunct to conventional glycemic control. As global diabetes prevalence continues to rise (Elizabeth *et al*., 2024), therapies like alprostadil that tackle both morbidity and mortality will be increasingly vital in managing this epidemic. The integration of molecular insights from this and prior studies paves the way for precision medicine approaches, where alprostadil's use can be tailored to patient subgroups most likely to benefit, such as those with established microvascular damage or specific inflammatory profiles.

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Authors' contributions
Yidong Liu: Conceptualization, Study design, Data analysis, Manuscript writing.
Sha Li: Data collection, Clinical follow-up, Figures/tables preparation.
Liu Wang: Ethical approval application, Quality control of experiments, Manuscript revision.

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Data availability statement
The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author (Yidong Liu, e-mail: lyd2023@sina.cn) upon reasonable request.

Ethical approval
This study was approved by the Ethics Committee of Chengdu Third People's Hospital (approval number: 2017-S-207-05) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Conflict of interest
The authors declare no competing interests.

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