Medical Policy

Subject: Outpatient Intravenous Insulin Therapy

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Description/Scope

This document addresses outpatient intravenous insulin therapy, also referred to as the following:

- Chronic intermittent intravenous insulin infusion therapy (CIIIT)
- Hepatic activation
- Metabolic activation therapy (MAT)
- Outpatient intravenous insulin therapy (OIVIT)
- Physiologic insulin resensitization (PIR)
- Pulsatile intravenous insulin therapy (PIVIT)
- Pulse insulin therapy (PIT)

Outpatient intravenous insulin therapy has been proposed as an adjunctive or alternative therapy for the treatment of type 1 diabetes.

Note: Please see the following for information on diabetes treatment:

- CG-DME-42 Continuous Glucose Monitoring Devices
- CG-DME-50 Automated Insulin Delivery Systems
- CG-DME-51 External Insulin Pumps

Position Statement

Investigational and Not Medically Necessary:

Outpatient intravenous insulin therapy is considered **investigational and not medically necessary** as a treatment for all indications, including diabetes.

Rationale

Individuals with type 1 diabetes require exogenous insulin therapy with or without oral medication therapy. Standard, optimal management of type 1 diabetes involves an individualized regimen of dietary, drug, and insulin therapy, with the goal of achieving target HbA1c concentrations of less than 7%. This goal has been shown to reduce microvascular and neuropathic complications of diabetes (American Diabetes Association, 2015). Different types of exogenous insulin are available with short-, medium-, and long-acting preparations typically combined to provide optimal coverage after and between meals. Commonly used oral medications include thiazolidinediones to increase glucose uptake in the muscle, liver, and gut, and metformin to suppress hepatic glucose production. Because of the many variables associated with optimal diabetic management, randomized controlled clinical trials are necessary to validate treatment effectiveness.

Outpatient intravenous insulin therapy, also referred to as CIIIT, hepatic activation therapy, MAT, OIVIT, PIR, PIVIT, or PIT, has been proposed treatment of diabetes that involves the delivery of insulin intravenously over a 5- to 7-hour period in a pulsatile fashion using a pump controlled by a computerized program. The dose of insulin is adjusted according to frequent blood glucose monitoring, and are proposed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections of insulin. It is proposed that this therapy results in improved glucose control through improved hepatic activation. Although the exact physiologic mechanism is unclear, Aoki, one of the principal investigators of MAT, proposes that in diabetics lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. Weekly 5- to 7-hour intravenous pulsatile infusions of insulin given while the individual ingests a carbohydrate meal are designed to increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes.

Aoki and colleagues (1995) studied the effect of CIIIT on hypertension control in 26 individuals with type 1 diabetes and associated hypertension and nephropathy. The 26 participants were randomly assigned to a control group or treatment group for 3 months and then crossed over to the opposite group for an additional 3 months. At baseline, all participants were being treated with 4 daily insulin injections and had achieved acceptable HbA1c levels of 7.4%. They also achieved acceptable baseline blood pressure control with medications adjusted according to a predetermined protocol. Treatment was begun with angiotensin converting enzyme inhibitors (ACEi). Individual regimens were compared by converting their dose to an “antihypertension medication dose unit” (AHM U) with the lowest recommended dose for each medication counting as one unit. While the study was randomized, it was not blinded in that sham CIIIT procedures were not performed. Therefore, those receiving CIIIT received more intense follow-up during this period. During the treatment phase, participants reported a significant decrease in the dosage of antihypertensive medicines. No difference in glycemic control was noted. Since all individuals had adequate blood pressure

control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Dailey and colleagues (2000) reported the effects of CIIIT on the progression of diabetic nephropathy in a prospective, non-randomized trial of 49 individuals with type 1 diabetes. A total of 26 participants were assigned to the control group, while 23 individuals were assigned to the treatment group who underwent weekly CIIIT. Both groups reported a similar significant decrease in HbA1c levels during the 18-month study period. The creatinine clearance declined in both groups, as expected, but the rate of decline in the treatment group was significantly less compared to the control group. Again, the clinical significance of this finding is uncertain particularly since the decrease in HbA1c was similar in both groups.

In a pilot study (Weinrauch, 2007), 10 individuals were treated with PIVIT and compared to a control group of 8 individuals treated with subcutaneous insulin. The investigators hypothesized that renal function would be preserved by mechanisms "involving cardiac autonomic function, cardiac mass, or efficiency or by hemostatic mechanisms." However, despite improvement of fuel oxidation noted by respiratory quotient, there was no significant difference between the control group and the treatment group in preservation of renal function.

In a randomized pilot study of PIVIT, Weinrauch (2010) reported the results of 65 evaluable participants out of 90 enrollees with type 1 diabetes and moderately severe (creatinine clearance greater than 30 mL/min; mean 58.2 mL/min PIVIT cohort and 63.5 mL/min control) nephropathy. All participants received standard therapy which included 3 to 4 insulin injections per day. Those randomized to the treatment group received additional weekly PIVIT with boluses of carbohydrates. Primary endpoints included decreased progression of diabetic renal disease and deterioration of the eye. During the follow-up period ranging from 6 to 22 months, the serum creatinine increased significantly from baseline in the control group (1.55 to 1.93; p=0.0038), but not in the PIVIT treatment group (1.62 to 1.71; p=0.1439). Although creatinine clearance decreased for both cohorts, the differences were not significant in the group receiving weekly PIVIT. Urine protein excretion did not significantly change at follow-up in either cohort. There were no statistically significant differences in the grade and occurrence of progressive retinopathy between the two groups. The authors concluded glycemia management was equally effective in both study groups and there was no beneficial retinal effect from PIVIT. Larger studies with longer follow-up are needed to further study the impact of PIVIT on renal preservation in type 1 diabetes.

Between 1995 and 2010 there were several studies that suggested CIIIT may improve glycemic control, slow progression of nephropathy or facilitate blood pressure control. However, these studies lacked adequate controls, randomization, and blinding, and the small sample sizes of the available studies preclude definitive conclusions regarding the health benefit of CIIIT. All other studies of CIIIT therapy were case series.

In 2009, Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) noting that "OIVIT does not improve health outcomes."

The 2024 American Diabetes Association's (ADA's) Standards of Care in Diabetes encompasses the latest clinical practice recommendations. This document aims to outline the key elements of diabetes management, setting general treatment objectives and guidelines, as well as providing tools to assess care quality. It does not address chronic intermittent intravenous insulin therapy, hepatic activation, outpatient intravenous insulin therapy, metabolic activation therapy, physiologic insulin resensitization, pulsatile intravenous insulin therapy, or pulse insulin therapy.

The American Association of Clinical Endocrinology (AACE) updated their clinical practice guideline for developing a diabetes mellitus comprehensive care plan in 2022. This guideline did not address chronic intermittent intravenous insulin therapy, hepatic activation, outpatient intravenous insulin therapy, metabolic activation therapy, physiologic insulin resensitization, pulsatile intravenous insulin therapy, or pulse insulin therapy.

At present, there is a lack of sufficient scientific evidence published in peer-reviewed medical literature to draw reasonable conclusions about the safety, efficacy, or improved net health outcomes of outpatient intravenous insulin therapy.

Background/Overview

Aside from standard diet, drug and insulin therapy, other treatment methods for type 1 diabetes have been proposed. Outpatient intravenous insulin therapy, also referred to as CIIIT, hepatic activation therapy, MAT, OIVIT, PIR, PIVIT, or PIT is one such treatment. Outpatient intravenous insulin therapy involves intravenous infusion of insulin over extended periods of time with the goal of improving physiological glucose control. Individuals receiving this therapy undergo intravenous insulin weekly for 5- to 7 hours at a time while eating a carbohydrate-rich meal. This is intended to increase concentrations of insulin in the portal vein of the kidney to stimulate the synthesis enzymes that are sensitive to insulin, which has been proposed to increase their ability to respond appropriately to carbohydrates, improve their glucose control, and decrease their diabetes symptoms.

Definitions

Diabetes mellitus: A variable disorder of carbohydrate metabolism caused by a combination of hereditary and environmental factors and usually characterized by inadequate secretion or utilization of insulin, by excessive urine production, by excessive amounts of sugar in the blood and urine, and by thirst, hunger, and loss of weight.

Insulin: A protein hormone that is synthesized in the pancreas from proinsulin and secreted by the beta cells of the islets of Langerhans, that is essential for the metabolism of carbohydrates, lipids, and proteins, that regulates blood sugar levels by facilitating the uptake of glucose into tissues, by promoting its conversion into glycogen, fatty acids, and triglycerides, and by reducing the release of glucose from the liver, and that when produced in insufficient quantities results in diabetes mellitus.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

HCPCS

G9147	Outpatient intravenous insulin treatment (OIVIT) either pulsatile or continuous, by any means, guided by the results of measurements for: respiratory quotient; and/or, urine urea nitrogen (UUN); and/or, arterial, venous or capillary glucose; and/or potassium concentration

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. Lancet. 1993; 342(8870):515-518.
2. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. Am J Med. 1995; 99(6):683-684.
3. Aoki TT, Grecu EO, Arcangeli MA, et al. Chronic intermittent intravenous insulin therapy: a new frontier in diabetes therapy. Diabetes Technol Ther. 2001; 3(1):111-123.
4. Aoki TT, Grecu EO, Prendergast JJ, et al. Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirement in IDDM subjects with hypertension and nephropathy. Diabetes Care.1995; 18(9):1260-1265.
5. Dailey GE, Boden GH, Creech RH, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism. 2000; 49(11):1491-1495.
6. Gill G, Williams G. Long term intermittent intravenous therapy and type 1 diabetes mellitus. Lancet.1993; 342(8878):1056-1058.
7. Weinrauch LA, Burger AJ, Aepfelbacher F, et al. A pilot study to test the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria. Metabolism. 2007; 56(11):1453-1457.
8. Weinrauch L, Sun J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism 2010; 59(10):1429-1434.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Diabetes Association Professional Practice Committee. Summary of Revisions: Standards of Care in Diabetes-2024. Diabetes Care. 2024 Jan 1;47 Suppl 1:S5-S10.
2. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022; 28(10):923-1049.
3. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination: Outpatient intravenous insulin treatment (40.7). Effective December 23, 2009. Available at: https://www.cms.gov/medicare-coverage-database/search.aspx . Accessed on October 14, 2024.
4. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and American college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015; 21 Suppl 1:1-87.
5. Powers MA, Bardsley J, Cypress M, et al. American Diabetes Association. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. July 2015. Available at: https://care.diabetesjournals.org/content/early/2015/06/02/dc15-0730. Accessed on October 14, 2024.

Websites for Additional Information

1. American Diabetes Association. Available at: http://www.diabetes.org/. Accessed on October 14, 2024.
2. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diabetes. Available at https://www.niddk.nih.gov/health-information/diabetes. Accessed on October 14, 2024.

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Document History

Status	Date	Action
New	11/14/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.