Kansas City

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Chronic Intermittent Intravenous Insulin Therapy (CIIIT)

Policy Number: 2.01.43
Origination: 3/2012
Last Review: 9/2014
Next Review: 3/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for chronic intermittent intravenous insulin therapy (CIIIT). This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Chronic intermittent intravenous insulin therapy is considered **investigational**.

Considerations

HCPCS code was created specific to this therapy:

- 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.

Description of Procedure or Service

Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dosage insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, it is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

Background

There are 3 main sites of insulin-mediated glucose homeostasis that must function in a coordinated fashion to maintain euglycemia: 1) insulin secretion by the pancreas; 2) glucose uptake, primarily in the muscle, liver, gut, and fat; and 3) hepatic glucose production. For example, in the fasting state, when insulin levels are low, the majority of glucose uptake is non-insulin mediated. Glucose uptake is then balanced by liver production of glucose, critical to nourish vital organs, such as the brain. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, as can be seen in diabetic patients, marked hyperglycemia may result. Different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (i.e., sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (i.e., pioglitazone [Actos®] and rosiglitazone [Avandia®]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (i.e., metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of the above classes of drugs, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy, with or without additional drug therapy with thiazolidinediones or metformin. Large-scale randomized studies have established that tight glucose control is associated with a decreased incidence of microvascular complications of diabetes (i.e., nephropathy, neuropathy, and retinopathy). Currently, the American Diabetics Association recommends a target hemoglobin A1c (HbA1c) concentration of less than 7%.

Chronic intermittent intravenous insulin therapy (CIIIT) also referred to as outpatient intravenous insulin therapy (OIVIT), hepatic activation, or metabolic activation, involves delivering insulin intravenously over a 6- to 7-hour period in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the dosages based on frequent blood glucose monitoring. The pulses are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections. This higher level of insulin is thought to more closely mimic the body's natural levels of insulin as they are delivered to the liver. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation.

CIIIT is typically delivered once weekly as outpatient therapy.

Regulatory Status
Any insulin infusion pump can be used for the purposes of CIIIT. Infusion pumps have received U.S. Food and Drug Administration (FDA) marketing clearance through the 510(k) process, as they are determined to be substantially equivalent to predicate devices for the delivery of intravenous medications.

Rationale

Literature Review

This policy was originally created in 2001 and was regularly updated with literature reviews through searches of the MEDLINE database, most recently through June 2, 2014. No new relevant research studies were identified in the most recent literature review. Following is a key summary of the literature to date, which primarily addresses whether chronic intermittent intravenous insulin therapy (CIIIT) improves glycemic control in diabetic patients and whether CIIIT reduces end organ damage associated with diabetes. No studies were identified that investigate the proposed mechanism of action of CIIIT in humans.

Does CIIIT improve glycemic control in diabetic patients?

Because of the many variables associated with diabetic management, randomized controlled trials (RCTs) are necessary to validate treatment effectiveness. A MEDLINE literature search did not identify any blinded randomized clinical trials focusing on the efficacy of CIIIT for glucose control.

In 1993, Aoki et al published a case series of 20 patients with "brittle" type 1 diabetes. All patients received 4 daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Throughout the study, patients remained in close contact with the clinic (at least once a week), during which appropriate adjustments in diet, insulin therapy, and activity were made. While the study reported a decrease in the HbA1c levels, the lack of a control group limits the interpretation of results. For example, the intense follow-up of the patients could have impacted results, regardless of any possible effects of the CIIIT. (1, 2)

Aoki et al also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1diabetes and associated hypertension and nephropathy. (3) The 26 patients 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 patients were being treated with 4 daily insulin injections and had achieved acceptable HbA1c levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (below 140/90 mm Hg) with a variety of medications (ie, angiotensin converting enzyme inhibitors, calcium channel blockers, loop diuretics, and alpha-2 agonists). While the study was randomized, it was not blinded in that sham CIIIT procedures were not performed. Therefore, those patients receiving CIIIT received more intense follow-up during this period. During the treatment phase, patients reported a significant decrease in dosage of antihypertensive medicines. No difference in glycemic control was noted. Because all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Does CIIIT reduce diabetic end-organ damage?

Because of the many variables associated with diabetic management, RCTs are necessary to validate treatment effectiveness. A MEDLINE literature search identified 2 RCTs focusing on the efficacy of CIIIT for reducing diabetic end organ complications.
In 2000, Dailey et al reported on the effect of CIIIT on the progression of diabetic nephropathy. (4) A total of 49 patients with type 1 diabetes were included. Of these, 26 were assigned to the control group, and 23 were assigned to the treatment group that underwent weekly CIIIT. Both groups reported a significant decrease in HbA1c 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 with the control group. Again, the clinical significance of this finding is uncertain; larger clinical trials that look at the end point of time to progression of renal failure are needed.

In 2010, Weinrauch et al published a study of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type I diabetes. (5) Patients were randomly allocated to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29) or standard therapy plus weekly CIIIT (n=36). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, diabetic control, and renal function (average creatinine 1.59 mg/dL, average creatinine clearance 60.6 mL/minute). Primary end points were progression of diabetic retinopathy and nephropathy. There was no significant difference in progression of diabetic retinopathy. Progression was noted in 18.8% of 122 eyes that were adequately evaluated (17.9% of 67 treated eyes, 20.0% of 55 controls; p=0.39). On average, serum creatinine increased in both groups; the increase was less in the treatment group (0.09 mg/dL vs 0.39 mg/dL, respectively; p=0.035). While average creatinine clearance fell less in the treatment group, the difference was not significant (-5.1 mL/minute vs -9.9 mL/minute, respectively; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown and requires further evaluation in trials involving a larger number of patients.

Ongoing Clinical Trials

A search of the online database ClinicalTrials.gov, in June 2014, identified the following studies evaluating the use of CIIIT.

- Multicenter Trial to Evaluate the Effects of Intensive Bolus Intravenous Insulin Delivery on Metabolic Integrity in Type 1 and Type 2 Diabetics Who Despite Tight Control and Proper Diet Still Suffer From Metabolic Problems (NCT01023165) – This is a nonrandomized Phase 3 trial to evaluate outcomes related to quality of life and diabetic complications in patients with diabetic complications who undergo weekly bolus insulin sessions. Enrollment is planned for 2000 subjects; the planned study completion date is November 2015.

- A Randomized Controlled Trial to Evaluate Early Intermittent Intensive Insulin Therapy as an Effective Treatment of Type 2 Diabetes: REmission Studies Evaluating Type 2 DM - Intermittent Insulin Therapy (RESET-IT) (NCT01755468) – This is a randomized, open-label trial to compare intermittent insulin therapy with continuous metformin therapy for patients with type 2 diabetes. Enrollment is planned for 148 subjects; the planned study completion date is December 2017.

Summary

Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dosage insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, it is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

It is hypothesized that CIIIT improves hepatic glucose regulation. A limited number of uncontrolled studies suggest that CIIIT may improve glycemic control. Two randomized trials report that CIIIT may

moderate the progression of nephropathy. However, the published studies are small and report benefits on intermediate outcomes only (ie, changes in laboratory values). This evidence does not permit definitive conclusions regarding the health benefits of CIIIT. Therefore, the technique is considered investigational.

Practice Guidelines and Position Statements

Clinical practice guidelines from professional associations, including the American Diabetes Association and the American Association of Clinical Endocrinologists, do not include CIIIT within each organization's clinical practice guidelines for diabetes. (6-8) The American College of Physicians published a clinical practice guideline in 2011 on the use of intensive insulin therapy for the management of glycemic control in hospitalized patients(9); the recommendations put forth in this guideline were based on earlier systematic review on this topic which did not include CIIIT. (10)

CIIIT is not a preventive service and is therefore not included in the U.S. Preventive Services Task Force recommendations for preventive services.

Medicare National Coverage

"Effective for claims with dates of service on and after December 23, 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that outpatient intravenous insulin therapy (OIVIT, ie, CIIIT) does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally noncovered under Medicare when furnished pursuant to an OIVIT regimen (see subsection A. above)."

References

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Billing Coding/Physician Documentation Information

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

Additional Policy Key Words

N/A

Policy Implementation/Update Information

3/1/12 New policy; considered investigational
9/1/12 No policy statement changes.
3/1/13 No policy statement changes.
9/1/13 No policy statement changes.
3/1/14 No policy statement changes.
9/1/14 No policy statement changes.
