Chronic Intermittent Intravenous Insulin Therapy

Title: Chronic Intermittent Intravenous Insulin Therapy

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<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:  • With type 1 diabetes</td>
<td>Interventions of interest are:  • Chronic intermittent intravenous insulin therapy</td>
<td>Comparators of interest are:  • Standard medical management</td>
<td>Relevant outcomes include:  • Symptoms  • Change in disease status  • Treatment-related morbidity</td>
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</table>

**DESCRIPTION**

Chronic intermittent intravenous insulin therapy (CIIT) 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.
OBJECTIVE
The objective of this policy is to evaluate whether the use of chronic intermittent intravenous insulin therapy improves glycemic control and end-organ damage outcomes for patients with type 1 diabetes, compared with standard insulin therapy.

BACKGROUND
Glucose Homeostasis
Insulin-mediated glucose homeostasis involves 3 primary functions which occur at 3 locations: (1) insulin secretion by the pancreas; (2) glucose uptake, primarily in the muscle, liver, gut, and fat; and (3) hepatic glucose production. In the fasting state, when insulin levels are low, most glucose uptake into cells is non-insulin-mediated. Glucose uptake is then balanced by liver production of glucose. 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.

Medications Used for Glucose Homeostasis in Diabetes
Diabetes is characterized by elevated blood glucose levels due to inadequate or absent insulin production (type 1 diabetes) or due to increased hepatic glucose production, decreased peripheral glucose uptake, and decreased insulin secretion (type 2 diabetes).

Different classes of diabetic drug therapy target different aspects of glucose metabolism. Various insulin secretagogues (eg, sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (eg, pioglitazone [Actos], rosiglitazone [Avandia]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (eg, metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of these classes of drugs, with or without additional insulin, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy. Standard insulin management involves use of subcutaneous injection to mimic a physiologic insulin profile. Intravenous insulin is used in the acute inpatient setting for the management of hyperglycemic emergencies (eg, diabetic ketoacidosis).

Chronic Intermittent Insulin Therapy
Several forms of chronic intermittent insulin therapy, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.

Chronic intermittent intravenous insulin therapy (CIIT)—also referred to as outpatient intravenous insulin therapy, pulsatile intravenous insulin therapy, hepatic activation therapy, or metabolic activation therapy—involves delivering insulin intravenously once weekly over several hours in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the dosages based on frequent blood glucose monitoring. CIIT is principally designed to normalize the hepatic metabolism of glucose. In a 1993 article describing the development of the technique, Aoki et al proposed that,
in patients with type 1 diabetes, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. The authors state: “We reasoned that if the liver of an IDDM [insulin-dependent diabetes mellitus; ie, type 1 diabetes] patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated,” and proposed that intermittent intravenous pulsatile infusions of insulin administered once weekly while the patient ingests a carbohydrate meal will increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. 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 because it is delivered to the liver. The goal of this therapy is improved glucose control through improved hepatic activation.

REGULATORY STATUS
Any insulin infusion pump can be used for the purposes of chronic intermittent intravenous insulin therapy. Infusion pumps have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: lZG.

POLICY
Chronic intermittent intravenous insulin therapy is considered experimental / investigational.

POLICY GUIDELINES
This policy does not apply to use of intravenous insulin infusions in the inpatient setting (ie, for the treatment of diabetic ketoacidosis or diabetic hyperosmolar coma).

RATIONALE
This evidence review was conducted through December 20, 2016.

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. Because of the many variables associated with management of diabetes, randomized controlled trials (RCTs) of CIIIT are necessary to permit conclusions about treatment effectiveness.

No studies were identified that investigate the proposed mechanism of action of CIIIT in humans.

CIIIT and Glycemic Control in Diabetic Patients
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 time appropriate adjustments in diet, insulin doses, and physical activity were made. While the study reported a decrease in the hemoglobin A1c (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 (1995) also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy.3 The 26 patients were randomly assigned to a control group or a 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 (<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.

Section Summary: CIIT and Glycemic Control in Diabetic Patients
One nonblinded RCT and 1 cases series reporting on the effect of CIIT on glycemic control in type 1 diabetic patients were identified. Both studies reported improvements: one in HbA1c compared with baseline, and the other in dose of antihypertensive medication in the treatment group compared with control. However, the lack of a blinded control comparator group in the RCT limits the conclusions that can be drawn.

CIIIT and Reductions in Diabetic End-Organ Damage
In 2000, Dailey et al reported on the effects of CIIIT on the progression of diabetic nephropathy.4 Their study included 49 type 1 diabetes patients with nephropathy who were following the Diabetes Control and Complications Trial intensive therapy (IT) regimen. Of these, 26 were assigned to the control group, which continued IT, and 23 were assigned to the treatment group that underwent weekly CIIIT in addition to IT. 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 than 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 1 diabetes.5 Patients were randomly allocated to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or standard therapy plus weekly CIIIT (n=36; treatment group). 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/min). 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 smaller in the treatment group than in the control 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/min vs -9.9 mL/min, respectively; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown.

**Section Summary: CIIIT and Reductions in Diabetic End-Organ Damage**

Two controlled studies focusing on the efficacy of CIIIT for reducing diabetic end-organ complications were identified. Both reported significant improvements in intermediate measures of glycemic control in each group from pre- to postintervention, but did not consistently report differences in clinically meaningful outcomes from the beginning of the studies to the end. Similarly, there were no significant differences between treatment groups in the RCT.

**SUMMARY OF EVIDENCE**

For individuals who have type 1 diabetes who receive chronic intermittent intravenous insulin therapy (CIIIT), the evidence includes 2 randomized controlled trials (RCTs) and uncontrolled studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. A limited number of uncontrolled studies have suggested that CIIIT might improve glycemic control. The 2 RCTs reported that CIIIT might moderate the progression of nephropathy or retinopathy. However, the published studies were small and reported improvements on intermediate outcomes only (ie, changes in laboratory values). The clinical significance of the differences reported in these studies is uncertain. Additionally, most published evidence appeared between 1993 and 2000 and, as a result, does not account for recent improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

Clinical practice guidelines from professional associations, including the American Diabetes Association (updated in 2017) and the American Association of Clinical Endocrinologists and American College of Endocrinology (updated in 2015), have not included chronic intermittent intravenous insulin therapy (CIIIT) in guidelines for managing type 1 diabetes.

The American College of Physicians updated its Best Practice Advice in 2014 on inpatient glycemic control, which provided some recommendations on the use of intensive insulin therapy, including:

- “Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140-200 mg/dL) if insulin therapy is used in SICU [surgical intensive care unit]/MICU [medical intensive care unit] patients.”
- “Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (140 mg/dL) because harms are likely to increase with lower blood glucose targets.”

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>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</td>
<td>2000</td>
<td>Nov 2015 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS

82948 Glucose; blood, reagent strip
94681 Oxygen uptake, expired gas analysis; including CO2 output, percentage oxygen extracted
96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
99070 Supplies and materials (except spectacles), provided by the physician or other qualified health care professional over and above those usually included with the office visit or other services rendered (list drugs, trays, supplies, or materials provided)
99211 Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician or other qualified health care professional. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.

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

J1817 Insulin for administration through DME (i.e., insulin pump) per 50 units

J7050 Infusion, normal saline solution, 250 cc

- There is no specific CPT code describing CIIIT. The following series of CPT codes and HCPCS J codes above are used to describe the various components of CIIIT. Some codes, such as the code for glucose testing, may be used more than once during a single session of CIIIT.

- There is a HCPCS code specific to this therapy: G9147.
Diagnoses
Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>12-09-2016</td>
<td>Policy added to the bcbsks.com web site on 11-09-2016 with an effective date of 12-09-2016.</td>
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REFERENCES