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Research Article

# Accelerated Intensive Insulin Therapy and its Benefits on Compliance and Glycemic Control

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## Abstract

**Background:** Intensive insulin therapy (IIT) simulates normal pancreatic function by closely matching the periodicity and amplitude of insulin secretion in healthy non-diabetic subjects. This is achieved by injecting intravenous (IV) insulin in a pulsatile manner and in a pattern matching the observed blood glucose level. This therapy has shown positive beneficial effects on secondary complications of diabetes. However, the duration of each session for this therapy has been associated with lower patient compliance and a high number of hyperglycemic events during insulin therapy.

**Objective:** We have demonstrated that a shorter IIT protocol duration can improve both patient compliance and reduce the incidence of hyperglycemic events during treatment.

**Method:** We analyzed the de-identified records of Type 1-2 diabetic patients treated at Diabetic Innovations, LLC. from 2016 - 2019 for reasons related to treatment stopping and discontinuance. A secondary analysis was done on the incidence of hyperglycemic events in patient that underwent both the original IIT protocol and the shortened protocol.

**Results:** We found that the duration of each treatment (4 hours) in the original protocol is one of the main causes of patients discontinuing their IIT. Analysis of patients who moved from the original to the shorter protocol showed that the shorter protocol with more frequent insulin pulses is associated with reduction in incidence of hyperglycemic events during IIT.

**Conclusion:** Reducing the length of the IIT protocol into 2 x 1-hour sessions, with 4 minute intervals between insulin pulses, can result in better glycemic control, in addition to potentially improving patient adherence to treatment.

***Keywords:*** *Diabetes; Insulin; Infusion; Intravenous Therapy; Hyperglycemic Events*

## Introduction

Since the discovery of insulin extracted from the pancreas in 1922, subcutaneous insulin injections remain a standard treatment for patients with diabetes. Despite the widespread use of subcuticular insulin, diabetes remains a progressive disease, with severe advanced complications including diabetic ulcers, neuropathy, and nephropathy [1]. There's an increasing amount of data that suggest that the cur-

rent insulin therapy is not effective in preventing long-term complications [1,2]. This lack of efficacy may be attributed to the method of administration for exogenous insulin [3].

After intensive studies and numerous published papers, evidence suggests it is not possible to obtain the concentration of insulin required for normal liver functioning through subcutaneous injections of insulin due to its limited absorption rate and blunted strength [4]. Thus, it was theorized that those enzymatic processes in a normal liver required to initiate carbohydrate metabolism can be "reactivated" in diabetic patients with proper signals, i.e. concurrent high level of oral glucose and intravenous insulin administration. This hypothesis leads to development of hepatic activation process via pulsed intravenous insulin delivery under controlled pressure [5].

In recent years, significant advancements have been made in intravenous pulsed insulin treatment by using an infusion pump that delivers microdoses of insulin intravenously, causing oscillations of insulin consistent with the amplitude of normal insulin secretion [6]. The advanced Intensive Insulin Therapy is an improvement over the original treatment [5]. It mimics both the periodicity and amplitude of normal pancreatic insulin release, which provides advantages in managing both type 1 and type 2 diabetes and associated secondary complications. The improved treatment involves two approximately 4-hour sessions in the first week, which is then reduced to one session weekly and over time reduced to every 2 - 3 weeks. In each session, the patient receives pulses of microdose intravenous insulin, while concurrent weight based oral glucose is administered according to a standard protocol and under medical supervision, typically on an outpatient basis [4,7]. This treatment has shown remarkable advantages for patients with both T1DM and T2DM in managing their complications, although there is not yet a large scale double blind controlled study for this treatment [8,9]. The precise insulin regimen used in this infusion therapy is also not finalized, with new dose regimen still developed as of 2020 [10]. However, the cycles of insulin infusion in the original protocol is given every 6 minutes, which does not match the insulin release pattern of healthy humans, where insulin is secreted from the pancreatic islets on average every 4 minutes [11]. The duration of therapy (4 hours per session) has also been associated with reduced patient compliance.

In this specific study, we will evaluate the deficiency of current Intensive Insulin Therapy regimen and the effects of reducing the duration of each session while increasing the frequency of insulin administration during each session from the standard time of 6-7 minutes between pulses to 4 minutes.

## Methods

### Ethical compliance

All procedures in this study were determined to be exempt, non-human research by Institutional Review Board at University of California Irvine.

### Study design

This retrospective, monocentric study was conducted at Diabetic Innovations, LLC. facility in Scottsdale, Arizona. Inclusion was restricted to patients that received IIT at Diabetic Innovations, LLC. facility in 2016 - 2019. The patient records were de-identified and used for blinded analysis by external analyst.

Primary analysis was done assessing the reasons for treatment discontinuance that was recorded as part of patient exit interview under standard procedure at the treatment center.

A secondary analysis was performed from subset of patients that received the original IIT treatment (3 hours with optional 2 x 30 minutes break) and then continued treatment but using the shortened IIT treatment (2 hours with optional 1 x 30 minutes break). Insulin pulse was changed from every 6 minutes to every 4 minutes. The incidence of hyperglycemic events in these patients was recorded per treatment and was divided in categories between 201 - 251 mg/dL, 251 - 301 mg/dL, or > 301 mg/dL.

## Results

During the evaluation period, a total of 82 patients were enrolled for IIT at Diabetic Innovations, LLC. facility between 2016 - 2019.

### Reasons for discontinuation of treatment

Of the 82 patients, there were 9 (11%) patients that are continuing their treatment. The remaining patients discontinued their treatments, with the reasoning provided in table 1.

| Reason of discontinuance | # of patients |
|---|---|
| Financial issues and/or lack of insurance coverage | 26 (32%) |
| Treatment lasts too long (4 hours per original regimen) | 26 (32%) |
| Patient moved and is too far to travel to facility for IIT | 6 (7%) |
| Decline to provide reason | 15 (18%) |
| Total | 73 (89%) |

***Table 1:*** *Reasons stated by patient for discontinuing intensive insulin therapy. Patients that decided to stop receiving treatment were requested to provide reason of discontinuance during their exit interview.*

Time was found to be a significant reason for discontinuance of the therapy (32% of patients). The original IIT protocol specified up to 4 hours per treatment, with each treatment consisting of 3 X 1-hour sessions, with an optional 30 minutes break in-between sessions. The patients would often leave during the third hour and cut their treatment short.

### Effects of shorter IIT protocol on incidence of hyperglycemic events during treatment

Of the 82 patients treated at Diabetic Innovations, LLC., 15 patients were originally treated with the 4-hours long treatment, but then were converted to 2.5-hours long treatment. These patients were diagnosed with either type 1 (8 patients) or type 2 diabetes (7 patients).

Following the change to the shorter protocol, these patients showed reduction in the incidence of hyperglycemic events between 201 - 251 mg/dL in 10 out of 15 patients (66%), between 251 - 301 mg/dL in 12 out of 15 patients (80%) and > 301 mg/dL in 12 out of 15 patients (80%) (Table 2).

Of these 15 patients that underwent both the original and the shortened IIT protocol, 3 (20%) discontinued their treatment for financial reasons, 2 (13%) because of moving too far from Diabetic Innovations, LLC. facility, and 1 (7%) wanted to go back to the longer protocol. This represents an increase of patient adherence to 60% in the shorter protocol, when compared to 32% in the original.

## Discussion

Reducing the duration of the IIT treatment, from the original 4 hours down to 2 hours from start to finish, has improved patient compliance. This is accomplished by increasing the number of pulses of insulin per 1-hour sessions (from one pulse every 6 minutes, to one pulse every 4 minutes). Our study showed that this resulted in better blood glucose control during treatment and especially after the patient is discharged at the end of treatment. In addition, this change in interval more closely matches the glucose response found in healthy non-diabetic patients.

The liver rapidly responds to fluctuations in insulin secretion, preferentially extracting insulin delivered in pulses [1]. Previous studies have showed that larger doses of insulin given in burst mass strongly predicted insulin clearance [1]. Insulin clearance increases with insulin concentration [4,12], which agrees with observations that the liver clears larger insulin secretory bursts to a greater extent than smaller insulin pulses, given that at least 70% of insulin secretion is pulsatile [1].

| | 201 - 251 mg/dL | | | 251 - 301 mg/dL | | | > 301 mg/dL | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient** | **Original** | **Modified** | **% change** | **Original** | **Modified** | **% change** | **Original** | **Modified** | **% change** |
| 1 | 2.13 | 3.80 | 78% | 1.16 | 1.00 | -14% | 0.69 | 0.00 | -100% |
| 2 | 2.50 | 1.67 | -33% | 1.43 | 1.00 | -30% | 0.39 | 0.33 | -15% |
| 3 | 2.32 | 2.08 | -10% | 1.21 | 0.33 | -73% | 0.46 | 0.08 | -83% |
| 4 | 2.29 | 0.94 | -59% | 0.43 | 0.06 | -87% | 0.00 | 0.00 | 0% |
| 5 | 2.04 | 2.14 | 5% | 0.85 | 1.29 | 52% | 0.21 | 0.00 | -100% |
| 6 | 4.52 | 2.29 | -49% | 1.71 | 1.00 | -42% | 0.31 | 0.00 | -100% |
| 7 | 1.08 | 1.00 | -7% | 0.73 | 0.00 | -100% | 0.24 | 0.00 | -100% |
| 8 | 2.45 | 2.00 | -18% | 0.90 | 0.00 | -100% | 0.10 | 0.00 | -100% |
| 9 | 4.41 | 1.09 | -75% | 2.12 | 0.35 | -83% | 0.48 | 0.06 | -88% |
| 10 | 4.26 | 4.78 | 12% | 3.52 | 1.33 | -62% | 1.42 | 0.78 | -45% |
| 11 | 4.94 | 4.81 | -3% | 1.72 | 1.25 | -27% | 0.40 | 0.06 | -85% |
| 12 | 3.02 | 2.83 | -6% | 1.88 | 2.33 | 24% | 0.73 | 1.00 | 37% |
| 13 | 2.47 | 1.42 | -43% | 1.56 | 0.21 | -87% | 0.34 | 0.12 | -65% |
| 14 | 1.86 | 2.33 | 25% | 0.77 | 1.00 | 30% | 0.45 | 0.50 | 11% |
| 15 | 0.08 | 0.75 | 793% | 0.06 | 0.00 | -100% | 0.05 | 0.00 | -100% |

***Table 2:*** *Mean incidence of hyperglycemic events per treatment. Patients originally received 3 sessions of 1 hour each, with 6 minutes interval between insulin pulses. These patients then were treated using the modified protocol of 2 sessions of 1 hour each, with 4 minutes interval between insulin pulses. Incidence of hyperglycemic events were categorized as between 201 - 251 mg/dL, 251 - 301 mg/dL, or > 301 mg/dL, and was averaged by the number of treatment specific to each patient. # of occurrences were the patients reduced their incidence of hyperglycemic incidence average is highlighted.*

There was a large incidence of hyperglycemic event under the original IIT protocol, which was reduced significantly by using the shortened protocol with more frequent insulin pulses. We believe that this is achieved by the increased match to the physiologic interval of pancreatic insulin secretion, where insulin is secreted from non-diabetic pancreatic islets in a pulsatile pattern with a mean pulse interval of 3.9 ± 0.1 min [8]. In addition, this may be affected by the increased insulin sensitivity of hepatocytes and adipocytes following pulsed insulin treatment [5,13,14]. In our experience, some patients improved within 3-6 months, while others that are severely insulin resistant can take longer 10 - 12 months or longer.

## Conclusion

The shortened protocol for intensive insulin therapy with more frequent (4 minutes vs 6 minutes) of insulin infusion provides a significant improvement by reducing hyperglycemic events during treatment, as well as increasing patient adherence to their treatment.

## Conflicts of Interest

Allison Cimler and John Elliott have previously treated patients under both the original and the modified therapy described in this manuscript.

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