

Treatment of Type 2 Diabetes Using Meal-Triggered Gastric Electrical Stimulation

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ABSTRACT: **Background:** The TANTALUS™ System (MetaCure Limited) is a minimally invasive implantable device for the treatment of type 2 diabetes. The system detects food intake by sensing gastric electrical variations and applies electrical stimulation to the gut synchronized to natural gastric activity. The system is commercially available in Europe and Israel and is in clinical trials in the United States. It has been tested in 132 patients worldwide to date.

Objectives: To re-analyze previously reported data from different studies. This retrospective analysis of the type 2 diabetes subpopulation analyzed the expected benefit and characterized the significance of baseline A1c in the determination of the expected clinical outcome.

Methods: From the total cohort of 132 patients implanted with the TANTALUS device in 10 different centers in Europe and the U.S., we identified 50 subjects (27 females, 23 males) who were obese with uncontrolled T2DM on a stable regime of oral medication for 3 months prior to implant. This population had similar inclusion/exclusion criteria as well as treatment protocols and were all treated for at least 24 weeks. The analysis was based on the A1c change compared to baseline.

Results: Data after 24 weeks demonstrated a reduction in A1c in 80% of the patients with average drop in A1c of 1.1 ± 0.1%. The average weight loss was 5.5 ± 0.7 kg.

Conclusions: The results suggest that the TANTALUS stimulation regime can improve glucose levels and induce moderate weight loss in obese T2DM patients

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or more oral drugs is usually prescribed. However, despite diet and/or pharmacological therapy, many T2DM patients are unsuccessful in achieving the recommended glycemic goal of HbA1c < 7.0 % [1]. Patient compliance with prescribed therapy is one of the major limiting factors in the ability to control blood glucose by oral or injectable agents. Additional medications for other common co-morbidities that typically accompany T2DM further increase the complexity of drug regimen and the challenge to patients' lifestyle.

The TANTALUS™ System (MetaCure Limited) presents a potential solution for some of these patients by introducing two novel features: automatic detection of patient food intake and electrical gastric contractility modulation [2]. This electrical stimulation is referred to as non-excitatory since the signals do not entrain the muscle, but rather maintain basic rhythm by synchronizing their delivery to sensed native slow wave activity. The result is an increase in the force of gastric contractions during stomach distension that was shown to increase vagal afferent activity in animals [3]. This enhancement of vagal afferents is similar to the normal process occurring with food intake or passive gastric distension, thereby imitating the natural satiation effect with a lower level of food-induced distension [4].

This concept of using electrical stimulation to control muscle contractility has been the basis for research since similar concepts were used in cardiac stimulation systems for the treatment of heart failure [5]. Modulation of muscle contractility is achieved by timing each stimulation signal to the refractory period of each slow wave. This effect is achieved without increasing the rate of electrical activity (no pacing).

The system was initially tested in a group of non-diabetic obese subjects and led to statistically significant weight loss [6]. A few additional studies have also included diabetic patients in testing the system [7-11]. Safety of the implantation procedure and stimulation treatment in patients was supported in global clinical studies with 132 subjects, with up to 3 years of documented clinical experience [6-9]. The majority of adverse events were unrelated to the device or procedure; however, most of these events that were procedure-related were consistent with those seen in similar laparoscopic procedures. A few cases of hypoglycemia were reported in subjects

Many type 2 diabetes mellitus patients, especially those in early stages, can manage their blood sugar effectively through diet, weight loss and physical activity. If these interventions are insufficient for effective control, oral medications are typically used. There are different classes of medications, and as the patient condition deteriorates a combination of two

T2DM = type 2 diabetes mellitus

who were being treated with hypoglycemic medications such as sulfonylurea in addition to TANTALUS.

The aim of this analysis was to evaluate the potential effect of the TANTALUS System on glycemic control and changes in body weight in the more focused subgroup of obese T2DM subjects who are unable to control blood glucose with the use of oral medications alone.

PATIENTS AND METHODS

A subgroup of 50 patients was identified from a total of 132 implanted patients using the following inclusion criteria: obesity (body mass index > 30) and presence of T2DM diagnosed and treated for at least 6 months but not more than 10 years.

All patients were treated with a stable regime of combined oral anti-diabetes medication prior to TANTALUS implant with no increase in the medication dose throughout the reported 3 months follow-up period. In addition, these subjects were required not to take any new medication or supplements that might affect the metabolism regardless of application of the device. No diet or exercise program was prescribed. All patients analyzed for this study received a TANTALUS implant and were treated for at least 24 weeks. A1c and weight measurements were taken several times during the study.

The implantation of the TANTALUS System [Figure 1] has been described previously [6]: three bipolar leads (Metacure Limited) were laparoscopically placed in the subserosa of the gastric wall. One electrode was located in the fundus for monitoring gastric distension with food intake. The other two leads were positioned at anterior and posterior sides of the antrum. These electrodes serve to monitor slow wave rate and to deliver GCM therapy. The TANTALUS system was programmed to initiate 45 minutes of GCM sessions upon detection of food intake. The patients were required to charge the system once a week for about 45 minutes using an external, non-invasive wireless charger. The charger is a portable battery-operated device that allows recharging at any time or place.

RESULTS

Average A1c dropped from 8.4 ± 0.1 to 7.3 ± 0.1 ($P < 0.01$). The majority of patients (80%, 40/50) presented with a reduction in A1c, with 52% of the patients (26/50) achieving the A1c target of 7% or lower (all patients had A1c > 7% at baseline). A statistically significant correlation ($P < 0.05$) was found between baseline A1c and the level of A1c drop. A simple regression analysis shows an additional drop of 0.4% in A1c at 24 weeks for each additional 1% at baseline.

GCM = gastric contractility modulation



Figure 1. The TANTALUS™ System

Ninety percent of the patients lost weight with an average weight loss of 5.5 ± 0.7 kg ($P < 0.01$). A weak correlation ($r^2 = 0.13$, $P < 0.01$) was found between weight loss and A1c drop. Many of the patients presented with other metabolic disorders (typical T2DM co-morbidities): 88% (44/50) presented with hypertension (systolic blood pressure > 130 mmHg or diastolic > 85 mmHg) at baseline. Those patients demonstrated reduced blood pressure from an average of 144/89 to 131/80 mmHg ($P < 0.01$).

DISCUSSION

The results of this analysis suggest that the delivery of non-excitatory GCM signals with the TANTALUS system is safe, well tolerated by patients, and has a significant impact on HbA1c and weight loss. This new treatment modality may hold promise for type 2 diabetes patients who are unable to achieve glycemic control in spite of optimal oral anti-diabetic drug therapy and are therefore indicated for injectable treatments such as insulin.

The data suggest that TANTALUS may become a new line of defense or an alternative to the use of insulin, providing

good glycemic control with minimal dependency on patient compliance and with a potential added benefit of weight loss and improved hypertension.

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