Implant for augmentation of cerebral blood flow trial 1: a pilot study evaluating the safety and effectiveness of the Ischaemic Stroke System for treatment of acute ischaemic stroke

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Introduction **In rat stroke models, sphenopalatine ganglion stimulation up to 24 h after stroke onset augments cerebral blood flow, reduces infarct volume and improves neurological deficits. The ischaemic stroke system 500 has been designed to stimulate the sphenopalatine ganglion in humans.**

Objectives **(1) To determine the safety and tolerability of the ischaemic stroke system 500 in acute ischaemic stroke within 24 h of stroke onset. (2) To determine the effectiveness of ischaemic stroke system 500 in acute ischaemic stroke treatment.**

Design/Methods **Implant for augmentation of cerebral blood flow trial-1 is a multi-national open-label study in patients of acute ischaemic stroke in the anterior circulation with National Institutes of Health Stroke Scales 7–20. The treatment initiation will be within 24 h of stroke onset. The ischaemic stroke system is implanted adjacent to the sphenopalatine ganglion via the greater palatine canal using local anaesthesia and a minimally invasive approach. The treatment protocol is constituted as 3–4 h of daily stimulation over 5–7 days.**

Conclusions **The implant for augmentation of cerebral blood flow trial-1 will determine the safety and tolerability of the ischaemic stroke system 500 in acute ischaemic stroke as reflected by the incidence of adverse events.**

Key words: ImpACT, ISS, protocol, stroke, treatment

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ISS: Investigational device. Limited by Federal (United States) law for investigational use.

Introduction

Treatment for acute ischaemic stroke (AIS) poses an imperative, unmet challenge. To date, intravenous recombinant tissue plasminogen activator (IV r-tPA) and mechanical recanalisation remain the only approved treatment modes. The fundamental limitation of these treatments is a short treatment window, up to 4·5 h from stroke onset for IV r-tPA (1, 2), and up to 8 h for the use of the recanalisation devices (3). Consequently, there is no direct treatment for the vast majority of stroke patients.

The ischaemic penumbra, clinically defined as the portion of the ischaemic region destined for infarction, but temporarily salvageable (4, 5), may be targeted within a prolonged therapeutic time window. Restoring blood flow to the penumbra potentially leads to reduced neurological damage. A favourable neurological outcome associated with spontaneous survival of hypoxic tissue was demonstrated even after 12 ± 48 h from stroke onset (6). More so, reperfusion has been shown to enhance angiogenesis in animal models and affect brain plasticity, suggesting improved functional restoration (7, 8).

Recently, the sphenopalatine ganglion (SPG) has been recognised as a source of vasodilating parasympathetic innervation to the anterior cerebral circulation. Studies in rodents, dogs and monkeys have demonstrated that stimulation of SPG neurons leads to a profound ipsilateral increase in the cerebral blood flow (CBF) as a result of arterial vasodilatation, and that this in turn leads to augmentation of tissue perfusion (9–13). The main neurotransmitters of this neuronal pathway are

acetylcholine, vasoactive intestinal polypeptide and nitric oxide (14–17). The physiological function and significance of this pathway is only beginning to be understood. Studies in rats demonstrated that while chronic sectioning of parasympathetic fibres does not appear to affect blood flow (11), spontaneously hypertensive rats with unilateral parasympathetic denervation showed impaired autoregulation of the ipsilateral cerebrovascular bed (18). When denervation is followed by focal cerebral ischaemia, the infarct volume is significantly larger than in nondenervated animals (18, 19). Accordingly, it is suggested that parasympathetic vasodilatation may have a protective effect in pathophysiological conditions involving hypoxia. Complementary to this, Henniger and Fisher, recently studied SPG stimulation in rat models of acute ischaemia using magnetic resonance imaging (MRI) (20). They demonstrated improved penumbral apparent diffusion coefficient (ADC) values, preservation of ADC/CBF-mismatch as well as attenuation of the final infarct volume in SPG-stimulated rats (20). Extensive studies (unpublished data) in rat stroke models have provided evidence that SPG stimulation improves neurological function even when initiated 24 h after stroke.

We hypothesised that stimulation of the SPG in patients with AIS in the anterior circulation will result in ipsilateral vasodilatation, leading to a significant increase of collateral blood flow, enhanced perfusion in the penumbra and improved prognosis. Implant for augmentation of CBF trial-1 (ImpACT-1) was designed as a pilot, prospective, multinational, open-label study aimed to assess the safety, tolerability and effectiveness of the ischaemic stroke system (ISS) in patients with AIS in the anterior circulation within 24 h of stroke onset.

Study design

The study is a prospective, multinational, open-label study in which a comparative group of patients is selected from a resource of clinical trial data: the NINDS r-tPA study on the basis of similar eligibility criteria.

Study objectives

The primary objective of this pilot study is the assessment of the safety of the ISS for the treatment of patients with AIS in the anterior circulation with a treatment time window of up to 24 h from stroke onset.

The secondary objective is to examine the effectiveness of the system in the treatment of AIS.

Study end-points

Primary

Assessment of the safety and tolerability of the ISS. The following parameters will be addressed: the need to stop the treatment sessions; the incidence of procedure complications; expected/unexpected adverse events (AE); and serious adverse events (SAE).

The survival and SAE profile at 90 days will be compared with the data from historical matched control patients.

Secondary

Effectiveness as measured by the distribution of modified Rankin Scale (mRS) scores at day 90; proportion of favourable outcome assessed using dichotomised mRS score (mRS 0–2 vs. 3–6); the proportion of favourable outcome using the National Institutes of Health Stroke Scales (NIHSS) defined as complete recovery (NIHSS 0 or 1) or an improvement of nine or more points in the NIHSS score at day 90; and change in mRS scores from day 7 to 90.

Subjects

Patients with known AIS within the last 24 h, who fulfil the eligibility criteria as specified. Because the primary end-point of ImpACT-1 is safety and tolerability, sample size calculations were not carried out.

Inclusion criteria

1. Age: ≥ 18 and ≤ 85 years of both genders.
2. Patients with symptoms and signs of an acute ischaemic hemispheric stroke within the anterior circulation.
3. NIHSS ≥ 7 and ≤ 20.
4. Treatment can be initiated within the first 24 h following stroke onset or since last seen normal.
5. Signed informed consent has been obtained from the patient him/herself or his/her legally authorised representative.

Exclusion criteria

General

1. Time interval since onset of symptoms undetermined.
2. Treatment with ISS cannot start within the first 24 h poststroke onset.
3. Any other imaging diagnosis including tumour, abscess, primary intracranial haemorrhage (ICH) or secondary haemorrhage (PH1, PH2) (H1 and H2 are allowed) (21), or symptoms suspicious for a subarachnoid haemorrhage, etc.
4. Clinical syndrome of an acute stroke due to lacunar infarct (pure motor hemiparesis, ataxic hemiparesis and sensorimotor stroke), unless brain imaging demonstrates a relevant lesion $> 1{\cdot}5$ cm in size.
5. A stroke in the posterior circulation.
6. Minor stroke with a nondisabling deficit or rapidly improving neurological symptoms with a high probability of a transient ischaemic attack.

7. Eligible for or treated with IV or IA t-PA or mechanical thrombolysis
8. Neurological deficit that has led to stupor or coma (NIHSS level of consciousness score ≥ 2).
9. History of stroke in the previous 6 months.
10. Preexisting disability; mRS > 2 upon screening.
11. Patients under oral anticoagulants or having received heparin within 48 h and/or with an elevated activated partial thromboplastin time (or international normalised ratio).
12. High clinical suspicion of septic embolus.
13. Severe cardiac disease: evidence of congestive heart failure (CHF) or has a history of end-stage cardiovascular disease (e.g. CHF NYHA Class III or IV or unstable angina).
14. Uncontrolled hypertension upon enrolment (systolic > 185 mmHg and/or diastolic > 110 mmHg).
15. Serious systemic infection.
16. Women known to be pregnant or having a positive or an indeterminate pregnancy test.
17. Patients with other implanted neural stimulator.
18. Orthodontics or nonhygienic condition/problems that prevent procedures within the mouth.
19. Life expectancy < 1 year from other causes.
20. Currently participating in any other clinical trial.
21. Patients unable or unwilling to follow protocol requirements.
22. Massive stroke, defined as an acute parenchymal hypodense lesion or effacement of cerebral sulci in over 2/3 of the MCA territory per CT (or equivalent per T2/Flair/DWI MRI).

Surgical
1. Maxillectomy of the operated side.
2. Previous surgery of the pterygopalatine fossa or the infra temporal fossa.
3. Large secondary cleft palate with or without reconstruction.

Device description

The ISS is an easy-to-use device intended for electrical stimulation of the SPG in order to augment cerebral perfusion in ischaemic stroke patients, who are not eligible for reperfusion therapy.

The ISS is comprised of two major components:
1. The implantable neural stimulator (INS) (Fig. 1).
2. The energy delivery control subsystem (EDC) (Fig. 2), divided into three parts:
- The controller
- The driver
- The transmitter

The INS is a 1-in.-long implant inserted through the greater palatine canal using a minimally invasive oral procedure under local anaesthesia. When implanted, the platinum–iridium electrode lies in the extracranial sphenopalatine fossa, in the vicinity of the SPG, and relays the stimulation pulse to the SPG (Fig. 3).

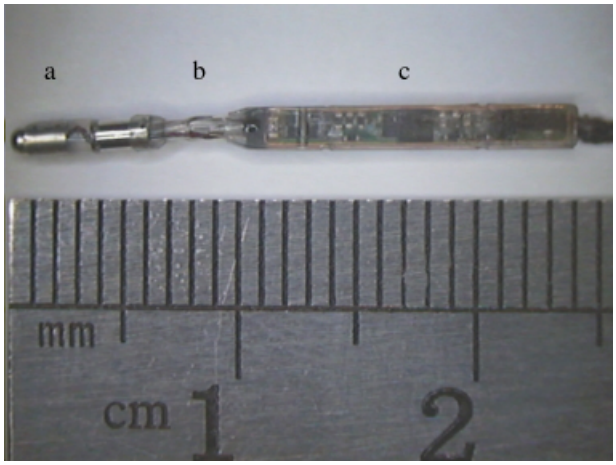

Fig. 1 The implantable neural stimulator (INS). The three parts of the INS are shown: (a) electrode , (b) body; and (c) receiver.

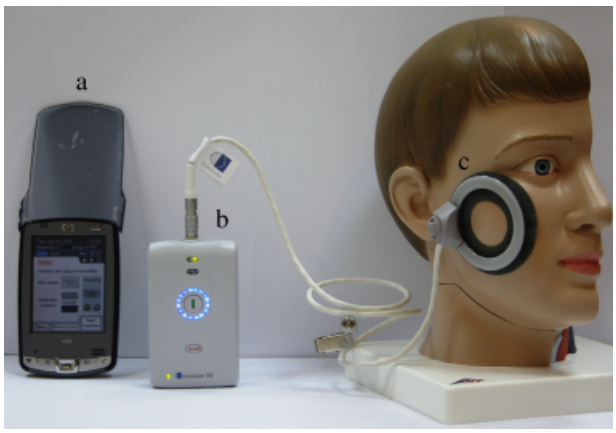

Fig. 2 The energy delivery control subsystem (EDC). The three parts of the EDC are shown: (a) controller; (b) driver; (c) transmitter.

In order to activate the implant, an external driver (Fig. 1b) transmits RF-energy via a transmitter coil (Fig. 1c) to an electronic circuit located in the proximal end of the implant. The transmitter is attached to the patient's cheek with a disposable, single use sticker for the duration of the treatment and removed after each treatment session. The transmitter receives constant feedback streams from the implant, indicating correct operation and signalling in case of signal failure and the need for repositioning the transmitter. A handheld computer (Fig. 1a) serves as controller, allowing the physician to control and monitor the treatment status.

The INS is removed simply by locating and gently pulling the excess thread that is left during implantation adjacent to the canal opening.

The implantable neural stimulator

The INS is composed of three major components (Fig. 1):
1. The INS electrode.

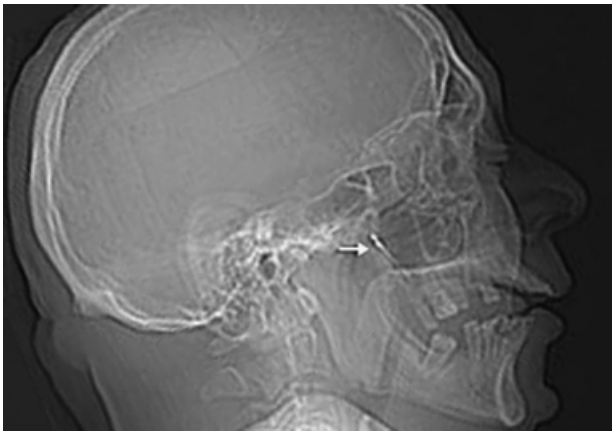

Fig. 3 The position of the implantable neural stimulator (INS). The position of the INS (arrow) is shown in a lateral view of the skull base.

2. The body of the INS: this part contains the wires through which the stimulation pulse is conveyed to the electrode.
3. The receiver (electrical circuit): this part receives the magnetic energy from the transmitter and outputs the stimulation pulse to the electrode.

The energy delivery control subsystem

The controller: The controller is an off-the-shelf, hand-held computer. The controller provides the user interface for the ISS and collects and archives the log files of the treatment sessions. During the operational phase, the controller communicates with the driver via a Bluetooth© communication.

The driver: The driver is the ISS component that generates and controls the energy delivered to the transmitter during a treatment session. The driver is physically connected to the transmitter and communicates with the controller in a wireless fashion.

The transmitter: The transmitter relays energy between the driver and the INS. It is physically connected to the driver. The transmitter is attached to the patient's cheek with a disposable, single-use, sticker. A headset-type transmitter (Fig. 2) acts as a fallback solution for patients who are found unsuitable for the default transmitter.

Implantation kit

The accessory implantation kit is composed of custom made conventional tools intended for use in the preparation of the greater palatine canal and the insertion of the INS (Fig. 4).

Stimulation parameters

Patients received SPG stimulation with parameters adjusted for their individual tolerability. Stimulation parameters ranged from 0·5 to 2·5 mA, 100–400 s at 10 Hz. The optimal stimulation protocol was studied for stimulation sessions of 3–4 h delivered for 5–7 days. The final stimulation protocol was a daily 4-h session for five consecutive days.

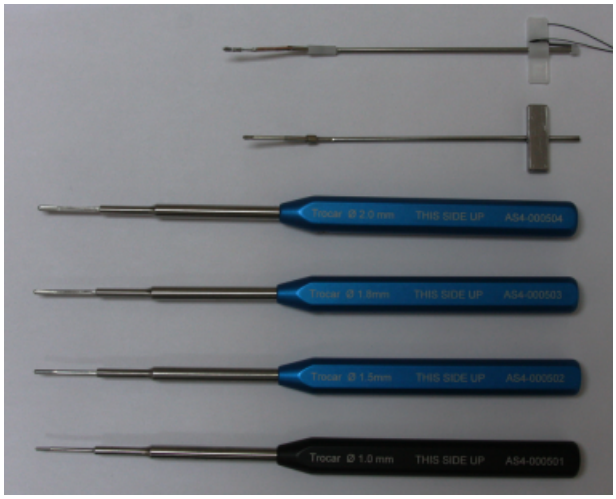

Fig. 4 The implantation kit.

Procedural protocol

Subjects with AIS in the anterior circulation who are eligible for treatment and who provide an informed consent will be enrolled.

Screening includes baseline medical history, routine laboratory tests as well as ECG and blood pressure (BP) measurements. Brain imaging will be performed to exclude haemorrhage. In addition, preexisting mRS, neurological history and NIHSS scoring will be recorded.

Subjects will be transferred to the implantation procedure facility for INS implantation, which will be performed by a trained physician. The ISS is implanted using local anaesthesia and a minimally invasive approach.

Treatment (SPG stimulation) will consist of 4 h of daily stimulation for a total of up to 5 days. Standard of care is adjunct to SPG stimulation treatment throughout the entire study period.

Safety will be evaluated following and during each activation session or at any time an AE is encountered. Safety assessments will consist of recording of all AEs. Severe adverse events are defined according to the ICH regulatory definition as an AE resulting in death; disability; life threatening; requiring intervention; prolonged hospitalisation; and congenital anomaly.

The relationship between AE/SAE and treatment will be defined.

The procedure related to AE reporting and management is fully outlined. The course of action will be in accordance with the severity and relationship with treatment. Specific time guidelines, communication mode and standard of operation are defined.

During hospitalisation, follow-up includes:

1. Neurological and clinical assessments using mRS and NIHSS obtained by a certified neurologist.

2. Routine physical examination including heart rate and BP, which will be recorded before, during and 1 h post the stimulation session.

At the end of the treatment, the INS will be explanted.

Follow-up will be performed at 30 ± 5 and at 90 ± 5 days poststroke onset and includes an interview for safety analysis and clinical and neurological assessment (mRS; NIHSS). Unscheduled visits may be performed at any time during the study at the subject's request or as deemed necessary.

Statistical analyses

The study hypotheses are that the use of the ISS is safe and tolerable and that it will improve the neurological outcome of ischaemic stroke patients.

The study is an open-label study in which a comparative group of patients will be selected from a resource of recent large-scale clinical trials. These studies include the NINDS r-tPA (22). Control subjects with a similar NIHSS range (7–20) at 24 h poststroke onset will be used for comparison.

Safety analysis will include all enrolled patients and will be based on the incidence of AEs, SAEs; and mortality. Survival and SAE profile at 90 days will be compared with the control patients. In addition, the safety of the implantation procedure will be measured by the need to stop treatment sessions as well as the incidence of procedure complications.

For effective assessment, the intent to treat (ITT) cohort is defined as patients who received at least one-treatment session and had at least one mRS follow-up. The per protocol cohort is defined as patients who received five-treatment sessions and who completed the 90-day follow-up.

The primary outcome measured at 90 days will be the distribution of mRS scores. It will be calculated by comparing the distribution of patients across mRS scores (0–6) between the ITT cohort and the historical matched control group (shift analysis).

The secondary outcome measures at 90 days will be:

Dichotomised mRS calculated by comparing the proportion of patients having a positive mRS outcome (defined as mRS 0–2) between the ITT cohort and the historical matched control group.

Dichotomised NIHSS calculated by comparing the proportion of patients having a positive NIHSS outcome (NIHSS of 0 or 1 or an improvement of at least 9 points from baseline) between the ITT cohort and the historical matched control group.

The change in mRS score from day 7 to 90 calculated by subtracting the latter from the former for each subject and comparing the deltas between the ITT cohort and the historical matched control group.

Outcome measures will be tested for statistical significance using the van-Elteren version of the two-tail Cochran–Mantel–Haenzel test, the χ^2-test and the Wilcoxon rank-sum test, respectively. Significance will be defined using an $\alpha = 0{\cdot}05$.

ImpACT-1 Investigators

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Conclusion

Sphenopalatine ganglion stimulation in animals has been shown to result in ipsilateral vasodilatation of the anterior circulation in the brain. While the functional physiological significance of this pathway is not fully understood, it is suggested to take part in a protective mechanism for specific pathological conditions such as ischaemia. This pilot study is designed to investigate the safety, tolerability and effectiveness of an investigational medical device, the ISS, in patients with acute stroke. Statistical analyses will compare study patients with historical matched controls.

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