UNIVERSITY OF BRISTOL

Prof A Levy BMEDSCI MB BS PhD FRCP
Prof of Endocrinology & Honorary Consultant Physician
GMC No: 2714413

Web site: http://www.bristolmedicalpro.com/
Skype address: bristolmedicalpro

Henry Wellcome Labs for Integrative Neuroscience & Endocrinology
University of Bristol
Dorothy Hodgkin Building
Whitson St, Bristol BS1 3NY
Telephone: 44-117-331-3115 Faximile:44-117-331-3116
e mail: a.levy@bris.ac.uk

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Ms Naaz Nathoo
North Somerset and South Bristol Ethics Committee
United Bristol Healthcare NHS Trust Headquarters
Marlborough Street
Bristol BS1 3NU

Re: Evaluation of VibraTip™: a simple & safe alternative to the tuning fork
Clinical evaluation of a medical device
Rec Ref No 08/H0106/133
23rd Jan 2009 (started) - 27th Feb 2009 (completed)

Primary objectives

The study was designed to provide evidence to support the clinical utility of an extremely simple, inexpensive and safe but nevertheless entirely novel method of testing vibration sense that has very high face validity. VibraTip™, is a key fob-sized device that has been specifically designed to overcome the limitations of tuning forks provides a constant source of gentle vibration using a vibrating motor (as used in mobile phones and vibrating wet razors) powered by a mercury- and lithium-free button cell in a clean, sealed, disposable unit.

The specific research question addressed was whether this device is at least as reliable as a tuning fork or monofilament (a single strand of nylon thread that buckles at a set pressure on the end) in identifying peripheral neuropathy. Tuning forks, which were first developed in the late 18th century by musicians and adopted by the medical profession in the early 20th century, have undergone no formal efficacy studies in any context. There is no agreement about an optimal pitch of vibration or consistent guidelines about how tuning forks should actually be used in clinical practice. As a source of vibration for clinical neurological use they are fundamentally flawed.

The hypothesis tested in this study was that by providing a clean source of consistent vibration that could be applied to the skin more gently, more discretely, more consistently and more rapidly than a tuning fork, VibraTip™ will be a safe and distinct improvement on currently available methods for assessing the presence or absence of peripheral neuropathy. The benefit to the patient and to the NHS is that early diagnosis of neuropathy helps to prevent complications and delays progression of the disease. It is anticipated that VibraTip™ will also be available to patients and will have great utility from an educational point of view. It will help to reduce the incidence of new onset of neuropathy and by being pocket size, unlike a tuning fork, will be available at the point of use.

Feasibility

The subjects required for the study attended the hospital in considerable numbers every week - attending not only one of several diabetic clinics, but also the podiatry clinic, hence the rapidity with which 100 consecutive subjects were collected. The ease with which subjects became available for this study also attests to the clinical relevance of the subject.
It was anticipated that the study from start to end would be completed within 6 weeks, and it was completed in 5. The study is a non-commercial evaluation of the efficacy of VibraTip™ as a uniform

source of gentle vibration for testing the preservation of vibration sense. It was anticipated that the maximum amplitude of vibration generated by VibraTip™ would be considerable less than that radiated by a small mobile phone on silent alert or a vibration wet razor, and very much less than that experience when using an electric toothbrush.
The primary objective was to determine whether the ability to detect vibrations derived from VibraTip™ correspond to the ability to detect vibration from a tuning fork or pressure from a monofilament.

Study Design

The study was cross sectional involving all patients attending a diabetic and a podiatry clinic at UHBristol over a 5 week period. Each patient at the clinic was asked if she/he would like to participate in the study. Subjects were then asked to take their shoes and socks off (if they had not already done so as part of their routine clinical evaluation) and were then tested for the presence of peripheral neuropathy using the following three methods:- VibraTip™, Monofilament, and tuning fork. The order in which the three methods were used was randomised using block randomisation. There were six different orders in which the tests were completed, which were allocated prior to the start of the study in blocks of 12. Patients received the allocation sequentially. Testing took approximately 5 minutes per patient including the explanation. Testing itself took seconds or a minute or two only. Patients wereaware of the results throughout the testing procedure, and had full access to the results. In each case, testing involved gently applying the stimulus to either the patient's left or right foot in 5 different places, each time on two occasions ("first time" and "second time"), for about two seconds, then asking the patient whether they felt the stimulus on the first or second occasion, saying 'this is the first', and 'this is the second'. On one of the two occasions, randomly, the damped tuning fork was applied (i.e. without vibration), the VibraTip™ without activating it or the monofilament held above the foot but not applied.

Justification of design

Sample size calculation

Assuming that the proportion of patients with neuropathy was 20% and that we were interested in showing that the agreement is at least 0.7 (good agreement) and that it is better than 0.4 (poor agreement), a large sample 5% level two-sided test of the null hypothesis that intraclass kappa is 0.70 will have 80% power to detect an alternative kappa of 0.40 when the sample size is 69. A sample of 100 patients was used. This will allow for the possibility of incomplete data and for the possibility of a lower rate of neuropathy as it gives 80% power or more for any sample with 13% or more diagnosed with neuropathy. In the event, as the clinic was an annual follow up clinic of insulin-treated and insulin-dependent diabetics and those attending the podiatry clinic, the prevalence of neuropathy was higher than anticipated.

Data collection

For each patient a data collection sheet was filled out detailing the order of the three methods used, whether the patient had a positive or negative test for the presence of neuropathy with each, and which of the prototype devices was used. Data was collected and will be retained in accordance with the Data Protection Act 1998.

Data handling and record keeping

Data from the data collection sheets was entered onto a computer spreadsheet. There will be no confidential information and the records will be entirely anonymous. Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 5 years following the end of the study.

Statistical analysis

The analysis will first look at agreement between the three methods, and then secondly look at diagnostic accuracy. Patients will receive a diagnosis of neuropathy or no neuropathy based on each of the

methods, tuning fork, monofilament and Vibratip. Agreement between the three methods will be examined using a Kappa statistics. Secondly patients will be ascribed an overall diagnosis using the best of three method using the three techniques. Using this overall diagnosis as a gold standard, the individual methods will then be compared against this diagnosis to investigate diagnostic accuracy again using a Kappa statistic, and also using the Mc Nemar's test to investigate whether any of the methods lead to increased rates of diagnosis.

Justification of Treatment/Procedure

Tuning forks Since the recognition at the beginning of the 20th century that the ability to detect vibration is a specific sensory modality 1-3 tuning forks applied directly to the skin have been used at the bedside as a source of vibration. There is little agreement about the optimal frequency of tuning fork 4 and they have several other specific drawbacks in use at the clinical interface:- They are cold to the touch and require pressure to impart vibration, both of which are independent sensations that impair the specificity of the test. Because of their size, tuning forks are difficult to carry in a pocket and difficult to use discretely, which leads to inappropriate cueing. They are designed to produce a set pitch rather than a set amplitude and vary in vibration intensity depending on how hard they are struck and how much time has elapsed since they were struck. This lead to confusion and increases the time required to make diagnoses. Lastly there is no precedent for autoclaving tuning forks or even wiping them between patients, and there are clearly increasing infection control imperatives that are not being addressed. Why bother to test? Testing vibration sense is an integral component of the clinical examination of the nervous system. Nerve dysfunction, often manifesting as loss of sensation and vibration sense in the feet and lower legs is common and particularly widespread in diabetics. Loss of sensation means that patients do not experience pain as a result of poorly fitting shoes, or climbing into a bath that is too hot, or from trauma such as standing on a nail. In addition, more subtle feedback signals such as the very slight discomfort that keeps you shifting your centre of gravity whilst sitting and while asleep in bed are not perceived, and tissues are very quickly damaged. If you sat absolutely still on a hard surface for a relatively short time (less than an hour), you would be danger of developing a pressure sore at the pressure points. Once damaged, the diabetic foot shows poor healing and if not carefully managed leads to ulceration, infection, amputation and even death. How big is the problem? The World Health Organization estimates that diabetes causes 5% of all deaths globally each year and affects 246 million people worldwide. The incidence of diabetes is escalating to epidemic proportions and by 2025, the figure is expected to reach 380 million. This is largely due to an increase in Type 2 diabetes that can be at least partly attributed to rising levels of obesity. In the US, there are currently 17.1 million patients diagnosed with diabetes (Type 1 and 2), or 6% of the population. The direct economic costs of diabetes (i.e. healthcare costs) is over $116 million dollars annually, whilst the indirect costs (i.e. lost days at work and lost productivity) amount to $58 billion dollars. These figures do not reflect the cost of other health complications experienced by diabetic patients 5. In England, there are an estimated 2.35 million people with diabetes and £3.5 billion per annum, or £9.6 million per day, is spent on treating diabetes and its complications. This represents 5% of the NHS budget 6 and remains very much in the news, as worldwide, a diabetic patient has an amputation every 30 seconds.

Inclusion criteria

Adult patients in the diabetes and podiatry clinics who speak English and have capacity are very well used to the involvement of many people in their care, and to the presence of medical students, trainees and people undertaking clinical studies. They are also 'professional patients', thanks to the chronicity of their condition, and tend to be very interested in work that might at some time be beneficial to them or to others who have or may develop their condition. A patient information sheet detailing the rationale for the study will be provided. The intervention planned is harmless and painless. Written consent was requested. One single patient gave verbal consent but refused to sign the consent form. He was not used in the study.

Exclusion criteria

There are no exclusion criteria other than practicality. In other words if a patient was a bilateral amputee

or had bilateral foot infections and complex bandaging (i.e. 4-layer pressure bandaging), then it would not be practical to ask him or her to participate. In the event, only two patients were excluded because it was thought to be too onerous for them to have dressings removed.

Good clinical practice

Research Governance, Monitoring and Ethics & R&D approval

The study was conducted in compliance with the Research Governance Framework for Health and Social Care and Good Clinical Practice (GCP). Data was collected in front of other clinical staff and as an entirely painless, harmless and rapid exercise with no prospect of disclosing clinical signs that were not already evident as part of routine assessment. There were no significant ethical issues of note. The study was monitored and audited in accordance with UHBristolNHSFT policy. All trial related documents will be made available on request for monitoring and audit by UHBristolNHSFT, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies. The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval. This study will be conducted in accordance with: • The Medicine for Human Use (Clinical Trials) Regulations 2004. • International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines • Research Governance Framework for Health and Social Care

Finance

The prototypes for VibraTip^{TM} will be made independently from the study. Monofilaments and tuning forks are already available in clinic. There will be no payment for participants in the study. The study is funded up to £1000.

Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

Safety Reporting

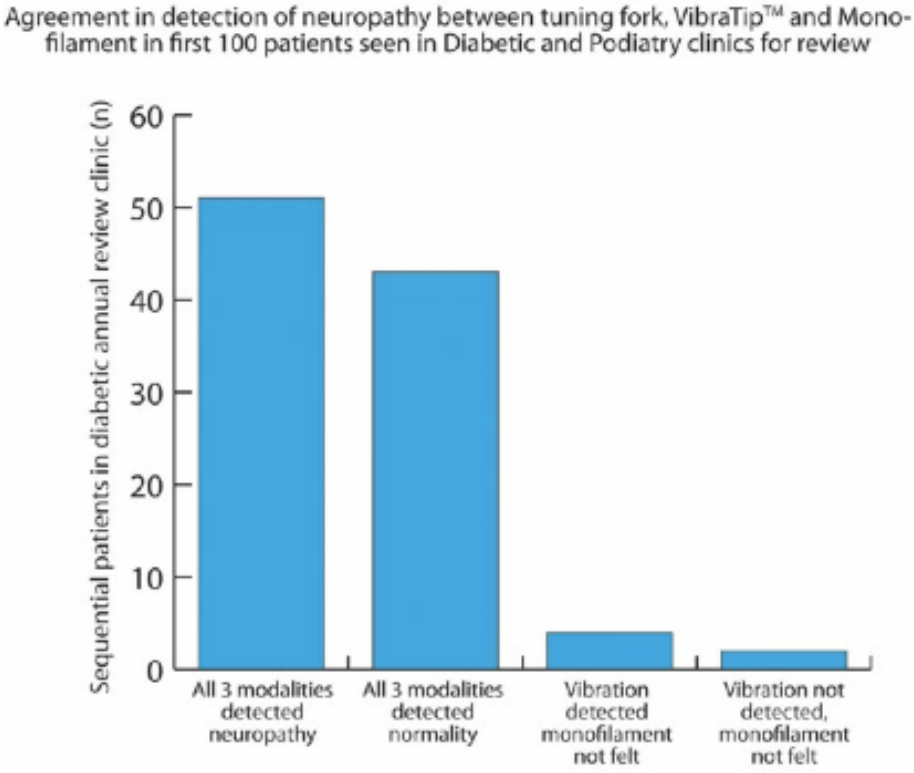
There were no adverse events in the study.

Reporting and dissemination

It is anticipated that the results of this study will be published as a short article or letter in the diabetes journals. Dissemination will also take the form of presentations in local, national and international meetings.

Results

All 3 detect neuropathy	51
All 3 detect no neuropathy	43
Vibration yes, filament no	4
Vibration no, monofilament yes	2



The comparison between VibraTip™ and tuning fork, and VibraTip™ and monofilament were analysed using a Kappa statistic for inter-rater reliability.

The VibraTip™, tuning fork and mono-filament were successfully presented to 100 patients who elicited a response for each of the methods. No patient was included more than once in this sample.

The results for the non-vibrating presentation of the VibraTip™ showed no patients who thought they could feel vibration when no such vibration was being applied. This was not the same for the tuning fork, as several patients stated that they could feel some vibration when the non-vibrating tuning fork was applied. The vibrating tuning fork and VibraTip™ were both felt by the same 55 of the 100 patients and not by the other 45 patients. This is complete agreement and gives a Kappa statistic for agreement of 1. However if the clinician give the tuning fork an extra hard hit with the patella hammer, some vibration was felt by several of the patients who did not feel it on the initial presentation. This was likely the result of vibration propagating further up the leg (bone conduction) and also because vibration of the tuning fork became clearly audible at high amplitude and would elicit a positive response to being able to hear it rather than feel it.

Comparison with the monofilament did not show complete agreement but this is in line with the results from the tuning fork. For the monofilament 53 patients were able to feel the sensation, of which 51 were the same as the vibratip results. This gave a Kappa value of 0.879 which indicates very good agreement and is identical to the agreement seen between the tuning fork and the monofilament in this set of patients.

Recorded comments

In certain circumstances, further comments were appended to the result forms. These are pretty self explanatory, and as follows

15 Hard bash on tuning fork was felt

16 Monofilament impalpable. Tuning fork palpable - VibraTip palpable 'in places'. VibraTip more in keeping really with the monofilament.
17 A really hard bang on tuning fork was palpable, but not palpable with monofilament or VibraTip
23 Not a very good witness. Did seem to feel monofilament on the pad of 4th toe on left and felt vibration from both sources there too, but otherwise clearly neuropathic
25 Neuropathy but able to feel monofilament and both sources of vibes on pads of 4th and 5th toes on the left foot
31 Listed as no neuropathy detected, but on the pad of the great toe, tuning fork was felt where the VibraTip wasn't. Monofilament felt
34 Neuropathy listed as not detected, although monofilament not felt in two places
37 Unreliable witness. Reported as neuropathy - only 2 or 10 monofilament
38 Reported as monofilament detected and vibes not, but all three were impalpable on the pad of the great toe
65 Needed to go back over all three for reliable result
66 Not the most reliable. Like several patients, reported the tuning fork 'vibrating' when it wasn't
67 Very unreliable, but clearly neuropathic
73 Not reliable. VibraTip noted to make the reliability issues much easier and certainly quicker to sort out. Many patients report 'slight' vibration when it isn't vibrating at all
74 Patchy but rather a poor witness. Device number 2 is bad
76 Unreliable but clearly neuropathic
77 Curiously, neuropathic everywhere but the pad of the great toe (right) was normal to vibes from both sources
86 Normal and reported as such but pad of great toe felt vibes but not monofilament
90 Difficult, quite unreliable but clearly neuropathic
91 Reported as normal but pad of great toe couldn't detect vibration
92 Patchy neuropathy
97 No vibration sense but felt monofilament
99 On pad of great toe, tuning fork palpable but vibratip wasn't

Summary

One of the 10 prototype devices did not function properly and was not included in the trial. The other devices were used randomly and about the same number of times during the trial. The most effective devices, or at least the ones that were the most simple to use, were those with buttons that operated completely silently. Several of the devices had buttons that 'creaked' when they were depressed and it was more difficult to elicit a 'creak' without activing the device to properly blind the stimulus applied. This is an issue that will be corrected when they are re-designed for manufacture.
Patients and staff were entertained and interested by the device. There were no problems at all with its use.

Andy Levy Thursday, March 19, 2009