Medipin outline cross-sectional study proposal to refine the identification of early small fibre damage in diabetic patients with distal polyneuropathy using a relative analogue scale to quantify cutaneous pinprick sensitivity in the rapid primary care setting with a novel device and instrument

This cross-sectional study is intended to demonstrate the existence of a clinically viable quantitative scale for neurological deficit in patients with diabetic peripheral neuropathy, whilst refining the clinical threshold identifying those at risk from serious complications, utilising a dedicated, cost efficient, single-use pinprick device with a rapid and logically modified application technique.

Clinical practice and research has largely relegated pinprick modality as relatively insensitive to neuropathic deficit because it tends to be employed in a binary, "on or off" fashion which produces typically false negative results. Sensory loss tends to be incremental and the test requires the patient to express only, IF they can feel, not HOW MUCH. Inevitably where pinprick perception has diminished, patients can still report a stimulus though, deprived of the facility to express magnitude, the test fails to reflect critical change. In consequence pinprick appears insensitive to neuropathy by virtue of it being applied to the wrong question. It is imperative to establish an instrument that promotes both consistency during testing and reproducibility between individual tests and clinicians. A number of devices, as modification away from conventional 'sharp blunt' testing, are available to facilitate this.

The instrument

The testing procedure will employ a cutaneous pinprick sensation technique substantially modified for the purpose. Representation of small diameter fibres by nociception is a highly sensitive modality for identifying early damage whilst the extent of deficit or specificity will be provided by the introduction of a verbal analogue scale (VAS) to quantify the degree of sensory loss consistent with the presence of clinical signs typical of peripheral neuropathy.

The procedure should involve simultaneous comparison with the data produced by ‘standard’ conventional low cost instruments, currently recommended to include the 10g Semmes-Weinstein monofilament and sensitive to large fibre neuropathy, for efficacy in detecting clinically significant neuropathy.

Rationale and Technique

Attempting to impose a device driven, 'standardized', level of stimulation across the population, even with a device that imparts a predictable level of force, simply won't work [1]. There are three basic reasons for this:

1. Pain is a state dependent phenomenon where individual subjects perceive stimuli idiosyncratically. There exists considerable variation in perception from day to day in the same patient dictated by mood and environment let alone between different members of the population.

2. There can be considerable inconsistency in application technique employed by a clinician during the same test let alone between clinicians in different tests.

3. Pain receptors are distributed randomly throughout the skin rendering consistent application of solitary stimuli in a nominated area challenging.

It is possible to circumvent these issues by employing a number of simple but logical modifications to conventional neurological technique:

a. The patient is made to act as his or her own control by comparing pinprick stimulus in a neutral or "normal" region to the potentially affected one. This will eliminate the need to impose some external "standard" which can't exist in anything but a crude sense. Simultaneously, it permits the expression of subtle sensory deficit rather than subscribing to the sharp/blunt scenario where, by definition of the question, only more advanced deficit can be reported. Vitally, all variations in circumstantial influences whether imposed by personal factors, environment or operator will affect different areas within the same patient to a similar degree, rendering all changes relative. Essentially, irrespective of setting, the patient's relative differences in sensation around the body between regions will remain relatively the same.[2]

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[1] *A.T. Shirgaonkar, M. Purva, I.F. Russell (2010); A double blind comparison of the variability of block levels assessed using a hand help Neurotip™ or a Neuropen® at elective caesarean section under spinal anaesthesia. International Journal of Obstetric Anesthesia 19, 61–66*

[2] *R. Rolke et al (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain 123 231–243).*

b. To significantly reduce error it is critical to provide the patient with an "average" or "normal" sense of stimulation peculiar to them. This is achieved using a technique in which multiple, rapid, but gentle applications are used continuously in the nominated area or region. This diminishes two sources of standard deviation associated with a single application by:

i. 'Levelling out' variation created by operator and patient error due to a process of sensory adaptation sometimes referred to as "wind-up". This is a frequency dependent increase in excitability of spinal cord neurons that reaches a plateau after about five stimuli [3] demonstrable from 60 BPM over $1cm^2$ [2]. Anecdotally, from a clinical perspective, 1 beat per second is probably unnaturally slow and the tendency amongst operators for this application appears well beyond this - probably between 200-250 bpm.

ii. Providing an increased probability of reliable stimulation of otherwise randomly distributed receptors.

Pinprick sensation is a particularly sensitive modality and comparison of the same modality in different regions affords a device by which patients can grade their idiosyncratic deficit quite discretely. This makes it possible to detect subtle sensory loss and to impose a verbal analogue representation for it. If what is felt in a "normal" or unaffected area can be demonstrated to the patient as representing a "5" on an arbitrary scale they can then ascribe a value for their sensation in the affected one. A subject with pre-existing deficit may say, for example, that the pin on their toes feels like a "2 or a 3" and it is expected that pre-existing physical evidence of neuropathic changes in the foot will be consistent with lower scores. In contrast subtle or early levels of pinprick deficit are not likely to be clinically significant suggesting the possibility of building a spectral picture on which a clinically critical threshold lies given a sufficiently credible study cohort. This scale may refine the specificity of currently assumed thresholds for so called "Loss of Protective Sensation" and in consideration that this is intended to be a simple, primary care technique that can be taught easily, it would be important to test it against that dictated by the 10g monofilament and other so called "gold standard" testing procedures as part of this study.

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[3] *Herrero JF, Laird 2000, JMA, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol ;61:169–203.*

In summary - Pinprick Instrument Methodology In Principle

1. Pinprick repetition – multiple application of the same stimulus around the same area narrows standard deviation by relegating operator handling and patient perception errors to generate a reliable '**Average'** stimulation [2]

2. Pinprick comparison – modality to modality between unaffected and affected areas establishes the patient as their own control to provide a personal '**Normal'** and automatic sense of gradation

3. The VAS enquiry promotes and refines patient-centred **quantification** that accommodates/compensates for variation from external factors and circumvents the need for an external standard

Procedure

To be undertaken in a population of 100 patients with a range of presentations varying from nil detected peripheral neuropathy though to neuropathic complication down to amputation.

The patient need not look away. The technique dictates that there is established a simple and logical process of self-reference throughout which the patient is actively participating. It is useful to note that maintained reinforcement from the clinician in the form of verbal cues to reiterate instruction serves to facilitate the consistency of this procedure and the patient will rapidly grasp the unambiguous task of comparison required of them by simple demonstration.

1. In a location assumed to be unaffected by pathology such as the knee or plantar surface of the wrist gently apply continuous pinprick stimuli to the skin - a few per second - covering an area of a few square centimetres moving around at random.

2. Whilst applying these stimuli instruct the patient that this normal pinprick represents a score of '5' which quickly establishes for them an 'average' response they can regard as a baseline for comparison.

3. Immediately compare the above to another area by repeating the technique in the nominated location whilst asking the patient to provide a comparative score.

4. If possible move continuously between locations maintaining consistent stimulation, where appropriate, asking the patient to provide feedback as the location changes.

5. Although it might be assumed that the arbitrary '5' in a "normal" area is a maximum value, patients may easily and instinctively express responses above as well as below. Hence '5' becomes a central reference value catering to hyperaesthetic or allodynic patients as well as accommodating idiosyncratic physiological variations.

*For convenience possibly to call this the **Pinprick Analogue Comparison Test***

B Jacobs - Updated 2021