Reviewer's report

Title: Norepinephrine-evoked pain in Fibromyalgia. A Randomized Study.

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Reviewer: Dr Andre Barkhuizen

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after revision, which I do not need to see

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1. This is a well thought out study based on a review of the literature and application of basic experimental design to test the hypothesis that the symptoms of fibromyalgia are sympathetically mediated. This study expands on prior work of this group demonstrating sympathetic overactivity in patients with fibromyalgia utilizing measurement of heart rate variability.

2. This study utilized subcutaneous norepinephrine as a cutaneous stimulant of sympathetic nerves. The authors used both a healthy pain free control group and a diseased control group with chronic musculoskeletal pain due to rheumatoid arthritis (RA). The RA group had similar pain level and stiffness to the fibromyalgia group.

3. The results confirm that NE evoked pain was present in more patients with fibromyalgia (80%) compared to controls (30% of both control groups). In addition the pain intensity was also greater in fibromyalgia compared to control groups. Another interesting finding was the spreading of pain to contiguous parts of the arm in close to 50% of fibromyalgia subjects. This spreading of pain seems similar to that found by Arendt-Nielsen when hypertonic saline was injected into the tibialis anterior muscle in patients with fibromyalgia.

4. It is unclear whether 24 hours was a sufficiently long period to be free of analgesics and anti-inflammatory medications prior to performing the study. If any patients were on long acting analgesics this may have abrogated their response to the NE injection. Similarly the presence of GABA-ergic agents, tricyclic antidepressants or mixed serotonin and norepinephrine reuptake inhibitors may have blunted the response to norepinephrine. Future studies should attempt to have adequate washout periods for all medications, which may have an effect on pain modulation.

5. Although not explicitly stated it is assumed that normal saline was used as vehicle for epinephrine. It must be noted that distilled water and hypertonic saline injected subcutaneously are both very painful injections even in healthy normal controls. The slightly greater rate of paresthesias produced by saline compared to norepinephrine may simply be due to small sample size, but it may also indicate that saline is not the ideal vehicle or control injectate.
6. The induction of pain, albeit less intense, in an equal number of RA and healthy controls reduces the likelihood that the test, as performed in this study, would be useful diagnostically. It is fairly easy to understand how RA patients with chronic joint inflammation have an element of sympathetically mediated pain. It is however more difficult to understand why subcutaneous norepinephrine induced pain in one third of healthy controls.

7. In summary, this study provides useful preliminary data to design future studies to further characterize the influence of the sympathetic nervous system in fibromyalgia. Greater care should be taken with prior medication use. As in this study, appropriate controls with chronic joint inflammation but without fibromyalgia should be studied in addition to the obligatory healthy control group. In addition attempts should be made to clearly isolate the effect of the injectate on the sympathetic nervous system rather than non-specific effects on the peripheral nervous system. Although rather invasive, repeating this study following sympathetic block or a sham block will provide irrefutable evidence that the pain produced by subcutaneous norepinephrine is indeed sympathetically mediated. In addition future studies should attempt to find a dose and mixture of injectate that more clearly distinguishes healthy controls from patients with fibromyalgia and other chronic painful conditions with a peripheral cause.

Specific questions to be addressed by authors:

1. Please provide a list of discontinued medications and their half-lives in both patient groups. In addition please provide number of patients on other centrally acting agents such as antidepressants, GABA-ergic agents such as neurontin, sedative hypnotics, etc. If numbers are sufficient please compare the induced pain level of those on centrally acting medications versus those not on them.
2. Please confirm that normal saline was vehicle for injection.
3. Last sentence of 1st paragraph following heading Background correct grammar: "..........remaining manifestations that this illness exhibits in different....."
4. Please rewrite the conclusion sentence so that it makes sense.
6. Reference 12 has incorrect year. It should read 1990.

Competing interests:

None declared.