and shape due to the plane of sectioning. While it is true that 54 μm thick sections will contain more continuous segments of innervation and vessels, long segments also occur parallel to the plane of sectioning within 14 μm thick sections. Many individual axons, which are typically very thin and varicose, penetrate and terminate among the DAPI labeled nuclei concentrated around the perimeters of the vessels. In both the thick and thin sections from control or CAPH biopsies, few if any such intimate vascular-related fibers can be seen separating back into the dermis to innervate other targets such as the epidermis. Our original publication showed additional double label combinations that documented several subtypes of these vascular-related fibers with all subtypes present in the control and CAPH subjects.

By contrast, both the 54 and 14 μm thick sections from the control biopsies show additional segments of nerves and individual axons that are clearly not in close association with the vasculature, but meander within the intervening dermis. Many of these profiles extend to the epidermal-dermal border, where there are no associated vessels, with some entering and ending in the epidermis (Supplementary Fig. 1A–E). There was no evidence of such non-vascular innervation or potential truncated proximal stumps in thick or thin sections of the CAPH subject biopsies (Supplementary Fig. 1F–I).

For these reasons, we have hypothesized that several intact varieties of sensory innervation affiliated with the vasculature in the upper dermis and dermal papillae, as well as with deeper vessels and sweat glands are the potential source of the existing tactile sensation in the CAPH subject. Given that this subject had impaired pain sensation from childhood, it seems likely that the missing innervation never developed or was eliminated quite early and that this subject learned to derive tactile perceptions from the existing varieties of sensory innervation on the vessels and sweat glands.

Indeed Nolano et al. [11] proposed that the sensory perivascular innervation likely monitors vascular dynamics thereby playing an important role in homeostasis [3]. We agree and suggest that if the vascular innervation in our CAPH subject is indeed the source of the neural input allowing for a fairly good degree of functional tactile discrimination, then we would propose that vascular innervation likely has the capability to monitor homeostasis with a higher degree of local resolution than has been previously appreciated. Potentially, this vascular innervation may also contribute to conscious tactile perception in normal individuals, as well as to chronic pain under pathological conditions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2010.08.027.

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Response to Drs. Bell and Moore commentary regarding the use of intravenous ketamine for CRPS

The authors would like thank Dr. Bell and Dr. Moore for their interest in our article "Outpatient Intravenous Ketamine for the Treatment of Complex Regional Pain Syndrome: A Double-Blind Placebo Controlled Study" recently published in Pain [6] and appreciate the opportunity to address the concerns and criticisms they raised regarding our publication [1].

Bell and Moore correctly state that the study was prematurely terminated. When the study was designed, our experience with outpatient intravenous ketamine was limited to doses of 25 mg/h

(100 mg over 4 h). Over the duration of this study (2 years) our experience with outpatient intravenous ketamine as well as the experiences of others demonstrated that doses of 200–250 mg over a 4 h period provided much greater pain relief lasting a longer period of time without complications. Since higher ketamine doses would provide much greater pain relief for a longer period of time without complications, it was felt that we should not continue treating patients at the low ketamine dose (principle of beneficence in clinical research). At that time, the study was stopped and the results on the group of 19 patients treated at the low ketamine dose were submitted for publication.

Bell and Moore correctly state that we did not specifically define our primary efficacy variables and did not provide details regarding the process of randomization. The primary efficacy variables of our study were the patients overall pain as determined by the activity watch and the short form McGill pain score. We choose the activity watch because it provided the greatest sampling of the patient overall pain score (at least 4 times per day for 21 days) prior to and following treatment. The McGill pain score was chosen because it is widely-used and has been shown to provide quantitative information that is sensitive and responsive to intervention. The process of randomization was as follows. A pseudo random number generator (RAND, in Microsoft Excel) was used to generate a column of random numbers from 0 to 1. Numbers between 0 and 0.5 were assigned a zero and numbers greater than 0.5 a one. Prior to the start of the study, a list of 48 patients in consecutive order (Pat001, Pat002, . . ., Pat048) was created. We then placed, adjacent to the patient list, six groups of eight numbers from the random number list such that each group would have four ones and four zeros. If the third patient to enter the study Pat003 was adjacent to a zero he/she was placed in the placebo group, if adjacent to a one he/she was placed in the ketamine group.

We do not agree with Bell and Moore assertion that our trial was not convincingly blinded, in fact, we feel that blinding was one of the strongest points about the study. The study was designed with an active placebo (midazolam and clonidine). Given that both ketamine and midazolam have psychomimetic effects and all study participants were ketamine naïve, it was our observation that neither the patient nor the examiner could correctly determine treatment assignation.

Drs. Bell and Moore incorrectly state that at least 23 different tests were performed and statistical significance should be adjusted for multiple testing to at least $p = 0.005$. We evaluated 14 tests, 16 when the McGill is split into sensory, affective and total (see Tables 2, 3 and 4). This discrepancy may have been caused by Drs. Bell and Moore counting every site a test was performed as a different test. Disregarding our disagreement over the number of tests, several parameters such as; the reductions in overall pain as determined by the activity watch ($p = 0.0019$) as well as the affective and total components of the McGill questionnaire at 3–4 weeks ($p = 0.0011$ and $p = 0.0038$) were significant to $p < 0.005$.

Drs. Bell and Moore state that ketamine is neurotoxic and its use can lead to memory impairment and cite two studies to support their allegation [2,5]. The first study is hard to interpret since the subjects were abusing other drugs as well as alcohol [2]. The second study did show up-regulation of the dopamine D1 receptor in chronic ketamine users; however it also demonstrated no significant performance differences in tests involving working memory, executive function, attention, reaction time, verbal learning and memory, fluency, motor function and intellectual function between healthy subjects and chronic ketamine users [5]. In addition, there are now approximately 80 patients who have undergone the ketamine coma protocol [3] in both Germany and Mexico with >50% complete remission for over 5 years. All these patients who had failed all the treatment modalities were narcotics addicted and had a greatly diminished quality of life. A group of these patients received extensive neuropsychology testing and showed no deficits [4].

We have seen no ketamine addiction problems or long term cognitive deficits in patients who have been treated with the 10 day outpatient regimen for over the past 8 years. These patients undergo intensive psychological evaluation prior to therapy and approximately 10% are excluded because of schizoid features, prior drug addiction, suicidal ideation or post traumatic stress disorders.

In their commentary, Drs. Bell and Moore raise the issue of the cost of intravenous ketamine as compared to alternative treatments such as sympathetic blocks. We feel that their confusion may stem from the fact that they incorrectly state that the study patients underwent 4-h daily ketamine infusions for 10 weeks, when our manuscript clearly states that the infusions were done over a 10 day period. In fact, the costs of 10 four-hour out-patient ketamine infusions are comparable to a series of fluoroscopy-guided sympathetic blocks. In addition, it appears that Drs. Bell and Moore are not familiar with the type of intractable CRPS patients enrolled in our study. We clearly specified that the CRPS patients in our study were severely affected and had failed standard therapies (antidepressants, anticonvulsants, blocks, physical therapy, psychiatric therapy, etc.). Ketamine worked when everything else had failed.

In conclusion, we view intravenous out-patient ketamine therapy as an additional treatment option that has been shown to be effective and safe when multidisciplinary and drug regimens have failed.

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