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Sodium channel $Na_v1.7$ immunoreactivity in painful human dental pulp and burning mouth syndrome

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Abstract

Background: Voltage gated sodium channels $Na_v1.7$ are involved in nociceptor nerve action potentials and are known to affect pain sensitivity in clinical genetic disorders.

Aims and Objectives: To study $Na_v1.7$ levels in dental pulpitis pain, an inflammatory condition, and burning mouth syndrome (BMS), considered a neuropathic orofacial pain disorder.

Methods: Two groups of patients were recruited for this study. One group consisted of patients with dental pulpitis pain (n = 5) and controls (n = 12), and the other patients with BMS (n = 7) and controls (n = 10). BMS patients were diagnosed according to the International Association for the Study of Pain criteria; a pain history was collected, including the visual analogue scale (VAS). Immunohistochemistry with visual intensity and computer image analysis were used to evaluate levels of $Na_v1.7$ in dental pulp tissue samples from the dental pulpitis group, and tongue biopsies from the BMS group.

Results: There was a significantly increased visual intensity score for $Na_v1.7$ in nerve fibres in the painful dental pulp specimens, compared to controls. Image analysis showed a trend for an increase of the $Na_v1.7$ immunoreactive % area in the painful pulp group, but this was not statistically significant. When expressed as a ratio of the neurofilament % area, there was a strong trend for an increase of $Na_v1.7$ in the painful pulp group. $Na_v1.7$ immunoreactive fibres were seen in abundance in the sub-mucosal layer of tongue biopsies, with no significant difference between BMS and controls.

Conclusion: $Na_v1.7$ sodium channel may play a significant role in inflammatory dental pain. Clinical trials with selective $Na_v1.7$ channel blockers should prioritise dental pulp pain rather than BMS.

Background

Orofacial pain conditions are common and debilitating. Few studies have investigated the role of novel key pain ion channels, such as $Na_v1.7$, in these conditions. Such studies may lead to the development of more effective treatments.

Dental pain is the most common symptom of diseased tooth pulp, often as a result of coronal caries of the tooth [1]. The mature human dental pulp is densely innervated with fibres that originate from the trigeminal ganglion [2]. The normal pulp seems insensitive to exteroceptive stimuli; however, in pathological states such as pulpitis (inflammation of the pulp), electrical, thermal, mechanical and chemical stimuli all produce a nociceptive response [3]. Primary and permanent tooth pulps contain 70-90% C-fibres, and thin myelinated A delta fibres [4]. The majority of nerve fibres terminate in the coronal region of the pulp, forming a subodontoblast plexus, with 40% terminating in the dentinal tubules close to the odontoblast processes [5]. Strong correlations have been reported between the afferent discharge frequency of human pulp nociceptors and pain levels [6].

Nociceptors within the oral mucosa have also been implicated in another orofacial pain condition, burning

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mouth syndrome (BMS). The International Association for the Study of Pain (IASP) defines BMS as a distinct neuropathic orofacial pain condition characterised by bilateral burning oral mucosal pain, usually affecting the anterior two thirds of the tongue with a lack of any visible signs of mucosal pathology, and of more than 6 months duration [7]. The pain intensity ranges from moderate to severe throughout the day and may last several years [8,9]. Initiation can be spontaneous or associated with systemic factors such as diabetes, nutritional deficiencies, hormonal changes, psychological disorders as well as local causes including oral infections, allergies, salivary gland dysfunction and dental treatment [10].

The underlying mechanisms involved in pain initiation and conduction in BMS and pulpitis are still not fully understood, but are likely to involve sodium ion channels. Voltage gated sodium (Na_v) channels are known to play a key role in elicitation of action potentials in neurons, including nociceptors [11]. There are 9 sub-types of sodium (Na_v) channels in humans, and changes in their expression may underlie hypersensitivity in pain states [12]. A subset of voltage-gated sodium channels that include $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$, have been shown to modulate pain [4,13]. These isoforms display unique expression patterns within specific tissues [12], and are up- or down-regulated after injury to the nervous system [11].

The voltage-gated sodium-channel type IX alpha subunit, known as $Na_v1.7$ and encoded by the gene SCN9A [14], is located in peripheral neurons and plays an important role in the action potential of these cells. $Na_v1.7$ is concentrated preferentially in rodent small diameter neurons [15]. The presence of $Na_v1.7$ sodium channel has been demonstrated in sensory neurons in human dorsal root ganglia (DRG), including the majority of small and medium-sized neuronal cell bodies, which include the nociceptors [16]. The accumulation of this channel has been demonstrated within the neurite tips of DRG and trigeminal ganglion neurons in culture [17]. Electrophysiological studies show that $Na_v1.7$ has a role in amplifying generator potentials [18].

The key role of $Na_v1.7$ channels in pain conduction was confirmed in recent studies of clinical genetic disorders. Gain-of-function mutations in $Na_v1.7$ have been shown to cause primary erythermalgia and familial rectal pain, recently renamed as paroxysmal extreme pain disorder [13,19], while loss-of-function mutations result in congenital insensitivity to pain [14]. Relatively few studies have evaluated expression of $Na_v1.7$ in acquired clinical pain states, and even fewer within trigeminal pain states [2,20-25]. One recent study investigated pain within the orofacial pain region and showed an increase in $Na_v1.7$ expression in pulpitis [22], while another study showed a decrease in $Na_v1.7$ in the neuropathic orofacial pain condition trigeminal neuralgia (TN) [26]. The aim of our study was to investigate whether $Na_v1.7$ has a role in BMS, considered a neuropathic orofacial pain disorder, and to compare this with dental pulpitis, an orofacial inflammatory pain condition.

Methods

Patients scheduled for dental extraction, and those diagnosed with burning mouth syndrome (BMS), at Kings College London Dental Institute, London, were included in this study. Patients gave informed consent before participating in the study, which had approval from the North East London Ethics Committee. All patients were recruited sequentially, none of whom were taking any medication at the time of the study.

Dental pulpitis

Seventeen permanent molar teeth were tested for positive neural vitality of the dental pulp one hour prior to extraction, using an electric pulp tester (analytic technology constant current at the mid-buccal surface of the tooth), and with ethyl chloride. The dental patients were divided into two groups, those with existing pain from the tooth (painful pulps; n = 5, with a mean age of 40.3 years [range 36-44 years]) and those with no history of or existing pain (controls; n = 12, with a mean age range of 37.3 years [range 23-51 years]). The gender distribution of the groups was M: F 1:1. All the dental pain in this study was attributable to pulpitis due to extensive dental caries of the molar tooth. Pulpitis was diagnosed by taking a full pain history and presence of pain on the day of extraction, vitality testing of the tooth and clinical radiography. The mean duration of pain was 2.9 weeks (range 0.5-8.0), and the indication for extraction of the non-painful teeth was pericoronitis.

All the teeth were removed by standard buccal approach under local or general anaesthesia. Subsequent to the extraction process (lasting less than 5 min), the teeth were sectioned vertically with a water-cooled drill and the pulp lifted out, and specimens immediately snap-frozen at -70°C.

Burning mouth syndrome

Patients attending Kings College London Dental Institute with a diagnosis of burning mouth syndrome (BMS; n = 7) in accordance with the International Association for the Study of Pain (IASP) criteria [27], and those attending for wisdom tooth removal under local analgesia (controls; n = 10), were invited to join this study in accordance with the North East London Ethics Committee approval guidelines. Efforts were made to age and sex-match the BMS patients with controls; however, although the age

ranges overlapped, BMS subjects were older than the controls. The mean age for the controls and the BMS patients was 40 years (range 16-79 years; M:F = 6:4) and 62 years (range 48-82 years; M:F = 5:5), respectively. The average duration of symptoms for the BMS group was 37.6 months. All patients were asked to report the degree of pain using the visual analogue scale (VAS) scoring system from 0 (no pain) to 10 (worst pain imaginable) prior to a lingual biopsy. The average pain score was 7.07 (range 5-10). All biopsies, including controls, were undertaken from the same site, on the right or left dorsal lingual mucosa lateral to the midline in the anterior third of the tongue, since all BMS patients had pain within this region.

Tongue punch biopsies were taken from BMS patients (disposable punch 3 × 3 mm Steifel CE 0120, Steifel Laboratories Ltd, Bucks, U.K.) under local anaesthesia. Control tongue punch biopsies were obtained from patients undergoing planned wisdom teeth surgery as a result of previous pericoronitis, which is localised mucosal inflammation around a partially erupted tooth. During recruitment of these control patients, a clinical history, examination and radiography were used to confirm this diagnosis. On the day of surgery, all control patients who attended for wisdom tooth removal were not in any pain (VAS = 0) as they were between episodes of pericoronitis. The control tongue biopsy was an additional procedure, which required no additional local anaesthesia. All tongue punch biopsies were immediately placed in liquid nitrogen, and subsequently transferred to -70°C storage until used for immunohistochemical analysis.

Immunohistochemistry

Frozen specimens were embedded in OCT medium (RA Lamb, London, UK) and sections of 12 μm thaw-mounted onto glass slides pre-coated with poly-L-lysine. Sections were immersion-fixed in fresh 4% paraformaldehyde in phosphate buffered saline (PBS) for 30 minutes, then endogenous peroxidases blocked by incubation with alcoholic 0.3% hydrogen peroxide for a further 30 minutes. Sections were incubated overnight with a monoclonal antibody to the structural neuronal marker neurofilament (Clone 2F11, Dako, Cambridge, U.K., used at a final titre of 1:10, 000) and a polyclonal antibody against $Na_v1.7$ (K241), whose specificity has been described by us previously [19,21]. Sites of primary antibody attachment were revealed using avidin-biotin peroxidase method (Vector Elite ABC method, Vectastain, Novacastra, Newcastle, UK). Preparations were counterstained in 1% w/v aqueous neutral red to visualise nuclei and photographed with an Olympus photomicroscope.

Analysis

A visual observation method of analysis for the evaluation of Na_v 1.7 in the subodontoblast plexus and submucosal region of tongue biopsies was adopted. This was in accordance with previously described methods [28,29]. A visual grading scale of intensity ranging between 0-3 (0 = nil, 1 = weak, 2 = moderate and 3 = strong immunoreactivity) was used. The mean values of readings obtained by two independent observers, each blinded, were used for final analysis. Computerised image analysis was also performed to quantify Na_v 1.7 immunoreactive area in the subodontoblast plexus of dental pulp, and submucosal region of tongue biopsies. Images were captured using an Olympus DP70 camera mounted to an Olympus BX50 microscope and analysed using analySIS (version 5.0). Positive Na_v 1.7 and neurofilaments immunostaining was highlighted by setting the grey-level detection limits to threshold and the area of highlighted immunoreactivity obtained as% area of the field scanned. Five random fields per tissue section were scanned and the mean value used in subsequent statistical analysis. The Mann-Whitney test was used for statistical analysis (P values < 0.05 were considered statistically significant). The ratio between Na_v 1.7 and neurofilaments in serial tissue sections was calculated and used to compare the results from the different groups. The Mann Whitney test was used to compare ratios between groups; *P* values less than 0.05 were considered significant.

Results

Figure 1 shows the presence of large numbers of nerve fibres within human tooth pulp that were immunoreactive for neurofilaments (Figure 1b, d). A subset of nerve fibres was also immunostained with the $Na_v1.7$ antibody (Figure 1a, c) in both non-painful and painful pulp groups. There was a significant increase in the visual intensity score for $Na_v1.7$ in the painful group compared

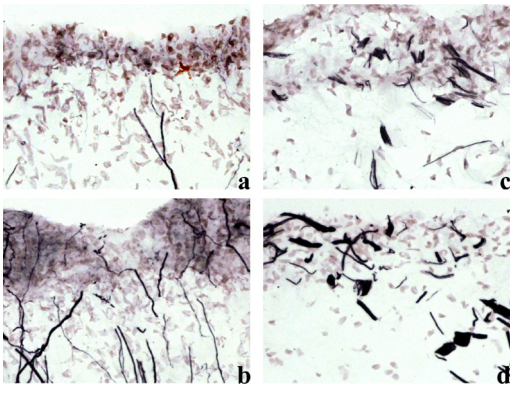

Figure 1 Immunoreactive nerve fibres in non-painful (left column) and painful (right column) human tooth pulp sections, within the subodontoblastic plexus region. Staining with antibodies to $Na_v1.7$ (Figures 1a and 1c) and neurofilament cocktail (Figures 1b and 1d). Magnification × 40.

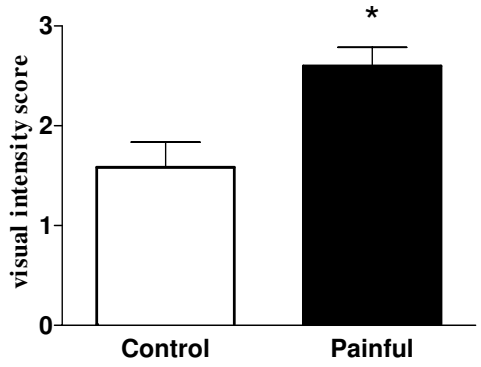

Figure 2 Visual intensity score of $Na_v1.7$ in tooth pulp (mean ± SEM). * P < 0.005.

to controls (Figure 2). By image analysis, there was a trend for an increase of the $Na_v1.7$ immunoreactive area in the painful group, but this was not statistically significant (Figure 3a). There was no difference between the neurofilament staining in these groups (Figure 3b), and when the results were expressed as a ratio of the neurofilament% area, there was also a strong trend for an increase of $Na_v1.7$ in the painful group (Figure 3c).

There was an abundance of $Na_v1.7$ immunoreactive fibres in the sub-mucosal layer of both control (Figure 4a) and BMS tongue biopsies (Figure 4b). No significant difference was observed between BMS and control biopsies with image analysis (Figure 4c). There was a trend for an increase in the visual intensity score for $Na_v1.7$ in the BMS compared to controls, but this was not statistically significant (Figure 4d).

Discussion

The role of ion channels has been implicated in subtypes of pain, such as neuropathic and inflammatory pain [11]. Our study aimed to investigate and compare the expression of $Na_v1.7$ sodium channel within two orofacial pain disorders, an inflammatory pain condition dental pulpitis, and burning mouth syndrome (BMS), considered a neuropathic condition.

This study showed a significant increase in the visual intensity levels of $Na_v1.7$ immunoreactivity within painful dental pulp, in accord with a previous study by Luo et al. (2008) [22]. The latter reported an increase within the axonal bundles [22], and in our study we observed increases within the subodontoblastic plexus. With over 900 axons known to enter the average human premolar tooth, less than half of these fibres that innervate the dental pulp (40%) terminate in dentinal tubules, close to the odontoblast process. The remaining fibres form the subodontoblastic plexus in the coronal aspect of the pulp tissue [2]. Our study has helped to localise the increased

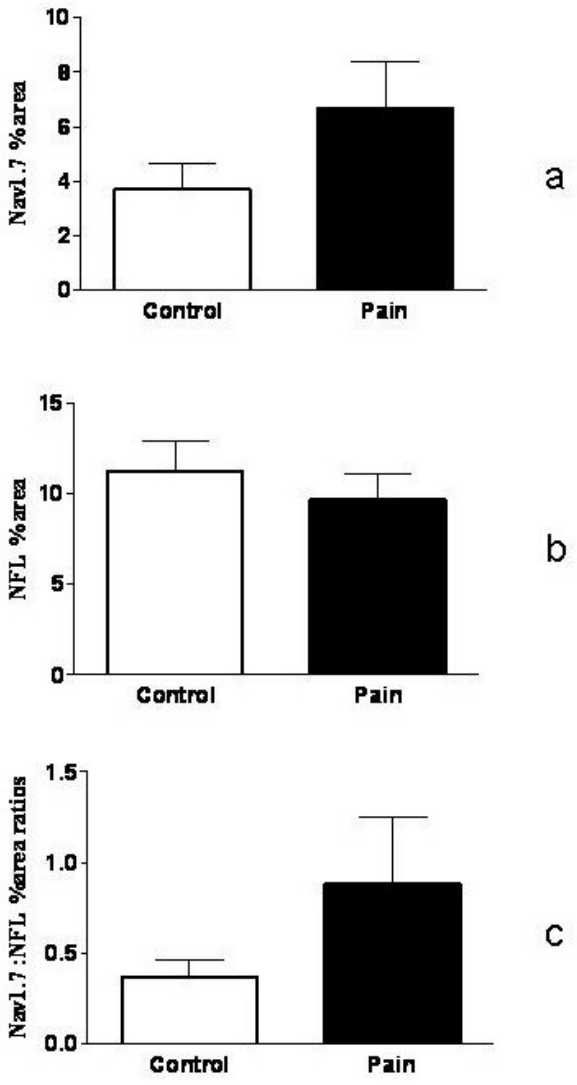

Figure 3 Image analysis of control and painful tooth pulp using antibodies to $Na_v1.7$ (Figure 3a), neurofilament (Figure 3b) and expressing the results as a ratio of $Na_v1.7$:NFL (Figure 3c).

expression of $Na_v1.7$ to the subodontoblastic plexus within painful pulp. These findings indicate a possible involvement of $Na_v1.7$ in toothache, and also suggest a potential role in human inflammatory pain conditions. The inflammatory mediators within pulp may up-regulate the expression of $Na_v1.7$, as may micro-organisms within the oral cavity by causing inflammation. It is unlikely that extracting teeth, or taking tongue biopsies, under local or general anaesthesia will affect Na_v channel expression; the acute effects of anaesthetics would not be expected to alter Na_v channel levels in the short term, as Na_v channels are synthesized in cell bodies and axonally transport to the nerve terminals where they are inserted

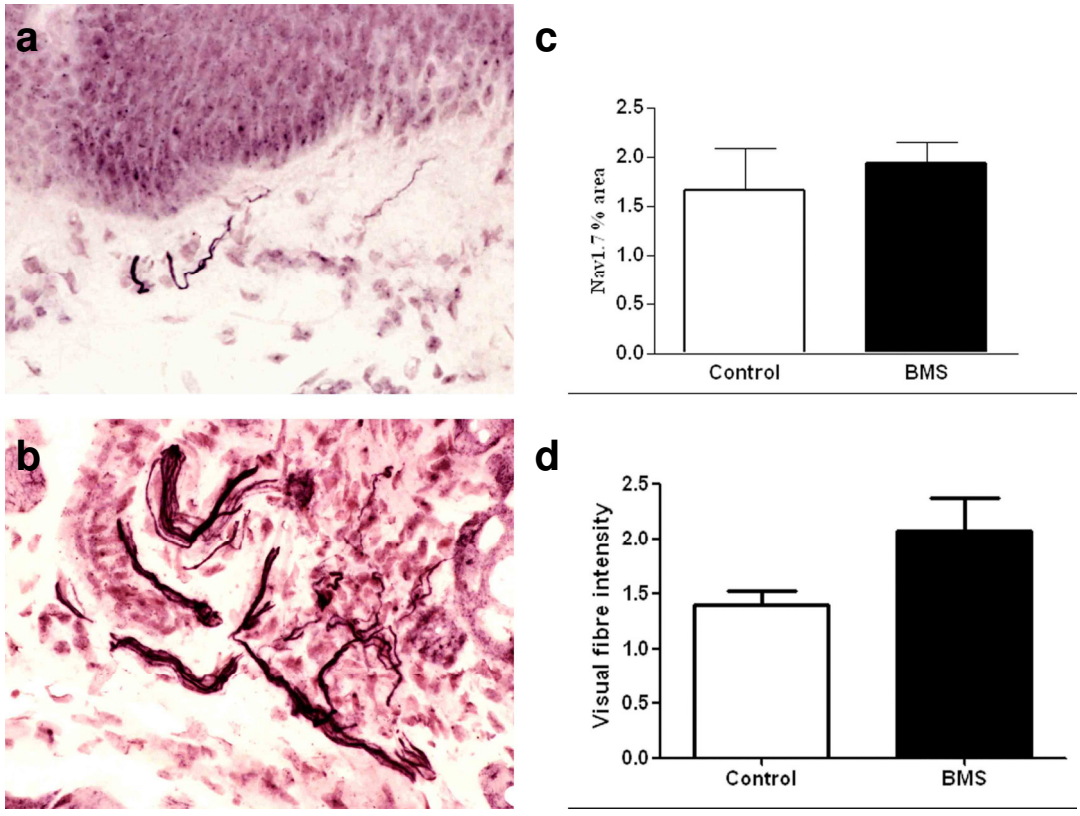

Figure 4 Immunoreactive $Na_v1.7$ nerve fibres in control tongue (Figure 4a) and burning mouth syndrome (Figure 4b), magnification × 40. The bar charts (Figure 4c) show the image analysis and visual intensity scores (Figure 4d) of the $Na_v1.7$ fibres in tongue (Mean ± SEM).

into membranes, a process with a turnover of several days.

Previous studies have demonstrated the role of other sodium channel isoforms within painful pulps. Renton et al. (2005) showed a significant increase in $Na_v1.8$ fibres as a proportion of neurofilament positive fibres within painful dental pulp specimens [2]. Wells et al. (2007) reported a significant increase in the immunoreactivity of $Na_v1.9$ channels in the axons of painful teeth compared to control teeth with no pain [25]. Padilla et al. (2007) also studied the expression of $Na_v1.9$, within rat and mouse trigeminal ganglion nerve endings [24]. $Na_v1.9$ was expressed in trigeminal ganglion neuronal somata (small and medium sized), and also along trigeminal afferent fibres and the terminal branches within lip skin and dental pulp.

The role of sodium channels has further been demonstrated in other inflammatory pain conditions. Strickland et al. (2008) investigated the changes in expression of $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ sodium channels in the rat model and showed that the dorsal root ganglia innervating the knee joint had increased expression of all three subtypes up to 28 days after the initial insult [30]. Our previous study demonstrated an increase of sodium channels $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ in hypersensitivity states of nasal mucosa in patients with allergic and non-allergic rhinitis [21]. These studies support a potential role of these sodium channels in chronic inflammatory pain and hypersensitivity [30].

Burning mouth syndrome (BMS) is defined as a distinct neuropathic orofacial pain condition affecting the oral mucosa according to the International Association for the Study of Pain (IASP). The classification of BMS as a neuropathic pain condition is supported by several previous studies which demonstrate the loss of intra-epithelial nerve fibres, and evidence of small fibre neuropathic changes [31,32]. The BMS patients who participated in this study were recruited in accordance to the International Association for the Study of Pain (IASP) in order to minimise any heterogeneity [27]. BMS patients reported moderate to severe pain intensity, which was similar to previous studies [7,8]. The expression of $Na_v1.7$ sodium

channel in sub-epithelial nerve fibres did not change significantly in BMS in this study. While efforts were made to match the BMS patients with controls and the age ranges overlap, the BMS subjects were older than the controls, and this needs to be taken into consideration. Our previous work also did not show a significant change in another sodium channel isoform $Na_v1.8$ in BMS, whereas the levels of the heat and capsaicin receptor, transient receptor potential Vanilloid (TRPV1), were increased [31].

As we did not observe a significant change in TRPV1 immunoreactivity levels in painful dental pulpitis compared to non-painful tooth pulp [33], there appears to be differential expression of sodium and TRP channels in trigeminal pain disorders - further studies are required to confirm the increase of $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ in inflammatory and TRPV1 in neuropathic trigeminal pain states. A recent investigation in trigeminal neuralgia, a neuropathic pain condition, demonstrated that $Na_v1.7$ levels were decreased. $Na_v1.7$ thus appears more likely to be involved in acquired inflammatory pain, rather than neuropathic pain, in trigeminal disorders [26].

The development of novel $Na_v1.7$ selective blockers remains a challenge, and a major pharmaceutical goal [34] - studies such as this may identify suitable patient cohorts for clinical trials with selective sodium channel antagonists.

Conclusions

The results of this study suggest that the $Na_v1.7$ sodium channel may play a role in inflammatory dental pain. Clinical trials with selective $Na_v1.7$ channel blockers may prioritise dental pulp pain rather than burning mouth syndrome.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KB and TR performed all the surgical procedures, extracted the tooth pulp, carried out all mucosal biopsies and assisted with interpretation of the data. YY performed the immunohistochemistry studies, and participated in the analysis of data and preparation of the manuscript. ZY assisted in drafting the manuscript. TR and PA conceived and coordinated the study, assisted with interpretation of results and helped write the manuscript. KB completed the writing of the manuscript. All authors read and approved the manuscript.

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