

Article

Multimodal Frequency Treatment for Facial Pain Caused by Chronic Rhinosinusitis: A Pilot Study

Michael Smith ¹, Philippe G. Berenger ², Peter Bonutti ³, Alisa P. Ramakrishnan ³, Justin Beyers ³ and Vivek Ramakrishnan ^{4,*}

¹ Sarah Bush Lincoln Health Center, 1000 Health Center Dr., Mattoon, IL 61938, USA; msmith@sblhs.org

² Department of Pain Management, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA; berengp@ccf.org

³ Bonutti Technologies, 2600 S Raney St., Effingham, IL 62401, USA; peter@bonutti.net (P.B.); alisa@bonuttiresearch.com (A.P.R.); jrbeyers@bonuttitechnologies.com (J.B.)

⁴ AxioSonic, 2600 S Raney St., Effingham, IL 62401, USA

* Correspondence: vivek@axiosonic.com; Tel.: +1-217-342-3400

Received: 1 August 2017; Accepted: 29 August 2017; Published: 4 September 2017

Abstract: Chronic rhinosinusitis (CRS) is a common disease that affects over 200 million patients worldwide. CRS often presents with facial pain, which is considered an important criterion for the diagnosis of CRS. A single-arm clinical study was designed to test the effect of simultaneous high (1 MHz) and low frequencies (70–80 Hz) on facial pain in 14 CRS patients at the Sarah Bush Lincoln Health Center, Mattoon, IL, USA. We used two quality of life (QOL) instruments to test the effect of multimodal frequencies on patients suffering from CRS: the Brief Pain Inventory Short Form (BPI-SF), and the Sino-Nasal Outcome Test (SNOT-22). Mean BPI-SF severity scores improved by 0.80 points (Wilcoxon rank sum test $p < 0.01$) in all 14 patients. In patients with baseline facial pain ($n = 9$), the scores improved by an average of 1.5 ($p < 0.01$) points in the pain severity domain and by 1.4 points in the pain interference domain. Additionally, the mean improvement in SNOT-22 scores was 14.11 ($p < 0.05$), which is above the minimal clinically-important difference (MCID) of nine points. Our pilot study indicates that multimodal vibration frequencies applied over the facial sinuses reduce pain, possibly through the reduction of the inflammatory response and modulation of the pain receptors. This study suggests the possibility that combining different frequencies could have an enhanced effect on reducing CRS-related facial pain.

Keywords: maxillary sinus; frontal sinus; chronic rhinosinusitis; facial pain; mechanical vibration; nociceptive modulation

1. Introduction

Chronic rhinosinusitis (CRS) is one of the most common conditions in North America, with almost 40 million patients [1]. Current research suggests that CRS is predominantly an inflammatory disease, with current therapies targeting inflammation within the sino-nasal cavity [2]. Symptoms of nasal congestion and facial pain significantly reduce the quality of life of CRS patients [3,4]. Many patients continue to experience pain after both medical and surgical management. Application of high frequency vibration to sinus regions in CRS patients has been shown to reduce pain and associated symptoms [5]. Chronic rhinosinusitis is characterized by the long-term presence of multiple symptoms including mucopurulent drainage and nasal congestion, and about 80% of CRS patients report facial pain/pressure [4,6,7]. Factors contributing to the pathophysiology of adult CRS include allergies, bacterial biofilms, asthma and exposure to various environmental pollutants [2,7–9]. Radiography or computed tomography (CT) scans are often used to identify mucosal thickening and to identify any comorbid factors such as anatomic abnormalities.

Treatment for CRS focuses on reducing inflammation and includes nasal irrigation, nasal corticosteroids [10], balloon sinuplasty and endoscopic sinus surgery [7,11]. Common pain relievers are also used [12]. Despite the best care, some patients will not respond to long-term medicinal therapy; these patients are recommended for endoscopic sinus surgery. Endoscopic sinus surgery carries some risks [13,14] and can be expensive [15]. Sinus surgery is also less effective for patients with mild symptoms [16], lower sinus microbial diversity [9], cystic fibrosis [17] or for eosinophilic CRS patients [18]. Chronic rhinosinusitis symptoms can continue for years [19], inflicting a significant financial burden [20] and a lower quality of life [4]. In one study, pain persisted for over two years after surgery in around 18% of patients [21]. Home-based, non-medicinal and non-intrusive treatment options are highly desirable both from a patient perspective and as a means to reduce burgeoning healthcare costs.

The causes of facial pain in CRS are unclear. Objective measures of disease severity do not correlate well with sinus pain [22,23]. One explanation is that stimulation in the sino-nasal cavity can cause referred pain, where pain is felt in a completely different location [24]. Another explanation is the observation that many patients complaining of sinus pain experience headaches or migraines [25,26]. Hypersensitization to pain from migraines could make innocuous stimuli more painful, which may contribute to the pain experienced by CRS patients [26,27]. Misuse of medication can also contribute to sinus pain [28].

Pain relief via cutaneous vibration has been demonstrated in chronic pain patients [29], osteoarthritis [30] and muscle pain [31]. Cutaneous vibration affects mechanoreceptors in the face [32,33], moderating pain by activating a pain gating pathway in the brainstem [34,35]. Though transcutaneous electrical stimulation can reduce headaches [36] and vibration has been used to reduce facial pain for injections [37], cutaneous vibration has not been tested on CRS patients.

Pain relief for CRS patients has been demonstrated using deep heating via application of 1-MHz frequency waves [38–40]. These high frequency waves raise deep tissue temperatures 1–5 °C [41], similar to the action of steam inhalation for nasal congestion [42]. High frequency waves may also reduce inflammation [43,44] and may also act on biofilms that have been hypothesized as a contributing factor in CRS [45]. A combination of cutaneous vibration and deep heat could more effectively alleviate facial pain associated with CRS, targeting both deep and surface mechano- and thermo-sensitive nerves.

CRS pain is usually reported as a single item in a larger suite of questions, affecting accurate interpretation of pain relief data [4]. Accurate measurements of pain are crucial to determining clinically-meaningful pain relief results [46,47]. The placebo effect is also strong in pain trials, increasing the need for accurate measurements [48]. The Brief Pain Inventory Short Form (BPI-SF) and the Short-Form McGill Pain Questionnaire are validated across many populations for use in pain studies, but have not been used to study the effect of vibration pain relief on CRS patients.

We combined cutaneous vibration at 70–80 Hz with deep heating at 1 MHz to test the effect of multimodal treatment on facial pain, quality of life and CRS symptoms in 14 patients with CRS. We hypothesized that cutaneous vibration would have an analgesic effect through stimulation of mechanosensors in the face, while deep heating would have effects similar to what has been observed in previous studies. Each patient was treated with a proprietary multimodal vibration therapy unit, designed by AxioSonic, with a specific transducer head that conforms to complex facial geometry. We used the BPI-SF to more accurately determine the extent of pain relief perceived by patients, while we used a similar measure used in a previous study (the Sino-Nasal Outcome Test, SNOT-22 instead of SNOT-20) for comparison and to quantify quality of life (QOL) changes due to CRS. Development of a cost-effective, non-medicinal and non-invasive therapy for CRS facial pain will be useful for both medical practitioners and patients.

2. Materials and Methods

2.1. Prospective Clinical Trial of Multimodal Frequencies for the Treatment of Chronic Rhinosinusitis Patients

This clinical trial was a prospective, single-arm study conducted at Sarah Bush Lincoln Health Center, Mattoon, IL, USA, from August–October 2016. Appropriate government and local reviews were obtained, including prior approval by the Medical Ethics and Institutional Review Board (IRB) committee at Sarah Bush Lincoln Health Center, Mattoon, IL, USA. All subjects gave written informed consent. Subjects who were included met the diagnostic criteria for CRS as defined by the American Academy of Otolaryngology–Head & Neck Surgery Foundation Clinical Practice Guidelines [7]. Patients were excluded who: had used immunosuppressive drugs for treatments besides CRS within 30 days of trial or who had a diagnosis of conditions that may interfere with the results of the study, such as: immotile cilia syndrome, cystic fibrosis, immune-deficiency, systemic autoimmune conditions with sinus involvement, had sino-nasal tumors or obstructive lesions, a history of facial trauma, uncontrolled diabetes, smoked or had cancer or brain tumor(s). Because the efficacy endpoints were related to pain and CRS symptoms, subjects were asked to make no changes to the pain or medications they were taking throughout the study.

Possible side effects of multimodal therapy on the face have not been reported in the literature, so our primary endpoint was safety, as measured by the proportion of patients with device-related serious adverse events. The secondary endpoints included facial pain as measured by the BPI-SF (pain severity and pain interference scores) and the Sino-Nasal Outcome Test-22 (SNOT-22) [16,49]. We used SNOT-22 scores to investigate changes in disease-related quality of life, because mechanical vibrations may improve CRS symptoms, as well as pain [43,50]. BPI-SF is a validated tool to measure clinical pain severity and interference and has become one of the most widely-used measurement tools for assessing clinical pain [51]. Questions are scored 0–10 [4,51], and averages are taken for six questions on severity of pain and for seven questions on interference with quality of life. The SNOT-22 questionnaire is a validated, widely-used 22-item tool used to assess CRS symptom severity [4]. Lower total scores (score range 0–110) indicate better overall symptom severity and quality of life [4]. Endoscopy was performed by Michael Smith before and after treatment to investigate possible changes in CRS symptom severity, and observations were noted.

Multimodal frequency treatments were administered using an AxioSonic therapeutic device (Figure 1) by trained clinical staff at the principal investigator's clinical site. The AxioSonic device is a hand-held portable device that can be administered either at home or at a clinic. The AxioSonic device operates at two simultaneous frequencies, one at 70–80 Hz and one at 1 MHz. The higher frequency wave has two settings for treatment: maxillary (1 W/cm^2 , 5 min duration) and frontal (0.5 W/cm^2 , 5-min duration). The device is coupled to the skin with the use of a gel. A proprietary cutaneous mechanical vibration treatment is activated when the applicator is adequately coupled to the skin. Each unit was independently calibrated to ensure acoustic intensity.

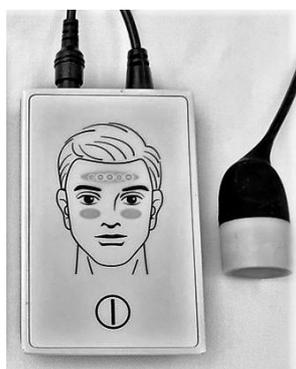


Figure 1. AxioSonic multimodal frequency treatment device.

The treatment regime consisted of three treatments per week for a total of six multimodal treatments over a two-week period (Figure 2). Each treatment session lasted a total of 15 min: 5 min on each maxillary sinus and 5 min on the frontal sinuses. Each unit was programmed to record total active usage time for each patient to ensure the units were functioning properly and to ensure treatment compliance. The study concluded for each participant 30 days after their last treatment with the AxioSonic device. All patients were treated with 3 treatments per week over the course of 2 weeks for a total of 6 treatments. All patients were followed for safety for 30 days after the last AxioSonic treatment session. Any adverse events were reported both with the number of patients experiencing events and the overall frequency of events. Adverse events were defined as any unfavorable and unintended diagnosis, symptom, sign, syndrome or disease occurring during the study, having been absent at baseline, or if present at baseline, appears to worsen. Because this was an initial assessment trial, no treatment control was included.

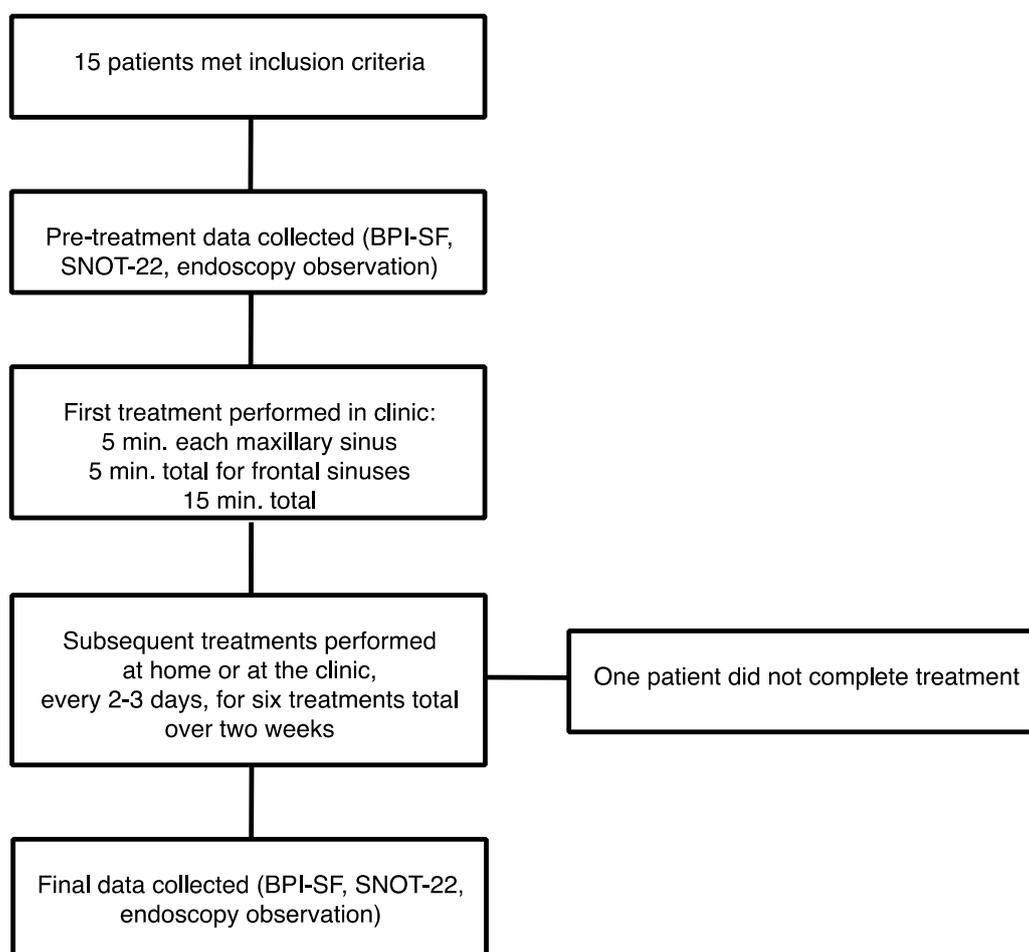


Figure 2. Clinical timeline. BPI-SF: Brief Pain Inventory Short Form; SNOT: Sino-Nasal Outcome Test.

Data analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA) and R Version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). We compared baseline to post-treatment scores with the Wilcoxon signed rank test to avoid violations of sphericity.

2.2. Analysis of Previously-Published Data

We were unable to find previous research that incorporated multiple analgesic frequencies to treat CRS pain. There are several studies that used 1-MHz frequencies to treat CRS symptoms, including pain [38–40,52–55], but only one was conducted in English with comparable data. We obtained raw

data for this study; it had a total of 20 patients treated with a 1-MHz frequency (1 W/cm² and 0.5 W/cm²) at a 10% duty cycle [40]. To evaluate the effect of their treatment, Young et al. [40] used the 20-question Sino-Nasal Outcome Test (SNOT-20), a list of questions where symptoms are rated 0–5. They also used a list of symptom-related questions, including pain, where each question was rated using a visual analog scale (1–7). We calculated standard statistical indices and estimated effect sizes using Cohen's *d*. Cohen's *d* is useful for quantifying the effectiveness of a particular intervention. It is a method of estimating the effectiveness of a treatment methodology, and is used to determine whether or not a significant difference in a study has a clinically-important outcome. It is calculated by dividing the difference in mean scores pre- and post-treatment by the standard deviation. Though other measures are also used, Cohen's *d* remains a useful tool in patient-reported outcome studies [56].

2.3. Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation as implemented by the Institutional Review Board for the Sarah Lincoln Bush Hospital (IRB00002130) and with the Helsinki Declaration of 1975, as revised in 2008.

3. Results

3.1. Clinical Trial Results

The average age of the 15 patients enrolled in this study was 60 years (34–83 years); six were male, and nine were female (Table 1). Subjects met inclusion and exclusion criteria. One patient was not considered in the final study because she did not continue treatment adequately after her device was damaged. Basic demographic data are presented in Table 1. Ten patients independently reported feelings of increased drainage and/or reduced pressure. Two patients specifically mentioned reduction in headache and pain. Most patients (13/14) felt that the treatment was helpful.

Table 1. Patient baseline demographic data. All patients maintained stable medication levels.

Patient Information	Value (SD*)
Patients enrolled	15
Patients completed study	14
Age (mean)	60 (12.64)
Male	6
Female	9
Diabetic (controlled)	3
Past sinus surgery	2
Hypertension	6
Patients reporting facial pain at the beginning of the study	9

* SD: standard deviation

Average post-treatment scores improved for both pain- and symptom-related domains (Tables 2 and 3). The treatment was more effective on patients with facial pain (Tables 2 and 3). Pain severity improved by one point on average for all patients and by 1.5 points for patients with facial pain (Figure 3). In the BPI-SF, there are seven questions relating to pain interference with daily life, called the interference domain. Patient mean scores in the interference domain improved from 2.0–0.89 for all patients (Table 4). Interestingly, the mean sleep domain scores of the BPI-SF interference assessment improved by 2.36 points in all subjects and by three points in subjects with pain at baseline.

Table 2. Changes in facial pain from Young et al. [40]. All 20 patients reported baseline facial pain. Mean scores, SD, mean change in scores, effect sizes (Cohen's *d*) and published *p*-values are included.

Item	Baseline	Post-Treatment	Change (SD)	Effect Size (Cohen's <i>d</i>)
Facial Pain (from SNOT-20)	2.20 (1.73)	1.45 (1.46)	0.75 (1.48)	0.51 *
Facial Pain Analog Scale	4 (2.12)	3 (1.67)	1 (1.65)	0.76
SNOT-20 total score	43.15 (24.75)	27.40 (21.18)	15.75 (17.41)	0.90 ***

*** $p < 0.001$, * $p < 0.05$.

Table 3. Treatment results for patients with baseline pain ($n = 9$). Mean scores, SD, mean change in scores, effect sizes (Cohen's *d*) and *p*-values are included.

Domain	Baseline	Post-Treatment	Change (SD)	Effect Size
BPI-SF Severity (Facial Pain)	2.78 (1.97)	1.28 (1.72)	1.50 (1.56)	0.96 **
BPI-SF Interference	2.65 (2.44)	1.25 (1.86)	1.40 (2.26)	0.62
SNOT-22 total score	47.11 (18.80)	33.00 (16.56)	14.11 (16.85)	0.84 *

** $p < 0.01$, * $p < 0.05$.

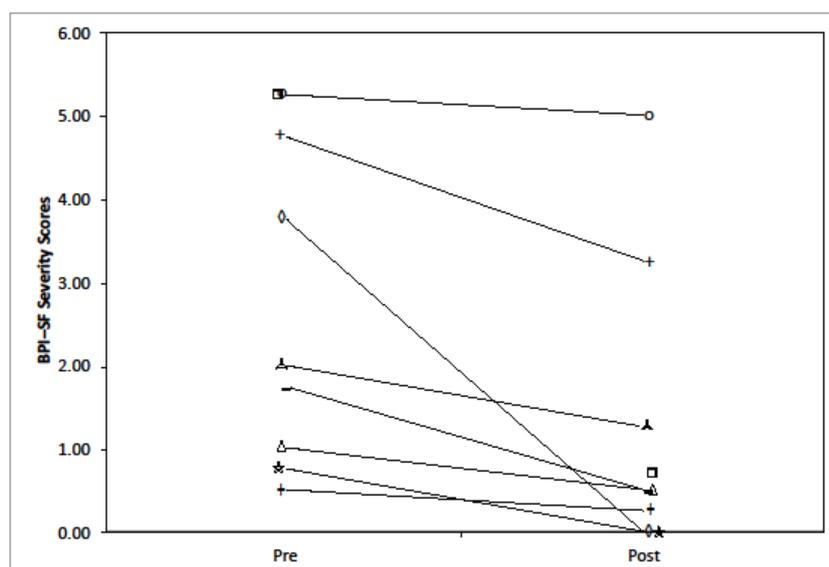


Figure 3. Improvement in BPI-SF severity domain pain scores for patients with baseline facial pain after six treatments.

Table 4. Treatment results for all patients ($n = 14$). Five patients reported no baseline facial pain. Mean scores, SD, effect sizes (Cohen's *d*) and *p*-values were calculated.

Domain	Baseline (SD)	Post-Treatment (SD)	Change (SD)	Effect Size
BPI-SF Severity (Facial Pain)	1.82 (2.00)	1.02 (1.62)	0.80 (1.52)	0.67 **
BPI-SF Interference	1.91 (2.11)	0.83 (1.51)	1.09 (1.78)	0.60 *
SNOT-22 total score	41.47 (17.56)	34.27 (15.73)	7.20 (19.18)	0.45

** $p < 0.01$, * $p < 0.05$.

Patient scores of overall symptom and quality of life as measured by SNOT-22 improved, with a medium effect size (Table 4 and Figure 4). The effect size of symptom improvement was larger (and statistically significant $p < 0.05$) for patients who reported pain at baseline (SNOT-22 $d = 0.84$, Table 3). Patients improved an average of 5.5 points in the symptoms domain of SNOT-22 (Questions 1–12) and an average of 3.14 points in the quality of life domain (Questions 13–22).

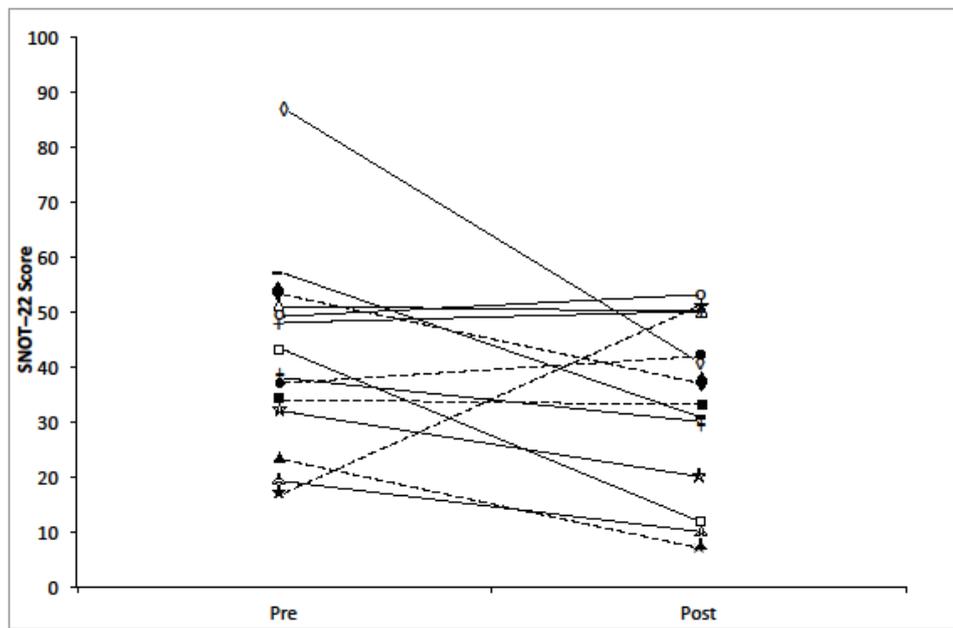


Figure 4. Change in SNOT-22 scores for all patients after six treatments. Patients with baseline facial pain are solid lines, and patients without baseline pain are dotted lines.

Total scores from BPI-SF and SNOT-22 were highly correlated (Figure 5), but there was one patient who reported a large decrease in quality of life using the SNOT-22 form that was not detected using the BPI-SF form. Similar questions are found in both forms, including quality of sleep, mood and productivity; it is unclear why the patient reported slight improvement on the BPI-SF form and a large decrease in quality of life on the SNOT-22 form.

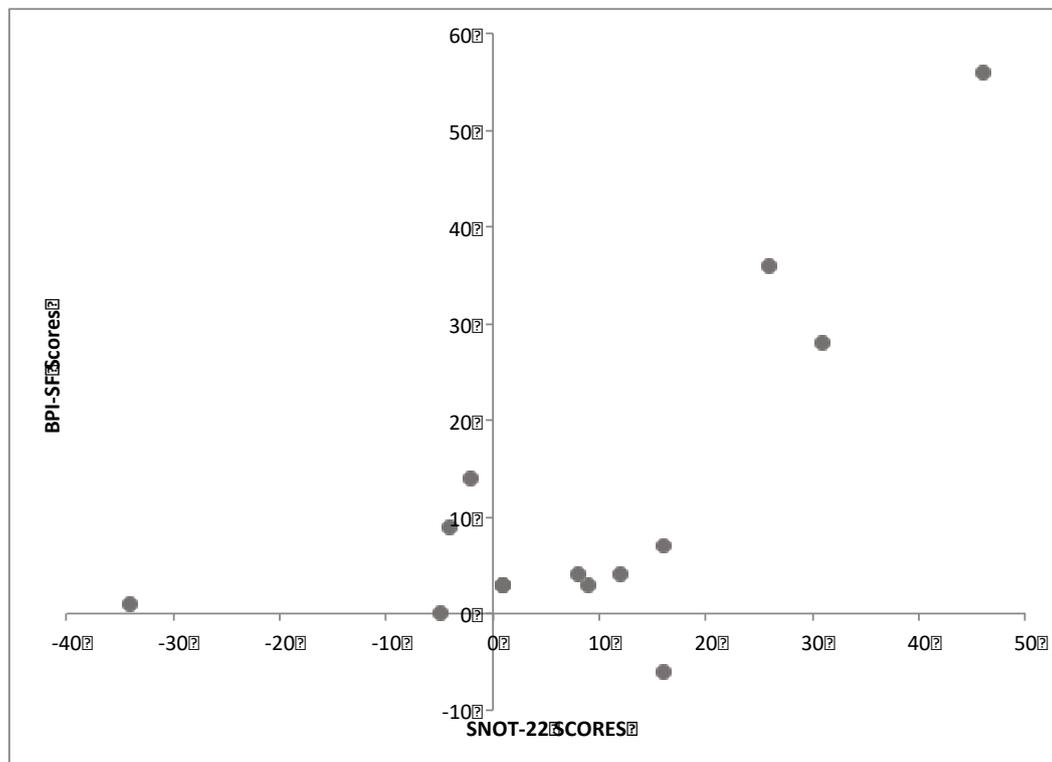


Figure 5. Correlation between SNOT-22 scores and BPI-SF scores ($R^2 = 0.51$).

Endoscopy results based on visual inspection by Michael Smith before and after treatment indicated reduced or completely resolved middle meatal edema in 13 out of 14 patients. Further studies with larger numbers of patients should include an objective scoring system, quantitative measures of edema and discharge, and based on our preliminary study, they should also focus on CRS patients that present with facial pain. No device-related adverse events were observed or reported for the 84 AxioSonic treatment sessions (six sessions for each of 14 patients), nor during the 30-day follow-up after the last AxioSonic treatment session. Overall, treatment of CRS pain with AxioSonic is safe, effective and has reduced side effects.

Effect sizes from Young et al. [40] were high and comparable to results from our paper for CRS symptoms (Table 2). All of these patients had pain of at least one on a scale of 0–7. When we compare results for patients that had facial pain, the AxioSonic multimodal treatment is more effective for treating pain.

4. Discussion

This study measured changes in CRS-related quality of life measurements including facial pain after treatment with multimodal frequency stimulation. Treatment with combined high frequency (1 MHz) and low frequency vibration (70–80 Hz) reduced both pain and quality of life measures. The effect size we observed for pain was larger than published results for a previous clinical trial that used only 1-MHz ultrasound frequency [40]. We also observed an improvement in the sleep subdomain of the SNOT-22, a crucial component of quality of life. There were no device-related adverse events. No research has yet reported effects of low frequency vibration (50–100 Hz) on CRS pain. Most of the published literature has focused on analgesia in the peripheral nervous system [30,31,57–60], though some research has reported success treating temporomandibular disorder pain [61,62]. Low frequency vibratory inhibition of nerves associated with the parasympathetic nervous system may be partly responsible for the beneficial effects of treatment [63,64]. The current study adds to previous research by testing the analgesic effects of vibrational neurostimulation for facial pain.

Several clinical trials have reported improvements in pain after treatment with 1-MHz ultrasound [40,52,54]. In a study by Ansari et al. [53], 95% of patients with facial pain at the beginning of the study reported significant improvement after the study. The facial pain effect size observed in our study ($d = 0.96$) was much higher than that estimated from Young et al.'s data ($d = 0.51$), likely due to the application of multimodal frequencies (70–80 Hz and 1 MHz) in the AxioSonic system. Our effect size for quality of life measures using the SNOT-22 questionnaire ($d = 0.45$) was lower than Young et al.'s paper [40] ($d = 0.9$). One possible reason for this discrepancy could be due to the fact most patients in Young et al.'s study [40] presented with facial pain, whereas in our study, five patients did not present with facial pain at the beginning of treatment. When we take patients presenting with facial pain into account, our symptom effect size ($d = 0.84$) is similar to Young et al. ($d = 0.90$) [40]. In addition, we used the pain-specific metric (BPI-SF) and the SNOT-22 questionnaires, had different treatment regimes, and our sample size was smaller, all of which can influence the end result. Chronic rhinosinusitis symptoms can have a negative impact on quality of life [47], especially in interference with sleep [65]. Lack of sleep is correlated with depression in CRS patients [3]. In our study, patients experienced better sleep after treatment and reported improvement in overall quality of life. In both questionnaires, the BPI-SF and the SNOT-22, patients reported increased ability for uninterrupted sleep. The observed effect size in questions related to sleep in the BPI-SF was $d = 0.64$ and $d = 0.61$ for SNOT-22 in all patients ($n = 14$). Treating CRS pain with vibrational stimulation could significantly decrease the burden of CRS on patients' quality of life.

Overall, the effect sizes we observed were largest for patients with facial pain, the main targeted symptom for AxioSonic multimodal treatment. Though this study only included nine patients with facial pain, the average change in SNOT-22 scores was 16.85 for those patients. This is larger than the minimal clinically-important difference (MCID) of 8.9 [66], indicating that patients with pain

due to CRS could benefit significantly from this treatment. Further clinical studies should test the relative benefits of different wavelengths and include a placebo control to quantify the effects of various treatments.

Vibratory analgesia is based on the observation that stimulation of afferent nerves with mechanical vibration reduces perceived pain [67,68]. The analgesic effect of vibration is likely due to both afferent and cortical processes [64,67,69]. Combining vibratory stimulation with either electrical or thermal stimulation increases the analgesia effect, probably due to the activation and recruitment of multiple types of receptors [30,31,57]. Vibratory analgesia of 70–80 Hz has been successfully used to reduce pain in various procedures, including IV insertion [59], blood collection [58] and experimentally-induced pain [70]. In a study on patients with temporomandibular disorder, 20-Hz vibration on the cheek reduced pain, but not as much as 100-Hz vibration [62]. Dual-stimulation therapy with application of both heat and vibration could alleviate CRS pain, as we observed in this study.

The reduction in quality of life reported by CRS patients may be mediated in part by the sphenopalatine (pterygopalatine) ganglion (SPG), near the maxillary sinuses and accessible through the rear of the nasal cavity. The SPG is involved in tissue inflammation, lacrimation, mucus production and other parasympathetic processes [71–74]. Low frequency neurostimulation (20 Hz, much lower than ultrasound frequencies) of the SPG or the Vidian nerve leads to vasodilation and associated inflammation [75,76]. Stimulation of the SPG at higher frequencies (50 Hz) resolves nasal congestion and swelling due to cluster headaches [77] and may alleviate similar symptoms in CRS patients, as well. Electrical stimulation and mechanical stimulation of peripheral nerves target similar types of nerves [57], and both electrical [78,79] and vibratory stimulation [30,62,80] have analgesic effects [29]. Combining treatment modalities could lead to amplified analgesia [57].

Vibratory stimulation at 70–80 Hz could reduce facial pain in CRS patients through multiple pathways, specifically by modulating the parasympathetic response. Neuromodulation through vibratory stimulus can affect the activity of large diameter nerve fibers, subsequently exciting inhibitory cells and reducing perceived pain [81]. Nerves associated with the SPG may also be involved, and vibration could modulate the parasympathetic response [64,82]. These mechanisms of action could explain the reduction in facial pain observed in our study and also the observation that over half of the patients in our study reported that the AxioSonic device helped increase mucous discharge possibly due to the thinning of bacterial biofilms [40]. Visual inspection by endoscopy as part of patients' routine care showed improved edema and reduction or clearing of purulent discharge, suggesting a reduced inflammatory response [83]. The deep heating and thermal effects of the 1-MHz waves could also contribute to an additional reduced inflammatory response [40]. Our AxioSonic device is hypothesized to work by a combination of modulating nociceptive receptors, deep heating and reducing inflammation.

5. Conclusions

Chronic rhinosinusitis has a negative impact on the quality of life of at least 14% of the population in the United States [84]. The data from our prospective clinical study support previous studies showing improvement in facial pain and overall CRS symptom scores in patients treated with ultrasound at a 1-MHz frequency. In addition, our studies show that adding an additional low frequency vibration at 70–80 Hz could improve the pain response in patients suffering from CRS and suggests that multimodal vibration treatment would benefit patients, with few side effects and no risk of antibiotic overuse.

Acknowledgments: We are grateful to James Bartley for providing us with data from previous studies, Tonya Bierman for help designing the device and Patrick Balsmann for help with the clinical trial.

Author Contributions: P.B. and V.R. helped design the study. M.S. performed the clinical trial. A.P.R. helped with the statistics and data analysis. J.B. designed the device, programmed the software and helped with the study. P.B. gave input on the neurobiology of pain. The final manuscript was written by A.P.R. and V.R. with inputs from all authors. All authors approved the final manuscript.

Conflicts of Interest: The multimodal frequency clinical trial was funded by AxioSonic. M.S. was the principal investigator of the study and designed the study with the input of P.B. and V.R. Data were collected at each site using paper clinical report forms. All investigators had unrestricted access to the data.

References

1. Blackwell, D.L.; Lucas, J.W. Tables of Summary Health Statistics for U.S. Adults: 2014 National Health Interview Survey. 2015. Available online: <http://www.cdc.gov/nchs/nhis/SHS/tables.htm> (accessed on 13 July 2017).
2. Fokkens, W.J.; Lund, V.J.; Mullol, J.; Bachert, C.; Alobid, I.; Baroody, F.; Cohen, N.; Cervin, A.; Douglas, R.; Gevaert, P.; et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology* **2012**, *50*, 1–298. [[PubMed](#)]
3. Cox, D.R.; Asbhy, S.; Mace, J.C.; DelGaudio, J.M.; Smith, T.L.; Orlandi, R.R.; Alt, J.A. The pain-depression dyad and the association with sleep dysfunction in chronic rhinosinusitis. *Int. Forum Allergy Rhinol.* **2017**, *7*, 56–63. [[CrossRef](#)] [[PubMed](#)]
4. DeConde, A.M.; Made, J.C.; Ashby, S.; Smith, T.L.; Orlandi, R.R.; Alt, J.A. Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. *Int. Forum Allergy Rhinol.* **2015**, *5*, 682–689. [[CrossRef](#)] [[PubMed](#)]
5. Bartley, J.; Ansari, N.N.; Naghdi, S. Therapeutic ultrasound as a treatment modality for chronic rhinosinusitis. *Curr. Infect. Dis. Rep.* **2014**, *16*, 398–404. [[CrossRef](#)] [[PubMed](#)]
6. Meltzer, E.O.; Hamilos, D.L. Rhinosinusitis diagnosis and management for the clinician: A synopsis of recent consensus guidelines. *Mayo Clin. Proc.* **2011**, *86*, 427–443. [[CrossRef](#)] [[PubMed](#)]
7. Rosenfeld, R.; Piccirillo, J.; Chandrasekhar, S.; Brook, I.; Kumar, K.; Kramper, M.; Orlandi, R.; Palmer, J.; Patel, Z.; Peters, A.; et al. Clinical practice guideline (update): Adult sinusitis. *Otolaryngol. Head Neck Surg.* **2015**, *152*, S1–S39. [[CrossRef](#)] [[PubMed](#)]
8. Lanza, D.C.; Kennedy, D.W. Adult rhinosinusitis defined. *Otolaryngol. Head Neck Surg.* **1997**, *117*, S1–S7. [[CrossRef](#)]
9. Ramakrishnan, V.R.; Hauser, L.J.; Feazel, L.M.; Ir, D.; Robertson, C.E.; Frank, D.N. Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome. *J. Allergy Clin. Immunol.* **2015**, *136*, 334–342. [[CrossRef](#)] [[PubMed](#)]
10. Schäcke, H.; Döcke, W.; Asdullah, K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol. Ther.* **2002**, *96*, 23–43. [[CrossRef](#)]
11. Patel, Z.M.; Thamboo, A.; Rudmik, L.; Nayak, J.V.; Smith, T.L.; Hwang, P.H. Surgical therapy vs continued medical therapy for medically refractory chronic rhinosinusitis: A systematic review and meta-analysis. *Int. Forum Allergy Rhinol.* **2017**, *7*, 119–127. [[CrossRef](#)] [[PubMed](#)]
12. Hinz, B.; Cheremina, O.; Brune, K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J.* **2008**, *22*, 383–390. [[CrossRef](#)] [[PubMed](#)]
13. Lund, V.J.; MacKay, I.S. Outcome assessment of endoscopic sinus surgery. *J. R. Soc. Med.* **1994**, *87*, 70–72. [[PubMed](#)]
14. Ragab, S.M.; Lund, V.J.; Scadding, G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: A prospective, randomised, controlled trial. *Laryngoscope* **2004**, *114*, 923–930. [[CrossRef](#)] [[PubMed](#)]
15. Friedman, M.; Schalch, P.; Lin, H.; Mazloom, N.; Neidich, M.; Joseph, N.J. Functional endoscopic dilatation of the sinuses: Patient satisfaction, postoperative pain, and cost. *Am. J. Rhinol.* **2008**, *22*, 204–209. [[CrossRef](#)] [[PubMed](#)]
16. Kennedy, J.L. Sino-nasal outcome test (SNOT-22): A predictor of postsurgical improvement in patients with chronic sinusitis. *Ann. Allergy Asthma Immunol.* **2013**, *111*, 246–251.e2. [[CrossRef](#)] [[PubMed](#)]
17. Chaaban, M.R.; Kejner, A.; Rowe, S.M.; Woodworth, B.A. Cystic fibrosis chronic rhinosinusitis: A comprehensive review. *Am. J. Rhinol. Allergy* **2013**, *27*, 387–395. [[CrossRef](#)] [[PubMed](#)]
18. Younis, R.T.; Ahmed, J. Predicting revision sinus surgery in allergic fungal and eosinophilic mucin chronic rhinosinusitis. *Laryngoscope* **2017**, *127*, 59–63. [[CrossRef](#)] [[PubMed](#)]

19. Benninger, M.S.; Ferguson, B.J.; Hadley, J.A.; Hamilos, D.L.; Jacobs, M.; Kennedy, D.W.; Lanza, D.C.; Marple, B.F.; Osguthorpe, J.D.; Stankiewicz, J.A.; et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol. Head Neck Surg.* **2003**, *129*, S1–S32. [[CrossRef](#)] [[PubMed](#)]
20. Bhattacharyya, N.; Orlandi, R.R.; Grebner, J.; Martinson, M. Cost burden of chronic rhinosinusitis: A claims-based study. *Otolaryngol. Head Neck Surg.* **2011**, *144*, 440–445. [[CrossRef](#)] [[PubMed](#)]
21. Jones, N.S.; Cooney, T.R. Facial pain and sinonasal surgery. *Rhinology* **2003**, *41*, 193–200. [[PubMed](#)]
22. Ryan, W.R.; Ramachandra, T.; Hwang, P.H. Correlations between symptoms, nasal endoscopy, and in-office computed tomography in post-surgical chronic rhinosinusitis patients. *Laryngoscope* **2011**, *121*, 674–678. [[CrossRef](#)] [[PubMed](#)]
23. Shields, G.; Seikaly, H.; LeBoeuf, M.; Guinto, F.; LeBoeuf, H.; Pincus, T.; Calhoun, K. Correlation between facial pain or headache and computed tomography in rhinosinusitis in Canadian and U.S. subjects. *Laryngoscope* **2003**, *113*, 943–945. [[CrossRef](#)] [[PubMed](#)]
24. Clerico, D.M. An experimental study of pain upon stimulation of the nasal and sinus cavities. *Am. J. Otolaryngol.* **2014**, *35*, 300–304. [[CrossRef](#)] [[PubMed](#)]
25. Mehle, M.E.; Schreiber, C.P. Sinus headache, migraine, and the otolaryngologist. *Otolaryngol. Head Neck Surg.* **2005**, *133*, 489–496. [[CrossRef](#)] [[PubMed](#)]
26. Jones, N.S. Sinus headaches: Avoiding over- and mis-diagnosis. *Expert Rev. Neurother.* **2009**, *9*, 439–444. [[CrossRef](#)] [[PubMed](#)]
27. Mehle, M.E.; Schreiber, C.P. What do we know about rhinogenic headache? *Otolaryngol. Clin. North Am.* **2014**, *47*, 255–268. [[CrossRef](#)] [[PubMed](#)]
28. Aaseth, K.; Grande, R.B.; Kværner, K.; Lundqvist, C.; Russell, M.B. Chronic rhinosinusitis gives a ninefold increased risk of chronic headache. *Cephalalgia* **2010**, *30*, 152–160. [[CrossRef](#)] [[PubMed](#)]
29. Lundeberg, T. The pain suppressive effect of vibratory stimulation and transcutaneous electrical nerve stimulation (TENS) as compared to aspirin. *Brain Res.* **1984**, *294*, 201–209. [[CrossRef](#)]
30. Kitay, G.S.; Koren, M.J.; Helfet, D.L.; Parides, M.K.; Markenson, J.A. Efficacy of combined local mechanical vibrations, continuous passive motion and thermotherapy in the management of osteoarthritis of the knee. *Osteoarthr. Cartil.* **2009**, *17*, 1269–1274. [[CrossRef](#)] [[PubMed](#)]
31. Gay, A.; Aimonetti, J.; Roll, J.; Ribot-Ciscar, E. Kinesthetic illusions attenuate experimental muscle pain, as do muscle and cutaneous stimulation. *Brain Res.* **2015**, *1615*, 148–156. [[CrossRef](#)] [[PubMed](#)]
32. Trulsson, M.; Essick, G.K. Sensations evoked by microstimulation of single mechanoreceptive afferents innervating the human face and mouth. *J. Neurophysiol.* **2010**, *103*, 1741–1747. [[CrossRef](#)] [[PubMed](#)]
33. Johansson, R.S.; Trulsson, M.; Olsson, K.Å.; Westbert, K.G. Mechanoreceptor activity from the human face and oral mucosa. *Exp. Brain Res.* **1988**, *72*, 204–208. [[CrossRef](#)] [[PubMed](#)]
34. Sessle, B.J. Acute and chronic craniofacial pain: Brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Crit. Rev. Oral Biol. Med.* **2000**, *11*, 57–91. [[CrossRef](#)] [[PubMed](#)]
35. Woolf, C.J. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain* **2011**, *152*, S2–S15. [[CrossRef](#)] [[PubMed](#)]
36. Miller, S.; Sinclair, A.J.; Davies, B.; Matharu, M. Neurostimulation in the treatment of primary headaches. *Pract. Neurol.* **2015**, *16*, 362–375. [[CrossRef](#)] [[PubMed](#)]
37. Nanitsos, E.; Vartuli, R.; Forte, A.; Dennison, P.J.; Peck, C.C. The effect of vibration on pain during local anaesthesia injections. *Aust. Dent. J.* **2009**, *52*, 94–100. [[CrossRef](#)] [[PubMed](#)]
38. Ansari, N.N.; Soofia, N.; Farhadi, M.; Jalaie, S. A preliminary study into the effect of low-intensity pulsed ultrasound on chronic maxillary and frontal sinusitis. *Physiother. Theory Pract.* **2007**, *23*, 211–218. [[CrossRef](#)] [[PubMed](#)]
39. Naghdi, S.; Ansari, N.N.; Farhadi, M. A clinical trial on the treatment of chronic rhinosinusitis with continuous ultrasound. *J. Phys. Ther. Sci.* **2008**, *20*, 233–238. [[CrossRef](#)]
40. Young, D.; Morton, R.; Bartley, J. Therapeutic ultrasound as treatment for chronic rhinosinusitis: Preliminary observations. *J. Laryngol. Otol.* **2010**, *124*, 495–499. [[CrossRef](#)] [[PubMed](#)]
41. Baker, K.G.; Robertson, V.J.; Duck, F.A. A review of therapeutic ultrasound: Biophysical effects. *Phys. Ther.* **2001**, *81*, 1351–1358. [[CrossRef](#)] [[PubMed](#)]
42. Tyrell, D.; Barrow, I.; Arthur, J. Local hyperthermia benefits natural and experimental common colds. *Br. Med. J.* **1989**, *298*, 1280–1283. [[CrossRef](#)]

43. Bartley, J.; Young, D. Ultrasound as a treatment for chronic rhinosinusitis. *Med. Hypotheses* **2009**, *73*, 15–17. [[CrossRef](#)] [[PubMed](#)]
44. Chung, J.-I.; Barua, S.; Choi, B.H.; Min, B.-H.; Han, H.C.; Baik, E.J. Anti-inflammatory effect of low intensity ultrasound (LIUS) on complete Freund's adjuvant-induced arthritis synovium. *Osteoarthr. Cartil.* **2012**, *20*, 314–322. [[CrossRef](#)] [[PubMed](#)]
45. Tan, N.C.; Foreman, A.; Jardeleza, C.; Douglas, R.; Tran, H.; Wormald, P.J. The multiplicity of *Staphylococcus aureus* in chronic rhinosinusitis: Correlating surface biofilm and intracellular residence. *Laryngoscope* **2012**, *122*, 1655–1660. [[CrossRef](#)] [[PubMed](#)]
46. Dworkin, R.H.; Turk, D.C.; Wyrwich, K.W.; Beaton, D.; Cleeland, C.S.; Farrar, J.T.; Haythornthwaite, J.A.; Jensen, M.P.; Kerns, R.D.; Ader, D.N.; et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J. Pain* **2007**, *9*, 105–121. [[CrossRef](#)] [[PubMed](#)]
47. Tarasidis, G.S.; DeConde, A.M.; Mace, J.C.; Ashby, S.; Smith, T.L.; Orlandi, R.R.; Alt, J.A. Cognitive dysfunction associated to pain and quality of life in chronic rhinosinusitis. *Int. Forum Allergy Rhinol.* **2015**, *5*, 1004–1009. [[CrossRef](#)] [[PubMed](#)]
48. Schedlowski, M.; Enck, P.; Rief, W.; Bingel, U. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. *Pharmacol. Rev.* **2015**, *67*, 697–730. [[CrossRef](#)] [[PubMed](#)]
49. DeConde, A.S.; Mace, J.C.; Bodner, T.; Hwang, P.H.; Rudmik, L.; Soler, Z.M.; Smith, T.L. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. *Int. Forum Allergy Rhinol.* **2014**, *4*, 972–979. [[CrossRef](#)] [[PubMed](#)]
50. Sanderson, M.J.; Dirksen, E.R. Mechanosensitivity of cultured ciliated cells from the mammalian respiratory tract: Implications for the regulation of mucociliary transport. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 7302–7306. [[CrossRef](#)] [[PubMed](#)]
51. Cleeland, C.S. Brief Pain Inventory User's Guide. 2009. Available online: https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf (accessed on 27 June 2017).
52. Ansari, N.N.; Fathali, M.; Naghdi, S.; Hasson, S.; Jalaie, S.; Rastak, M.S. A randomized, double-blind clinical trial comparing the effects of continuous and pulsed ultrasound in patients with chronic rhinosinusitis. *Physiother. Theory Pract.* **2012**, *28*, 85–94. [[CrossRef](#)] [[PubMed](#)]
53. Ansari, N.N.; Naghdi, S.; Farhadi, M. Physiotherapy for chronic rhinosinusitis: The use of continuous ultrasound. *Int. J. Ther. Rehabil.* **2007**, *14*, 306–310. [[CrossRef](#)]
54. Ansari, N.N.; Naghdi, S.; Fathali, M.; Bartley, J.; Rastak, M.S. A randomized clinical trial comparing pulsed ultrasound and erythromycin phonophoresis in the treatment of patients with chronic rhinosinusitis. *Physiother. Theory Pract.* **2015**, *32*, 166–172. [[CrossRef](#)] [[PubMed](#)]
55. Høsoien, E.; Lund, A.B.; Vasseljen, O. Similar effect of therapeutic ultrasound and antibiotics for acute bacterial rhinosinusitis: a randomized trial. *J. Physiother.* **2010**, *56*, 27–32. [[CrossRef](#)]
56. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Lawrence Earlbaum Associates: Hillsdale, NH, USA, 1988.
57. Guieu, R.; Tardy-Gervet, M.; Roll, J. Analgesic effects of vibration and transcutaneous electrical nerve stimulation applied separately and simultaneously to patients with chronic pain. *Can. J. Neurol. Sci.* **1991**, *18*, 113–119. [[CrossRef](#)] [[PubMed](#)]
58. İnal, S.; Kelleci, M. Relief of pain during blood specimen collection in pediatric patients. *MCN* **2012**, *37*, 339–345. [[CrossRef](#)]
59. Moadad, N.; Kozman, K.; Shahine, R.; Ohanian, S.; Badr, L.K. Distraction using the BUZZY for children during an IV insertion. *J. Pediatr. Nurs.* **2016**, *31*, 64–72. [[CrossRef](#)] [[PubMed](#)]
60. Taddio, A.; Shah, V.; McMurtry, C.M.; MacDonald, N.E.; Ipp, M.; Riddell, R.P.; Noel, M.; Chambers, C.T. Procedural and physical interventions for vaccine injections. *Clin. J. Pain* **2015**, *31*, S20–S37. [[CrossRef](#)] [[PubMed](#)]
61. Hara, E.S.; Witzel, A.L.; De Luca, C.E.P.; Ballester, R.Y.; Kuboki, T.; Bolzan, M.C. A novel vibratory stimulation-based occlusal splint for alleviation of TMD painful symptoms: a pilot study. *J. Oral Rehabil.* **2013**, *40*, 179–184. [[CrossRef](#)] [[PubMed](#)]
62. Roy, E.A.; Hollins, M.; Maixner, W. Reduction of TMD pain by high-frequency vibration: A spatial and temporal analysis. *Pain* **2003**, *101*, 267–274. [[CrossRef](#)]

63. Rocha, W.A.; Rodrigues, K.M.; Pereira, R.R.; Nogueira, B.V.; Gonçalves, W.L. Acute effects of therapeutic 1-MHz ultrasound on nasal unblocking of subjects with chronic rhinosinusitis. *Braz. J. Otorhinolaryngol.* **2011**, *77*, 7–12. [[CrossRef](#)] [[PubMed](#)]
64. West, S.J.; Bannister, K.; Dickenson, A.H.; Bennett, D.L. Circuitry and plasticity of the dorsal horn—Toward a better understanding of neuropathic pain. *Neuroscience* **2015**, *300*, 254–275. [[CrossRef](#)] [[PubMed](#)]
65. Craig, T.J.; Ferguson, B.J.; Krouse, J.H. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. *Am. J. Otolaryngol.* **2008**, *29*, 209–217. [[CrossRef](#)] [[PubMed](#)]
66. Hopkins, C.; Gillett, S.; Slack, R.; Lund, V.J.; Browne, J.P. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin. Otolaryngol.* **2009**, *34*, 447–454. [[CrossRef](#)] [[PubMed](#)]
67. Duan, B.; Cheng, L.; Bourane, S.; Britz, O.; Padilla, C.; Garcia-Campmany, L.; Krashes, M.; Knowlton, W.; Velasquez, T.; Ren, X.; et al. Identification of spinal circuits transmitting and gating mechanical pain. *Cell* **2014**, *159*, 1417–1432. [[CrossRef](#)] [[PubMed](#)]
68. Melzack, R.; Wall, P.D. Pain mechanisms: A new theory. *Science* **1965**, *150*, 971–979. [[CrossRef](#)] [[PubMed](#)]
69. Vierck, C.J.; Whitsel, B.L.; Favorov, O.V.; Brown, A.W.; Tommerdahl, M. Role of primary somatosensory cortex in the coding of pain. *Pain* **2013**, *154*, 334–344. [[CrossRef](#)] [[PubMed](#)]
70. Hollins, M.; McDermott, K.; Harper, D. How does vibration reduce pain? *Perception* **2014**, *43*, 70–84. [[CrossRef](#)] [[PubMed](#)]
71. Day, M. Sympathetic blocks: The evidence. *Pain Practice* **2008**, *8*, 98–109. [[CrossRef](#)] [[PubMed](#)]
72. Felisati, G.; Arnone, F.; Lozza, P.; Leone, M.; Curone, M.; Bussone, G. Sphenopalatine endoscopic ganglion block: A revision of a traditional technique for cluster headache. *Laryngoscope* **2006**, *16*, 1447–1450. [[CrossRef](#)] [[PubMed](#)]
73. Khan, S.; Schoenen, J.; Ashina, M. Sphenopalatine ganglion neuromodulation in migraine: What is the rationale? *Cephalalgia* **2014**, *34*, 382–391. [[CrossRef](#)] [[PubMed](#)]
74. Robbins, M.S.; Robertson, C.E.; Kaplan, E.; Ailani, J.; Charleston, L.; Kuruvilla, D.; Blumenfeld, A.; Berliner, R.; Rosen, N.L.; Duarte, R.; et al. The sphenopalatine ganglion: Anatomy, pathophysiology, and therapeutic targeting in headache. *Headache* **2015**, *56*, 240–258. [[CrossRef](#)] [[PubMed](#)]
75. Talman, W.T.; Corr, J.; Dragon, D.N.; Wang, D. Parasympathetic stimulation elicits cerebral vasodilatation in rat. *Auton. Neurosci.* **2007**, *133*, 153–157. [[CrossRef](#)] [[PubMed](#)]
76. Uddman, R.; Malm, L.; Fahrenkrug, J.; Sundler, F. Vip increases in nasal blood during stimulation of the Vidian nerve. *Acta Otolaryngol.* **1981**, *91*, 135–138. [[CrossRef](#)]
77. Ansarinia, M.; Rezai, A.; Tepper, S.J.; Steiner, C.P.; Stump, J.; Stanton-Hicks, M.; Machado, A.; Narouze, S. Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. *Headache* **2010**, *50*, 1164–1174. [[CrossRef](#)] [[PubMed](#)]
78. Bjordal, J.M.; Johnson, M.I.; Lopes-Martins, R.A.; Bogen, B.; Chow, R.; Ljunggren, A.E. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskelet. Disord.* **2006**, *8*, 51. [[CrossRef](#)] [[PubMed](#)]
79. Johnson, M.; Martinson, M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials. *Pain* **2007**, *130*, 157–165. [[CrossRef](#)] [[PubMed](#)]
80. Lobre, W.D.; Callegari, B.J.; Gardner, G.; Marsh, C.M.; Bush, A.C.; Dunn, W.J. Pain control in orthodontics using a micropulse vibration device: A randomized clinical trial. *Angle Orthod.* **2015**, *86*, 625–630. [[CrossRef](#)] [[PubMed](#)]
81. Mücke, M.; Cuhls, H.; Radbruch, L.; Weigl, T.; Rolke, R. Evidence of heterosynaptic LTD in the human nociceptive system: Superficial skin neuromodulation using a matrix electrode reduces deep pain sensitivity. *PLoS ONE* **2014**, *9*, e107718. [[CrossRef](#)] [[PubMed](#)]
82. Peirs, C.; Seal, R.P. Neural circuits for pain: Recent advances and current views. *Science* **2017**, *354*, 578–584. [[CrossRef](#)] [[PubMed](#)]
83. Smith, M.; Sarah Bush Lincoln Health Center, Matoon, IL, USA. Personal Communication, 2016.
84. Van Cauwenberge, P.; Watelet, J.B. Epidemiology of chronic rhinosinusitis. *Thorax* **2000**, *55*, S20–S21. [[CrossRef](#)] [[PubMed](#)]

