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Effectiveness of nasal irrigation for chronic rhinosinusitis and fatigue in patients with Gulf War illness: Protocol for a randomized controlled trial☆,☆☆

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ABSTRACT

Introduction: Gulf War Illness (GWI) affects 1 in 7 returned Persian Gulf War veterans. Quality-of-life impact is large; there is no cure. Chronic sinus symptoms and fatigue are common. Nasal irrigation with saline (NI-S) or xylitol (NI-X) improve sinus symptoms and fatigue in the general population. This trial will assess the effect of NI-S and NI-X on sinus and fatigue symptoms, economic outcomes and pro-inflammatory milieu among participants with GWI.
Methods: 75 participants (age 35 to 65 years, 25 in each of three arms) with GWI will be recruited from the Veteran's Administration and the community. They will use routine care for sinus symptoms and fatigue and be randomized to continued usual care alone or additional therapy with NI-S or NI-X. Participants will be able to adjust specific elements of the NI procedure. The primary outcome (Sinonasal Outcome Test, SNOT-20) and other self-reported assessments will occur at baseline, 8 and 26 weeks; lab assessment of pro-inflammatory cellular and cytokine profiles will occur at baseline and 26 weeks. Other outcomes will include fatigue-specific and overall health-related quality of life, pro-inflammatory cellular and cytokine profiles, cost-effectiveness and participant satisfaction.
Results: Baseline demographic and clinical data from the first 10 participants show effective participant recruitment, enrollment, randomization, retention and data collection.
Conclusion: Early study conduct suggests that our participant-oriented approach will yield high rates of participant adherence and data capture, facilitating robust analysis. Results of this study will clarify the value of NI for chronic sinus symptoms and fatigue among patients with GWI.
Clinical trial registration: clinicaltrials.gov identifier NCT01700725.

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1. Introduction

Of the 700,000 veterans who returned from the Persian Gulf conflict of 1990–91 (Desert Shield/Desert Storm), up to 100,000 are affected by Gulf War Illness (GWI) [1,2]. Symptoms and co-morbidities span multiple organ systems; the first and third most common complaints have been reported to be chronic upper respiratory complaints (with nasal congestion reported by 47% of patients) and fatigue (41%) [3,4].

The etiology of chronic upper respiratory complaints and fatigue among patients with GWI is unclear. In the general population, chronic upper respiratory symptoms are primarily caused by infectious, irritant and allergic agents. Chronic symptoms change the nasal mucosa, predisposing it to further insult. Fatigue is often concomitant with URI symptoms [5]. Change in the concentration of pro-inflammatory biomarkers in serum and nasal mucosa has been associated with both fatigue [6] and chronic upper respiratory infection [7] in the general population. In spite of substantial research [8], and conflict about the status and relevance of that research [9], the cause and optimal treatment of GWI remain poorly understood. Therapy has focused on symptomatic treatment. The US Department of Defense (DoD) Gulf War Illness Research Program (GWIRP) has called for investigation of therapy to treat GWI [8].

Nasal irrigation (NI) is an adjunctive treatment for chronic upper respiratory symptoms for a variety of conditions that bathes the nasal cavity with liquid [10,11]. Two solutions have been assessed, saline (NI-S) and xylitol (NI-X). NI-S originated in the Ayurvedic medical tradition. Chronic rhinosinusitis (CRS) is the most common indication for NI-S [10]. The Cochrane Collaboration concluded that NI-S is appropriate adjunctive therapy for the symptoms of chronic rhinosinusitis [12]. An element of successful clinical use of NI-S has been patient-centered control of some elements of the irrigation protocol, including the frequency of irrigations and salinity, and has led to improved patient self-management of symptoms and QoL, and decreased side effects [13]. NI-X has a shorter clinical and cultural history, with medical use spanning only a few decades [14]. Xylitol is a naturally occurring, non-absorbed, five-carbon sugar reported to increase the effectiveness of resident natural killer cells in the nasal mucosa when used topically [15]. Xylitol has been reported to prevent dental caries [16] and acute otitis media [17]. It has been assessed for chronic upper respiratory symptoms in limited trials [12]. Neither NI-S nor NI-X has been assessed for GWI, and neither has been studied using assessment of pro-inflammatory biomarkers.

The primary aim of this study is to determine whether nasal irrigation using a participant controlled protocol improves upper respiratory and fatigue symptoms among participants with GWI. We hypothesize that routine care plus either form of NI will be more effective than routine care alone.

Our secondary aims are:

a) To explore whether use of NI is associated with changes in the inflammatory marker concentration nasal in mucus and serum.
b) To explore whether use of NI is cost-effective and satisfying to participants.
c) To explore the ability of pretreatment psychosocial and clinical characteristics to predict which patients will benefit most from the two forms of NI.

2. Materials and methods

2.1. Study design

The study is a 26-week, three-arm randomized controlled trial (RCT) to assess the comparative effectiveness of three therapeutic approaches in patients with GWI affected by CRS and fatigue. All groups will utilize routine care for their symptoms of CRS and fatigue. Group 1 will add NI with saline (NI-S) twice daily and Group 2 will add NI with xylitol (NI-X) twice daily to their usual care regimen. Group 3 will continue to use routine care only.

2.2. Eligibility

Eligibility is based on self-report. Potential participants will be initially screened by phone and then in person at a later date. Inclusion criteria include (1) deployment to the Persian Gulf for the purpose of Operation Desert Shield or Operation Desert Storm during the first Gulf War (1990–1991); and (2) a diagnosis of GWI as based on a modified application of the "Kansas" GWI case definition [4]. The modification to this case definition involves making some of the exclusionary diagnoses relative, rather than absolute, if persons are stable with respect to the condition, and symptoms are well controlled/in remission, and have not resulted in hospitalizations within five years prior to enrollment. These diagnoses include diabetes, heart disease, stroke, melanoma, alcohol or drug dependence, depression, cancer, liver disease, posttraumatic stress and bipolar disorders: (personal communication with content expert Lea Steele, 8-26-12) [4]; (3) Eligible participants must also have a diagnosis of CRS which is defined by the presence for more than 12 weeks of 2 or more major factors (facial pain, nasal obstruction/purulence, hypo/anosmia, purulence in the nasal cavity) or one major and two minor factors (fever, headache, cough, fatigue, ear pain, dental pain, ear pain/fullness); and (4) self-reported average daily sinus and fatigue ratings of moderate to severe grades over the past month [22] as indicated by at least 3 points on a 0–10 ordinal response symptom severity scale [22] (Table 1).

Exclusion criteria include self-reported pregnancy; current use of NI, neurological or musculoskeletal conditions that could facilitate aspiration, or patients who otherwise cannot physically perform the NI procedure; anatomical abnormalities detected on CT or nasal endoscopy concerning for neoplasm perforations; and unstable psychiatric illness and competency as determined by psychiatric evaluation prior to enrollment. "Kansas definition" exclusions of lupus, multiple sclerosis, schizophrenia, active cancer treatment and presence of cognitive or physical impairments following a stroke remain absolute exclusionary criteria.

2.3. Recruitment and consent

Veterans will be recruited from the Madison and surrounding area. Recruitment from VA hospitals is based on an active duty screen which identifies veterans who were in the first Gulf War, and on an ICD-9 billing record screen to identify those diagnosed with CRS (473.*) and fatigue (780.7), or multiple episodes of acute rhinosinusitis (461.9) in the past two years. Potentially eligible participants receive a letter with an 'opt-in/