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RESEARCH ARTICLE

Potential Clinical Benefits of Combination of Black Seed, Licorice, and Turmeric Supplements within the Treatment Regimens of Bell's Palsy

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ABSTRACT

Bell's palsy can be considered as one of the most resistant and idiopathic neuromuscular facial diseases. It has not any specific effective treatments up to date in 2021. The aim of this article is to introduce this new randomized controlled trial (RCT) which has the major objective of determining the proposed favorable positive effects and outcomes of integrating the triple herbal mixture of the black seed, licorice, and turmeric (in secure adequate doses) with the standard treatment (the standard of care) on the recovery of Bell's palsy patients. The anticipated findings of this study are the faster recovery and enhanced nerve regeneration in Bell's palsy patients taking appropriate doses of the black seed, licorice, and turmeric supplements within the treatment protocols.

Abbreviations

H-B: House-Brackmann; RCT: Randomized Controlled Trial; AFT: Accelerated Failure Time; DoH: Declaration of Helsinki; GCP: Good Clinical Practice; MoHP: The Egyptian Ministry of Health & Population

Justification and Significance

Bell's palsy (idiopathic acute sudden one-sided facial paralysis) is one of the most resistant and mysterious diseases, among neuromuscular diseases, with no specific effective treatments thus far [1,2]. The degenerative (nonregenerative) nature of the facial nerve lesion is the most challenging core point in Bell's palsy treatment. Conventional standard treatment regimens do not provide complete and/or fast facial nerve regeneration in almost all cases [1-3]. Although, the incidence, epidemiology, and treatment of Bell's palsy disease have been investigated and discussed in several literature articles, but the resulted and available information and data are very scanty, insufficient, and usually with paradoxical findings [4]. As a result of absence of specific and fixed standardized treatment protocols for this challenging disease, diverse medical specialties (e.g., neurologists, neurosurgeons, medical internists, physical therapists, otorhinolaryngologists, clinical pharmacists, dentists, and herbalists) are often involved in putting the treatment plans and regimens with distinct perspectives and points of view. Clinical trials in herbal medicine (mainly for the enhancement of resistant diseases management through the effective incorporation of natural herbs) are a very interesting and rich area in clinical research. To date at the middle of 2021, no clinical studies have

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furnished any evidence of the efficacy of using or integrating complementary herbal medicine for effectively curing Bell's palsy disorder [3]. Therefore, putting successful comprehensive management protocols of Bell's palsy is still a demanding strategic goal and endeavor for the relevant clinical researchers and medical professionals. We propose, for the first time, integrating a triple herbal mixture of the black seed, licorice, and turmeric (a unique formula of safe potential antifacial palsy herbal drugs) along with the traditional pharmacotherapeutic and physiotherapeutic treatment protocols for the sake of rapid and complete recovery in Bell's palsy patients of all ages. Our general aim is to help in designing a novel standardized management plan and protocol for the effective and successful treatment of Bell's palsy patients.

Specific Aim and Hypothesis

The proposed study has the following direct objective:

- **Specific aim:** To determine the proposed favorable positive effects and outcomes of combining the triple herbal mixture of the black seed, licorice, and turmeric (in safe adequate doses) with the standard treatment on the recovery of Bell's palsy patients.

The research question of the current proposal is very optimal, since it is an unanswered novel and important question which can be conducted and solved in a very feasible interventional clinical trial. The proposed study has the following direct main hypothesis:

- **Primary hypothesis:** We mainly hypothesize that adding the safe and bioactive black seed/licorice/turmeric supplements with the standard treatment regimens is associated with clinically-significant shorter recovery times and enhanced facial nerve regeneration (i.e., significantly-better disease recovery outcomes) as compared to using the standard conventional treatments alone in Bell's palsy patients.

Background

To date, Bell's palsy is still idiopathic and very confusing. It ranges in severity from slight weakness to total irritating paralysis of facial muscles (significant intense facial distortion) [1,5,6]. Different facial nerve grading systems are used to assess the degree of Bell's palsy severity/improvement, e.g., the gross House-Brackmann (H-B), weighted regional Sunnybrook, and unweighted regional Yanagihara scoring systems [7]. Clinical improvement occurs instantaneously within 3-4 weeks in about 85% of cases; however, about 15-30% of patients are reported to remain with several degrees of long-lasting debilitating sequelaes (functional/physical/psychological effects) [5,6,8]. According to the literature, the mean time to recovery (complete or almost complete) is about 3.5 months [6,8]. Standard treatment regimens of Bell's palsy disease comprise both conventional pharmacotherapeutic treatments, which include, e.g., corticosteroids (such as prednisolone), antiviral agents (such as acyclovir; there are some pathologic and clinical evidences that this palsy may be directly linked to certain viruses like herpes simplex, varicella zoster, and influenza viruses), vitamin B complex supplements, anticonvulsant drugs (such as carbamazepine), anti-inflammatory/analgesic agents (such as ibuprofen), antioxidant supplements, multivitamin/multimineral supplements (including zinc), and other nerve tonics; and traditional physiotherapy [1,2]. Herbal medicine is of special importance in the treatment of neuromuscular diseases [2,3]. Black seed, licorice, and turmeric herbs with their major extremely potent bioactive ingredients (thymoquinone, glycyrrhizin, and curcumin, respectively) have excellent beneficial bioactivities (e.g., anti-inflammatory, antioxidant, antiviral, neuroprotective, and antimicrobial activities) that are ultimately needed in any Bell's palsy case [9-11]. These previously-mentioned knowledge and data establish the backbone of this current research.

Research rationale

Conceptually, the study is based on making use of the potent multiple activities of three of the most known and safe medicinal herbs, the black seed, licorice, and turmeric, mainly through their approved-use effective chemical compounds (thymoquinone, glycyrrhizin, and curcumin, respectively) which are known for their successful potent anti-inflammatory, antioxidant, antiviral, and neuroprotective bioactivities [3,9-11], to address the issues accompanying the standard treatment in Bell's palsy patients (e.g., severe facial inflammatory status, very slow facial nerve recovery, incomplete facial nerve regeneration, and intense facial distortion) [1,5,6,8].

Research Design and Methodology

Study design, settings, and sampling technique

The proposed design of this clinical study is a 1:1, multicenter, double-blinded, two-arm, parallel, randomized controlled trial (RCT), aiming to determine the beneficial effects of combining the proposed triple herbal mixture (black seed/licorice/turmeric) within the treatment regimen of Bell's palsy patients in effectively reducing the recovery time. The H-B grading system will be the major Bell's palsy scoring system used for the evaluation of the cases [12]. We are suggesting enrolling Bell's palsy patients mainly from various governmental hospitals (neurology and physiotherapy departments) of at least 8 cities from different governorates in Egypt over a one-year period of follow-up.

Subjects' eligibility

We propose to enroll patients of both genders according to the following eligibility criteria:

- **Inclusion criteria:** Patients affected by an acute onset of unexpected unilateral facial paralysis with no known or detectable causes, together with those of recurrent episodes of Bell's palsy.
- **Exclusion criteria:** Patients < 15 years old or > 75 years old, suffering from hypertension/heart disease, sensitive/allergic to any of the herbal mixture ingredients/standard treatment medications, with bilateral facial paralysis, with concurrent neuromuscular and neurologic diseases, and/or having known inflammatory/neoplastic conditions.

Methods and outcomes

Patients will be randomly assigned into two groups; the intervention group, which will receive the same suggested daily oral doses of black seed/licorice/turmeric supplements (administered as capsules of the crude powders; at least 1 gm/day of each herbal drug) with the standard pharmacotherapeutic (consists of all the previously-mentioned conventional medications in the specified doses according to the patient's age/weight/healthy condition) and physiotherapeutic (fixed items in all patients as much as possible [13]) treatment, and the comparator group, which will receive the same standard pharmacotherapeutic/physiotherapeutic treatment alone (all patients will be weekly monitored). The primary objective outcome is the faster times to disease recovery (with almost complete facial nerve regeneration) compared to known normal conventional rates. The presence/absence of complete nerve regeneration (or the ordinal degree of nerve degeneration) can be considered as the secondary outcome. The H-B facial nerve grading system will be used as the major assessment tool to measure both outcomes during and at the end of the one-year follow-up [12,14].

Sample size and statistical analysis

The mean complete facial function recovery time is conventionally about 3.5 months in 70-85% of the cases [5,6,8]. We assume, at least, 30% reduction in the time to complete recovery. A minimum of 180 patients (90 per each group) is needed to have an 80% chance of detecting, as significant at the 5% level, a decrease in the mean recovery time from 3.5 months in the control group to nearly 2.5 months in the interventional group (calculated using StataIC 16). The resulted data will be coded and analyzed using StataIC 16. Supposing normal distribution of the data, a suitable accelerated failure time (AFT) model and logistic regression will be used for analysis of the data of the primary and secondary outcomes (time to recovery and presence/absence of almost complete nerve regeneration), respectively. We will check for residual differences in patients' characteristics after randomization and adjust for potential confounders in the analysis phase using, mainly, the multiple regression analyses.

Ethical considerations

The study protocol totally adheres to the Declaration of Helsinki (DoH) and Good Clinical Practice (GCP) Guidelines. The entire research plan and protocol will be extensively reviewed by the ethics committees of the Egyptian Ministry of Health & Population (MoHP) and the relevant hospitals in order to be approved and ratified; the informed consent will be signed and obtained from each patient or his/her legal representative(s) in accordance with the patient's condition.

Study limitations

This RCT will only determine the efficacy of the titled triple herbal mixture on a low-dosage scale. Also, the study protocol was designed without putting into consideration the possible additive/inhibitory effects resulted from other daily spices present in the patients' meals. Future studies are planned to resolve both limitations.

Anticipated Results

The integration of the black seed, licorice, and turmeric supplements within the treatment regimens for Bell's palsy is expected to be associated with faster recovery and enhanced nerve regrowth (i.e., clinically-meaningful and significant outcomes).

Declarations

Ethics approval and consent to participate

The trial will receive ethical clearance (under registration) from the local ethics committees of the participating sites (eight sites), as well as from the Egyptian MoHP Research Ethics Committee (MoHP REC). All participants will provide informed consent before the initial screening and also before trial inclusion (i.e., a two-step procedure).

Authors' contributions

The entire study protocol and manuscript were designed and written by a single author (Dr. Amgad M. Rabie).

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Author's information

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