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Original Article

Physical Medicine and Rehabilitation Section

Effects of Royal Jelly Supplementation on Dry Mouth Sensation in Patients with Normal Saliva Function: A Randomised Clinical Study

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ABSTRACT

Introduction: In several cases, dry mouth sensation with normal salivary function is not diagnosed as an abnormality and this condition has no standardised treatments. Moreover, it is significantly associated with psychological disorders such as depression, trait anxiety and perceived stress. Based on recent studies, daily oral royal jelly supplementation (1000 mg) for eight weeks has beneficial effects on menopausal symptoms such as anxiety. However, there are no studies on the effects of royal jelly supplementation on dry mouth sensation in patients with normal salivary function. Further, only few clinical trials have long-term follow-up greater than eight weeks.

Aim: To evaluate the effects of royal jelly tablets on dry mouth sensation in patients with normal salivary function.

Materials and Methods: This randomised, double-blind, crossover clinical trial included 15 adults with an unstimulated salivary flow of >0.1 mL/min who had a chief complaint of dry mouth sensation and those without any salivary gland disease. This study was performed at Tokyo Medical and Dental University Hospital, Tokyo, Japan, between November 2019 and April 2020. The royal jelly tablet contained 400 mg of enzyme-treated royal jelly powder and each participant received either two tablets of enzyme-treated royal jelly (800 mg) or placebo daily for 12 weeks. The Visual Analogue Scale (VAS) was used to evaluate objective dry mouth sensation and the Japanese version of the Hospital Anxiety and Depression Scale (HADS) and General Health Questionnaire 12 (GHQ-12) were applied to assess psychological status and social dysfunction. The differences in VAS, HADS and GHQ-12 scores over time between the enzyme-treated royal jelly and placebo groups were analysed using repeated-measure analysis of variance and the post-hoc paired t-test.

Results: The 4- and 12-week VAS scores between the enzyme-treated royal jelly and placebo groups significantly differed (p-value=0.041 and 0.043, respectively). The 12-week HADS and GHQ-12 scores between the enzyme-treated royal jelly tablet and placebo groups differed significantly (p-value=0.040 and 0.046, respectively). Moreover, the HADS scores of the enzyme-treated royal jelly tablet group significantly decreased.

Conclusion: Daily supplementation with enzyme-treated royal jelly (800 mg) for 12 weeks was effective against dry mouth sensation in patients with normal saliva function.

Keywords: Burning mouth syndrome, Normal salivary function, Psychological disorders

INTRODUCTION

Several patients with an unstimulated salivary flow of >0.1 mL/min based on the saliva secretion test and those who do not have autoimmune diseases including Sjogren's syndrome and salivary gland diseases complain of dry mouth sensation. In most cases, dry mouth sensation with normal salivary function is not diagnosed as an abnormality inspite of suffering from dry mouth sensation. Moreover, it has no detailed studies focussing on the dry mouth sensation with normal saliva function and there are no established standardised treatments.

Recent studies have shown that the anxiety and depression scores of patients who have an unstimulated salivary flow of >0.1 mL/min who presented with subjective dry mouth sensation were significantly higher than those without subjective dry mouth sensation [1,2]. Further, dry mouth sensation is significantly associated with psychological disorders such as depression, trait anxiety and perceived stress in patients with normal salivary function [1].

Royal jelly, a viscous jelly-like natural substance, is produced by the mandibular and hypopharyngeal glands of honeybees (*Apis mellifera*). It comprises water (50%-60%), proteins (18%), carbohydrates (15%), lipids (3%-6%), mineral salts (1.5%) and vitamins and it is non cytotoxic [3]. In addition, it can be easily purchased from different stores and is widely used as a natural nutritional supplement. Recent studies have shown that daily supplementation with oral royal jelly (1000 mg) for eight weeks has beneficial effects on menopausal symptoms such as anxiety [4,5]. However, there are no studies on the effect of royal jelly supplementation on dry mouth sensation in individuals with normal salivary function. Moreover, only few clinical trials have long-term follow-up greater than eight weeks.

This clinical study aimed to evaluate the effects of royal jelly-containing tablet on dry mouth sensation in patients with normal saliva function.

MATERIALS AND METHODS

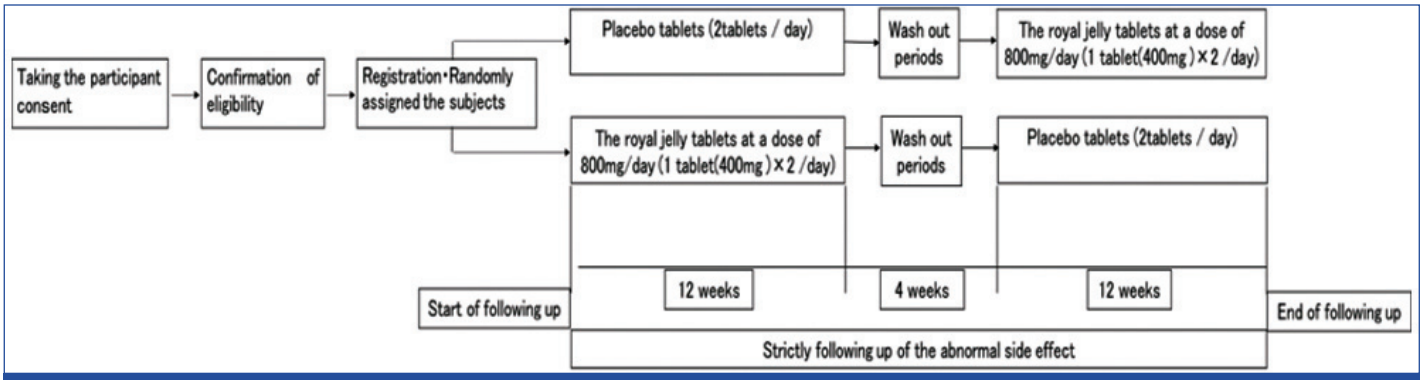
This study was randomised, double-blind, crossover clinical trial and performed according to the Declaration of Helsinki and was approved by the Ethical Committee for Human Research (no. D2019-021) and Certified Clinical Research Review Board (NR2019-002) of Tokyo Medical and Dental University. This study was performed at Tokyo Medical and Dental University Hospital between November 2019 and April 2020. Moreover, the trial is registered in the Japan Registry of Clinical Trials.gov protocol registration system (ID: jRCTs031190067). All patients provided a written informed consent before participation.

Inclusion criteria: Adults who were atleast 20 years of age and could visit the department and provide a written informed consent, those with an unstimulated salivary flow of >0.1 mL/min based on the saliva secretion test [1,2], those without autoimmune diseases including Sjogren's syndrome and salivary gland diseases and those who were not taking royal jelly products at the start of this study were included in the study.

Exclusion criteria: Adults who developed drug and food allergies, those with a history of asthma and those who did not provide consent were excluded from the study.

Sample size: The sample size was estimated using an effect size in the range of d=0.7, two-sided test with α=0.05 and a power of 0.8. Based on the results, the crossover design required a sample size of 11. With consideration of dropouts due to severe side-effects, 15 randomised patients were included [4].

Study procedure: The size, shape and colour of the powdered enzyme-treated royal jelly and placebo tablets were similar and their packaging was labelled as A or B by the person except for the researchers and the participants. If the participants initially received packages labelled with A, then they were provided with packages labelled with B after the wash-out period. The researchers and the participants of this research were blinded to the packaging labels and didn't know whether the packages labelled A was enzyme-treated royal jelly or placebo tablets. Each participant was assigned randomly to two groups based on randomisation codes, which were selected by a computer using dynamic allocation (with a balanced marginal distribution algorithm) [Table/Fig-1].



[Table/Fig-1]: Protocol of this clinical trial.

The enzyme-treated royal jelly (lot.YRP-M-190315-2) was standardised to contain 3.5% 10-Hydroxy-Trans-2-Decenoic Acid (10H2DA) and 0.6% 10-hydroxydecanoic acid and was obtained from Yamada Bee Company, Inc. (Okayama, Japan). One royal jelly tablet contained 400 mg of enzyme-treated royal jelly powder.

The VAS was used to evaluate objective dry mouth feeling, with a score of 100 representing dryness and 0 no dryness.

Psychological status was assessed using the Japanese version of the HADS [6], which had two subscales (anxiety with seven questions and depression with seven questions). Each subscale was scored on a scale from 0 to 3. Then, the total score of the seven questions was calculated. The anxiety and depression subscales were scored from 0 to 21. According to Zigmond AS et al., scores of 0-7 represent a non case of psychiatric morbidity; scores of 8-10, a doubtful or borderline case and scores of 11-21, a definite case [6].

Psychological distress and social dysfunction were evaluated using the Japanese version of the GHQ-12 [7]. The GHQ-12 assesses two factors (psychological distress and social dysfunction). Each response was scored on a scale from 0 to 1 and the score of the 12 questions was calculated. If the score is ≥4, psychological distress and social dysfunction were considered. Higher scores are indicative of worsened psychological distress and social dysfunction.

STATISTICAL ANALYSIS

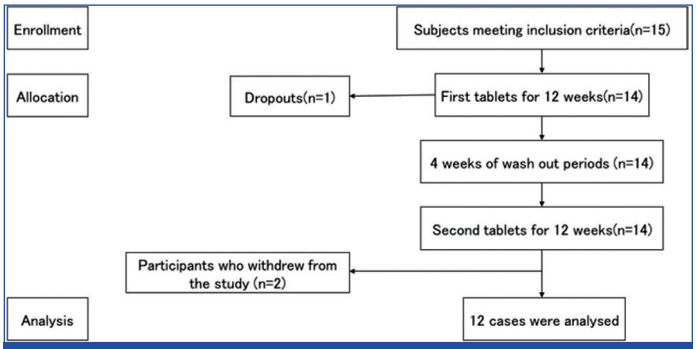
The VAS, HADS and GHQ-12 scores at the start of placebo or enzyme-treated royal jelly supplementation was used as the baseline data. Each score of the placebo or enzyme-treated royal jelly groups at 4/8/12 weeks-each score at the base period of the placebo or enzyme-treated royal jelly groups was calculated. The differences in VAS, HADS and GHQ-12 scores over time between the enzyme-treated royal jelly and placebo groups was analysed using repeated-measure analysis of variance and the post-hoc paired t-tests. The differences at each examination point was analysed with the t-test. For all analyses, a 5% significance level was used to determine statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 25.0J, IBM, Armonk, NY).

RESULTS

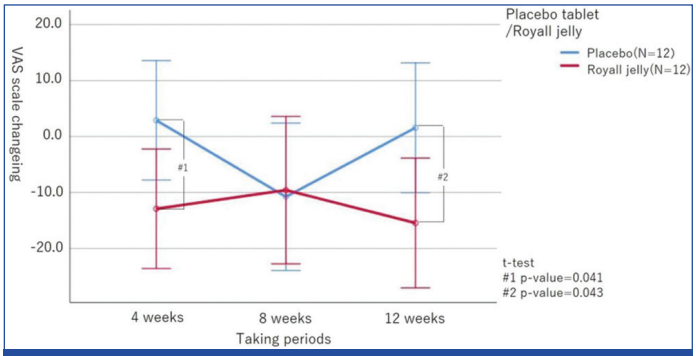
Demographic characteristics of the participants:

In total, 15 participants met the inclusion criteria. Among them, one was lost to follow-up due to lack of contact and two participants withdrew from the study. Finally, 12 patients were analysed. The compliance rate of all participants was 100% and any allergic reactions or abnormal side-effects were not observed. [Table/Fig-2] shows the CONSORT flowchart.

VAS scores: [Table/Fig-3] presents the VAS scores. There were no significant differences in terms of VAS scores between the placebo (p-value=0.570) and enzyme-treated royal jelly (p-value=0.308) groups.



[Table/Fig-2]: Data analysis-CONSORT diagram.



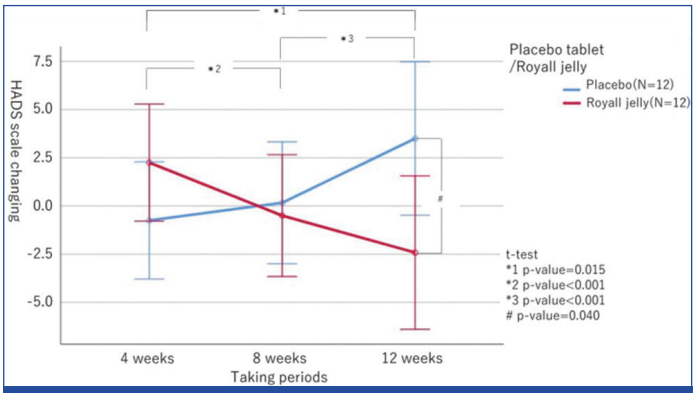
[Table/Fig-3]: Changes in the trend of Visual Analogue Scale (VAS) scores over time.

The 4 and 12-week VAS scores between the enzyme-treated royal jelly and placebo groups significantly differed (p-value=0.041 and 0.043, respectively). However, there were no significant differences in terms of the 8-week VAS scores between the two groups (p-value=0.896).

HADS score:

[Table/Fig-4] shows the HADS scores. There were no significant differences in terms of HADS scores over time in the placebo group (p-value=0.058). However, the HADS scores of the enzyme-treated

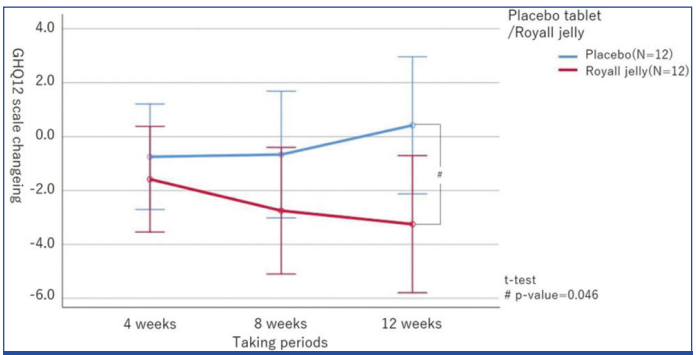
royal jelly group significantly decreased over time (p-value=0.002). There were significant differences in terms of HADS scores in the enzyme-treated royal jelly group between 4 and 8 weeks (p-value <0.001), between 4 and 12 weeks (p-value=0.015) and between 8 and 12 weeks (p-value <0.001). The 12-week HADS scores significantly differed between the enzyme-treated royal jelly and placebo groups (p-value=0.040).



[Table/Fig-4]: Changes in the trend of Hospital Anxiety and Depression Scale (HADS) scores over time.

GHQ12 score:

[Table/Fig-5] depicts the GHQ-12 scores. There were no significant differences over time in terms of the GHQ-12 scores of the placebo group (p-value=0.191) and the GHQ-12 scores of the enzyme-treated royal jelly group (p-value=0.072). Differences in GHQ-12 scores between enzyme-treated royal jelly and placebo at the evaluation period of 4 weeks (p-value=0.539) and 8 weeks (p-value=0.207) were not significant, however, the 12-week GHQ-12 scores between the enzyme-treated royal jelly and placebo groups significantly differed (p-value=0.046).



[Table/Fig-5]: Changes in the trend of General Health Questionnaire 12 (GHQ-12) scores over time.

DISCUSSION

Royal jelly contains a unique component, 10H2DA, an unsaturated fatty acid [8]. A 10H2DA is one of the main bioactive components of royal jelly and comprises most of the royal jelly lipid content (0.75%-3.39%) [9,10]. Sharif SN and Darsareh F showed that daily supplementation with oral royal jelly (1000 mg) for eight weeks was effective against menopausal symptoms [5]. However, there are no reports on royal jelly's efficacy against dry mouth sensation in individuals with normal saliva function. From the results of this study, it is considered that royal jelly supplements are effective for depression and anxiety associated with the subjective dry mouth sensation and oral administration of royal jelly tablets at 12 weeks may be effective for treating dry mouth sensation. This is the first double-blind, randomised, placebo controlled, clinical trial on the effects of royal jelly supplementation on dry mouth sensation in patients with normal saliva function. Bergdahl M and Bergdahl J revealed that although there are several unknown factors, depression, stress and anxiety have complex interactions with subjective dry mouth sensation in individuals with normal salivary function [2].

Recent studies have reported about burning mouth syndrome, which is defined as a burning sensation or as pain in the oral mucosa [11-14]. This syndrome has been typically described by patients as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations [12] and as a condition that has an aetiologically complex association with pathophysiological factors, particularly depression and anxiety [11,14]. Burning mouth syndrome commonly affects the tongue (specifically the tip and lateral borders), lips and hard and soft palate. Moreover, patients experience clinically unremitting oral mucosal pain and dysgeusia, in addition to burning sensation [11]. Dry mouth sensation is considered a symptom of burning mouth syndrome in patients with normal salivary function [9-12,15]. Petruzzi M et al., reported a pilot study of capsaicin administration for burning mouth syndrome, however, standard treatment and medication for dry mouth sensation in individuals belonging to burning mouth syndrome has not been established and still been studied [14].

In this study, based on the evaluation performed using the VAS scale, dry mouth sensation significantly improved at 4 and 12 weeks with royal jelly tablet supplementation. However, the VAS scale scores over time were unstable. This finding might be attributed to oral symptoms, other than dry mouth sensation, caused by depression and anxiety. Other uncomfortable oral sensations caused by burning mouth syndrome may intricately disturb the score using the VAS and the score of the VAS cannot accurately purely reflect the degree of subjective dry mouth sensation.

Ito S et al., showed that 10H2DA was effective in improving the stress-induced symptoms of depression and anxiety in animal models [8].

Only few clinical trials on burning mouth syndrome had long-term follow-up greater than two months [16,17]. Therefore, further studies on dry mouth sensation in patients with normal saliva function should be conducted. The present study revealed that royal jelly supplementation (800 mg dairy) for 12 weeks is effective against psychological stress (anxiety and depression) and social activity disorder in patients with normal saliva function who presented with subjective dry mouth sensation. Nevertheless, further developmental studies must be performed in the future.

The addition of burning mouth syndrome as an exclusion criterion is extremely challenging and difficult as it has many clinical symptoms and its diagnosis is based on the subjective histories of patients [12]. In relation to these reasons, in this study, the presence of burning mouth syndrome was not included as a screening item in the exclusion criteria and only patients with normal salivary function who presented with dry mouth sensation were included.

The treatment of burning mouth syndrome is challenging for oral health care professionals [12] and the condition has no standard therapy. Some clinical trials have been reported that drug therapy with capsaicin, alpha-lipoic acid, clonazepam and antidepressants and psychotherapy could be effective against burning mouth syndrome [9-11]. However, there is no effective protocol for all patients and these drugs have side-effects [16]. Therefore, further developmental studies assessing the effects of royal jelly on burning mouth syndrome caused by depression and anxiety should be conducted in the future.

Limitation(s)

The current study had some limitations. First, only a limited number of participants were included. Second, information on the lower effective dose and dose dependency was unclear. Third, only patients with normal salivary function who presented with dry mouth sensation were included. Fourth, the detailed mechanism and component of royal jelly were not evaluated.

CONCLUSION(S)

This study reveals that 12 weeks of royal jelly tablets (800 mg dairy) administration is effective for psychological stress (anxiety

and depression) in patients who suffer from subjective dry mouth sensation with normal saliva function. Further developmental studies assessing the effects of royal jelly on oral diseases caused by depression and anxiety could be conducted in the future.

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