Synsepalum dulcificum And Variable taste Occurring after Radiation (SAVOR) Trial

Parker A. Velargo, MD; Sandeep Samant, MD, FRCS
University of Tennessee Department of Otolaryngology/ Head & Neck Surgery

ABSTRACT

Objectives:
Postirradiation gustatory dysfunction (PIGD), which may cause malnutrition, is common in patients with head/neck cancer undergoing radiation therapy (XRT). *Synsepalum dulcificum* (miracle fruit) changes taste transduction mechanisms of certain substances. This investigation addresses whether *S. dulcificum* can improve PIGD and result in weight augmentation in head/neck cancer patients.

Study Design:
Double blind randomized prospective clinical trial.

Methods:
Sixteen patients meeting criteria were separated into 2 groups based on timing after XRT. In a double-blind randomized fashion, patients were assigned miracle fruit or placebo. A series of taste batteries/questionnaires were performed. Patients were given a 1-month supply of test substance. We measured pre- and posttrial weight.

Results:
Fifty-six percent of patients subjectively reported that sweet tastes were most adversely affected by XRT; however, objectively all patients correctly identified sweet tastes while approximately one-third of patients answered sour, umami, or bitter tastes incorrectly. The majority of patients in both groups had a positive response to sour tastes with *S. dulcificum* when compared to placebo (not statistically significant). Weight gain was slightly greater in group two with *S. dulcificum* when compared to placebo (not statistically significant). Inter-group analyses did not yield significant differences.

Conclusions:
In the treatment of PIGD, *S. dulcificum* may be an effective treatment for patients with sour dysfunction but may not be effective in augmenting weight. It appears to work similarly in irradiation patients regardless of time after radiation. A larger N may help to obtain more significant findings.

CONTACT

Parker A. Velargo, MD
University of Tennessee
Dept. of Otolaryngology/ Head & Neck Surgery
Email: pvelargo@uthsc.edu
Phone: 901-448-5885
Website: www.uthsc.edu/otolaryngology

INTRODUCTION

An astounding 75% of patients with head and neck cancer undergoing radiation therapy complain of taste dysfunction broadly termed “post-irradiation gustatory dysfunction”, which can include hypogeusia (partial taste loss), ageuisia (complete taste loss), and/ or dysgeusia (distorted taste).[6,12] While post-irradiation gustatory dysfunction is often transient, gradually returning to near-normal levels within 6-12 months after radiation therapy, some patients may retain residual hypogeusia or dysgeuisa permanently.[4,5,16,17] According to one study, taste dysfunction has the greatest impact on a patient’s quality of life.[13] Additionally, it has been well established that post-irradiation gustatory dysfunction is a contributing factor to malnutrition in patients who may already be cachectic from head and neck cancer and its treatment.[1,3,4,5] Malnutrition coupled with its effects, such as a decreased immune system and poor healing and recovery, has been associated with an increased mortality rate.[4,14,15]

Recalling that radiation predominantly imparts cell death via damage to DNA, proliferative cell populations in addition to the cancer, such as taste cells, are most sensitive to its effects. Taste thresholds begin to increase when patients are treated with as little as 2-4 Gy.[16] Radiation doses between 10-40 Gy result in either complete taste bud destruction or at least a 30-50% reduction of taste cell volume.[23] Thus, the number of taste buds that degenerate is directly proportional to the size of the radiation dose.[3] Several studies compare the impact that radiation therapy has on patients’ ability to identify the basic taste qualities. One study concluded that bitter and salty tastes were severely impacted by radiation therapy while sweet and sour tastes were more robust.[4,22] Another study performed four years later by the same investigator, Mossman, reported that bitter and acidic flavors were more severely impacted by radiation therapy than were salty and sweet flavors.[5,12] It is worth stressing again, that while post-irradiation gustatory dysfunction is often transient, some patients may retain residual hypogeusia or dysgeuisa permanently.[4,5,16,17] Although radiation therapy has a profound impact on taste, what if there was a way to improve or mask post-irradiation gustatory dysfunction?

Synsepalum dulcificum, known more commonly as the “miracle fruit", may be the answer to this question. This fruit was first discovered in the early 18th century in West Africa by a French cartographer and navigator named Reynaud Des Marchais; however, it was not until Dr. William Freeman Daniell, a British Army surgeon and botanist stationed at an outpost in West Africa, published an article in the Pharmaceutical Journal, Vol. XI in 1852, that the miracle fruit and its effects were popularized.[27] The miracle fruit, when ripened, is a small tasteless red fruit measuring approximately 1.5 cm in length and 8 mm in width (Figure 1A). Although its exact mechanism of action remains uncertain, its active substance (found in the pulp of the fruit), miraculin, is a glycoprotein, which according to Göran Hellekant, a miraculin researcher and professor of physiology and pharmacology at the University of Minnesota, changes the structure of taste cells.[30] The taste transduction mechanisms of taste cells are thus altered with changes in shape such that sour and bitter pathways are transformed into sweet pathways “tricking” the brain into thinking sour and bitter foods actually taste sweet. On average, this sensation lasts between 30 minutes and 2 hours.[27] This ability of the miracle fruit can have profound implications in post-irradiated head and neck cancer patients exhibiting residual taste dysfunction.

Thus, this investigation will address whether *Synsepalum dulcificum* can improve or mask post-irradiation gustatory dysfunction and aid in nutritional augmentation in head and neck cancer patients.

METHODS

Full IRB approval was obtained prior to starting this double-blind randomized prospective clinical trial.

Two groups of patients were studied. Group one included those patients who were in an early post-irradiation period (2-4 months post-irradiation) such that miraculin’s effects could be studied prior to peak taste recovery, which usually occurs between 6-12 months. Group two included those patients who were in a late post-irradiation period (6 months or later) such that miraculin’s effects could be studied during peak taste recovery.

Inclusion Criteria:
Patients: over the age of 18 years, with cancers limited to head and neck region, receiving a minimum of 54 Gy

Exclusion Criteria:
Documented anosmia, recipient of nutrition via feeding tube, recipient of radiation therapy to the nasal cavity or ethmoid areas, resection of more than 50% of oral tongue, patients with known lesions of cranial nerves VII, IX, or X, documented allergy to red dye #40

Selected patients (Table 1) had a baseline weight checked and then took a pre-testing questionnaire. Afterwards, they underwent baseline taste testing using a taste quality battery, received the test substance, participated in random taste testing using a taste quality battery, and performed a post-tasting questionnaire.

Patients were given an ample one-month supply (30 teaspoons) of the test substance with instructions on use. At the end of one month, the patient returned to the clinic, had a weight check, the amount of remaining test substance was calculated, patients completed an end of study questionnaire (Figure 2), and patients were informed of whether they were given the placebo or the miracle fruit. .

Test substances: Red dyed Sugar (Domino® granulated sugar combined with Betty Crocker® red dye #40 "Classic Gel Food Colors" and distilled water) vs. miracle fruit granules (Figure 1B; obtained from www.miraclefruitusa.com) -- given in ¼ teaspoon doses.

Test substances looked identical in appearance thus allowing for the blinding of the investigator as well as the patient. A random numerical number was assigned to plastic zip bags containing 1 teaspoon of the test substance. A separate database was used to store the actual test substance identity of each bag based on number. Each patient was randomly assigned a bag of test substance, the number on the bag was used as the identifying number during testing for future analysis using the database.

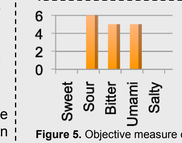

Figure 5. Objective measure of the five major taste qualities

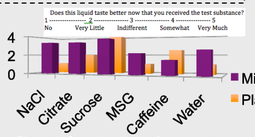

Figure 6. Group I analysis of response to miracle fruit

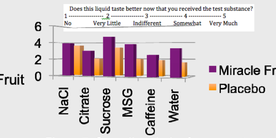

Figure 7. Group II analysis of response to miracle fruit

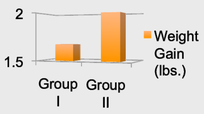

Figure 8. Inter-group analysis of weight gain

Figure 1. *Synsepalum dulcificum* (miracle fruit) in natural form (A) and granulated form (B).

	Group I	Group II
N	**8**	**8**
Male	7	5
Female	1	3
Median Age	**64**	**61**
Site of cancer:		
Oral cavity	2	0
Oropharynx	3	4
Larynx	1	2
Parotid	2	2
Miracle Fruit	**5**	**4**
Placebo	**3**	**4**

Table 1. Study participants

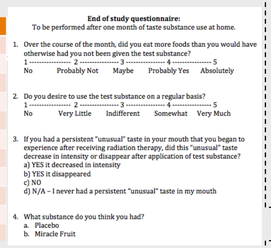

Figure 2. End of study questionnaire

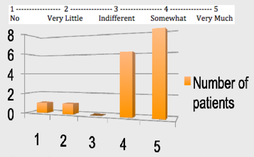

Figure 3. Have you lost the desire to eat certain foods because of a change in your taste ***after*** you received radiation therapy?

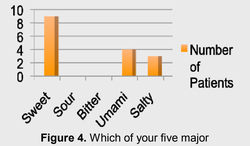

Figure 4. Which of your five major taste qualities has been most affected by radiation therapy?

RESULTS

Eighty-eight percent of patients reported that they lost the desire to eat certain foods because of a change in taste after radiation therapy.

Fifty-six percent of patients subjectively reported that sweet tastes were most adversely affected by XRT (Figure 4); however, objectively all patients correctly identified sweet tastes while approximately one-third of patients answered sour, umami, or bitter tastes incorrectly (Figure 5).

The majority of patients in both groups had a positive response to sour tastes with *S. dulcificum* when compared to placebo (not statistically significant). Positive response is defined as a substance tasting better after application of the miracle fruit and resulting in the desire to eat more foods of that taste quality if access to the test substance were granted. See Figures 6 & 7.

Only six patients (out of eighteen) stated in the end of study questionnaire that they ate more foods than they would have otherwise had they not been given the test substance. Miracle fruit was administered to five of these six patients.

Fifty-seven percent of patients who received the miracle fruit assumed they had placebo when asked at the end of the study prior to un-blinding while eighty-three percent of patients who received the placebo assumed they, in fact, had the placebo.

Weight gain was slightly greater in group two with *S. dulcificum* when compared to placebo (2 lbs. vs. 1.75 lbs., respectively -- not statistically significant), but weight gain was slightly greater in group one with placebo when compared to miracle fruit (3 lbs. vs. 1.67 lbs., respectively -- not statistically significant). Inter-group analyses did not yield significant differences (Figure 8).

CONCLUSIONS

At this time the data suggest that while there is no significant difference in PIGD between groups, the miracle fruit may be effective in treating PIGD of sour tastes. It appears that the miracle fruit may work similarly in irradiated patients regardless of time after radiation. Moreover, the data suggest that there is no significant change in weight with use of the miracle fruit.

The low N of this study is a weakness that cannot be ignored. Efforts are being made to continue enrollment and participation in the study.

REFERENCES

1. Vissink, et. al. Prevention and Treatment of the Consequences of Head and Neck Radiotherapy. *Critical Reviews in Oral Biology and Medicine*. 2003; 14; 213-225.
2. Smutzer, et. al. A Test For Measuring Gustatory Function. *The Laryngoscope*. 2008; 118; 1411-1416.
3. Nelson, G.M. Biology of Taste Buds and the Clinical Problem of Taste Loss. *The Anatomical Record*. 1998; 253; 70-78.
4. Mirza, et. al. Gustatory Impairment in Patients Undergoind Head and Neck Irradiation. *The Laryngoscope*. 2008; 118; 24-31.
5. Vissink, et. al. Oral Sequelae of Head and Neck Radiotherapy. *Critical Reviews in Oral Biology and Medicine*. 2003; 14; 199-212.
6. Yamashita, et. al. Taste Dysfunction in Patients Receving Radiotherapy. *Wiley InterScience*. 2006; 10.1002; 508-516.
7. Sandow, et. al. Taste Loss and Recovery Following Radiation Therapy. *Journal of Dental Research*. 2006; 85 (7); 609-611.
8. Yamashita, et. al. Umami Taste Dysfunction in Patients Receving Radiotherapy for Head and Neck Cancer. *Journal of Oral Oncology*. 2009; 45; 19-23.
9. Epstein, et. al. Adverse Events Associated with Concurrent Chemoradiation Therapy in Patients with Head and Neck Cancer. *Archives of Otolaryngology/ Head and Neck Surgery*. 2009. 135 (12); 1209-1217.
10. Flint, et. al. Cummings Otolaryngology: Head and Neck Surgery. 5th Edition. 2010.
11. Bailey, et. al. Head & Neck Surgery – Otolaryngology. 4th edition. 2006.
12. Mossman K, Shatzman A, Chenchanick J. Long-term effects of radiotherapy on taste and salivary function in man. Int J Radiat Oncol Biol Phys 1982; 8:991–997.
13. Donaldson SS. Nutritional consequences of radiotherapy. *Cancer Res* 1977;37:2407–2413.
14. Epstein JB, Emerton S, Kolbinson DA. Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck* 1999;21:1–11.
15. Hess MA. Taste: the neglected nutritional factor. *J Am Diet Assoc* 1997;97:5–7.
16. Conger AD. Loss and recovery of taste acuity in patients irradiated to the oral cavity. *Radiat Res* 1973;53:338–347.
17. Vissink JA, Beard JF, Larson RA, et al. A prospective pilot study to evaluate a new dental assessment and treatment paradigm for patients scheduled to undergo intensive chemotherapy for cancer. *Cancer* 1999;85:1843–1848.
18. Catalanotto FA, Sweeney EA. Salivary sodium and potassium concentrations in adrenalectomized rats. *Behav Biol* 1978;24:467–473.
19. Kuten A, Ben-Aryeh H, Bierdicevsky I. Oral side effects of head and neck irradiation: correlation between clinical manifestations a laboratory data. *Int J Radiat Oncol Biol Phys* 1986;12:401–405.
20. Zheng WK, Inokuchi A, Yamamoto T, Komiyama S. Taste dysfunction in irradiated patients with head and neck cancer. *Fukuoka Igaku Zasshi. 2002*; 93(4):64-76.
21. Kinnamon SC, Margolskee RF; Mechanisms of Taste Transduction. *Curr Opin Neurobiol* 6; 506-513. 1996.
22. Mossman KL, Henkin RI. Radiation-induced changes in taste acuity in cancer patients. *Int J Radiat Oncol Biol Phys* 1978;5:521–528.
23. Conger AD, Wells MA (1969) Radiation and aging effect on taste structure and function. *Radiat Res* 37:31–49.
24. DeWys WD, Walters K. Abnormalities of taste sensation in cancer patients. *Cancer* 36:1888-1896. 1975.
25. Slater, J. To Make Lemons into Lemonade, Try 'Miracle Fruit'. *Wall Street Journal*. March 30, 2007.
26. Farrell P, Bracken K. A Tiny Fruit That Tricks the Tongue. *The New York Times*. May 8, 2008.
27. Mozie, Curtis. Miracle Fruit University. *www.themiraclefruitman.com*. 2010.
28. Theerasilp S, Kurihara Y. Complete Purification and Characterizationof the Taste-modifying Protein, Miraculin, from Miracle Fruit. *Journal of Biological Chemistry*. Vol. 263, No. 23, Issue of August 15, pp. 11536-11539, 1988.
29. Brouwer, JN. et. al. The Sweetness-Inducing Effect of Miraculin. *J. Physiol.* (1983), 337, pp. 221-240.
30. Rowe, A. Super Lettuce Turns Sour Sweet. *Wired Magazine*. December 7, 2006.
31. Park, M. Miracle Fruit Turns Sour Things Sweet. *CNN Health* March 25, 2009.
32. Doty RL, Hawit BR. Objective Assessment of Terbinafine Induced Taste Loss. *Laryngoscope* 2005;115:2035–2037.