Taste and Smell Alterations in Patients undergoing Hematopoietic Stem Cell Transplantations

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Abstract

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Background: Alterations in the chemosensory functions of taste and smell are common side effects experienced by patients undergoing standard oncology treatment. However, minimal data exists in patients undergoing hematopoietic stem cell transplantation (HSCT). Furthermore, most HSCT studies have focused solely on gustatory function and have been conducted only following completion of treatment.

Aim: This study aimed to assess the magnitude and characteristics of gustatory and olfactory (chemosensory) function in patients receiving HSCT at the Seattle Cancer Care Alliance (SCCA) using objective and subjective chemosensory testing methods. We examined the relationship between chemosensory function and Quality of Life (QOL).

Methods: In a prospective cohort study, patients aged 18+; scheduled to undergo HSCT at the SCCA were tested for gustatory and olfactory functions at three time points: pre-transplant (baseline) and then on day 30 and day 80 post HSCT. Gustatory function was assessed following the procedures of the Rapid Screening test used by the Monell-Jefferson Taste and Smell Clinic, modified to use the general Labeled Magnitude Scale for response. Olfactory testing was conducted using the NIH Toolbox Odor Identification Test. Self-assessment of taste and smell function was performed using two different survey instruments: the Taste and Smell

survey (Heald et al., 1998) and the EORTC QLQ-C30 & EORTC QLQ – H&N35. QOL was also assessed using the EORTC QLQ-C30 & EORTC QLQ – H&N35.

Results: Twenty-nine patients were enrolled in the study between August 2014 and March 2015. A total of twenty-three patients were included in the analysis after exclusion of patients who were not tested at day 30 post-HSCT. Sixteen participants were tested at baseline, day 30 and day 80.

The primary finding of this study is the decreased sensitivity (hypoguesia) for citric acid on day 30 and day 80 following HSCT; citric acid intensity was partially recovered by day 80. Increased sensitivity (hyperguesia) to a single concentration of sucrose at day 30 and a single concentration of NaCl at day 80 were also observed. Olfactory identification scores were unchanged from baseline to day 30.

Results of the QOL data analysis indicated that most patients' quality of life was reduced at 30 days post-transplant; however, quality of life was restored to an acceptable level of functioning and symptoms by 80 days after HSCT. Notably, some areas remain impaired, such as social functioning and dry mouth.

Conclusion: Patient reports of altered taste function were collaborated by objective testing. Taste was not reduced across the board, however. Rather, specific declines in sour (citric acid) perception were noted. Selective hypersensitivity was seen for some taste solutions. No obvious issues were found with olfactory function in relation to HSCT.

It would be helpful if future investigations confirm our results with a larger number of patients. That would aid in developing food products and/or nutritional supplements that appeal to patients experiencing altered taste functions post HSCT.

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I also wish to thank all faculty members of the University Of Washington, Department Of Oral Medicine who have given me the tools necessary to become a well-trained clinician and researcher.

This thesis wouldn't have been possible without the unconditional love and support of my family, who have always believed in me and encouraged me to fulfill my ambitions. It is because of many sacrifices made by my dear husband, Hisham, and my loving sons, Ahmed and Yusouf, that I'm able to achieve this goal.

Lastly, I offer my regards and blessings to all of those who supported me in any respect during the completion of this research study.

DEDICATION

To the loving memory of my father

To my mother for her endless love and encouragement

To my husband, who has supported me in all my endeavors

To my sons, Ahmed and Yusouf, who make life enjoyable

Chapter I: Background and Significance

Hematopoietic stem cell transplantation (HSCT) is widely used as a potentially therapeutic treatment for patients with several malignant and non-malignant hematological diseases and congenital immune deficiencies (Copelan, 2006).

HSCT patients undergo preparative conditioning therapy consisting of chemotherapy, combination chemotherapy, chemo/radiation or radiation alone in order to provide immune suppression and to eliminate the maximum number of cancer cells with the least amount of toxicity (Hamadani *et al.,* 2011).

Stem cell sources include peripheral blood stem cells (PBSC), bone marrow transplant (BMT), and cord blood. Donor types include autologous/allogeneic/syngeneic. Conditioning types include myeloblative, nonmyeloblative, and reduced intensity conditioning.

The intensive conditioning regimens are associated with significant side effects such as anorexia, nausea, vomiting, diarrhea, or mucositis in the acute phase of transplant (Gratwohl *et al*., 2010). This can lead to a limiting of voluntary nutritional intake placing the patient at risk of malnutrition.

Loss or change in taste perception is also a frequent complaint among most patients undergoing HSCT, particularly the allogeneic type. Taste alterations often have a negative effect on the quality of life of HSCT patients and their nutrition status by increasing association of certain tastes with nausea that accompanies chemotherapy, decreasing food enjoyment, and reducing their overall nutritional intake (McIssac T., 2008).

Alteration in the sense of taste among HSCT patients may also be associated with weight loss due to a decrease in overall food intake. Lenssen and colleagues (1990)

reported nutritional problems in 23% and weight loss in 28% of 192 patients in the first year after allogeneic bone marrow transplantation (BMT). High prevalence (66% at day 50) of eating disorders has been found among HSCT patients (n=64) in a longitudinal study in the Netherlands (Iestra *et al.,* 2002). Taste alterations were mentioned as one of the symptoms most strongly associated with eating difficulties among study participants. They occurred in 61% of the patients at day 50 and remained in 7% at day 350 (Iestra *et al.,* 2002).

A limited number of studies have focused on studying taste alterations among HSCT patients. Some studies investigated taste disorder in association to HSCT, while others were looking at recovery of the taste function after HSCT; summary of some of the studies is provided in Table (1).

Marinone *et al.* (1991) observed late and selective taste disorders in allogeneic transplant patients. The researchers conducted objective evaluation in patients undergoing HSCT (Autologus=8 and Allogeneic=15) after transplantation and in twenty normal subjects to determine threshold for the 4 basic tastes. Allogeneic HSCT recipients showed a significant hypogeusia for salt (Pearson's chi square p= 0.0002), and sour (Pearson's chi square p=0.001).

Boer *et al.* (2010) reported taste alteration in three groups of patients for sweet and salty tastes up to 3 years after ablative or reduced intensity HSCT. Group I (n=20) up to 150 days after HSCT, Group II (n=20) between 151 and 1095 days of HSCT, Group III (n=21) more than 1095 days of HSCT. Taste acuity was measured by taste thresholds for the four basic tastes (NaCl, Sucrose, Citric Acid, and Caffeine). This was performed by using 5ml of 4 different solutions, each of the solutions were then created

at 3 different concentrations. Their finding suggests that taste changes can be permanent and can also occur as a late complication of HSCT.

A recent study by Hull and colleagues (2012) found reduction in taste in 20% of the study participants, n=18. Eighty-eight survivors of allogeneic HSCT, were examined between 6 months and 6 years post-HSCT using a standardized questionnaire with no objective taste testing. The study does not report information about the exact time of taste recovery.

Mattsson and colleagues (1992) observed recovery of taste acuity to the control values in 80% of patients (n=26) one year after allogeneic HSCT. Patients were asked to complete a questionnaire on the subjective assessment of taste and taste related changes. Taste perception was registered before and three times after transplantation. Of the four examined taste modalities, the most frequently recorded change was a raised threshold for salt. The group tested 2-5 years after HSCT had normal values for taste acuity (Mattsson et al., 1992).

In a survey study, taste changes appeared to have recovered by day 90-100 (post-transplant) (Epstein *et al*., 2002). Changes of taste intensity in this study among patients undergoing allogeneic HSCT (N=50) were detected by reporting either increase or decrease of taste of salt, sweet, sour, and bitter.

In a retrospective study, alterations in taste perception tended to be more prevalent after allogeneic HSCT compared to after autologous HSCT with 58.1% vs. 45.5% (Federrman *et al.*, 2009). A significant difference in recovery time was also observed, with a subjective improvement of symptoms, after a median of 60 days (range,

3-365) after autologous HSCT vs. 120 days after allogeneic HSCT (range, 30-600) (p= 0.03).

Table 1: Summary of Literature Review

Name of the Study	No of Patients	Method of Evaluation	Conclusions
Barale *et al.* (1982)	11(6-15yrs) 20 normal children (sex matched and age similar)	Recognition thresholds were determined using the Up-Down Staircase method	Only minor changes in taste thresholds were demonstrated in this study
Marinone *et al.* (1991)	15 Allogeneic 8 Autologous	Cross sectional Taste acuity evaluation to obtain detection and recognition threshold	Late and selective taste disorders are observed in allogeneic BMT patients
Mattsson *et al.* (1992)	26 Allogeneic 10 long survivors of BMT	Subjective and objective assessment of taste and taste related changes	About 80% of the patients taste acuity had recovered to the control values one year after transplantation.
Epstein *et al.* (2002)	(50) Allogeneic	(QLQ-C30) Survey to assess Taste and smell alterations following HSCT	Taste changes recovered in large degree by day 90-100
Federmann *et al.* (2009)	(148) Allogeneic (33) Autologous	Clinical data were gathered from patients'charts, changes in taste perception on a semi-quantitative visual analogue scale	71% of the pts. reported moderate to severe changes
Boer *et al.* (2010)	(61) Allogeneic Low intensity HSCT (3)different groups	Survey & detection and recognition threshold	Taste alterations only for the sweet and salty tastes up to 3 years after HSCT
Cohen *et al.* (2012)	(10) children (7) Allogeneic (3) Autologous	Taste and smell detection and identification Tests	Taste and smell dysfunctions were transient and resolved within 2 months post-transplant.

Significance of the study

There is no consensus as to the duration of taste dysfunction in post HSCT patients. Two of the studies discussed in the literature review section concluded that taste dysfunction in patients undergoing HSCT was a short-term problem, which resolved with time (Marinone *et al.,* 1991,Mattsson *et al.,* 1992). While other studies determined that it is a problem of a persistent nature (Federrman *et al.* 2009, Boer *et al.* 2010).

There is also no agreement between previous investigations regarding disturbances in taste intensities and modalities following HSCT. This is partly because of differences in the taste testing methodologies and study population between earlier studies. In order to understand the extent of the problem of taste dysfunction in patients undergoing HSCT, it is necessary to objectively measure taste perception in this population using pre and post- HSCT taste testing methods. A prospective study would help clarify the relationship between taste dysfunction and time.

In addition, there has been a focus on assessing taste dysfunction alone. Taste and smell senses are both integrated in the perception of flavor and palatability of food, and dysfunction in one of these senses can lead to varied compensatory dietary habits. Therefore, gathering data on the impact of taste and smell dysfunction on food selection and eating habits will be a helpful tool in exploring more about dysfunction. It is also reasonable to assess the Quality of life (QOL) of HSCT patients, as taste alterations have previously been shown to negatively affect QOL of HSCT patients (Epstein *et al,* 2002).

Hypothesis

There are expected alterations in chemosensory functions in HSCT patients. We also hypothesized that QOL scores would negatively change in relation to HSCT.

However, we expect that unfavorable alterations in chemosensory functions and QOL scores would be transient and would recover by the end of the study timeframe.

Aims of the Study

1. To assess the magnitude and characteristics of taste and smell (chemosensory) dysfunction in patients receiving HSCT.
2. To examine the relationship between chemosensory functions and QOL.
3. To determine if patients' perception of chemosensory function is reflected in clinical chemosensory test results.

Chapter II: Materials and Methods

Study participants:

The patients included in the study were all scheduled to undergo HSCT at Seattle Cancer Care Alliance (SCCA) (Seattle, Washington State, USA). Participants receiving stems cells from any source were considered eligible for this study. All conditioning regimes and diagnosis were eligible. The enrollment started in August 2014 and was completed in May 2015.

Eligible patients completed a routine pre-transplant examination at SCCA's Oral Medicine clinic. Potential subjects were approached and informed of the study by the Oral Medicine clinic staff personnel during this examination. Participants were recruited into the study if they were older than 18 years, were able to eat and drink by mouth, and spoke and understood English. Also, participants must have been registered to receive myeloablative or non-myeloblative conditioning therapy prior to HSCT.

Participants were excluded if they had self-reported allergy to quinine, as well as patients who were in-patients at the time of testing.

SCCA-Fred Hutchinson Cancer Research Center Ethics Committee approved the protocol (FHCRC Data Repository protocol #884). Informed consent was obtained from the participants.

Data Collection Methods:

Overview:

Data were collected pre HSCT to establish levels of function at baseline and post HSCT at days 30 and 80.

Data collection methods included:

(A) Two Validated quality of life instruments EORTC QLQ-C30 & EORTC QLQ – H&N35

(B) Taste and Smell Survey (Parts A & B)

(C) Olfactory testing

(D) Gustatory testing

(E) Demographic and health status

Study participants were asked to complete two validated quality of life instruments: EORTC QLQ-C30 **(Appendix 1)** & EORTC QLQ - H&N35 **(Appendix 2).** EORTC QLQ - H&N35 has one question each on taste and smell. They were also asked to complete the Taste and Smell Survey (Parts A & B) **(Appendix 3)**

All participants also completed one session of taste and smell objective testing prior to conditioning for HSCT to establish a baseline for sensory function. The follow up test was repeated after 30 (+/- 5) days. A subsequent visit at day 80 (+/- 5) days was also planned.

Testing Protocol:

a. Validated quality of life instruments: EORTC QLQ-C30 & EORTC QLQ - H&N35

1. EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Study Group has developed a measurement strategy for the assessment of quality of life (QOL) of cancer patients in clinical trials.

The EORTC QLQ-C30 (version 3.0)156 is a core questionnaire that assesses how patients with cancer have perceived their health related quality of life (HRQOL) during the past week. It contains 30 items distributed over 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea or vomiting), and 1 global health-status/quality of life scale. This questionnaire also contains 6 single items addressing further cancer symptoms (dyspnoea, appetite loss, insomnia, constipation, and diarrhea) and the financial impact of the disease. Each item has 4 response alternatives: 1) "Not at all", 2) "A little", 3) "Quite a bit", and 4) "Very much", except the global health-status/quality of life scale, which has the response alternatives based on a marking on a categorical scale ranging between 1) "Very poor" and 7) "Excellent". The QLQ-C30 has been tested and shown good validity and reliability [Aaronson *et al.* (1993), Groenvold *et al.* (1997), Hjermstad *et al.* (1995)].

2. EORTC QLQ- H&N35

The current version of the Head and Neck module, the QLQ-H&N35 (version 1.0) includes 35 items and has been translated into 11 languages, following the EORTC Quality of Life Study Group guidelines. This module has been validated by Bjordal and colleagues (1999).

The QLQ-H&N35 comprises seven subscales: pain (4 questions), swallowing (5 questions), senses (2 questions), speech (3 questions), social eating (4 questions), social contact (5 questions), and sexuality (2 questions). In addition, 11 individual topics were evaluated taking into account the anatomic site, symptoms, and treatment (dental problems, mouth opening, dry mouth, poor salivation, coughing, sense of illness, analgesic use, nutrition difficulties, gastric tube, and weight loss or gain).

The time frame of the module is "during the past week". Items No1 to No 30 are scored on four-point Likert-type categorical scales ("not at all," "a little," "quite a bit," "very much"). Items No 31 to No 35 have a "no/yes" response format. The scores are transformed into 0-to-100 scales, with a high score implying a high level of symptoms or problems.

The EORTC QLQ-H&N 35 was administered to all patients, and scored using standardized procedures. The questionnaire resulted in 18 quality of life summary scores.

The QLQ-H&N35 survey was selected for use in the current study because of its common use in cancer research, in particular the area of head and neck cancer. This facilitates comparing and interpreting results from this study across studies and different populations. Moreover, The EORTC QLQ-H&N 35 has established standards by addressing questions related to the quality of life of patients with Head and neck cancer. It also has established face validity.

b. Self-assessment of taste and smell function

Taste and Smell Survey (Parts A & B)

Study participants were asked to complete the Taste and Smell Survey (Parts A & B). A subjective taste and smell questionnaire is an easy and useful tool for identifying taste and smell alterations in the clinical setting. Heald and colleagues (1998) developed

the taste and smell survey to evaluate chemosensory function in AIDS patients and it has been used recently with advanced cancer patients (Hutton *et al.,* 2007).

The advantages of implementing the taste and smell survey (Parts A and B) are:

1. It includes specific questions addressing changes in taste and smell among study participants and the effect these chemosensory changes have had on their quality of life.

2. The survey yields a numerical chemosensory complaint score (CCS), which can be used to group patients into those with mild, moderate and severe chemosensory complaints (Hutton *et al.,* 2007).

3. The CCS can be compared with clinical taste and smell tests' scores to verify if patient perception accurately characterizes chemosensory changes.

c. Olfactory testing:

Olfactory testing was conducted using the National Institute of Health (NIH) Toolbox Odor Identification test.

This test assesses a person's ability to identify various odors. It has been validated by Dalton *et al.* (2013). The selected odors are lemon, play doh, chocolate, bubble gum, popcorn, coffee, smoke, natural gas, and flower.

Scratch 'n' sniff cards were used to test the sense of smell. After scratching the cards one at a time, participants were asked to identify which of four pictures (representing the correct and 3 distractor odor sources), matches the odor they have just smelled.

The smell test takes approximately 4 to 5 minutes to administer and is recommended for ages 3-85.

The odor ID test was scored by summing the number of correct responses across the nine odor cards.

d. Gustatory testing

Gustatory testing closely followed the procedures of the Rapid Screening Taste Test (RSTT) used by the Monell-Jefferson Taste and Smell Clinic, modified to use the General Labeled Magnitude Scale (GLMS) as the response scale.

Participants were first oriented to the use of the GLMS (Figure 1)

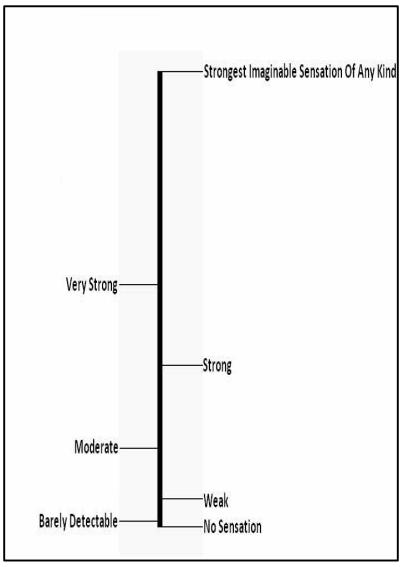

Figure 1: The General Labeled Magnitude Scale (GLMS)

Participants rated the intensity of three different concentrations each of chemicals representing the four basic taste modalities: sweet (sucrose), salty (NaCl), bitter (quinine), and sour (citric acid). Solutions were presented in one of two randomized orders (order A at baseline and day 80, order B at day 30).The sweet solutions were made of sucrose in the following molar (M) concentrations: 1.0 M, 0.32 M, and 0.1 M. The salty samples were made from sodium chloride (1.0 M, 0.32 M, and 0.1 M). Sour samples were made from citric acid (0.018 M, 0.0056 M and 0.0018 M). Bitter samples were made from quinine hydrochloride (0.001 M, 0.00032 M, and 0.0001 M). Distilled water was also administered as one of the 13 tastants. Stimuli were prepared fresh weekly from USP-grade or food-grade chemicals and Earth H2O brand distilled water.

When not in use, stimuli were stored under refrigeration and were warmed to room temperature prior to testing.

Procedure:

Participants were presented with 10 ml of each solution in a 30 ml medicine cup. Participants sipped the entire amount of each solution, swished it around in the mouth, and then expectorated the solution into a cup. Participants were first asked to state whether the solution was sweet, salty, sour, bitter, or had no taste. Because people tended to confuse bitter and sour, participants were asked to use the word *sour* to describe a "lemon-like" taste and *bitter* to describe a taste "like black coffee, medicine, or tonic water". After identifying the taste, participants rated the intensity of each taste on the general labeled magnitude scale.

Taste intensity data were scored as mm marked along the GLMS scale. Detailed description about the experimenter's instructions to study participants is provided in Appendix 4.

E. Other variables

Demographic information collected from the electronic health records of participants included age, sex, hematologic diagnosis, stem cell source, donor relationship, degree of Human Leukocyte Antigen (HLA) match, history of prior transplant, and conditioning regimen (ORCA, University of Washington Medical Center, Seattle, WA USA; Powerchart, Cerner Corporation, Kansas City, MO USA).

Chapter III: Analysis

Statistical Analysis was performed for subjects who completed the first and second testing (n=23).

Descriptive statistics were calculated for patient demographics, clinical diagnosis, types of conditioning, and GVHD prophylaxis. Paired t-tests were used to test for differences in Odor ID scores from baseline to day 30. ANOVA's were used to assess for main effects of test time (baseline versus day 30) or solution concentration (low, medium, high), and for time by concentration interactions. When significant time by solution concentration interactions were observed, Newman-Keuls post-hoc testing was used to assess for changes in taste intensity at each solution concentration. A separate ANOVA was conducted for each of the four basic tastes. In order to assess whether observed decreases in taste function recovered, a subgroup analysis was additionally conducted for the sixteen patients who completed day 80 testing.

Quality of life was examined individually in order to identify participants reporting frequent or infrequent problems with senses (taste and smell), eating, and weight loss.

Chapter IV: Results:

Patient demographics:

Twenty-nine patients were enrolled in the study between August 2014 and March 2015. A total of twenty-three patients were included in the analysis after exclusion of patients who didn't complete the study or refused to do the follow-up testing due to several reasons (e.g., being unwell at the time of assessment); flow chart to demonstrate the withdrawal reasons (Figure 2)

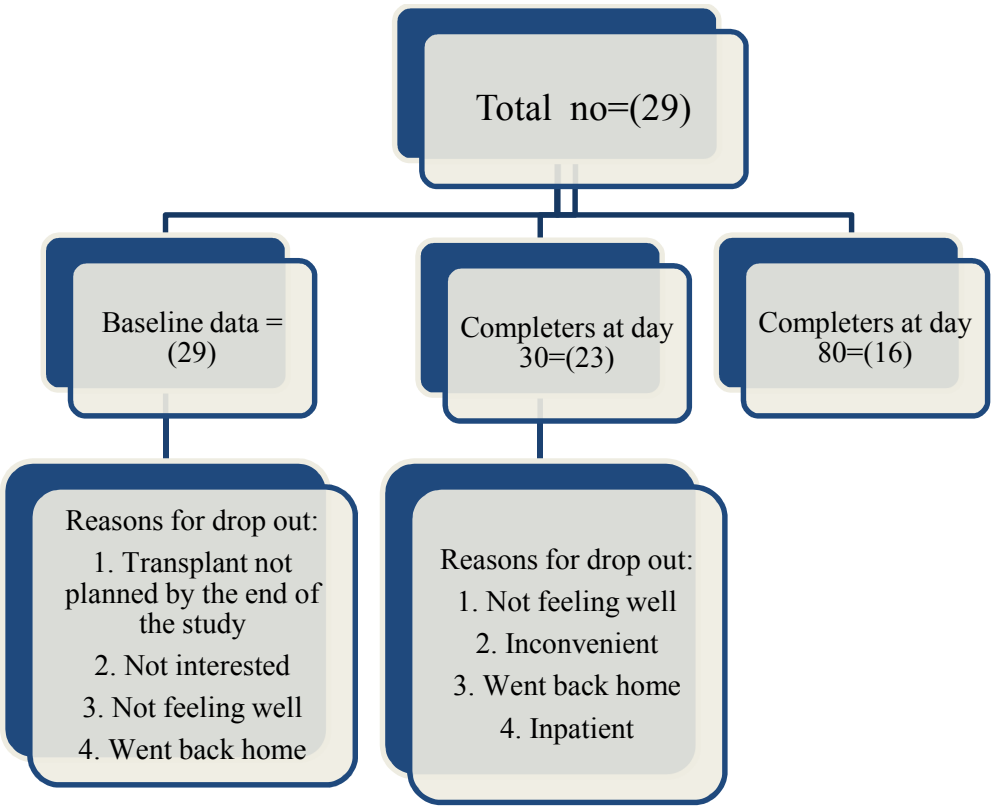

Figure 2: Flow Diagram of Patients

Demographic and clinical characteristics of the 23 (20 for MAC and 3 for RIC) included patients are shown in Table 2. There were more females than males at baseline (14 vs 9) and ages ranged between 73 and 26 years old (mean=50). The largest diagnostic groups were acute myeloid leukemia (26%) and multiple myeloma (22%).

Patients received different conditioning regimens depending on diagnosis and the transplant protocol (Table 2).

Patients were hospitalized a median of 19 (range= 0-35) days. Peripheral blood stem cells were the most common stem cell source (87%). The majority of donors were not related to the recipient (39%). Matched unrelated donors (MURDs) were the most common donor group with respect to HLA-classification (26% of total donors).

HSCT Protocols: Eight distinct MAC (24 patients) and RIC conditioning protocols (2 patients) were utilized in our cohort. Six different prophylactic GVHD regimens were used with the most common prescribed prophylactic medications were primarily cyclosporine (CSP, Neoral)/ mycophenolate mofetil (MMF).

Graft versus host disease (GVHD): Twelve allogeneic participants developed GVHD (skin +/or gastrointestinal) after HSCT. One autologous participant developed pseudo GVHD by day 28 which resolved later on.

Table 2: Demographics

		n (%)
Sex	Male	9 (39)
	Female	14 (61)
Age at transplantation	Mean	50
	Median	49
	Range	47
Diagnosis	AML	6(26)
	MM	5(22)
	MDS	3(13)
	ALL	3(13)
	Mantle Cell, Non-Hodgkin's Lymphoma	1(4)
	Diffuse Large B-Cell Lymphoma	1(4)
	B-Cell Follicular Lymphoma Stage III	1(4)
	Myelofibrosis	1(4)
	Blastic plasmacytoid dendritic cell neoplasm	1(4)
	CML	1(4)
Transplant Type	Autologus	7(30)
	Allogeneic	16(69)
Conditioning Protocol	Myeloablative	20(87)
	RIC	3(13)
Source of stem cells	PBSC	20(87)
	Cord blood transplant	2(9)
Donor	MRD	5(22)
	MURD	6(26)
	MMRD	1(4)
	MMURD	3(13)
Conditioning protocols	Myeloablative Bu/Cy	5(22)
	Myeloablative MEL	4(17)
	Myeloablative Flu, treosulfan	3(13)
	Myeloablative TBI/Cy	3(13)
	Myeloablative BEAM	2(9)
	Nonmyeloablative Flu/Cy/TBI.	2(9)
	Myeloablative Radiolabeled Anti-CD45/TBI/Flu	1(4)
	Myeloablative Cy/TBI/ etoposide (VP16)	1(4)
	Myeloablative Flu/Cy/TBI	1(4)
	Nonmyeloablative Y-90 DOTA Bioten/Flu/TBI	1(4)
GVHD Prophylaxis protocol	Cyclosporine, Mycophenolate Mofetil	6(26)
	Methotrexate, Tacrolimus	4(17)
	Cyclosporine, Methotrexate	2(9)
	Methotrexate, Tacrolimus, Abatacept	2(9)
	Mycophenolate Mofetil, Tacrolimus	1(4)
	Cyclophosphamide, Mycophenolate Mofetil, Tacrolimus	1(4)
GVHD	GVHD (GI +/or Skin)	12(53)
	Pseudo GVHD	1(4)

ALL= acute lymphoblastic leukemia; AML= acute myelogenous leukemia; CLL= chronic lymphoblastic leukemia; CML= chronic myelogenous leukemia; CMML= chronic myelomonocytic leukemia; MDS= myelodysplastic syndrome; MMRD= mismatched related donor; MMURD= mismatched unrelated donor; MRD= matched related donor; MURD= matched unrelated donor; PBSC= peripheral blood stem cell; RIC= reduced intensity conditioning; TBI= total body irradiation; Bu= busulfan; Cy= cyclophosphamide; MEL= melphalan; Flu= fludarabine; Beam= carmustine, etoposide, cytarabine, melphalan

Clinical Chemosensory Assessments

Odor Identification Test:

Patients in the study were given an odor ID score based on their performance in the odor test.

Graph (1) reveals the average performance of all the patients at baseline alongside their average performance at day 30. The scores for the odor test ranged from 7-9 on a scale of 9 across the patient group. Odor identification score did not change from baseline to day 30 ($p = 0.56$).

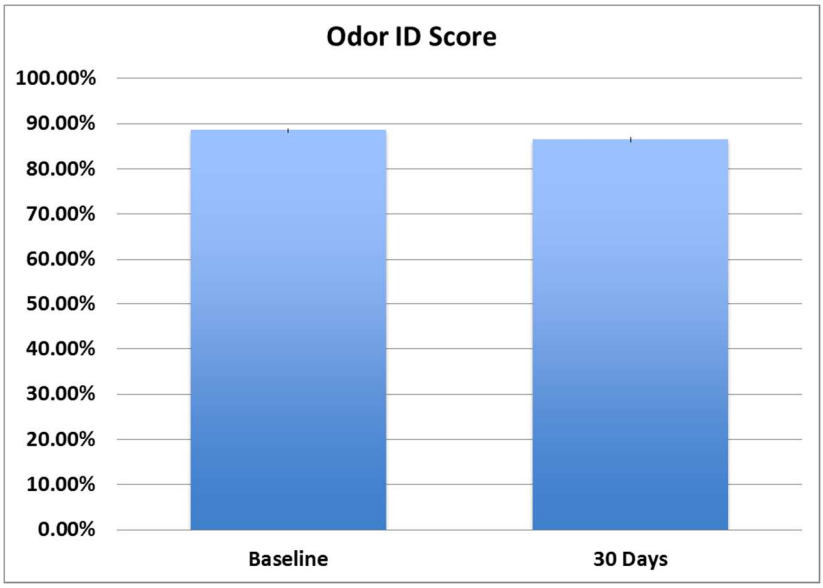

Figure 3: Odor Identification Test Scores at Baseline and at Day 30

Gustatory Testing:

Data gathered from the gustatory testing is depicted in Graphs (2-5). Taste intensity data was plotted from baseline to day 30 for each concentration of a solution (low, medium, high), to show their relationship to intensity scores on the GLMS scale. For NaCl, there was a significant effect of concentration [$F(2, 44) = 99.24$, $p < 0.001$] and a significant concentration by time interaction [$F(2,44) = 3.96$, $p < 0.05$]. The middle concentration of NaCl was rated significantly lower on day 30 compared with baseline (Newman-Keuls, $p < 0.02$).

We also observed decreased ratings for 0.018 M citric acid (high concentration) and 0.0056 M citric acid (medium concentration) [Main effect of concentration, $F(2, 44) = 71.8$, $p < 0.0001$, main effect of time, $F(1,22) = 24.8$, $p < 0.0001$, and a significant concentration by time interaction, $F(2,44) = 5.53$, $p < 0.02$. Both middle ($p < 0.01$) and high ($p < 0.001$) concentrations were rated significantly lower at time 2 (Newman-Keuls post hoc tests).]

For quinine, there was a significant main effect of solution concentration [$F(2,44) = 57.6$, $p < 0.0001$], but no main effect of time or any time by concentration interactions to indicate that quinine intensity changed following HSCT. For sucrose there was a significant main effect of concentration $F(2,44) = 69.3$, $p < 0.0001$ and a concentration by time interaction $F(2, 44) = 5.39$, $p < 0.01$. The middle concentration of sucrose was significantly *higher* at time 2 than at baseline (Newman-Keuls, $p < 0.01$).

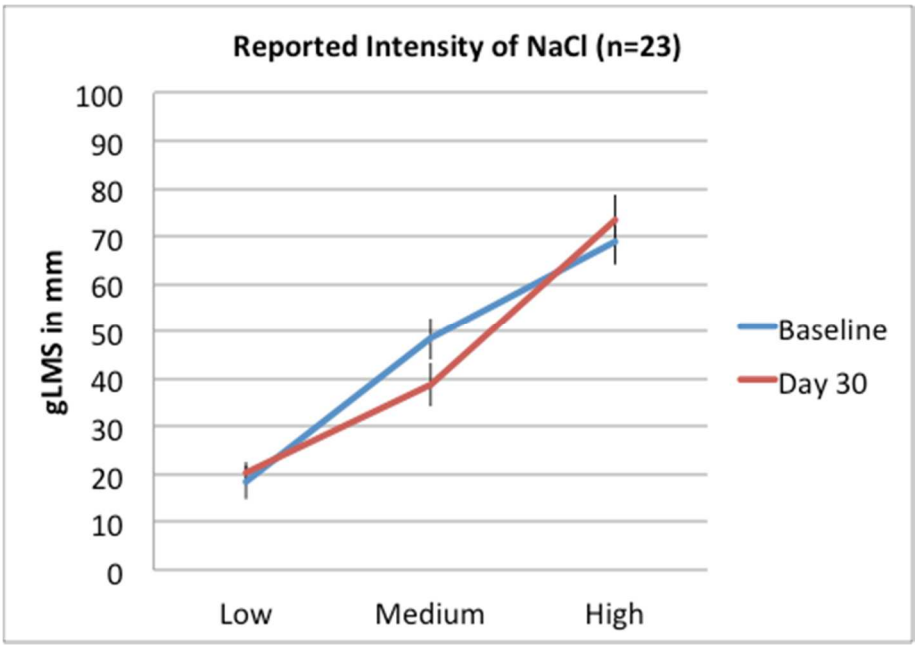

Figure 4: Reported Intensity of NaCl at day 30

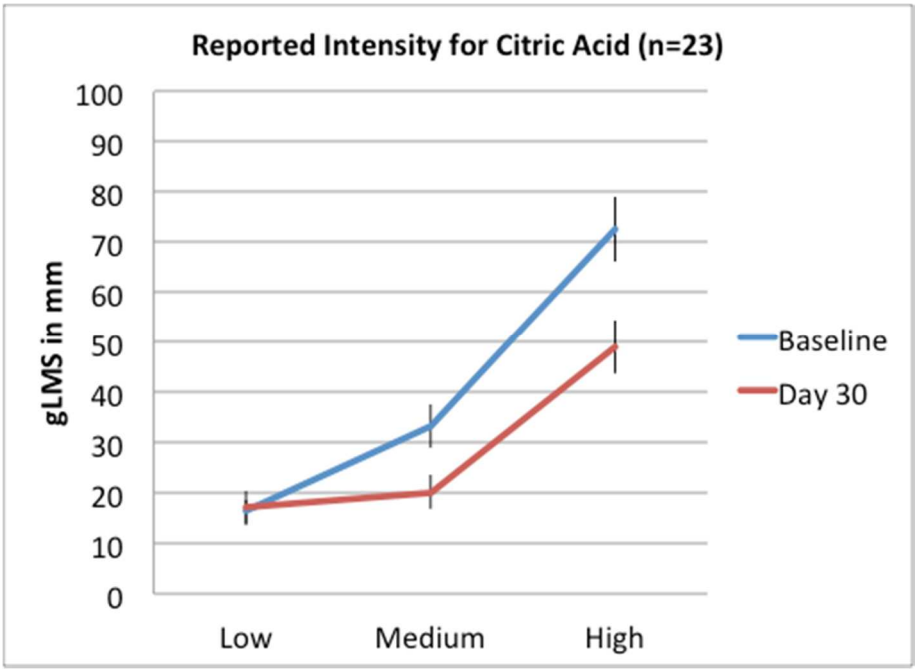

Figure 5: Reported intensity of Citric Acid at day 30

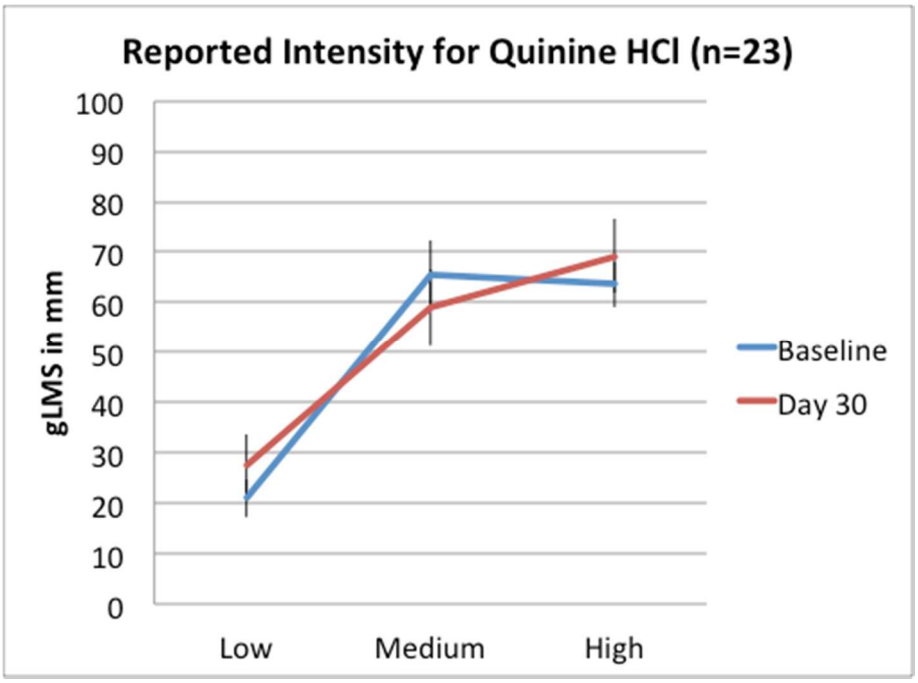

Figure 6: Reported intensity of Quinine HCl at day 30

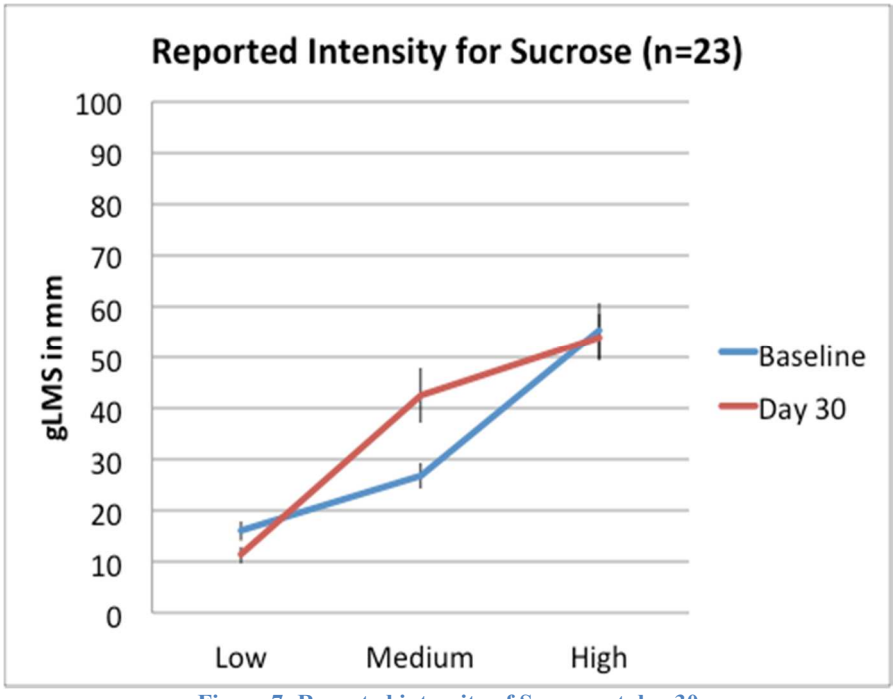

Figure 7: Reported intensity of Sucrose at day 30

Subgroup analysis for 16 patients who completed the study until day 80:

For the subgroup analysis (including only the 16 patients completing the study through day 80), the decreased perception of 0.018 M Citric Acid and increased perception of 0.1 M sucrose were still evident. Though diminished taste perception for 0.1 M NaCl and 0.0056 M Citric Acid did not reach statistical significance when analyzing data from only those 16 participants. The perception of 0.018 M Citric Acid partially recovered by Day 80, whereas 0.1 M sucrose perception returned to baseline levels. There was also some evidence for enhanced sensitivity to 1 M NaCl at Day 80.

Graphs 6-9 show taste intensity data for each taste modality plotted at three time points (baseline, day 30, and day 80)

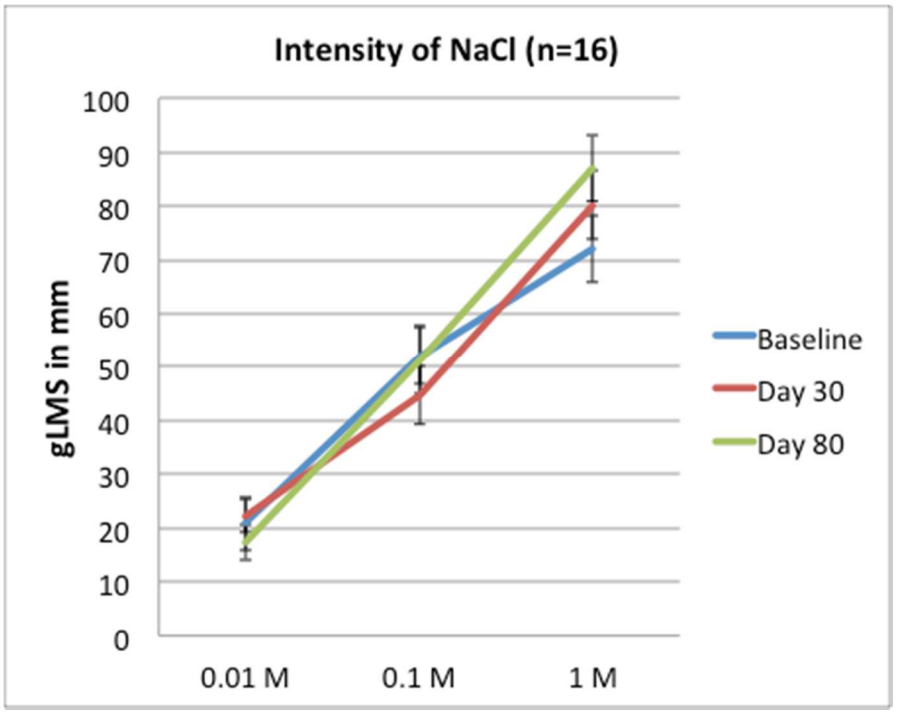

Figure 8: Reported intensity for NaCl

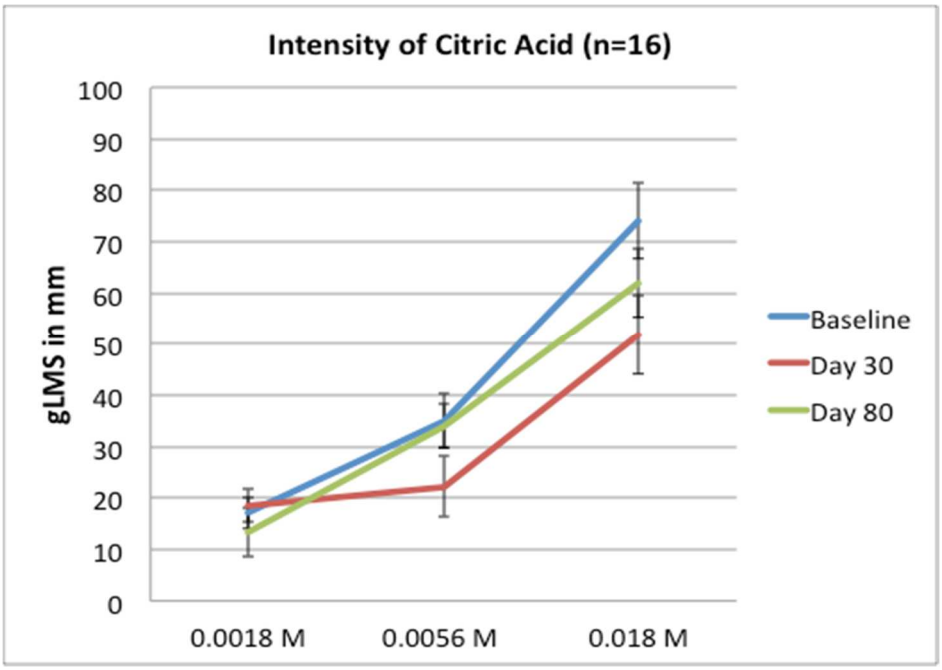

Figure 9: Reported Intensity for Citric Acid at three time points

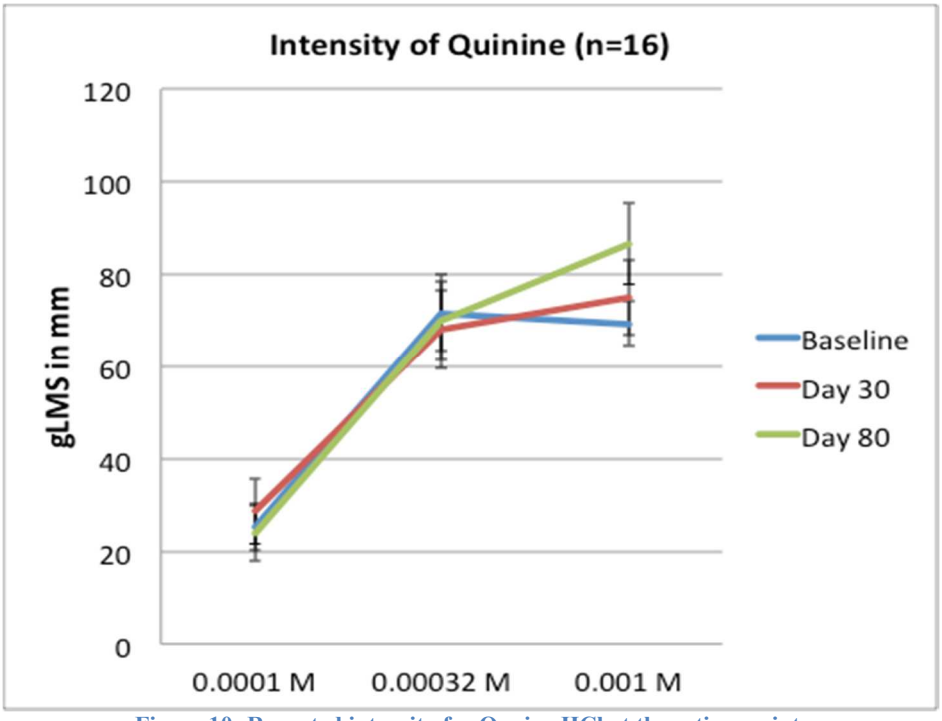

Figure 10: Reported intensity for Qunine HCl at three time points

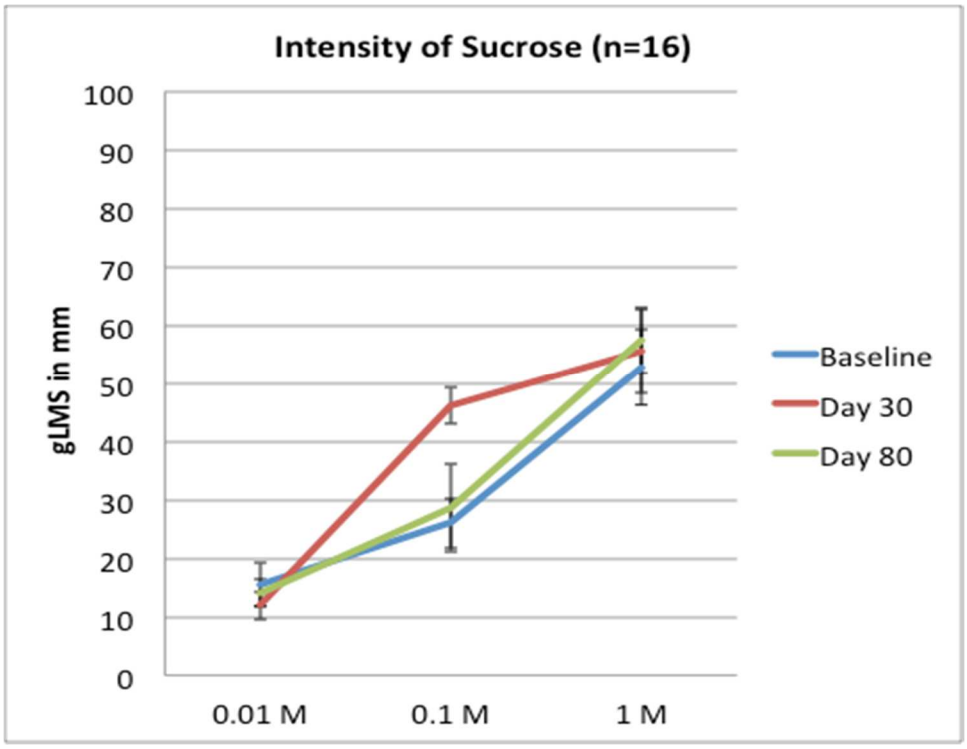

Figure 11: Reported Intensity for Sucrose at three time points

Quality of Life:

All patients in the study were also given the EORTC QLQ-C30 & EORTC QLQ - H&N35 surveys. The average scores and standard deviations for selected domains (relevant to gustatory or olfactory function) are depicted below in Table 3. The highest symptom scores and lowest function scores were experienced 30 days after HSCT. Thereafter, the levels of symptoms decreased and levels of functioning increased, hence returning to baseline levels by day 80.

Exceptions from this pattern were dry mouth and sticky saliva problems. These symptoms increased over the whole time period.

Table 3: Mean (SD) values for the EORTC QLQ

	Baseline n=23	**Day 30 after HSCT** n=23	**Day 80 after HSCT** n=16
Functional scales[a]			
Physical	88 (12.1)	78.6 (19.1)	84.7 (9.5)
Role	83.3 (16.6)	63.8 (24.95)	70.8 (23.96)
Emotional	81.5 (14.8)	82.6 (15.9)	83.3 (24.6)
Cognitive	78.9 (19.6)	76.8 (24.9)	87.5 (18.8)
Social	57.9 (24)	56.5 (24.9)	65.6 (28.9)
Global QOL	68.1 (15)	57.6 (19.1)	61.97 (24.3)
Symptom scales[b]			
Appetite loss	10.1 (18.6)	33.3 (26.6)	18.8 (20.97)
Nausea and vomiting	7.96 (13.2)	18.1 (18.1)	6.2 (11.97)
Pain H&N	3.6 (7.9)	7.6 (18.3)	1 (2.8)
Swallowing	1.1 (2.9)	9.4 (18.3)	0.5 (2.1)
Dry Mouth	18.8 (29.9)	36.2 (31.6)	41.7 (33.3)
Sticky saliva	13 (24.1)	24.6 (25.1)	24.99 (22.8)
Weight loss	13 (34.4)	56.5 (50.7)	31.3 (47.9)
Senses problems (taste and smell)	1.5 (4.8)	30.4 (30)	10.4 (14.8)

[a]Scores range from 0 to 100, with higher scores representing higher levels of functioning

[b]Scores range from 0 to 100, with higher scores representing higher levels of symptoms

Chapter V: Discussion:

Gustatory functions (Supra-threshold Taste Test Performance)

Gustatory function testing (both pre and post-HSCT) revealed normal upward trends in taste intensity scores as the concentrations of chemicals (sucrose, citric acid, quinine and NaCl) increased, indicating proper gustatory function in relation to differentiating between intensities of concentrations.

We observed decreased sensitivity (hypogeusia) for both medium and high concentrations of citric acid on day 30, as well as decreased sensitivity for a medium concentration of NaCl. The subgroup analysis indicated that decrease in citric acid perception may only partially recover by day 80. This finding is consistent with results from Marinone *et al.,* (1991*)* who reported that the thresholds for sour tastes significantly increased in 15 adult patients at 4 - 51 months after HSCT compared with those in 20 healthy subjects.

Heightened ratings (hypergeusia) for 0.1 M sucrose (medium concentration) were observed at day 30. This finding is in contrary to results from Boer *et al.,* (2010), who reported taste alteration in three groups of patients for sweet and salty tastes up to 3 years after ablative or reduced intensity HSCT. Group I (n=20) up to 150 days after HSCT, Group II (n=20) between 151 and 1095 days of HSCT, Group III (n=21) more than 1095 days of HSCT. The intensity of the sweet solution in the high and low concentrations was a challenging to be determined for those patients ($p = 0.04$ and $p = 0.05$ respectively). For the medium salty concentration and high sucrose concentration the tastes were difficult to be determined only by Group I ($p = 0.08$ and $p = 0.07$ respectively). Differences between our results and those of Boer *et al., (*2010) may be related to differences in the taste testing methodology or any other variables.

We also found increased ratings (hypergeusia) of 1 M (high) concentration of NaCl at day 80. This finding is in contrary to results from [Marinone *et al.,* (1991), Mattsson *et al.,* (1992)], who reported raised threshold for salt after HSCT.

This finding is also different to results from Barale *et al*., (1982), who assessed the recognition thresholds for the four tastes in 11 children who had undergone HSCT and found that the threshold for salty taste significantly increased 2 days after transplantation and returned to the pretreatment level 45 days after transplantation. However, the rapid resolution of chemosensory deficits in young children compared to adults may be related to a more rapid regeneration of taste receptors during childhood.

The observation that HSCT differentially impacted perception of sour, salty, bitter, and sweet tastes may be due to differences in cellular transduction mechanisms for each of the 4 basic taste qualities. It may also be explained by changes in recovery rate of taste receptor cells.

Taste molecules are detected by chemo-sensitive taste receptors in the taste buds. Taste receptors are located on the anterior and posterior tongue, the palate and the epiglottis. Each taste bud may comprise 50 to 100 taste receptors (Fábián *et al.,* 2015).

The taste bud cells have been assorted into three major groups: Type I, II, and III cells. There are also basal cells in the taste buds; also termed type IV cells. The role of type I receptors in salty taste sensation has recently been suggested. However, the mechanism of how these cells detect taste remains unclear. Sweet and bitter perception involve G-protein coupled receptors, which are expressed by Type II taste cells. While, type III taste cells are thought to be involved with sour perception (Chaudhari & Roper , 2010).

Direct damage to taste buds may have been induced by cytotoxic antineoplastic treatment through a higher rate of cell turnover. This is believed to be the basis of taste changes during chemotherapy and radiotherapy cancer treatment (Hovan *et al.,* 2010).

Antineoplastic drugs may also affect taste by causing disruption of taste sensation conduction or by inhibiting synaptic reuptake (Doty & Bromley, 2004). Further analysis is needed to assess the relationship between antineoplastic interventions, medications and taste alterations.

Another plausible explanation for alterations of taste perception may be related to the expected reduction in salivary flow in HSCT patients. It is known that reduced salivary flow (hyposalivation) is associated with alterations in oral flora constituents and that may affect the sense of taste (Fernando *et al.,* 1995). However, the exact mechanism of how salivary composition affects taste perception is still under investigation (Fábián *et al.*, 2015). Future objective investigation may lead to new findings in the relationship between salivary flow and taste chemosensory function.

Olfactory function

At baseline, smell scores from study participants were very similar to the ones found for the national norm in the NIH Toolbox study and indicated no major impairment at baseline.

We didn't observe any differences in odor identification scores from baseline to day 30. This may reflect a lack of damage to the olfactory system. This finding may also suggest the need for a more sensitive technique for assessment of olfactory changes than the methodology we used in this study.

Quantitative testing of olfactory function of HSCT patients in the present study was performed using the NIH Toolbox for olfactory testing which is a brief, inexpensive

and easy-to-administer assessment. This method includes presenting study participants with familiar odorants at supra-threshold concentrations (i.e., above the detection level for most subjects). This technique is less sensitive than detection threshold olfactory testing but it requires less time to administer (Doty *et al.,* 1996). Detection threshold for an odorant is the concentration at which an individual a) can just detect the odor's presence, or b) can discriminate it from a sample of odorless air. (Doty *et al.*1996). We also could have assessed olfactory intensity as we did for taste.

Future threshold olfactory testing may contribute new knowledge about the nature of alterations in the smell sense.

Quality of life

Quality of Life was assessed using the EORTC QLQ-C30 & EORTC QLQ - H&N35. Our study population had most symptoms and worst functioning 1 month after HSCT. This is accordance with results from (Andresson *et al.,* 2009), who reported similar findings with the exception of substantial differences between patients undergoing myeloablative conditioning (MAC) and patients undergoing reduced intensity conditioning (RIC). The MAC group deteriorated in 20 symptom scales compared with 8 in the RIC group. In our investigation, most of our patients (n=20) have received MAC.

Subgroup analysis in our study showed that patients (n=16) had recovered reasonably well 80 days following HSCT, concerning physical, social, emotional, role and cognitive function. One exception is the social domain. It is observed that social functioning was low from start, and even if it improved over time, it was still impaired 80 days following HSCT. One reason is long hospitalization and frequent visits at the outpatient clinics after HSCT, which limits patient's social life.

Symptoms related to the mouth and the digestive system such as dry mouth, swallowing, appetite loss, nausea and vomiting, and senses problems dramatically increased in one month following HSCT. These problems decreased over time except dry mouth, which even increased over the whole time period. This finding is consistent with results from (Andresson *et al.,* 2009), who reported the persistence of mouth dryness in patients undergoing myeloablative conditioning (n=25) one year after HSCT.

It is plausible that mouth dryness is related to the type of conditioning. Most of study participants received myeloablative treatment, with 9 of them received Total Body Irradiation (TBI).

Limitations

The study has several limitations. First, there is lack of information about taste perception and salivary flow rate. It is thought that if saliva flow adaptation is disrupted, taste sensitivity is decreased (Vissink *et al.,* 2003). Saliva could have been collected during taste evaluation; however that was not possible given the nature of this pilot study. Further research would benefit from collecting information about association between salivary flow rate and taste changes.

Second, no data were collected about the presence of mucositis and oral candidiasis, which may alter chemosensory functions in this population.

Lastly, we were able to get significant results by performing statistical analysis on twenty-three recruited participants at baseline and at day 30 following transplant. Only sixteen participants were capable of continuing the study until day 80 (+/- 5 days). It is a challenge to keep participants in such a study without expecting them to drop because of sickness, re-hospitalization after HSCT or death. Future studies may benefit from

recruiting more participants into the study at baseline to overcome the possibility of patients who decide to withdraw.

Strengths of the study

One of the strengths of this study is its longitudinal prospective design, which helps determine the timeline around the loss, recovery, and/or alteration in taste and smell function that may result from HSCT.

This study is the first study to objectively assess both smell and taste functions in HSCT patients prior to their transplant and at two time intervals after HSCT. The study also combined self-assessment of taste and smell function with a comprehensive set of clinical chemosensory test procedures.

Self-assessment of taste and smell function was performed using two different survey instruments; one of them (the Taste and smell survey) contains open-ended questions. The Taste and smell survey collected rich qualitative data, which are planned for analysis in the future. The other survey instrument is the EORTC QLQ-C30 & EORTC QLQ - H&N35, which is an internationally validated data collection tool.

Assessment of gustatory perception was performed using the rapid screen method of supra-threshold testing, which is brief (approximately 5 minutes), available at minimal cost, reliable, validated, and readily administered on a large scale (Coldwell et al., 2013). The advantages of using the supra-threshold testing made it more convincing to choose it over any other technique.

Generally, assessment of taste sensitivity is performed using a variety of techniques including:

1. Subjective ratings of intensity for supra-threshold stimuli, 2) absolute detection thresholds (the lowest concentration subjects can reliably discriminate from water),

3) recognition thresholds (the minimum concentration at which the quality of a stimulus (e.g. sweet, sour) can be identified and 4)differential thresholds(the smallest increase in supra-threshold stimulus concentration that can be detected) (Bartoshuk 1978).

Evaluation of olfactory changes was done using the NIH odor identification assessment. This method is an easy, brief and fun task. It also doesn't require much instruction. And, it represents the most ecologically valid role of olfaction in everyday life

Practical implications

There are several practical implications of this study:

1. We observed statistically significant differences between baseline and day 30 and day 80 after HSCT for selected intensities of different taste modalities. Accordingly, patients who complain of these changes should be encouraged to experiment with foods and try everything in order to learn what tastes good. Food seasoning and flavor enhancers could help with improving taste modality recognition and nutritional status *"e.g., using lemon juice to enhance sourness"*. The goal is to decrease overall chemosensory complaints to help improve patient's quality of life, nutritional status, and compliance with medication.
2. Chemosensory-related changes may result in increased intake of specific foods and this can be challenging. For example, the fact that sucrose perception is recovered or enhanced by day 30 may increase sweet consumptions. Accordingly, this may exacerbate problems with dental caries in HSCT patients (Mattes *et al.,* 1990). Controlling dental diseases in this population is very important to avoid the need for future dental procedures.

3. Our study results showed that there is a concern with taste function in the early transplant period (+/- 5 days time frame) for selected taste modalities. This was largely resolved within 2.5 months. Study results may suggest that difficulty to maintain an adequate diet during the recovery period beyond 2 months is not due to chemosensory disorders. Accordingly, other contributing factors should be explored in order to increase dietary intake among patients undergoing HSCT.
4. Finally, it might be valuable to design and administer a very short taste and smell questionnaire to identify chemosensory alterations in the clinical setting. Such a survey is a fast and low-burden tool and it may aid in preventing malnourishment, weight loss and poor QOL.

Future research

Future investigation should explore the relationship between chemosensory alterations and nutritional choices. Such an investigation would be helpful in predicting possible weight changes and interventions for chemosensory distortions.

Preliminary analysis of the Taste and Smell Survey (data not shown here), revealed that many subjects complained of the interference of antineoplastic and prescription medications with their sense of taste and smell. Future research is needed to evaluate the effect of each medication on the senses of taste and smell. Results of such an investigation would be particularly important for patients suffering from cachexia in post HSCT period.

GVHD is a major complication in stem cell transplant recipients and can affect many organs, including the oral cavity (Imanguli *et al.,* 2006). Such complication is reported to have a morbidity and mortality incidence of 40–70% (Socie *et al.,* 2003). It would be interesting to explore relationships between GVHD and taste abnormalities

using the supra-threshold taste testing.

Finally, our sample included a diverse group with a variety of diagnosis, treatment and demographics. There may be other factors that cause chemosensory alterations observed in this study. More research needed to determine the exact origin of taste and smell changes in this population.

Conclusion

The results presented here expand the current knowledge of chemosensory dysfunction in patients receiving HSCT. It is reasonable to conclude that there is some concern with taste perceptions for selected taste intensities and modalities in the early post-transplant period. This was largely resolved within 2.5 months.

Decreased sensitivity (hypogeusia) was observed for both medium and high concentrations of citric acid on day 30, as well as decreased sensitivity for a medium concentration of NaCl. The subgroup analysis indicated that decrease in citric acid perception may only partially recover by day 80. Increased sensitivity (hyperguesia) of medium concentration for sucrose was detected at day 30. The subgroup analysis showed that increase in sucrose perception was not fully recovered by day 80.

The observed alterations in taste perceptions in this group of patients may possibly be explained by changes in number, recovery rate, and structure of taste receptors. It is also plausible that HSCT affects the reestablishment of synaptic connections of chemosensory functions.

It would be helpful if future investigations confirm our results with a larger number of patients. That would aid in developing food products and/or nutritional supplements that appeal to patients experiencing altered taste functions post HSCT.

We didn't find significant differences in odor identification scores from baseline to day 30. Results of the QOL data analysis indicated that most patients reached an acceptable level of functioning and symptoms during the first 80 days after HSCT. However, some areas remain impaired, such as social functioning and dry mouth.

Further investigation may lead us to better understanding the exact biological mechanism behind chemosensory alterations in relation to HSCT. Such an investigation is necessary for avoidance of nutritional disturbances and compliance with medication intake.

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Appendix 1: EORTC QLQ-C30 (version 3)

ENGLISH

Appendix 1

Participant Number: Date: / / (month/day/year)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

[redacted]

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 2: EORTC QLQ-H&N35

Appendix 2

Participant Number: Date: / / (month/day/year)

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Appendix 3: Taste and Smell Survey- Part A&B

TASTE AND SMELL SURVEY- PART A

Participant Number: _____ Date:__ /__ /__ (month/day/year)

The purpose of this survey is to see how health conditions affect the senses of taste and smell. Please answer the following questions as best as you can.

1. Have you noticed any changes in your sense of taste? Yes No

   If yes, please describe:

_____

2. Have you noticed any changes in your sense of smell? Yes No

   If yes, please describe:

_____

3. Have you ever noticed that a food tastes different than it used to? Yes No

   If yes, please describe:

_____

4. Have you ever noticed that a food smells different than it used to? Yes No

   If yes, please describe:

_____

5. I have a persistent bad taste in my mouth (circle Best answer)
   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent taste is (circle ALL that apply)
   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (specify) _____

7. Do specific drugs interfere with your sense of taste? Yes No

   If yes, which ones?

_____

8. Do some drugs taste worse than others? Yes No

   If yes, which ones?

_____

9. Do specific drugs interfere with your sense of smell? Yes No

If yes, which ones?

---

10. Do some drugs smell worse than others? Yes No

If yes, which ones?

---

11. Comparing my sense of taste now to the way it was before I was diagnosed with my condition:

a. Salt tastes (Circle BEST answer)

1) stronger

2) as strong

3) weaker

4) I cannot taste it at all

b. Sweet (sugar) tastes (Circle BEST answer)

1) stronger

2) as strong

3) weaker

4) I cannot taste it at all

c. Sour (lemon or vinegar) tastes (Circle BEST answer)

1) stronger

2) as strong

3) weaker

4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (Circle BEST answer)

1) stronger

2) as strong

3) weaker

4) I cannot taste it at all

12. Comparing my sense of smell now to the way it was before I was diagnosed with my condition:

Odors are

1) stronger

2) as strong

3) weaker

4) I cannot taste it at all

13. Over the past 3 months, I would rate my abnormal sense of taste as: (Circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

14. How has your abnormal sense of taste affected your quality of life?

---

15. Over the past 3 months, I would rate my abnormal sense of smell as: (Circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

16. How has your abnormal sense of smell affected your quality of life?

TASTE AND SMELL SURVEY - PART B

Participant Number: _____ Date:___/___/____ (month/day/year)

The purpose of this part of the survey is to determine if there are factors other than your health condition that influence your sense of taste and smell. Please answer the following questions as best as you can.

1. Do you wear dentures?	Yes	No
2. Have you had mouth and/or gum infections in the past two years?	Yes	No
3. Are you currently bothered by hay fever and/or allergies?	Yes	No
4. Are you currently bothered by your sinuses?	Yes	No
5. Does your sense of smell change from day to day?	Yes	No
6. Does your sense of taste change from day to day?	Yes	No
7. Has a doctor previously diagnosed you with any taste or smell problems?	Yes	No
8. Before your health condition, did you have any problems with your sense of taste or smell?	Yes	No
9. Do you smell "phantom odors"; you can smell something but the source of smell is nowhere near you?	Yes	No
10. Are you currently a smoker?	Yes	No
11. If you are not a current smoker, are you a former smoker?	Yes	No
12. Does a caregiver prepare the majority of your meals?	Yes	No
13. Do you prepare the majority of your meals?	Yes	No
14. Do you eat your meals alone?	Yes	No
15. Do you taste "phantom taste"; taste something when there is nothing in your mouth?	Yes	No

Some symptoms or problems can affect your ability to eat. Please indicate the extent to which you experienced these symptoms or problems in the past week, using a scale from one to five, where 1 represents "not at all" and 5 represents "very often"

	Not at all				Very often
15. Do you have pain or soreness in your mouth?	1	2	3	4	5
16. Do you have pain in your jaw?	1	2	3	4	5
17. Do you have pain in your throat?	1	2	3	4	5
18. Do you have problems swallowing liquids?	1	2	3	4	5
19. Do you have problems swallowing pureed foods? e.g. applesauce	1	2	3	4	5
20. Do you have problems swallowing solid foods?	1	2	3	4	5
21. Do you have a dry mouth?	1	2	3	4	5
22. Do you have sticky saliva?	1	2	3	4	5
23. Do you have trouble eating?	1	2	3	4	5
24. Do you suffer from constipation?	1	2	3	4	5
25. Do you enjoy your meals?	1	2	3	4	5
26. Do you feel hungry at meal time?	1	2	3	4	5

Appendix 4: Instructions for using the General Labeled Magnitude Scale (GLMS)

The experimenter directed the study participant as follows:
"I am going to ask you to use this rating scale to rate how weak or strong some sensations are to you. Some of these sensations you will experience. Some of these sensations are what you recall experiencing.

This scale ranges from "no sensation" at the bottom to "strongest imaginable sensation of any kind" at the top.

(Experimenter points to the bottom and draws finger up the scale to the top)

"Any kind" means that you can use this scale to judge the strength of any kind of experience – how sweet is the taste, how loud is the sound, or how bright is the light?

"Strongest imaginable" refers to the strength of any kind of experience (such as loudness or brightness), even sensations that might be painful.

Now, please use this scale to rate the brightness of the light in this room. How strong or intense is the brightness to you?

- First, choose the word on the scale that describes how bright. (word _____)

  Is the brightness you experience more than (word) but not (next descriptor above)? Or is the brightness you experience less than (word) but not (next descriptor below)?

  Your rating can fall anywhere on the line between (word) and the next descriptor. Like fine tuning your rating.

• Now, please remember the brightness of a dimly lit restaurant, where the only light is from candles on the tables. Would you say the intensity of a dimly lit restaurant is less bright or brighter than the light in this room? Less bright Brighter

– Choose the word on the scale that describes the brightness of a dimly lit restaurant.

(Experimenter assesses if they pick a word descriptor that matches their assessment of less bright or brighter.)

– Fine-tune your rating.

"Please rate the strength of these recalled or remembered sensations."

1. Loudness of a whisper
2. Loudness of a conversation
3. Loudest sound you have ever heard

Each participant was next tested with three concentrations each of sweet, salty, sour, and bitter tastants. The concentrations were presented at weak, moderate, and strong levels of taste intensity. The order of presentation was systematically varied. Distilled water serves as an additional stimulus, a solvent for the tastants, and was also used to rinse between stimulus presentations.