Effect of Concord Grape Juice on Chemotherapy-Induced Nausea and Vomiting: Results of a Pilot Study

Gail L. Ingersoll, EdD, RN, FAAN, FNAP, Amy Wasilewski, RN, MS, Michele Haller, RN, MS, Kishan Pandya, MD, John Bennett, MD, Hua He, PhD, Claire Hoffmire, BS, and Cynthia Berry, RN, BSN

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Purpose/Objectives: To determine the feasibility of administering a flavonoid-rich adjunctive treatment (Concord grape juice) for the management of chemotherapy-induced nausea and vomiting (CINV); to evaluate the usefulness of existing measures for assessing CINV frequency and severity, quality of life, control over life events, and psychological state; to identify any actual or potential adverse events associated with frequent grape juice intake; and to provide preliminary data concerning the effect of Concord grape juice on CINV, quality of life, perceived control over life events, and psychological state.

Design: Double-blind, randomized clinical trial.

Setting: A cancer center in an academic health science center in the northeastern United States.

Sample: 77 adult patients with cancer receiving moderately or highly emetogenic chemotherapy agents.

Methods: Participants drank 4 oz. of grape juice or placebo prior to meals for one week following each of four chemotherapy treatment cycles. They recorded frequency, duration, and distress of nausea, vomiting, and retching daily, beginning the evening of chemotherapy administration and continuing for seven days. Data were analyzed with generalized estimating equations methodology to model differences between groups over time.

Main Research Variables: Nausea and vomiting frequency, duration, and distress; quality of life; control over decision making; and psychological state.

Findings: Nausea and vomiting frequency, duration, and distress were lower for experimental group members, although a high attrition rate (50%) resulted in insufficient power to detect statistically significant differences over time. Greater levels of anxiety, depression, and hostility at baseline were related to nausea and vomiting, quality of life, and perceived control over decision making.

Conclusions: The effect of grape juice flavonoids on CINV should be investigated further with a larger sample to determine whether preliminary findings are supported. Alterations to the study protocol will be necessary to decrease attrition.

Implications for Nursing: Flavonoid-rich fruits and vegetables may provide additional protection against CINV. If the compounds work, they would offer a low-cost, readily available adjunctive treatment for the management of CINV.

The management of chemotherapy-induced nausea and vomiting (CINV) has improved significantly with the use of selective $5HT_3$-receptor antagonists, which are effective for managing acute nausea (Hesketh, 2008); the more recent addition of neurokinin-1-receptor (NK_1) antagonists, which are more effective for the treatment of delayed nausea (Dando & Perry, 2004; Sanger & Andrews, 2006); and the publication of evidence-based standards of practice (Kris et al., 2006). Even with these combination drugs and the use of the American Society of Clinical Oncology's guidelines (Kris et al., 2006), uncontrolled nausea still is reported in 36% (Waqar et al., 2008) to 59% (Cohen, de Moor, Eisenberg, Ming, & Hu, 2007) of treated patients and in 75% of patients not receiving prophylactic NK_1 antagonist (aprepitant) therapy (Erazo Valle, Wisniewski, Figueroa Vadillo, Burke, & Martinez Corona, 2006).

The mechanisms for CINV are not fully understood, although some theories focus on the relationship between the small intestine's endocrine and enterochromaffin cells, which release serotonin (5-hydroxytryptamin [5-HT]) in response to chemotherapy-related damage to the duodenal mucosa (Saito, Takano, & Kamiya, 2003). The serotonin released from the duodenum binds to vagal afferent $5\text{-}HT_3$ receptors, which then transmit the afferent impulses to the emetic center in the brain (Hogan & Grant, 1997). This process is responsible for early nausea and vomiting during the first 24 hours of drug administration. Delayed nausea and vomiting result from more complex responses and the combined effect of serotonin release and disrupted gut motility (Carelle et al., 2002). Cellular damage and breakdown in the stomach and small intestine also contribute to delayed nausea and vomiting (Baker, Morzorati, & Ellett, 2005).

Absorbed toxic materials circulating in the blood, including those associated with chemotherapeutic agents, also can act directly on the area postrema of the brain where the blood-brain barrier is relatively permeable

and emesis is stimulated. The mechanism for this action is poorly understood, but ablation of the area has resulted in reduced emesis from chemotherapy, radiation, and renal failure (Sanger & Andrews, 2006).

Nonpharmacologic Management of Chemotherapy-Induced Nausea and Vomiting

Nonpharmacologic approaches to the control of CINV have focused primarily on the use of acupuncture or acustimulation and massage or aromatherapy, with mixed results (Ezzo et al., 2006; Oncology Nursing Society, 2008). A few studies have examined progressive muscle relaxation, music therapy, education, support, and ginger therapy, although limitations in sample size and research design make confirmation of the regimens' effects difficult (Oncology Nursing Society, 2008). Another potential adjunctive therapy is oral administration of flavonoids, which are low-molecular-weight polyphenol metabolites of plant origin that have antioxidant properties and other beneficial effects, including bacterial growth inhibition (Jayaprakasha, Selvi, & Sakariah, 2003) and reductions in inflammation (Bhat & Pezzuto, 2002), cell destruction (Shoskes, Jones, & Shahed, 2000), and tumor growth (Sharma, Tyagi, Singh, Chan, & Agarwal, 2004; Singh, Tyagi, Dhanalakshmi, Agarwal, & Agarwal, 2004). In one study, oral administration of grape extract flavonoids to rats resulted in an 82% reduction in gastric mucosa ulceration (Saito, Hosoyama, Ariga, Kataoka, & Yamaji, 1998). Flavonoids also have demonstrated long-term favorable effects on cancer risk (Han, 2007) and have synergistic effects against inflammation and tissue injury when administered in combination with immunosuppressive (Shoskes et al., 2000), antifungal (Zheng et al., 1993), and anticancer agents (Sharma et al., 2004).

As polyphenols, flavonoids act as scavengers of free radicals and inhibit free-radical-mediated damage to cells and tissue (Korkina & Afanas'ev, 1997). They do so by binding to heavy metal ions, which catalyze the processes, leading to the appearance of free radicals (Havsteen, 1983). A number of flavonoids also chelate trace metals and support the body's natural antioxidant defenses (Pietta, 2000).

Reports differ concerning the absorption of flavonoids from dietary sources. Some studies have provided clear evidence of absorption sufficient to support antioxidant capabilities (Hollman, de Vries, van Leeuwen, Mengelers, & Katan, 1995; Pietta, 2000; Spencer et al., 1999), whereas others have suggested that the binding of flavonoids to plasma proteins prevents the possibility of cellular impact (Boulton, Walle, & Walle, 1997). The observed transfer of flavonoids across the blood-brain barrier (Mitsunaga et al., 2000), however, suggests that a cellular-level exchange is possible. Moreover, Hollman et al. (1995) and Hollman and Katan (1998) demonstrated the absorption of 24%–52% of orally administered quercetin (a flavonoid found in moderate to high amounts in grapes and other fruits and vegetables). The study by Hollman et al. (1995) also determined that flavonoid compounds are absorbed most effectively when transported by a glucose carrier, which occurs with the ingestion of an effectively absorbed fruit juice, such as grape juice (Perman, 1996).

The current authors hypothesized that the flavonoids present in Concord grape juice would decrease the severity of chemotherapy-produced cellular damage, thereby reducing the generation of afferent impulses and decreasing the incidence and severity of CINV. To test this hypothesis, they conducted a pilot study of the effect of Concord grape juice on CINV in adults receiving moderately or highly emetogenic agents for the treatment of cancer.

Methods

Design

A double-blind, randomized clinical trial was conducted in a large cancer center within an academic health science center in the northeastern United States. The aims of the study were to: (a) determine the feasibility of administering a flavonoid-rich adjunctive treatment (Concord grape juice) for the management of CINV; (b) evaluate the usefulness of existing measures for assessing CINV frequency and severity, quality of life (QOL), control over life events, and psychological state; (c) identify any actual or potential adverse events from drinking grape juice three or four times per day; and (d) provide preliminary data concerning the effect of Concord grape juice on CINV, QOL, perceived control over life events, and psychological state.

Sample and Setting

Seventy-seven adult patients with cancer without evidence of neurologic involvement; diabetes; head, neck, or brain tumors; pregnancy; bleeding disorders; anticoagulant therapy; allergy to food dyes or grape products; or inability to drink or swallow grape juice or placebo were enrolled. No further exclusion criteria were set based on type of cancer or treatment received. Participants had to be cognitively aware of the study requirements and able to complete self-report forms. The sample size for the study was estimated with repeated-measures estimation techniques and an effect size of 0.8, a significance level of 0.05, and an attrition rate of 20%, resulting in a sample size of 76, or 38 each in the experimental and control groups.

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Instruments

Both groups maintained daily logs in which they recorded the amount of grape juice or placebo consumed. They also completed self-report instruments measuring symptom experience (daily), psychological state (at baseline and final week), QOL (at baseline and final week), perceived control over decision making (at baseline), and perception of cancer treatment experience (final data collection period). In addition, data concerning usual and weekly food intake were collected through a food frequency questionnaire, which listed foods likely to enhance (flavonoid-rich) or hinder (protein-rich) intervention outcome. The tool was reviewed for completeness and accuracy by a nutritionist and modified based on feedback.

Symptom experience (CINV): CINV was measured by the Rhodes' Revised Index of Nausea and Vomiting (INV-R), which assessed all three components of symptom experience (pattern of symptom experience, pattern of symptom distress, and pattern of symptom occurrence) (Rhodes & McDaniel, 1999; Rhodes, Watson, & Johnson, 1984). The eight-item INV-R measures: (a) duration, frequency, and distress associated with nausea; (b) frequency, distress, and amount of emesis associated with vomiting; and (c) frequency and distress associated with retching. Scores for items are summed to provide an overall symptom experience index, with higher scores indicating greater frequency, duration, and distress. Previous versions of the INV-R have been used successfully with patients in oncology, obstetrics, and ambulatory surgery settings (Fetzer, Hand, Bouchard, Smith, & Jenkins, 2004; Rhodes & McDaniel, 1999; Zhou, O'Brien, & Soeken, 2001). Acceptable internal consistency reliability ($\alpha = 0.98$) and concurrent ($r = 0.87$), (Rhodes & McDaniel, 1999), construct, and discriminant validity estimates have been reported (Rhodes, Watson, Johnson, Madsen, & Beck, 1987). Factor analysis findings vary, with some investigators reporting a single factor structure (Fetzer et al., 2004) and others reporting three distinct factors of nausea, vomiting, and retching (Rhodes et al., 1987; Zhou et al., 2001). For the current study, the researchers altered the period covered for the symptom experience from the recommended 12 hours (Rhodes et al., 1984) to 24 hours. This was done to reduce the burden associated with completing a form daily for seven days for each of four treatment cycles.

Flavonoid-enhancing or -depleting food intake: Flavonoid-enhancing or -depleting food intake was measured by food inventories that assessed usual (historical) and current (previous week) intake of flavonoid-rich and high-protein foods (greater than 10 g per standard serving) (Pennington, 1998). This information was collected because diets composed of foods with high flavonoid content may artificially inflate the effect of the grape juice or produce an unintended effect in the placebo group. Diets rich in high-protein foods, on the other hand, may reduce the effectiveness of the grape juice as a result of the tendency of proteins to bind with polyphenols (Hollman et al., 1995). For each food listed, participants circled whether they ate the food never, once a month, once a week, or daily for usual intake; and never, 2–3 times, 4–6 times, or daily for weekly intake (treatment cycles 2, 3, and 4).

Psychological state: Psychological state was measured by the 132-item state form of the Multiple Affect Adjective Checklist, Revised (MAACL-R). The MAACL-R is a widely used measure of anxiety, depression, hostility, positive affect, and sensation seeking (Zuckerman & Lubin, 1985). This instrument was chosen over other anxiety and depression scales because of its inclusion of a positive affect dimension, which contributes on its own to favorable stress response (Folkman & Moskowitz, 2000). Comprehensive reliability and validity testing has been conducted, and internal consistency reliability for the subscales ranges from 0.5 (for the sensation seeking scale) to 0.95 (for the positive affect scale). Anxiety scores on the MAACL-R are negatively associated with patient participation in care. Increased satisfaction with services, on the other hand, is negatively associated with anxiety and depression (Littlefield, Chang, & Adams, 1990).

Perceived control: Perceived control was measured by the seven-item Pearlin and Schooler Mastery Scale, which measures an individual's perception that "life chances" are under personal control rather than the result of fatalistic ruling (Pearlin & Schooler, 1978). The instrument has been used extensively and has a reported coefficient alpha of 0.76. A study by Zautra, Reich, and Newsom (1995) found that the seven items split into two subscales, one that measures control over positive outcomes and one that measures fatalism.

Quality of life: QOL was measured by the McGill Quality-of-Life Questionnaire (MQOL), a 16-item scale measuring subjective well-being and containing four subscales that assess physical symptoms, psychological symptoms, existential well-being, and emotional support. A single-item global assessment scale is included (Cohen, Hassan, Lapointe, & Mount, 1996). Internal consistency reliability estimates range from 0.84–0.87 for the subscales; the overall coefficient alpha is 0.89. The MQOL differs from other QOL scales by its inclusion of an existential component, which is highly predictive of overall well-being (Cohen, Mount, Tomas, & Mount, 1996; Cohen et al., 1997). The existential component focuses on concerns about death, freedom, isolation, and the question of meaning. The instrument developers suggested that this aspect of QOL is important for people with life-threatening illnesses (Cohen, Hassan, et al., 1996).

Perception of the cancer treatment experience: Perception of the cancer treatment experience was measured by an investigator-developed scale derived

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from previous instruments discussed in the literature. Because no comprehensive cancer experience survey was available, the researchers chose to develop their own 25-item scale. The areas included in the survey focused on interpersonal manner of care providers, technical quality of care, accessibility of care, cost, physical environment, availability of resources (Ware, Snyder, Wright, & Davies, 1983), trust in care provider, continuity of care, inclusion in decision making, individualization of care (Radwin, 2000), accuracy and completeness of information provided, and provision of counseling and support (Sitzia & Wood, 1999). A Likert-type format was used to promote consistency of response options across instruments. Several negatively worded items were included to prevent response set and were reverse-coded during data analysis. The scale was reviewed by a panel of experts prior to its use and was determined to be consistent with clinical experience with patients with cancer. Experts were asked to identify the constructs to which the items referred and to recommend changes as needed. Item revisions were made based on feedback.

Procedures

The university's institutional review board approved the study and confirmed the protection of participants' rights. Once approval was obtained, the researchers began enrolling people who met eligibility criteria. All participants were required to sign a consent form prior to randomization to the experimental or control group. Members of the experimental group were instructed to drink 4 oz. of chilled Concord grape juice 30 minutes prior to meals and an additional 4 oz. as needed for nausea. Members of the control group received a placebo that contained no fruit juice and was composed of water, sweeteners, food-grade acids, natural grape essence, and food coloring (personal communication, D. Mark, January 21, 2003). Blind taste-testing was conducted with healthy volunteers at the cancer center prior to the study to ensure that taste differences would not result in unblinding.

Both groups received standard medical management of CINV; the grape juice or placebo intervention served as an adjunct to rather than a replacement for usual CINV therapy. Information about type of cancer, chemotherapy, and prescribed antiemetic medications was extracted from medical records.

Participants were asked to drink the grape juice or placebo for one week following each of four chemotherapy treatment cycles. When they arrived for treatment, they received a week's supply of grape juice or placebo and data collection forms. They were instructed to begin drinking the grape juice or placebo the evening of the treatment day and to record juice intake and symptoms at that time. Participants were encouraged to denote whether they drank all or a portion of the grape juice or placebo and to note whether they drank an additional dose because of nausea. When self-report forms were mailed to the study office, participants were sent a $10 gift card to a local grocery store.

If participants assigned to the experimental group followed the study protocol, grape juice consumption for the week following each chemotherapy cycle was estimated at 84–112 oz. per cycle, resulting in a daily flavonoid intake of 720–960 mg, or 4.8–6.4 times the usual phenolic intake of 150 mg per day (Prior & Cao, 2000). Total weekly flavonoid intake for members of the experimental group was estimated at 5,040–6,720 mg, as compared to 1,050 mg for members of the control group. If participants drank more or less juice than requested in the study protocol, the researchers expected their flavonoid intake to vary accordingly.

Data Analysis

Data analysis consisted of initial descriptive and group comparison techniques (analysis of variance and chi square) to describe the characteristics of the sample and any differences according to group (e.g., age, gender, admitting diagnosis). Instruments also were assessed for internal consistency reliability; more expansive testing was not done because of insufficient sample size.

Initial data analysis procedures were followed by correlations and data displays to examine relationships between nausea frequency, nausea distress, vomiting frequency, vomiting distress, and vomiting amount at different time cycles. The relationships between variables and time cycles also were compared. Generalized estimating equations methodology was used to model differences between groups over time for the five primary outcomes of interest (nausea frequency, nausea distress, vomiting frequency, vomiting distress, and vomiting amount) and the summed adverse event score by including the treatment and the interaction of treatment and time cycle in the model. Treatment by cycle interaction was used to determine whether the differences between groups changed over time. When the interaction was not significant, it was removed from the model. In each of the models, the outcome was treated as continuous and the identity link function was used.

The control group served as the reference, with a negative coefficient for the grape juice group indicating a better outcome than the control group. The coefficient can be interpreted as the number of units increased (for positive coefficient) or decreased (for negative coefficient) in the corresponding outcome for the treatment group.

Results

Seventy-seven people were enrolled in the study, but only 38 (49%) completed all four cycles of the intervention.

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A significantly greater number of experimental group members withdrew (58% versus 41%; p = 0.03). No differences were seen for emetogenicity of chemotherapeutic agent or reason for withdrawal. Patients with a diagnosis of breast cancer had a 50% withdrawal rate; the number of patients with other admitting diagnoses (30%) was too small for comparative analysis. Most of the withdrawals from the study (81%) were patients receiving a combination of doxorubicin and cyclophosphamide, which, in combination, are defined as highly emetogenic (Roila, Hesketh, Herrstedt, & the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer, 2006). Forty-two percent of participants who withdrew were receiving a combination of dexamethasone and granisetron for prevention of CINV. Only 17 (22%) participants (9 who withdrew, 8 who did not) received aprepitant as one of their prescribed antiemetic medications. This is likely a reflection of the time period of the study and the changes in recommended treatment approaches during that time.

Characteristics of participants enrolled in the study were similar between the experimental and control groups. As noted in Table 1, the sample was overrepresented by women, which is reflective of the large breast cancer population treated at the study site. For all but two of the baseline measures (usual protein intake and physical symptom bother over previous two days), characteristics (age, psychological state, perception of control over environment, and QOL) were similar between groups. In the two measures that differed, usual protein intake (p = 0.01) and bother by physical symptoms (p = 0.009), mean scores were greater for members of the control group.

Psychometric evaluation of measures indicated that internal consistency reliability estimates for the subscales were consistent with previous research. The lowest coefficient alphas were noted for the hostility (0.52) and sensation seeking (0.54) subscales of the MAACL-R, which was unexpected in light of the extent of prior research with the scale. Scores for the remaining subscales were within acceptable limits (anxiety = 0.82; depression = 0.76; positive affect = 0.93). Coefficient alphas for control over practice (0.75), QOL (0.86), and the investigator-developed perception of cancer treatment experience (0.8) met minimum reliability estimates (Nunnally, 1978).

An interesting finding with the INV-R was the variation in coefficient alpha according to day of measurement. As the frequency of nausea and vomiting increased, the scale became more internally consistent. On day 1 of the cycle, the alpha was 0.71; on day 2, it rose to 0.75, and on day 3, it was 0.84. This finding is likely related to the increased association between item dimensions (i.e., those who were vomiting also were reporting nausea and retching and were distressed by each symptom) and the increased distress when symptoms persisted for more than one day.

Table 1. Sample Characteristics

	Grape Juice (N = 40)		Placebo (N = 37)	
Variable	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**
Age (years)	54.1	12.4	54.5	12.7
Variable	**n**	**%**	**n**	**%**
Gender				
Female	32	80	30	81
Primary admitting diagnosis				
Breast cancer	27	68	27	73
Lung cancer	3	8	2	5
Lymphoma	1	3	4	11
Non-Hodgkin lymphoma	3	8	1	3
Prostate cancer	–	–	2	5
Colon cancer	1	3	1	3
Other[a]	5	13	–	–
Chemotherapy regimen[b]				
Doxorubicin	29	73	27	73
Cyclophosphamide	20	50	27	73
Rituximab	4	10	4	11
Docetaxel	1	3	6	16
Carboplatin	2	5	3	8
Paclitaxel	3	8	1	3
Vincristine	2	5	2	5
Cisplatin	3	8	–	–
Etoposide	3	8	–	–
Other (one each per drug)	8	20	5	14
Antiemetic regimen[b] (in descending order of frequency [total for both groups])				
Dexamethasone	36	90	30	81
Granisetron	33	83	28	76
Prochlorperazine	26	65	19	51
Aprepitant	9	23	8	22
Lorazepam	4	10	4	11
Ondansetron	6	15	1	3
Diphenhydramine	2	5	4	11
Cimetidine	2	5	3	8
Palonosetron	2	5	–	–
Total number of cycles enrolled in study				
1 or fewer	18	45	10	27
2	3	8	2	5
3	2	5	3	5
4	17	43	22	60
Reasons for withdrawing[c]				
Nausea	9	43	5	36
Indigestion or gastrointestinal distress	4	19	4	29
Sweetness of drink	4	19	2	14
Difficulty remembering or demands of study	2	10	2	14
Other adverse event (nonrelated)	2	10	1	7

[a] One each for acute myeloid leukemia, metastatic melanoma, hairy cell leukemia, urethral cancer, and gastrointestinal cancer

[b] Some members of the experimental and control groups were receiving more than one chemotherapeutic agent and/or more than one antiemetic regimen simultaneously.

[c] 39 participants did not complete the study, and 4 of them did not provide a reason for withdrawal.

Note. Because of rounding, not all percentages total 100.

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Thirty-four percent of the people enrolled in the study reported nausea on one or more days following administration of chemotherapy. This was despite the administration of two antiemetic drugs to 94% (n = 72) and three antiemetic drugs to nearly half. Moreover, the nausea persisted until day 7 (n = 15), with the greatest numbers of episodes reported on days 2 (n = 26), 4 (n = 19), 5 (n = 19), and 6 (n = 20). Only four vomited (5%), 3 from the experimental group and 1 from the control group. Potential intervention-related adverse events in the study included infrequent reports of gastric distress or indigestion (n = 7). No other adverse reactions were described.

Initial analyses of clinical outcomes showed some differences according to group over time. Because of attrition, however, statistically significant differences were not seen for the majority of outcomes. Analyses indicated that, compared to the control group, the grape juice group exhibited a reduction in mean response for nausea frequency, nausea distress, and vomiting distress. On average, the grape juice treatment reduced 0.64 time of nausea frequency, 0.98 unit of nausea distress, 0.11 unit of vomiting distress, and 0.33 unit of vomiting amount. Although not attaining statistical significance, the treatment effects were all in the hypothesized direction. Only one outcome produced unexpected results: Vomiting frequency increased 0.13 time for members of the experimental group.

Low positive correlations were seen between total number of days in which nausea occurred and baseline MAACL-R anxiety ($r = 0.32$; $p = 0.005$), depression ($r = 0.35$; $p = 0.002$), hostility ($r = 0.25$; $p = 0.03$), and dysphoria ($r = 0.37$; $p = 0.001$) scores, suggesting that the number of days with nausea was related to a negative psychological state. A trend was seen for depression and total number of days with vomiting ($r = 0.21$; $p = 0.06$). Scores for the MAACL-R's three positive indicators (positive affect, sensation seeking, and positive affect/sensation seeking) were not related to nausea and vomiting. A low negative and significant relationship was seen between the total number of days nauseated and QOL ($r = -0.25$; $p = 0.03$). No relationship was seen between usual and weekly food intake and CINV. However, a moderate and positive relationship was seen between flavonoid and protein intake ($r = 0.54$; $p < 0.0001$), suggesting that participants who ate diets rich in flavonoids also ate diets rich in proteins.

Some differences for psychological distress were seen between the experimental and control groups, with levels of anxiety and depression higher for members of the control group at the final data collection point (see Table 2). These findings were supported by individual ratings within the MQOL: Members of the experimental group rated extent of depression, nervousness, and sadness lower than members of the control group; they also rated their perception of the future as higher. None of the differences was statistically significant, however. The differences for positive affect score and for perception of cancer treatment experience were small.

Discussion

Findings from this small pilot study are useful for determining whether to proceed to a more expansive study of the effect of Concord grape juice on CINV. Although the withdrawal rate was high, the information obtained can be used to prepare for a larger, full-scale study. The pilot study also demonstrated that the instruments used to collect data are sensitive to differences within and across groups and are understandable by patients with cancer undergoing treatment.

Of note in this pilot study is the finding that 34% of the participants experienced nausea over the course of their treatment experience and that many of them reported episodes of delayed nausea and vomiting. These numbers are consistent with published reports of frequency (Hesketh et al., 2003) and delayed response (Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Dibble, Israel, Nussey, Casey, & Luce, 2003; Grunberg et al., 2004) and suggest that, despite recent changes to the management of CINV, nausea and (to a lesser extent) vomiting persist.

Although the differences between groups in CINV frequency, severity, and distress were not significant, the differences were in the hypothesized direction. Experimental groups had a slightly lower level of frequency, severity, and distress during their second, third, and fourth chemotherapy treatments. Additional research is needed to determine whether significant differences can be seen with a sample of sufficient size to detect differences across groups.

The reason for the significant differences between control group and experimental group anxiety and depression scores at the final data collection point is unknown. These outcome indicators, which were assessed with a more finite tool than the instrument used to measure CINV, may be an important distinguisher between favorable and unfavorable cancer treatment experience. The negative relationships between psychological state (i.e., level of anxiety, depression, and hostility) and QOL and overall treatment experience are consistent with published reports in the literature (Ballatori & Roila, 2003; Bloechl-Daum et al., 2006; Chou, Lin, Cooney, Walker, & Riggs, 2003; Colagiuri et al., 2008). Because the psychological and QOL variables were collected prior to the reporting of CINV, these factors appear to be potential predictors of nausea and vomiting following administration of chemotherapeutic agents.

The unexpected increase in the coefficient alpha for the INV-R over time is consistent with the findings of a study by Zhou et al. (2001), in which the distress

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Table 2. Comparison of Experimental and Control Group Findings

Variable	Grape Juice (N = 40) $\bar{X}$	SD	Confidence Interval	Placebo (N = 37) $\bar{X}$	SD	Confidence Interval	p
Chemotherapy-induced nausea and vomiting[a]							
Week 1	1.6	2.3	0.5–2.6	1.7	2.7	0.6–2.8	0.84
Week 2	1.7	2.2	0.6–2.8	2.1	3.4	0.6–3.5	0.71
Week 3	0.9	2	–0.2–2.1	1.7	2.3	0.7–2.7	0.29
Week 4	1.6	2.3	0.3–2.9	2	3	0.5–3.5	0.67
Baseline anxiety	2.4	2.5	1.5–3.2	3.3	2.8	2.3–4.2	0.13
Final anxiety	0.19	0.75	–0.2–0.6	2.3	2.8	1.2–3.5	0.005
Baseline depression	0.4	1.2	0–0.8	0.8	1.3	0.4–1.3	0.11
Final depression	0	0	0	0.83	1.3	0.3–1.4	0.02
Baseline positive affect	9.9	6.6	7.8–12	9.8	6.7	7.6–12	0.94
Final positive affect	11.5	5.2	8.8–14.2	10.2	6.5	7.5–12.9	0.49
Baseline perceived control	3.4	0.5	3.3–3.6	3.4	0.1	3.2–3.6	0.67
Baseline quality of life	7.8	1.3	7.4–8.2	7.7	1.2	7.3–8.1	0.74
Final quality of life	8.1	0.54	7.9–8.4	7.6	1.3	7.1–8.2	0.13
Final perception of cancer treatment experience	3.8	0.22	3.6–3.9	3.7	0.25	3.6–3.8	0.54

[a] Lower overall mean score indicates less frequency, duration, and distress. Range = 0–4.

associated with symptoms was dependent upon the degree of symptom severity. In the current study, the presence of symptoms increased over time, resulting in the symptoms being perceived as more severe and the level of distress rising as well. The relationships between the measures became more internally consistent, resulting in the higher alpha.

Limitations

The most serious limitation of this study is the high attrition rate over time, which resulted in insufficient power to detect differences between groups. The researchers originally used an effect size of 0.8 when estimating sample size and ended up with effect sizes that ranged from 0.03–0.61. With an attrition rate greater than 50%, the researchers would have needed 200 members per group to have sufficient power to detect significant differences.

Although no differences were seen between the baseline characteristics and treatment regimens for those who stayed and those who left, the dropout rate suggests that either the intervention itself was undesirable or participation in the study was too much of a burden. Several participants reported that the demands of the study, in combination with everything else they were experiencing, were too much for them to handle, resulting in their withdrawal. A few participants commented that the sweetness of the juice or placebo made it difficult to drink when they were nauseated. This problem may necessitate the use of an alternate form of grape flavonoids (e.g., tablet, capsule) if the taste of the juice or placebo is unacceptable when patients experience any nausea or vomiting.

The second limitation is the study's reliance on self-report measures, which may have resulted in participants over- or under-reporting symptoms and juice or placebo intake and their responding in socially acceptable ways. However, because of the frequency of data collection and the need to assess participants' perceptions as well as response to intervention, this approach was deemed most reasonable. In addition, the variation in responses across participants suggests that the measures served the purpose of gathering information from participants who received a home-based daily intervention.

The third limitation is the use of a time frame (24 hours) for recording CINV that differed from the INV-R tool developers' recommended 12 hours (Rhodes et al., 1984). The time difference may have altered the validity of the scale, although the original testing of the tool did not clarify the effect of time period on validity estimates. Consequently, the authors do not believe that the 24-hour versus 12-hour time frame adversely affected the data obtained.

The fourth limitation is participant enrollment at a single cancer center, which may have resulted in the investigation of a nonrepresentative group of patients with cancer in general. Indeed, the sample's overenrollment of women receiving treatment for breast cancer

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suggests that the study is limited in its generalizability to the target setting and to the population of patients with cancer as a whole. Further research is planned with additional cancer treatment locations to address this concern.

Conclusion

The findings of this small pilot study suggest that continued investigation of the effect of flavonoids on CINV is warranted. The importance of psychological state also demands further exploration of its effect on the measures used to address CINV and other cancer treatment outcomes.

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Gail L. Ingersoll, EdD, RN, FAAN, FNAP, is the director of the Clinical Nursing Research Center and the Loretta Ford Professor of Nursing, and Amy Wasilewski, RN, MS, is a clinical nurse specialist in ambulatory nursing, both at the University of Rochester Medical Center in New York; Michele Haller, RN, MS, is a nurse manager in the Ambulatory Oncology Center, Kishan Pandya, MD, is the medical director of the Hematology/Oncology and Clinical Trials Office and a professor of medicine, and John Bennett, MD, is a professor of medicine, all at the James P. Wilmot Cancer Center in Rochester; Hua He, PhD, is a research assistant professor in biostatistics and computational biology at the University of Rochester Medical Center; Claire Hoffmire, BS, is a doctoral student in Community and Preventive Medicine at the University of Rochester; and Cynthia Berry, RN, BSN, is a nurse leader at the University of Rochester Medical Center. The grape juice and placebo for this study were provided by Welch Foods Inc. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Ingersoll can be reached at gail_ingersoll@urmc.rochester.edu, with copy to editor at ONFEditor@ons.org. (Submitted January 2009. Accepted for publication May 24, 2009.)

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