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Effect of Oral Cryotherapy on Combination Chemotherapy-induced Oral Mucositis: A Randomized Clinical Trial

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Abstract

Background: This study assesses the effect of oral cryotherapy on the incidence and severity of chemotherapy-induced oral mucositis in combined chemotherapy regimens.

Methods: This was a randomized controlled trial that enrolled 80 cancer patients. We evaluated the primary oral status of all patients prior to chemotherapy. Patients were divided into two groups, experimental and control. The experimental group was given ice to place in their mouths from 5 min before to 5 min after chemotherapy.The control group received no intervention. Both groups were treated with the following chemotherapy regimens: i) 5- fluorouracil + leucovorin; ii) cyclophosphamide + adriamycin + 5-fluorouracil; or iii) cyclophosphamide + methotrexate + fluorouracil. World Health Organization and patient-based oral mucositis scales were used for evaluation.

Results: According to the WHO based Oral Mucositis Scale, the incidence of oral mucositis in the intervention group (45%) was significantly lower than the control group (77.5%; *P*=0.01). The incidence of oral mucositis in the intervention group based on the Patient-Judged Oral Mucositis Scale was lower than the control group. The findings of this study indicated that patients who underwent cryotherapy had less severe oral mucositis based on both WHO (*P*=0.01) and patient oral mucositis scales (*P*=0.001).

Conclusion: Oral cryotherapy because of its ease of application, tolerability and lack of side effects makes it an important resource for reducing the incidence and severity of oral mucositis. The role of oncology nurses is crucial to the application and success of oral cryotherapy.

Keywords: Oral cryotherapy, Oral cooling, Mucositis, Stomatitis, Chemotherapy

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Introduction

Oral mucositis (OM) is a common complication of cancer therapy. Mucositis results from damage to the mucosal epithelium after delivery of chemotherapy or radiation designed to treat the cancer.[1] Under normal conditions, oral mucosa and normal saliva activity are two important barriers that prevent invasion by microorganisms.Nevertheless, in the presence of chemotherapic drugs this barrier becomes disrupted.

Oral mucositis disrupts the function and integrity of the oral cavity, which affects functional status and quality of life.[2,3] Oral mucositis is linked to clinical morbidity, pain, malnutrition, and local and systemic infections.[4] Treatment delays and dosage adjustments can also occur resulting in dose reductions in subsequent cycles of chemotherapy or even discontinuation of treatment. Dose reductions have been seen in 60% of patients and discontinuation of regimens in about 30%.[5]

The type of chemotherapeutic agents that are used, the specific dose, route, and frequency of administration, and whether the chemotherapy is given as monotherapy or in combination with other agents and modalities of treatment significantly affect the degree of injury.[6]

Various chemotherapy cycles and previous exposure to chemotherapy agents increases the risk of oral mucositis.[7] Chemotherapy for the treatment of solid tumors such as breast and colorectal leads to the development of mucositis in 5% to 40% of patients. Of these, 5% to 15% have WHO grades 3 to 4 mucositis.[6] Chemotherapy drug regimens such as 5-fluorouracil(5-FU)have a high rate of mucositis (20%–50%), as domethotrexate (MTX) and other antimetabolites which have 20%–60% rates of alimentary tract mucositis, in particular OM.[8]

Several methods have been proposed for preventing chemotherapy-induced oral complications.[9] The revision of the Multinational Association of Supportive Care in Cancer, 2007 (MASCC) guideline has recommendations for the use of palifermin for OM associated with stem cell transplantation, amifostine for radiation proctitis, and cryotherapy for mucositis associated with high-dose melphalan.[10] In addition, there have been several reports of reduced chemotherapy-induced OM by cryotherapy.[3,11-19]

Oral cryotherapy is the application of ice chips or ice-cold water to the mouth. Oral cryotherapy for chemotherapy-induced OM requires that patients suck on ice chips before, during, and after infusions of mucotoxic drugs.[4] The theory underlying oral cryotherapy is that ice can constrict the blood vessels of the oral cavity membranes, therefore decreasing exposure of the oral mucosa to mucotoxic agents.[1,4,16,19-21] Cryotherapyis the most conventional and easy-to-use preventive method, at least for 5-FU-based bolus therapy, and appears to have implications for other chemotherapy regimens as well, such as edatrexate and melphalan.[22] Studies have provided support for the use of cryotherapy with high-dose melphalan.[1,11,18,20] According to a report of the ESMO Guidelines Working Group, oral cryotherapy (30 min) is recommended for the prevention of OM in patients receiving bolus 5-FU chemotherapy [II, A] and 20-30 min of oral cryotherapyis suggested to decrease mucositisin patients treated with bolus doses of edatrexate[IV, B].[8] For oral cryotherapy, the effectiveness is limited to single chemotherapy agents that have a short half-life. The majority of evidence to date is for 5-FU and high-dose melphalan. To date, this simple method has not been used in combination chemotherapy regimens such as5-FU with leucovorin (MAYO); the combination of cyclophosphamid, adriamycin and 5-fluorouracil (CAF); or the combination of cyclophosphamid, methotrexate and fluorouracil (CMF).

According to the results of systematic reviews by Worthington et al. in 2007 and 2010, several interventions have been found to be somewhat beneficial at preventing or reducing the severity of mucositis associated with cancer treatment. However the strength of the evidence was variable and implications for practice include consideration that the benefit of cryotherapy may be specific for certain cancer types and treatments. According to

Worthington,"There is a need for well designed and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent".[23,24] There is a lack of studies that report on the use of cryotherapy in patients who undergo combined chemotherapy regimens. In addition, in the nursing literature related to mucositis management, standard treatment and maintenance practices for mucositis prevention are quite limited. Yet, as the primary caregivers for the patients, nurses should have a central position in the prevention and management of mucositis.

This study was conducted to evaluate the effectiveness of cryotherapy to reduce the incidence and severity of chemotherapy-induced OM in patients treated with the combination chemotherapy regimens, MAYO, CAF and CMF. The hypothesis underlying this study was that a preventive oral cryotherapy systematically applied to cancer patients during chemotherapy would reduce the occurrence of oral ulcerative lesions, and alleviate the severity of OM and OM-related pain.

Materials and Methods

Research design

This study was a randomized, controlled clinical trial that consisted of two groups, experimental (EXP, n=40) and control (CTR, n=40). Randomization was performed by the use of a random numbers table, which gave an equal chance for patients to be assigned to either the EXP or CTR group. In order to ensure homogeneity of patients participating in the study, a questionnaire was administered prior to the application of cryotherapy. The questionnaire included sociodemographic, individual, illness-specific features, and oral cavity status. Variables controlled through homogeneity included ethnicity (all were Iranian), cancer type (all were breast or colorectal), course of chemotherapy (all were in the first course) and number of patients in each group (n=40 for each group).

This study examined the administration of ice chips to the oral cavity of the EXP group before, during, and after intravenous administration of chemotherapy. The primary objective was to determine whether the use of oral cryotherapy could reduce the incidence of chemotherapy-induced OM. The secondary objective was to determine whether the use of oral cryotherapy could reduce the severity of chemotherapy-induced OM.

Table 1. World Health Organization mucositis grades.

Description	Grade
None	0
Erythema, painful ulcers, mild sore throat	1
Painful erythema, painful ulcers, edema of the oral mucosa, but able to eat solid food	2
Painful erythema, painful ulcers, painful edema of the oral mucosa that interferes with eating solid food	3
Need for parenteral or enteric support due to very severe stomatitis	4

Sample and setting

This study was conducted from March 2007–April 2008 with cancer patients (breast and colorectal) who received outpatient chemotherapy at two oncology hospital chemotherapy units affiliated with Mashhad University of Medical Science (MUMS) in Iran, after Institutional Review Board approval. Patients were provided with informed consent for the study using a protocol and consent forms approved by the Research Ethics Committee of MUMS. A total of 80 patients with pathological diagnoses of breast and colorectal cancer who were under combination chemotherapy with MAYO, CAF and CMF regimens were enrolled. The Mayo regimen consisted of 5-FU at a dose of 425 mg/m^2 and leucovorin at a dose of 25 mg/m^2 for five consecutive days, to be repeated every 28 days. The CAF regimen consisted of cyclophosphamid(500 mg/m^2), adriamycin(50 mg/m^2) and 5-FU(500 mg/m^2) for the first day of the cycle, which was repeated every 21 days. The CMF regimen consisted of cyclophosphamid(600 mg/m^2), MTX(40 mg/m^2) and 5-FU (600 mg/m^2) administered on the first day of the cycle and

Table 2. Demographic characteristics.

Properties		Control group N (%)	Cryotherapy group N (%)	Total N (%)	test
Age (years)	Mean (SD)	63.25 (15.06)	59.50 (12.35)	61.37 (13.81)	T=1.217, df=78, *P*=0.227
	Min-max	32-88			
Tooth status	Artificial	16 (40)	17 (42.5)	33 (42.2)	X=2.741, Df=2, *P*=0.253
	Natural	16 (40)	20 (50)	36 (45)	
	Partial	8 (20)	3 (7.5)	11 (13.7)	
Smoking habit	Yes	16 (40)	13 (32.5)	29 (36.3)	X=0.487, Df=1, *P*=0.485
	No	24 (60)	27 (67.5)	51 (63.7)	
Mouthwash use	None	19 (47.5)	16 (40)	35 (43.7)	MannWhitney, Z= 1.251, *P*=0.792
	One or more	21 (52.5)	24 (60)	45 (56.2)	
Brushing habit	None	17 (42.5)	17 (42.5)	34 (42.5)	MannWhitney, Z=1.521, *P*=0.946
	One or more	23 (57.5)	23 (57.5)	46 (57.5)	
Malignancy	Colorectal	18 (45)	22 (55)	40 (50)	X=0.800, Df=1, *P*=0.371
	Breast	22 (55)	18 (45)	40 (50)	
Regimen	CMF	5 (12.5)	6 (15)	11 (13.7)	X^2=1.353, Df=2, *P*=0.508
	CAF	17 (42.5)	12 (30)	29 (36.2)	
	MAYO	18 (45)	22 (55)	40(50)	

repeated every 28 days. Mean infusion times were as follows: CAF- and CMF-based regimens (25 to 35 min) and Mayo regimen (about 20 min).

Eligibility criteria included the following: i) ability to undergo the standard dose of chemotherapy regimens; ii) normal laboratory levels that included complete blood counts (CBC); iii) normal kidney and hepatic function as evidenced by liver (ALT and AST) and renal function tests (BUN and Cr); and iv) the patient or his/her primary caregiver must be able to read and write.

Patients were excluded if: i) they previously underwent their first round of chemotherapy; ii) did not undergo a combined course of chemotherapy; iii) were treated with head and neck radiotherapy; and iv) were diabetic.

Tools

The questionnaire and tools used for collection of data in this study included a data collection form, WHO Mucositis Scale (Table 1), Patient-Judged Mucositis Grading, and Oral Assessment Guide (OAG).

Data collection form

The data collection form was developed by researchers following an extensive, relevant literature review of OM and chemotherapy. This form was comprised of demographic data, factors that affect OM, disease-specific properties and questions about the patient that might influence the development of OM after chemotherapy. A committee of experts that included two oncologists, two dentists, and two nurses assessed content validity of the data collection form, which was determined to be 0.89.The items included in the form were as follows: age and sex of the patient, systemic diseases, oral prosthesis, smoking and drinking status, caries, periodontal diseases, regular brushing habits, mouth dryness and the status of the sensation of taste, inappropriate nutritional habits, daily liquid consumption, weight, diarrhea and vomiting status, other medications and laboratory findings.

World Health Organization (WHO) Mucositis Scale and Patient-Judged Mucositis Grading Scale

One of the simplest established grading systems that incorporates both subjective and objective criteria is the WHO grading system.[25] The validity of the WHO Mucositis Scale has been established in several studies.

The Patient-Judged Mucositis Grading Scale is a modified version of the WHO Mucositis Scale

originally developed by Mahmood et al.[16] in the US and has also been used by Papadeas[17] and Karagozoglu.[15] It involves consideration of the general physical and nutritional status of the patient as well as an inspection of the oral cavity. Patient-judged mucositis grades have been used to measure the incidence and severity of OM. This scale has been prepared for daily recording by patients of both groups and used from the first until the last day of the initial chemotherapy course. Its content is the same as the WHO scale, however the phrases have been modified for patient comprehension. Patients recorded their daily symptoms. At the end of the first course of chemotherapy, this questionnaire was collected and the maximum score considered as the mucositis grade.

Oral Assessment Guide (OAG)

Eilers' OAG uses eight categories to assess chemotherapy-related changes: voice, swallowing, lips, tongue, saliva, mucous membranes, gingival, and teeth or dentures. Assessment changes are graded on a severity scale of 1–3, with 3 being the worst. The total score on the OAG ranges from 8, which is normal for all categories, to 24, which signifies breakdown in all categories.[26] We have used this tool to assess the oral status of all patients before the intervention. The validity of OAG has been established in several studies.

Reliability of tools

We conducted a pilot study with 20 randomly selected participants. Inter-rater reliability was used for reliability assessments of the WHO Mucositis Scale, Patient-Judged Mucositis Grading Scale and OAG. Four trained research assistants (two committee members) and two dentists were used for data collection. To establish the level of agreement on OM assessment, all research assistants examined 20 patients. Respectively, inter-rater reliability by intra-class correlation coefficient was established at 0.86 for the WHO Mucositis Scale, 0.78 for the Patient-Judged Mucositis Grading Scale, and 0.83for OAG.

Table 3. WHO Mucositis Grading result.

Result Group	None	Oral mucositis	Total
	N (%)	N (%)	N (%)
Study(EXP)	22 (55.0)	18 (45.0)	40 (50.0)
Control (CTR)	9 (22.5)	31 (77.5)	40 (50.0)
Total	31 (38.8)	49 (61.2)	80(100.0)

Chi-square=8.901, df=1, *P*=0.003

Administration of cryotherapy

The cryotherapyice chips used were prepared in a manner that would not cause irritation to patients' oral cavities and could easily be moved to every corner of the mouth. The ice chips were given to the patients in the EXP group from 5 min before until 5 min after chemotherapy (mean time: 20 – 45 min). Cryotherapy was maintained depending on the characteristics of the chemotherapy protocol and the duration of infusion. This timeline was determined based on the half-lives of the drugs.[15,17,27] Patients were informed of the importance of keeping the oral cavity constantly cool. As the ice chips melted they were replaced by new ones. Cryotherapy was used in patients who received the MAYO regimen during the initial five days of chemotherapy. Cryotherapy was used before, during and after the drug infusion. If the patients had any prosthetic teeth, they were asked to remove them before cryotherapy. Oral cryotherapy was well-tolerated and the majority of patients reported that they managed to keep their oral cavities constantly cooled for most of the chemotherapy treatment.

Procedures

Before the first chemotherapy course, the investigator completed the data collection form after face-to-face interviews with all study participants, after which OAG was used to evaluate oral status prior to chemotherapy. In this study, oral cryotherapy was used for only one cycle of chemotherapy. Nurses and patients both assessed mucositis through the first cycle of chemotherapy (one month). Patients were instructed on the daily assessment and grading of their oral cavity status. Signs and symptoms were documented on the Patient-Judged Mucositis

Grading form, which was given to the patients. Forms were collected when patients returned for their second course of chemotherapy. The WHO Mucositis Scale was used to make an oral evaluation for mucositis in patients. Studies have shown that symptoms of mucositis develop 5-10 or 7-14 days following chemotherapy, and decrease within 2-3 weeks after chemotherapy. In this study, we assessed patients who underwent the single-day course of chemotherapy on days 7, 14, and 21; those who underwent chemotherapy for five consecutive days were assessed on days 1 through 5, 14, and 21 days after chemotherapy.

Ethical consideration

Written informed consent was initially obtained from the patients for their participation in the study, prior to administration of the questionnaires. Participation was voluntary and patients could withdraw from the study at any time. Approval was obtained from the Ethics Committee of the Mashhad University of Medical Science.

Data analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS), version 15.0. Descriptive statistics using frequency (%) and mean (SD) were employed to summarize the socio-demographic and clinical characteristics, as well as the intensity of oral dysfunction. Differences in oral dysfunction and distress by cancer site and type of cancer therapy were analyzed through Kruskall–Wallis tests (chi-square and *P*-value) and paired comparisons (post hoctests) were computed by using Mann–Whitney U-tests (Z and *P*-value). A nominal significance level of 5% was used. In the WHO Mucositis Scale and Patient-Judged Mucositis Grading scores from 0 to 4 were used: 0 (lack of mucositis), 1 (mild), 2 (moderate), 3 and 4 (severe).

Results

Patient characteristics

A total of 80 patients were enrolled. There were no differences in terms of age, sex, BMI, educational status, teeth status, treatment regimen, and malignancy between both groups. Patients' mean age was 61.37±13.81 years and BMI was 24.93. There were 60% female patients and 36.3% of patients were smokers. Patients had the following characteristics: loose teeth (31.3%), broken teeth (41.3%), and good oral health (31.3%). In the EXP group, 65% had poor oral hygiene. Table 2 shows some of the properties in the two comparison groups.

(Table 2: Demographic characteristics of the participants)

Table 4. Patient-Judged Mucositis grading result.

Result			
Group	**None**	**Mucositis**	**Total**
	N (%)	N (%)	N (%)
Study	24 (60.0)	16 (40.0)	40 (50.0)
Control	11 (27.5)	29 (72.5)	40 (50.0)
Total	35 (43.8)	45 (56.3)	80 (100.0)

Chi-square=8.584, df=1, *P*=0.003

Because of the importance of concurrent medication in oral mucosal status, all patients were assessed and classified according to their current medication usage. There were 50% who reported they took no additional medications. However, other participants reported taking the following classes of medications: anti-seizure medications and sedatives (6%); anti-hypertensives (17%); and anti-histamines (4%). The remainder of participants (13%) stated they did not regularly take medications. According to the chi-square test, there was no difference between the two groups (*P*=0.161).

Oral cryotherapy was well tolerated. Although 8(20%) patients complained of chills during oral cryotherapy, there was no discontinuation of therapy.

Incidence and severity of mucositis

Based on the WHO Mucositis Assessment Scale, 61.2% of patients suffered from mucositis. According to the Patient-Judged Mucositis Grading Scale, 56.2% of patients had mucositis. There was no grade 4 mucositis in either group based on both grading scales. According to the WHO Mucositis Assessment Scale, 55% of patients were free from OM in the EXP group compared with 22.5% in the CTR group, which was statistically significant according to the chi-

square test(Table 3; *P*=0.001).

(Table 3: WHO mucositis assessment scale Result)

According to the Patients-Judged Mucositis Grading Scale, the percentage of patients who did not suffer from mucositis was significantly higher in the EXP group. The rate of patients with mucositis was 40% in the EXP group compared to 77.5% in the CTR group, which was statistically significant (Table 4; *P*=0.01).

(Table 4: Patient- Judged Mucositis Grading Result)

According to the WHO Mucositis Assessment Scale, 20% of patients had grade 3mucositisin the EXP group and 40% in the CTR group. The difference between both groups was statistically different (Table 5; *P*=0.01).

(Table 5: mucositis severity in WHO Mucositis Grading scale)

According to the Patient-Judged Mucositis Grading Scale, the rate of patients with mucositis grade 3 was 20% in the EXP group and 47.5% in the CTR group, which was statistically significant (Table 6; *P*=0.001).

(Table 6: mucositis severity in Patient- Judged Mucositis Grading Result)

Table 5.Mucositis severity according to WHO Mucositis.

	Grading Scale		
Group	**Study**	**Control**	**Total**
Severity	N (%)	N (%)	N (%)
0 and 1	22 (55.0)	9 (22.5)	31 (66.3)
2	10 (25)	15 (37.5)	25 (43.7)
3	8 (20.0)	16 (40.0)	24 (30.0)
Total	40 (100.0)	40 (100.0)	80 (100.0)

Mann-Whitney: Z=3.097, *P*=0.002

Discussion

Oral mucositis is a major complication of antineoplastic drug therapy that affects patients' quality of life, morbidity and mortality as well as the cost of caring for patients with cancer. Cryotherapy, reportedly, has been helpful in reducing the incidence and severity of chemotherapy-induced mucositis due to reductions in mucosal blood flow during chemotherapy administration.

In the present study, oral cryotherapy during chemotherapy was assessed. Based on the WHO scale, the incidence of mucositis was 61.2% and the rate of grade 3 mucositis was 20% in the EXP group and 40% in the CTR group. Based on the Patient-Judged Mucositis Grading Scale, the incidence of mucositis was 56.2% and the rate of grade 3 mucositis was 20% in the EXP group and 47.5% in the CTR group. Based on both grading scales, there was no grade 4 mucositis noted. The results of this study demonstrated that the incidence and severity of chemotherapy-induced mucositis in the cryotherapy group decreased based on both scales, which confirmed earlier research.[1,3,12-17,19]

According to studies oral cryotherapy significantly decreased the incidence and severity of chemotherapy-induced stomatitis.[15,17] A Svanberg study showed that patients who received oral cryotherapy had less evidence of mucositis, decreased use of i.v. opioids, decreased hospitalization time, need for less total parenteral nutrition and increased levels of S-albumin.[3,12]

In contrast, the result of a study by Gori stated that cryotherapy during MTX administration did not reduce severe OM in patients who underwent myeloablative allergenic HSCT(Hematopoietic Stem Cell Transplantation).[28] The reason oral cryotherapy did not seem to help MTX-induced mucositis was probably related to the long half-life of MTX, as opposed to the shorter half-life of other agents. Presumably, this was a consequence of a different causative mechanism for mucositis in patients who have undergone bone marrow suppressive chemotherapy. In bone marrow suppressive regimens, mucositis occurs because of a decrease in blood nutrophil levels (neutropenia) and pervasion of mouth flora across the broken epithelial barrier that causes infection and mouth soreness (indirect mucositis).[29,30]

Oral mucositis can be exacerbated when chemotherapy drugs are given in high doses and frequent repetitive schedules, and can be even more damaging when they are given in combinations with other chemotherapeutic agents or ionizing irradiation.[31]

In the present study, the percent of patients treated with the various regimens in the EXP group was as follows: Mayo (55%), CAF (30%),and CMF(15%). The percent of patients treated with the various regimens from the CTR group were: Mayo (45%), CAF (42.5%) and CMF (12.5%) but the difference was not statistically significant between the groups (Table 2). In these regimens, because of drug synergy, oral mucosal toxicity can rise and therefore the rate of mucositis was higher in CTR group. In contrast, the rate of mucositis in the EXP group was 50% percent less than the CTR group. We applied ice chips for 30-60 min; this time course was determined according to the agent's plasma half-life. According to previous reports of patients who received cryotherapy following standard dose chemotherapy it has been shown that increasing the time of application did not lead to greater protection.[15,17,27,32] The optimum duration and intensity of cryotherapy requires further investigation.

Patients with poor oral hygiene are more susceptible to mucositis and have longer recovery times. Dodd has assessed mucositis risk factors and observed increased mucositis in patients with poor oral hygiene.[33] In the current study, 45% of patients in the EXP group had mucositis. There were 65% of patients in the EXP group with poor oral hygiene, whereas 76.4% of patients that had poor oral hygiene also had mucositis. Therefore, based on the Dodd study, one cause for mucositis in the cryotherapy group was possibly poor oral hygiene.

Conclusion

Due to its ease of application, tolerability, and lack of side effects, oral cryotherapy is recommended for alleviating and decreasing the incidence of mucositis and its severity. This recommendation is congruent with the Multinational Association of Supportive Care in Cancer (MASCC) guidelines.[9,24,34]

Nursing Implication: In consideration of the valid body of knowledge about oral cryotherapy, it is time for applying them to the practice and oncology nurses are crucial to application of the evidence in those areas. Nurses caring for patients treated with chemotherapy should place high priority to prevent oral mucositis by implication of oral cryotherapy at least for MAYO, CAF, CMF regimens. Finally, our findings support the positive effect of oral cryotherapy on reduction of incidence and severity of this debilitating side effect of single or combination chemotherapy. Therefore, utilization of this simple method recommended for the practice. We recommended other Researcher nurse to conduct a well designed study with large sample size to evaluating the effect of oral cryotherapy on oral mucositis in newer chemotherapy regimens.

Table 6. Mucositis severity according to Patient-Judged Mucositis Scale.

Group	Study	Control	Total
Severity	N (%)	N (%)	N (%)
0 and 1	24 (60.0)	11 (27.5)	35 (43.8)
2	8 (20.0)	10 (25.0)	18 (22.5)
3	8 (20.0)	19 (47.5)	27 (33.7)
Total	40 (100.0)	40 (100.0)	80 (100.0)

Test: Mann-Whitney: Z=3.151, *P*=0.002

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