Original Paper

Study on the Clinical Significance and Related Factors of Thirst and Xerostomia in Maintenance Hemodialysis Patients

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Key Words

Hemodialysis • Thirst • Xerostomia • Inter dialytic weight gain • Quality of life

Abstract

Aims: To analyse the clinical significance and related factors of thirst and xerostomia and to find methods to alleviate thirst and xerostomia in maintenance hemodialysis (MHD) patients. **Methods:** Forty-two MHD patients were included for observational study and eleven patients were enrolled for crossover trial. Thirst was assessed by 100-mm visual analog scales (VAS) and dialysis thirst inventory (DTI). Meanwhile, xerostomia was assessed by VAS and xerostomia inventory (XI). Depression, kidney disease quality of life (KDQOL), salivary flow rates and inter dialytic weight gain (IDWG) were measured. Data were analyzed by ANOVA and correlation coefficient was used to assess the correlations between continuous variables. The results of crossover trial were investigated by two-sample T-tests. **Results:** Strong positive correlations among DTI, VAS thirst score, XI and VAS xerostomia score were found ($P=0.000$). Daily IDWG was positively correlated with VAS thirst score ($r=0.315$, $P=0.042$) and DTI ($r=0.391$, $P=0.010$). UWS (unstimulated whole saliva) was negatively correlated with VAS xerostomia score ($r=-0.308$, $P=0.048$). Residual urine output was negatively correlated with DTI ($r=-0.402$, $P=0.008$), VAS xerostomia score ($r=-0.461$, $P=0.002$) and XI ($r=-0.403$, $P=0.008$). In the crossover trial, DTI, XI, IDWG2d, IDWG3d, VAS thirst and xerostomia score were significantly reduced by the use of chewing gum ($P=0.000$, 0.001 , 0.009 , 0.017 , 0.038 , 0.001). The VAS thirst score, DTI and IDWG3d were significantly reduced by receiving straw ($P=0.016$, 0.003 , 0.049). **Conclusion:** Thirst and xerostomia might affect the quality of life in MHD patients. Both chewing gum and straw could decrease thirst and IDWG.

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Introduction

Most patients with end-stage renal disease (ESRD) under hemodialysis appear multiple complications, especially cardiovascular disease [1]. High fluid intake from daily diet leads to high inter dialytic weight gain (IDWG) in patients during dialysis session. Long-term

noncompliance to the fluid-restricted diet may bring patients chronic fluid-overload and induce complications including hypertension, acute pulmonary oedema, congestive heart failure and cardiovascular comorbidity [2, 3]. Previous studies have shown that, even though patients are aware of the complications, about 80% patients refuse to comply with restrictions on liquids [2, 4-6]. Thus, patients taking maintenance hemodialysis (MHD) have to pay attention to daily diet and accept strict fluid intake restrictions.

Researches find that a considerable number of MHD patients suffered from thirst, xerostomia and saliva reduction simultaneously [7-9]. Factors including high sodium intake, potassium depletion, increased blood urea, sugar and high angiotensin II (AngII) levels and psychologic factors, may cause thirst and high fluid intake of MHD patients [2, 4, 7, 10-14]. MHD patients with thirst may have high fluid intake [4, 14]. Xerostomia, another potential dipsogenic factor, is caused by the reduction of salivary flow, which leads to thirst and excess IDWG. Some studies [15, 16] observe that there exist an intimate association among thirst, xerostomia and IDWG in MHD patients. Bots et al. [17] evaluated the effects of chewing gum or saliva substitute on thirst, xerostomia and IDWG and found no change in IDWG index. Pilocarpine significantly alleviated the increased thirst and large IDWG in MHD patients during three-month clinical trial [18]. These findings suggest that saliva substitutes or gustatory and masticatory stimulations can potentially be applied to decrease thirst and xerostomia in the therapy of MHD patients, which may also increase the compliance to the fluid-restricted diet and result in a decreased IDWG and an improved quality of life subsequently.

In our study, we investigated the clinical significance and related factors between thirst and xerostomia, and the relationship among thirst, xerostomia and quality of life. The potential effects of using sugar-free chewing gum and straw on xerostomia, thirst and IDWG in MHD patients were also concluded in our study, which may provide a unique way on the improvement for MHD patients.

Materials and Methods

Patients and study protocol

This study was approved by ethics committees of the No.5 Hospital of Shanghai, Fudan University, Shanghai, China, and adhered to the Declaration of Helsinki. Informed consent was also obtained from each participant. The inclusion criteria were as follows: ≥ 5 months on hemodialysis (HD); ≥ 18 years of age; mentally and physically being able to participate and complete the study; with stable clinical conditions including stable dry weight and hematocrit. Patients who were possessing hemodynamic instability preventing sufficient ultrafiltration, hospitalization within the preceding 3-month, dementia or terminal diseases, logistic impossibility of investigation, and unwilling to participate in this study were excluded.

Finally, forty-two MHD patients undergoing HD were included in our study and observed in the dialysis center of the No.5 Hospital of Shanghai. Age, gender, underlying diseases, HD duration, dry weight, body mass index, urine output and blood pressure were recorded. The use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) was also recorded. Weekly removal of urea by dialysis (Kt / Vweek), normalized protein catabolic rate (nPCR), routine blood test, plasma osmotic pressure, and biochemistry values were measured.

The crossover trial lasted for 6 weeks. In total, eleven patients randomly received either chewing gum or straw to restrict fluid in the first 2 weeks. After a wash-out period of 2 weeks, another regimen (chewing gum or straw) was carried out for the last 2 weeks. The xylitol sugar-free gum with minty flavor (Extra, Wrigley) and plastic straws with a diameter of 3mm were selected and given to the patients. The participants were instructed to chew one piece of gum gently, for at least 10 minutes, six times a day and as desired throughout the day when the mouth felt dry or when they were thirsty, from 6-10 pieces approximately. The straws were used to take a little water when patients were thirsty. Thirst and xerostomia were assessed at baseline and after each treatment period as well as salivary flow rates. The mean blood pressure and IDWG were also calculated during each study period.

Assessment of thirst and xerostomia

Thirst was assessed by the dialysis thirst inventory (DTI) and 100-mm self-rating visual analog scales (VAS). DTI quantified the occurrence of thirst before, during and after dialysis, and perceived thirst during day and night [17]. Each item had a 5 point Likert-type scale ('never' = 1 to 'very often' = 5). The responses to the five items were summed, which results in a score ranging from 5 (never thirsty) to 25 (very often thirsty). VAS was defined as the negative and the positive on the left and right, respectively (*e.g.*, 100 mm = extremely thirsty) [18].

Xerostomia was assessed by XI (xerostomia inventory) and VAS during the dialysis session. XI is a validated questionnaire consisted of 11 items, each with a 5 point Likert-scale ('never' = 1 to 'very often' = 5) [17]. All participants completed XI and the responses to the 11 items were added, which resulted in a score ranging from 11 (no dry mouth) to 55 (extremely dry mouth) [18].

Saliva collection

In the observational study, unstimulated whole saliva (UWS) was collected before dialysis. All subjects were instructed to refrain from smoking, eating, drinking or tooth brushing at least 1h prior to saliva collection. UWS was collected for 5 min using an established spitting technique [19, 20]. In the crossover trial, UWS and paraffin chewing-stimulated whole saliva (PC-SWS) were both collected before analysis. The method of collecting PC-SWS was the same as that of collecting UWS. During the saliva collection period, the subjects chewed a piece of tasteless parafilm (5 × 5cm, 0.30g; Parafilm 'M'; American National CAL, Chicago, IL, USA) at their natural pace. Saliva volumes were determined gravimetrically (assuming 1g = 1mL), with saliva flow rates expressed in milliliters per minute (mL/min). The saliva collection was performed by a trained investigator who was blind to all clinical data [17].

Assessment of IDWG

Participants were weighed before and after each dialysis session. IDWG was defined as the amount of fluid (kg) removed during the dialysis session [17]. IDWG% was obtained by dividing IDWG by the patient's target dry weight. The IDWG was expressed as daily IDWG, daily IDWG%, IDWG for 2 day (IDWG 2d) and for 3 day (IDWG 3d) as indicated. The target dry weight of patient was determined according to standard clinical criteria and was reviewed continuously by nephrologists. To get better assessment of the changes of IDWG, we set the ultrafiltration rate according to the IDWG in each dialysis session and corrected the post-dialysis body weight to the target dry weight. Given that patients we recruited were with stable dry weight during our study, the post-dialysis body weights were comparable with target dry weights [18]. Meanwhile, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were also detected.

Assessment of KDQOL

The Kidney Disease Quality of Life (KDQOL) [21] was assessed using the short version of the validated KDQOL-SF™ Version 1.3 Scoring Program(v3.0) (Copyright ©UCLA Division Of General Internal Medicine and Health Services Research, 2000). This questionnaire contains 80 items, which included Kidney Disease Target Area (KDTA, 44 items) and Short Form 36 (SF-36, 36 items). The item scores were aggregated without weighting and transformed linearly to a 0–100 range. Patients with higher scores had better states.

Statistical analysis

In our study, data were expressed as mean ± SD. The data were classified with regard to gender, age (<65 and ≥65 years), residual urine output (yes / no) and diabetics (yes / no). Data were analyzed by ANOVA and spearman correlation coefficient was used to assess the correlations between continuous variables. Factors including multiple linear regressions with stepwise selection were identified and independently associated with the score of VAS thirst, DTI, VAS xerostomia, and XI. The multivariate analyses were repeated forcing all variables left in the stepwise selection model, together with gender, age, the presence of diabetes, use of ACEI or ARB, nPCR, sodium, and potassium into the final regression model. In the crossover trial, the period effect and the influence of the order in which the subjects received the therapy (treatment-period interaction) were investigated with two-sample T-tests. Since no treatment-period interaction was found, we compared the effect of each therapy (chewing gum and straw) with the main baseline variables using the general linear model of ANOVA (repeated measures design, followed by paired T-tests as post-hoc

Table 1. Clinical data of 42 MHD patients in the cross-sectional study

	Mean (SD)
Age (years)	65.2 (10.9)
Male gender	57.1% (n=24)
Residual urine output	42.9% (n=18)
Full denture	16.7% (n=7)
Current smoker	4.8% (n=2)
Alcohol use	9.5% (n=4)
Educational level	
Primary school	38.1% (n=16)
Junior school	38.1% (n=16)
Senior school	11.9% (n=5)
University	11.9% (n=5)
Diabetes type 1 or 2	23.8% (n=10)
Time on HD (months)	38.5 (25.4)
HD sessions per week	
2	9.5% (n=4)
3	90.5% (n=38)
HD sessions per week	
Dry weight (kg)	57.7 (11.8)
Body mass index (kg/m ²)	20.7 (3.3)
Daily IDWG (kg/d)	0.9 (0.4)
Daily IDWG%	1.6 (0.7)
Pre-HD SBP (mmHg)	147.0 (20.4)
Pre-HD DBP (mmHg)	82.0 (12.0)
Pre-HD MAP (mmHg)	103.2 (13.7)
Hemoglobin(g/L)	96.4 (14.0)
Serum albumin (g/L)	42.4 (3.6)
Kt/V	1.4 (0.3)
nPCR (g/kg/day)	1.3 (0.3)
DTI	10.4 (5.9)
VAS thirst score	33.7 (31.0)
XI	19.5 (7.9)
VAS xerostomia score	34.1 (27.8)
UWS (mL/min)	0.26 (0.21)

procedure). All statistical analyses were conducted using the statistical software package SPSS 13.0 at the two-tailed significance level of 0.05.

Results

Observational study

Forty-two MHD patients (24 men and 18 women) were enrolled in the observational study. The mean age was 65.2 ± 10.9 years, and these patients were on HD for 38.8 ± 25.4 months. Causes for the chronic renal failure were glomerulonephritis (28.5%), hypertension (21.4%), diabetes (23.8%), lupus nephritis (4.8%), gouty nephropathy (4.8%) and unknown (16.7%). The clinical characteristics and pre-dialytic biochemical data at baseline were presented in Table 1.

Thirteen patients (30.9%) were reported to appear thirst during daytime (fairly to very often). The mean DTI and VAS thirst score of the patients were 10.4 ± 5.9 and 33.7 ± 31.0 , respectively. A subjective dry mouth was present in 69% of the patients. The mean XI and VAS xerostomia score of the patients were 19.5 ± 7.9 and 34.1 ± 27.8 , respectively. About 26.2% patients of the study were reported to have problems with eating dry food, and 23.8% of the patients sipped liquids to aid in swallowing food. The mean UWS was 0.26 ± 0.21 mL / min. Normal values (0.25-0.50 mL / min) were reported in 38.1% of the patients. Hyposalivation (UWS < 0.15mL / min) was found in 40.5% of the cases.

Women had higher XI scores (22.2 ± 8.5) than men (17.4 ± 6.8 ; $P = 0.048$). Participants with residual urine output reported significant lower scores of DTI, VAS thirst, XI and VAS xerostomia than subjects without residual urine output ($P < 0.05$, Table 2). DTI, VAS thirst score, XI and VAS xerostomia score were correlated with each other (Table3, $P=0.000$).

Correlates of DTI, VAS thirst score, XI, and VAS xerostomia score in the observational study were analysed (Table 4). Daily IDWG was positively correlated with VAS thirst score ($r = 0.315$, $P = 0.042$) and DTI ($r = 0.391$, $P = 0.010$). Daily IDWG% was positively correlated with VAS thirst score ($r = 0.519$, $P = 0.000$), DTI ($r = 0.490$, $P = 0.001$), VAS xerostomia score ($r = 0.384$, $P = 0.012$) and XI ($r = 0.319$, $P = 0.040$). Residual urine output was negatively correlated with DTI ($r = -0.402$, $P = 0.008$), VAS xerostomia score ($r = -0.461$, $P=0.002$) and XI ($r = -0.403$, $P = 0.008$). Dry weight was negatively correlated with DTI ($r = -0.317$, $P = 0.041$), VAS xerostomia score ($r = -0.405$, $P = 0.008$) and XI ($r = -0.403$ $P = 0.008$). UWS was negatively correlated with VAS xerostomia score ($r = -0.308$, $P = 0.048$). The results of multiple linear regression analyses revealed that XI, VAS xerostomia score and daily IDWG% were independently associated with DTI and VAS thirst score. No significant correlation was observed between UWS and IDWG. No significant interaction of gender, age, the presence of diabetes, use of ACEI or ARB was observed for thirst, xerostomia, IDWG, or salivary flow rate (data not shown).

The mean score of KDQOL-SF was 61.6 ± 14.4 . The mean score of SF-36 and KDTA were 60.8 ± 22.5 and 62.4 ± 10.7 , respectively. Compared with patients in low VAS thirst score

Table 2. Measurement of DTI, VAS thirst, XI, VAS xerostomia, UWS, Daily IDWG and Daily IDWG% (data were expressed as mean $\pm$ SD)

	n	DTI (5-25)	VAS Thirst score	XI (11-55)	VAS xerostomia score	UWS (mL/min)	Daily IDWG (Kg)	Daily IDWG%
Gender								
Male	24	9.8 $\pm$ 6.4	32.3 $\pm$ 33.9	17.4 $\pm$ 6.8	27.4 $\pm$ 25.6	0.28 $\pm$ 0.20	1.0 $\pm$ 0.4	1.6 $\pm$ 0.7
Female	18	11.1 $\pm$ 5.4	35.4 $\pm$ 27.4	22.2 $\pm$ 8.5 ^a	43.0 $\pm$ 28.9	0.24 $\pm$ 0.21	0.8 $\pm$ 0.4	1.6 $\pm$ 0.7
Age group								
$\geq$ 65 years	27	9.9 $\pm$ 6.1	27.1 $\pm$ 31.0	18.3 $\pm$ 7.0	30.9 $\pm$ 25.9	0.26 $\pm$ 0.20	1.5 $\pm$ 0.6	0.8 $\pm$ 0.3
<65 years	15	11.3 $\pm$ 5.8	45.5 $\pm$ 28.3	21.5 $\pm$ 9.2	39.9 $\pm$ 1.0	0.26 $\pm$ 0.23	1.8 $\pm$ 0.9	1.1 $\pm$ 0.5
Urine output/d								
$\geq$ 100mL	18	7.8 $\pm$ 5.2	22.6 $\pm$ 31.6	16.2 $\pm$ 8.2	20.1 $\pm$ 28.2	0.32 $\pm$ 0.21 ^b	1.5 $\pm$ 0.8	0.9 $\pm$ 0.4
<100mL	24	12.3 $\pm$ 5.8 ^a	42.0 $\pm$ 28.4 ^a	21.9 $\pm$ 6.9 ^a	44.6 $\pm$ 22.9	0.22 $\pm$ 0.19	1.7 $\pm$ 0.6	0.9 $\pm$ 0.3
DM								
No	32	10.1 $\pm$ 5.8	33.9 $\pm$ 32.2	18.4 $\pm$ 7.3	30.8 $\pm$ 27.3	0.27 $\pm$ 0.22	1.62 $\pm$ 0.79	0.9 $\pm$ 0.4
Yes	10	11.4 $\pm$ 6.6	33.0 $\pm$ 28.2	22.7 $\pm$ 9.2	44.5 $\pm$ 28.4	0.22 $\pm$ 0.14	1.63 $\pm$ 0.36	1.0 $\pm$ 0.3

Data were analysed by ANOVA. ^a: $P < 0.05$; ^b: $P < 0.01$. Abbreviation: DM, diabetes miltetus

Table 3. Correlations of DTI, VAS thirst score, XI and VAS xerostomia score in the observational study

	DTI		VAS thirst score		XI		VAS xerostomia score	
	r	P	r	P	r	P	r	P
DTI	1	—	0.840	0.000	0.682	0.000	0.759	0.000
VAS Thirst score	0.840	0.000	1	—	0.577	0.000	0.654	0.000
XI	0.682	0.000	0.577	0.000	1	—	0.977	0.000

Table 4. Correlates of DTI, VAS thirst score, XI, and VAS xerostomia score in the observational study

	DTI		VAS thirst score		XI		VAS xerostomia score	
	r	P	r	P	r	P	r	P
UWS	-0.149	0.348	-0.170	0.281	-0.293	0.060	-0.308	0.048
Daily IDWG	0.315	0.042	0.391	0.010	0.124	0.434	0.180	0.255
Daily IDWG%	0.490	0.001	0.519	0.000	0.319	0.040	0.384	0.012
Urine output	-0.402	0.008	-0.295	0.058	-0.403	0.008	-0.461	0.002
Dry weight	-0.317	0.041	-0.214	0.173	-0.403	0.008	-0.405	0.008
SDS	0.362	0.019	0.361	0.019	0.396	0.010	0.401	0.009

Abbreviation: SDS, self-rating depression scale

(<50) group, high VAS thirst score (>50) group had significant lower scores in many items of KDQOL-SF (Table 5). VAS thirst score, DTI, VAS xerostomia score and XI were negatively related with many items of KDQOL-SF (Table 6,7), such as symptom/problems list (SPL), effects of kidney disease (EKD), overall health (OH) and emotional well-being (EWB). Multiple linear regression analyses showed that XI score, age and SDS were independent determinants for KDQOL.

Crossover study

In total, eleven MHD patients were enrolled and randomized to two groups: chewing gum and straw for 2 weeks. There were no significant difference in age, gender, time on HD, parameters of biochemistry, hemoglobin, Kt / V and nPCR between the two groups. What's more, no obvious difference was found in the level of xerostomia, thirst, IDWG and blood pressure. However, significant treatment effects were observed for thirst and xerostomia (Table 8). The use of chewing gum decreased the VAS thirst score (70.7 $\pm$ 17.1 to 61.1 $\pm$ 22.0, $P = 0.038$), DTI (19.3 $\pm$ 3.4 to 14.3 $\pm$ 4.8, $P = 0.000$), VAS xerostomia score (54.6 $\pm$ 19.6 to 44.6 $\pm$ 20.0, $P = 0.001$) and XI (32.2 $\pm$ 9.4 to 27.3 $\pm$ 11.7, $P = 0.001$). The use of straw also had a positive overall effect on the DTI ($P = 0.016$) and VAS thirst score ($P = 0.003$) during the crossover clinical trial. When patients treated with chewing gum, IDWG2d decreased from

Table 5. Comparison of items of KDQOL stratified with VAS Thirst score[#]

	VAS thirst score<50 (n=30)	VAS thirst score≥50 (n=12)	Test type	P
Symptom/problems list (SPL)	88.5±10.3	72.7±23.3	t=2.263	0.042
Burden of kidney disease (BKD)	73.5±17.7	59.1±24.9	t=2.12	0.040
Overall health (OH) ¹	60.0 (50.0,72.5)	50.0 (30.0,60.0)	Z=-2.448 ²	0.016
Emotional well-being (EWB)	82.9±12.5	64.0±25.8	t=2.430	0.030
Social function (SOCF)	75.8±24.3	54.2±37.8	t=2.212	0.033
SF-12 physical health (SF12MH)	52.9±7.8	45.2±13.3	t=2.331	0.025
Short Form 36 (SF-36)	65.4±19.4	49.2±26.3	t=2.203	0.033
Kidney Disease Target Area (KDTA)	64.9±8.2	56.0±13.6	t=2.615	0.013
KDQOL-SF	65.1±11.3	53.3±18.0	t=2.572	0.014

[#]The table only lists the items of KDQOL which had different comparison stratified with VAS thirst;
¹, median (P25, P75); ², Mann-Whitney U

Table 6. Correlates of VAS thirst score, DTI with items of KDQOL in the observational study

	VAS thirst score (r)	P	DTI	P
Symptom/problems list (SPL)	-0.442	0.003	-0.547	0.000
Effects of kidney disease (EKD)	-0.342	0.027	-0.464	0.002
Burden of kidney disease (BKD)	-0.220	0.162	-0.417	0.006
Overall health (OH)	-0.426	0.005	-0.425	0.005
General health (GH)	-0.277	0.076	-0.433	0.004
Emotional well-being (EWB)	-0.464	0.002	-0.565	0.000
Social function (SOCF)	-0.299	0.054	-0.325	0.036
Energy/Fatigue (EF)	-0.248	0.113	-0.430	0.004
SF-12 physical health (SF12PH)	-0.166	0.292	-0.332	0.032
SF-12 physical health (SF12MH)	-0.303	0.051	-0.358	0.020
Kidney Disease Target Area (KDTA)	-0.370	0.016	-0.473	0.002
Short Form 36 (SF-36)	-0.296	0.057	-0.435	0.004
KDQOL-SF	-0.351	0.023	-0.484	0.001

Table 7. Correlates of VAS xerostomia score, XI with items of KDQOL in the observational study

	VAS xerostomia score (r)	P	XI	P
Symptom/problems list (SPL)	-0.464	0.002	-0.451	0.003
Effects of kidney disease (EKD)	-0.441	0.003	-0.425	0.005
Burden of kidney disease (BKD)	-0.372	0.015	-0.348	0.024
Overall health (OH)	-0.532	0.000	-0.494	0.001
Role limitations-physical (RPL)	-0.312	0.044	-0.301	0.052
General health (GH)	-0.580	0.000	-0.559	0.000
Emotional well-being (EWB)	-0.470	0.002	-0.446	0.003
Social function (SOCF)	-0.319	0.040	-0.306	0.049
Energy/Fatigue (EF)	-0.472	0.002	-0.477	0.001
SF-12 physical health (SF12PH)	-0.385	0.012	-0.407	0.007
SF-12 physical health (SF12MH)	-0.384	0.012	-0.387	0.011
Kidney Disease Target Area (KDTA)	-0.460	0.002	-0.451	0.003
Short Form 36 (SF-36)	-0.500	0.001	-0.519	0.000
KDQOL-SF	-0.519	0.000	-0.527	0.000

2.78 ± 0.66 kg to 2.43 ± 0.70 kg ($P = 0.009$) and IDWG3d decreased from 3.17 ± 0.89 kg to 2.88 ± 0.65 kg ($P = 0.017$). The IDWG3d also decreased by the use of straw to control water intake ($P = 0.049$). Treatment with chewing gum and straw did not influence UWS, PC-SWS, MAP, SBP and DBP during the crossover clinical trial.

Table 8. The effect of the two treatment modalities on the main outcome variables in 11 MHD patients

	Baseline	Chewing gum	<i>P</i>	Straw	<i>P</i>
VAS thirst	70.7±17.1	61.1±22.0	0.038	59.4±21.7	0.016
DTI	19.3±3.4	14.3±4.8	0.000	15.6±5.3	0.003
VAS xerostomia	54.6±19.6	44.6±20.0	0.001	54.4±18.0	NS
XI	32.2±9.4	27.3±11.7	0.001	30.0±10.1	NS
UWS	0.20±0.16	0.24±0.24	NS	0.21±0.15	NS
PC-SWS	0.59±0.28	0.67±0.39	NS	0.57±0.37	NS
IDWG2d (kg)	2.78±0.66	2.43±0.70	0.009	2.60±0.86	NS
IDWG3d (kg)	3.17±0.89	2.88±0.65	0.017	2.94±0.71	0.049
Daily IDWG (kg)	1.17±0.36	1.10±0.35	NS	1.14±0.39	NS
Daily IDWG%	2.08±0.49	1.95±0.44	NS	2.01±0.48	NS
SBP(mmHg)	148.57±13.66	146.27±15.81	NS	146.77±15.24	NS
DBP(mmHg)	87.89±6.61	86.80±8.08	NS	86.08±8.81	NS
MAP(mmHg)	108.12±8.43	106.62±10.35	NS	106.31±10.52	NS

Compared with the treatment of straw during the crossover clinical trial, the VAS xerostomia score significantly decreased by the use of chewing gum ($P = 0.06$). Between the two interventions, no difference was found in DTI, VAS thirst score, XI, UWS, PC-SWS, IDWG, MAP, SBP and DBP (Table 9).

Discussion

Researches have found that a large number of MHD patients are accompanied with thirst, xerostomia and saliva reduction [7-9]. In our study, high thirst scores were observed in 30.9% MHD patients, which was lower than some other studies [16-18], which might be caused by lacking of enough cases. Meanwhile, a relatively large proportion of the MHD patients in our study had a dry mouth (69%), which was in agreement with previous studies [16, 22]. But the xerostomia scores in MHD patients in our study were lower than patients in other studies [16, 23]. MHD patients might have a light dipsia of lower degree, which might cause a lower score in XI xerostomia score.

General exocrine gland dysfunction had been described in MHD patients, including the reduced acid secretion, impaired peptic secretion, dry eyes, and cutaneous xerosis [9, 24, 25]. Measurement of UWS was the most reliable method for quantifying the salivary function [26]. The UWS index ($0.26 \pm 0.21 \text{ mL / min}$) of our patients was normal compared with healthy individuals (0.25 to 0.5 mL / min) [27] and to other studies in MHD patients [22]. In our study, 48.24% MHD patients were hyposalivation ($\text{UWS} \leq 0.16 \text{ mL / min}$). The calculated mean rates were normal due to a few HD patients with high flow rates. UWS didn't present a relationship with dialysis months, suggesting that dialysis might not affect saliva function. The mean salivary flow rates of patients in our study were significantly higher than that of patients received radiotherapy for head and neck tumors (0.113 mL / min) [28], which was also accorded with recent study that salivary glands maintained their secretory capacity in patients under UWS and chewing-stimulating [17].

Thirst and xerostomia are related to UWS and the dysfunction of saliva can cause xerostomia [8, 9, 16, 18, 22]. In our study, we did not find the relationship between thirst and UWS, suggesting that thirst might not be mainly caused by salivary flow rates reduction. Some studies observed thirst and xerostomia were significantly related to age, gender, depression, anxiety and stress [29, 30]. Other study showed MHD patients under the age of 65 years had much higher XI scores [16]. Our research showed that SDS score had an apparent relationship with thirst and xerostomia score, and XI score of female patients was significantly higher than male patients, and thirst and xerostomia were rarer in elder patients.

Table 9. Comparison of the effect of the two treatment modalities (chewing gum and straw for 2 weeks) on the main outcome variables

		First stage (2weeks)	Second stage (2weeks)	P
VAS thirst score	C-S	57.8±25.5	54.2±25.6	0.853
	S-C	65.6±16.6	65.0±19.0	
DTI	C-S	14.2±6.5	15.0±5.6	0.179
	S-C	16.4±5.6	14.4±2.3	
VAS xerostomia score	C-S	40.7±14.1	51.8±15.6	0.006
	S-C	57.4±22.1	49.2±26.6	
XI	C-S	31.5±14.4	32.7±12.7	0.075
	S-C	26.8±5.5	22.2±4.9	
UWS	C-S	0.26±0.27	0.27±0.17	0.583
	S-C	0.15±0.11	0.22±0.24	
PC-SWS	C-S	0.67±0.37	0.60±0.37	0.096
	S-C	0.54±0.40	0.67±0.45	
IDWG2d	C-S	2.13±0.43	2.35±0.46	0.078
	S-C	2.90±1.17	2.79±0.84	
IDWG3d	C-S	2.65±0.46	2.74±0.51	0.565
	S-C	3.17±0.90	3.15±0.79	
Daily IDWG	C-S	0.99±0.24	1.06±0.28	0.415
	S-C	1.24±0.51	1.23±0.44	
Daily IDWG%	C-S	2.00±0.47	2.11±0.38	0.503
	S-C	1.89±0.59	1.90±0.45	
SBP	C-S	139.07±11.60	139.72±13.64	0.819
	S-C	155.23±13.58	154.92±16.89	
DBP	C-S	82.18±6.00	81.00±7.25	0.724
	S-C	92.18±6.55	92.33±6.91	
MAP	C-S	101.14±7.32	100.57±8.73	0.880
	S-C	113.20±8.53	113.19±10.10	

C, chewing gum; S, use of straw

In our study, DTI, XI and VAS xerostomia score were negatively related to residual urine output, which was similar to the result of previous study [17]. We also observed no correlation between thirst, xerostomia, IDWG, or salivary flow rate and the use of ACEI or ARB. One recent study also found chronic ACEI therapy was not effective in reducing thirst and IDWG [31, 32]. We found significant relationships among thirst, xerostomia and IDWG, suggesting that xerostomia and thirst might be one of the reasons that lead to higher fluid intake. Studies have showed thirst had a positive relation to IDWG [7,

33]. Bots et al. found thirst and xerostomia were associated with greater IDWG [16, 33]. Thus, alleviating xerostomia and thirst might be an intervention to decrease IDWG in MHD patients.

On the other hand, although there was a relationship among thirst, xerostomia and IDWG, no conclusion could provide an evidence that thirst and xerostomia leading to drinking or high IDWG. Some patients feel very thirsty but have the willpower to strict fluid intake restrictions. These patients may be very thirsty, but still have low IDWG [10]. López-Gómez et al. [34] reported that a greater IDWG was directly associated with a better nutritional status. Therefore, the percent of IDWG results in better long-term prognosis of the patients. The beneficial effects of IDWG on the nutritional status and prognosis were greater than the negative aspects that depended on its effects on blood pressure.

The KDQOL has been developed as a self-report measure for individuals with kidney disease and on dialysis and the psychometric properties of the KDQOL-SF proved to be benefiting [21, 35]. In our study, thirst and xerostomia were significantly negative correlation with many items of KDQOL-SF. What's more, XI and SDS were independent determinants for KDQOL. For patients on HD, a good correlation was observed between HRQOL and the levels of anxiety and depression [36, 37]. Taskapan et al. found that all indices of quality of life decreased in MHD patients with depression [38]. Furthermore, renal transplantation enhanced salivary flow and decreased symptoms of xerostomia and thirst, and hence enhanced the potential to improve the quality of life of affected individuals [39]. Therefore alleviating thirst and xerostomia in MHD patients might improve their quality of life.

Patients on daily HD were less thirsty and also showed less fluctuation in body fluid volume [40]. But this therapy might not be used generally. In addition, xerostomia can be reduced by either stimulation of the saliva secretion (mechanical, gustatory, or pharmacologic)

or palliative care using mouthwashes or saliva substitutes [17, 24, 25]. In our crossover trial, the using of chewing gum for 2 weeks among MHD patients significantly reduced both thirst and xerostomia, which was agreed with other studies that investigated the effect of chewing gum on xerostomia in both MHD patients and other patient populations, such as rheumatic patients [41] or in patients with a malignant disease [17, 42, 43]. Furthermore, the use of straws to restrict fluid reduced perceived thirst in MHD patients but had no effect on xerostomia, which was similarly to the effect of saliva substitutes. Interestingly, we also found a minimal objective reduction in IDWG, which might not according perfectly with previous study that no change was found in IDWG [17]. However, some scholars had the view of their long-term use might irritate the oral tissue [11, 42, 44, 45]. In the 3-month clinical trial, Sung et al. found pilocarpine significantly alleviated the exaggerated thirst and large IDWG in MHD patients [18]. Therefore, the 2-week period might be short, and a longer study might affect fluid intake more significantly.

However, there were several limitations to our interventional trial. One potential limitation of this study was the lack of blinding. However, this was unavoidable in this crossover design in which the participant received two potential active agents (chewing gum and straw). In addition, only clinically stable patients were enrolled in our study. Therefore, it remained uncertain whether our findings could be generalized to individuals with multiple concurrent diseases.

Conclusion

Thirst was correlated with daily IDWG, daily IDWG%, SDS, residual urine output and dry weight. UWS was negatively correlated with VAS xerostomia score. Xerostomia and IDWG were independently associated with thirst. Thirst and xerostomia were negatively correlated with many factors of KDQOL-SF. Besides, thirst and xerostomia might affect the quality of life in MHD patients. Chewing gum could alleviate thirst and xerostomia and the use of straw to restrict fluid could also alleviate thirst. Both of them could decrease IDWG. The use of chewing gum or straw could be considered as a clinical tool to assist MHD patients in improving compliance to the fluid intake restrictions, reducing cardiovascular diseases, avoiding possibly negative effect nutrition and improving their quality of life as well.

Conflict of Interests

We have no conflict of interest to state.

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