KEY WORDS
Medication adherence, Dental caries, Caries risk assessment, CAMBRA, Chlorhexidine, Xylitol, Fluoride mouthwash, Fluoride gel

Randomized controlled trial

ADHERENCE TO CARIES-PREVENTION THERAPY BY AT-RISK ADULTS: A RANDOMIZED FACTORIAL TRIAL

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PURPOSE. To evaluate the adherence to therapy by patients classified as being at high risk of caries.

MATERIALS AND METHODS. A randomized factorial trial with one-month follow-up was conducted. Adult patients at high risk of caries were recruited from a private dental practice. They were randomized according to a factorial trial design to use one or more of the following: fluoride mouthwash, chlorhexidine mouthwash, fluoride gel, and/or xylitol chewing-gum. At baseline, each patient was asked to score their oral health from 1 to 10. One month later, patients were contacted by telephone by another operator for interview regarding their use of the prescribed products, and once again to rate their oral health from 1 to 10. Asymmetric discordance and agreement between assigned therapy and therapy undertaken were performed respectively using the McNemar test and K-statistic.

RESULTS. Twenty-three patients were randomized, but there were three drop-outs. Only 11 of the remaining 20 participants (55%) adhered to the assigned therapy, while nine patients (45%) did not (95%CI from 23 to 68%). Six patients (30%) took at least one of the four therapies not prescribed them. Considering abstention from non-prescribed treatments, therefore, only 6 patients (30%; 95%CI from 12 to 54%) fully adhered to the therapy prescribed. Thus, 14 out of the 20 participants failed to fully adhere to the therapy prescribed (70%; 95% CI from 46 to 88%). Asymmetric discordance was significant for chlorhexidine mouthwash (four out of nine patients did not use the mouthwash, P = 0.0455) and for fluoride gel (five out of 11 patients did not use the gel, P = 0.0253), while it was non-significant for xylitol chewing-gum (P = 0.3173) and fluoride mouthwash (P = 1.0). Agreement was moderate for chlorhexidine mouthwash (K = 0.58), fluoride gel (K = 0.52), and xylitol chewing-gum (K = 0.60), and fair for fluoride mouthwash (K = 0.40). Patient satisfaction with therapy was 7.7 ± 2.4, but was not linked to any of the four treatments assigned: fluoride mouthwash (P = 0.7699), chlorhexidine (P = 0.8980), xylitol (P = 0.6203), fluoride gel (P = 0.3885). An increase in satisfaction with oral hygiene was observed (P = 0.0003), but was not associated with the treatment prescribed.

CONCLUSIONS. Adherence to therapy was rather low. After one month, many patients (about 45%) were not adhering to the prescribed therapy. Some treatments appear to have stimulated greater adherence than others.

CONFLICT OF INTEREST STATEMENT
The authors declare that they have completely self-funded the study, and that there are no conflicts of interest.

INTRODUCTION

Adherence is the extent to which a person's behaviour coincides with medical or health advice[1]. It is a key factor in successful treatment, and most studies have reported a significant correlation between adherence to therapy and clinical outcome[2].

For people with chronic diseases, management of their conditions is fundamental to minimizing their impact, improving health outcomes, preventing further disability, and reducing healthcare costs. However, only about half of patients with chronic conditions take their medications as prescribed, making medication adherence improvement a priority for the public health service[3,4]. Although many adherence studies have investigated this aspect in chronic systemic diseases[5], several studies have been done in the dentistry field[6-13].

One method of determining whether a patient is at high risk of developing a carious lesion is Caries Management by Risk Assessment-CAMBRA[14,15]. The caries management plan for each individual is based upon reducing the caries risk factors and enhancing the protective factors with the additional aid of behaviour modification[16]. Common recommendations consist of the use of gel containing fluoride, mouthwash containing fluoride, mouthwash containing chlorhexidine, and/or chewing-gum containing xylitol[17]. However, few studies have been conducted on adherence to caries-prevention protocols in adult patients[18,19].

Hence, the purpose of this randomized factorial trial was to estimate adherence to four different caries-prevention protocols (use of gel containing fluoride, mouthwash containing fluoride, mouthwash containing chlorhexidine, chewing-gum containing xylitol) in adult patients at high risk of caries, and to assess any discrepancies between therapy prescribed and that actually undertaken by the patient.

MATERIALS AND METHODS

Trial design

This study was designed in accordance with the CONSORT 2010 guidelines for reporting parallel-group randomized controlled trials[20] and with the design, analysis, and presentation of factorial randomized controlled trials[21]. It was a single-centred, examiner-blind, randomized clinical trial with four-factorial design. The four factors, at two levels each, were:

- Fluoride mouthwash (FM) yes or no;
- Chlorhexidine mouthwash (CM) yes or no;
- Fluoride gel (FG) yes or no;
- Xylitol chewing-gum (XC) yes or no.

Eligibility criteria for participants

The investigation was carried out from June to October 2015. During this period, 23 patients seeking oral hygiene procedures in a private practice in Campi Bisenzio, Florence, Italy, were consecutively recruited for the study.

The inclusion criteria used for selection were:

- Age between 18 and 85 years;
- Presence of at least 20 teeth;
- High risk of developing dental caries according to CAMBRA risk assessment[14,15], i.e., one or more white spots or one or more restorations carried out in the preceding 3 years, or one or more carious lesions on the enamel or dentin (clinically or radiographically detectable). According to the CAMBRA, an individual with caries lesions either currently or in the recent past is at high risk of future caries by default[15].

The exclusion criteria were:
- Patients with manual inability to perform dental care;
- Patients with neurological disorders;
- Pregnant women.

Informed written consent was obtained from all patients recruited for the study.

Interventions

An oral hygiene session was performed before the start of the study. Demographic and clinical data were collected. Each patient was asked to express an opinion regarding their oral hygiene, giving it a score from 0 to 10 (VAS), with 0 meaning very bad oral hygiene and 10 very good oral hygiene.
After a professional scale and polish, the envelope with the randomization code was opened by an operator (MG).
On the basis of the code assigned, the patients were told which of the following product(s) they should use at home in addition to their daily home oral care routine (toothbrush, fluoride toothpaste, interdental cleaning aids):
- Mouthwash containing fluoride (FM) at a fluoride concentration of 0.05%;
- Mouthwash containing chlorhexidine (CM) at a chlorhexidine concentration of 0.12%;
- Gel containing fluoride (FG) at a NaF concentration of 1.1%;
- Chewing-gum containing xylitol (XC).

Each patient was prescribed a combination of the products according to the randomization scheme. Following a full factorial randomization model, all combinations of therapies were possible. In fact, with four factors 16 combinations of therapies were possible, from no assigned treatment to all four assigned treatments.
The operator (MG) informed and explained to the patient the methods and timing relating to the assumption of the products. In addition, the patient received a leaflet with written information on how to use the products and some trade names of the prescribed products. The purchase of the products was the responsibility of the patient.
- For the FM the concentration of fluoride was 0.05%. The patient was required to rinse his/her mouth for approximately 60 seconds once a day[14].
- For the CM the concentration of chlorhexidine was 0.12%. The patient was required to rinse his/her mouth for approximately 60 seconds once a day and for only one week per month[14].
- For the FG the concentration of NaF was 1.1%. The impressions of the dental arches were taken and two custom trays were prepared on the shape of the patient's dental arches. The patient was asked to insert the gel inside both trays and insert them in the mouth for a maximum of 5 minutes once a week.
- For the XC the patient was prescribed to chew four chewing gums a day for at least 5 minutes each.

One month later, the patients were contacted by telephone by another blinded operator (DF) who was unaware of their randomization code and therefore blind to their prescribed treatment. The operator asked the participant whether they were taking each of the four treatments (to respond "yes" or "no" to each). Each patient was then asked to express an opinion regarding their oral hygiene, scoring it from 0 to 10 (VAS) as above. In addition, each patient was asked to express their level of satisfaction with the prescribed therapy (from 0 = no satisfaction to 10 = maximum satisfaction).

Outcome measures

The aim of this study was to estimate the percentage of adherence to therapy by patients classified as being at high risk of caries. Full adherence to therapy included not taking non-prescribed treatments. For each treatment, asymmetric discordance and agreement between treatment prescribed and treatment taken was to be evaluated. A secondary aim was to evaluate whether patient satisfaction with the prescribed therapy at one month was linked to the treatment prescribed.

Sample size

To estimate a confidence interval at 95% with a 20% margin of error for adherence to treatment, at least 32 patients were required, considering a 20% drop-out. Unfortunately, only 23 patients could be included and randomized to treatment.

Random sequence

Four computer-generated lists of random numbers (one for each factor) were used for participant allocation. Blocked randomization was applied to include 16 patients in each level of each factor.

Allocation concealment and blinding

The allocation sequence was concealed from the researcher (MN) enrolling and assessing participants in sequentially numbered, opaque, sealed, and stapled envelopes. The envelopes were opened by the operator (MG) only after professional oral hygiene. Outcome assessors (DF) were kept blinded to the allocation.

Statistical methods

Descriptive statistics were calculated (by MN) using mean and standard deviation for quantitative data and frequency and percentage for qualitative data. The percentage and 95% confidence interval (95% CI) were calculated on the total of patients who did not adhere to the assigned therapy. The same calculation was made considering those not taking non-prescribed treatments (full adherence).

McNemar testing was performed to evaluate the asymmetry of mismatch between prescription and use for each treatment. The k-statistic and 95% CI were calculated to estimate the agreement between prescription and use for each treatment. K values were interpreted according to Landis and Koch[22].

A linear model was constructed to test the association between the four treatments performed and patient satisfaction with the therapy prescribed. A similar analysis was also carried out for the change in self-assigned oral hygiene score, using oral hygiene score at the baseline as covariate. Intention-to-treat analysis was carried out, and a sensitivity-per-protocol analysis was performed.

MedCalc software version 12.7.5.0 (MedCalc Software, bvba, Ostend, Belgium) and JMP software version 13.0 (SAS Institute Inc.) were used for the analysis.

RESULTS

Participant flow and recruitment

Twenty-three patients were consecutively enrolled in the trial and randomized in a factorial four-factor, two-level study. Two patients for each factor were randomized to XC; FM+FG; FM+XC; FG+XC; FM+CM+FG; FM+FG+XC; CM+FG+XC. Only one patient for each factor was randomized to None; FM; CM; FG; FM+CM; CM+FG; CM+XC; FM+CM+XC; FM+CM+FG+XC.

On average, each patient received 2.1 treatments (SD 0.9), with a range from 0 to 4 treatments. Eight patients (35%) received at least 3 treatments. In total, 12 patients were prescribed FM, 10 CM, 13 FG, and 13 XC. Three patients dropped out and did not respond to repeated telephone calls. They had been randomized to FM+XC, CM+XC, and FM+FG+XC, respectively.

Baseline data

Twenty-three consecutive patients were included in the study. Their average age was 41.8 years (standard deviation 15.5 years) with a range from 19 to 73 years. The sample consisted of 15 males (65%) and eight females (35%). Nine were smokers (39%). Their average baseline self-assigned oral hygiene score was 6.7 (SD 1.5), ranging from 4 to 10.

Outcomes and estimation

At follow-up one month after randomization, three patients had dropped out. Hence the data from 20 participants was analysed. Only 11 adhered (55%) to the prescribed therapy, while nine (45%) did not (95%CI from 23 to 68%). Six patients (30%) took at least one of the four therapies not prescribed. Therefore, only six patients (30%; 95%CI from 12 to 54%) fully adhered to the prescribed therapy (including not taking non-prescribed treatments), whereas 14 out of 20 did not (70%; 95% CI from 46 to 88%).

Adherence to FM is reported in **TABLE 1**. Seven out of 10 patients adhered to the prescribed FM. The McNemar test result was not significant (P = 1.0), thereby revealing no asymmetric discordance between randomization and FM use. The agreement between prescription and use was fair (K = 0.40; 95% CI from 0.00 to 0.80) because three patients took the fluoride mouthwash although it was not prescribed to them.

Adherence to CM is reported in **TABLE 2**. Five out of nine patients adhered to CM as prescri-

TABLE 1 RANDOMIZATION AND USE OF FLUORIDE MOUTHWASH (FM). MCNEMAR: P = 1.0. K = 0.40 (95% CI FROM 0.00 TO 0.80)

	Intake of FM		
	Intake of FM	No intake of FM	Total
Randomization			
Randomized to FM	7 (70%)	3 (30%)	10
No randomized to FM	3 (30%)	7 (70%)	10

TABLE 2 RANDOMIZATION AND USE OF CHLORHEXIDINE MOUTHWASH (CM). MCNEMAR: P = 0.0455. K = 0.58 (95% CI FROM 0.24 TO 0.91)

	Intake of CM		
	Intake of CM	No intake of CM	Total
Randomization			
CM prescribed	5 (56%)	4 (44%)	9
CM not prescribed	0 (0%)	11 (100%)	11

bed. The McNemar test result was significant (P = 0.0455), thereby showing an asymmetric discordance between CM prescription and use. While four out of nine patients did not use the prescribed treatment, none of those who were not instructed to do so used chlorhexidine mouthwash. The agreement between prescription and use was moderate (K = 0.58; 95% CI from 0.24 to 0.91).

Adherence to FG is reported in **TABLE 3**. Six out of 11 patients adhered to the FG prescription. The McNemar test result was significant (P = 0.0253), revealing an asymmetric discordance between FG prescription and use. While five out of 11 patients did not take the prescribed treatment, none of those who were not prescribed it used the fluoride gel. The agreement between randomization and intake was moderate (K = 0.52; 95% CI from 0.20 to 0.84).

Adherence to XC is reported in **TABLE 4**. Nine out of 10 patients took the XC as prescribed. A non-significant McNemar score (P = 0.3173) revealed no asymmetric discordance between randomization and FM intake. The agreement between prescription and use was moderate (K = 0.60; 95% CI from 0.26 to 0.94) because three patients used the xylitol chewing-gum although it was not prescribed to them.

Patient satisfaction with therapy was 7.7 on average (SD 2.4), ranging from 0 to 10. There was no link between patient satisfaction and any of the four treatments (**TABLE 5**). Participants' self-assigned oral hygiene score one month after randomization was on average 7.6 (SD 1.3). There was a significant increase in satisfaction from baseline (0.8; SD 0.8; 95% CI from 0.4 to 1.2; P = 0.0003, paired t-test), but this was not associated with the therapy prescribed (**TABLE 6**): FM (0.2; 95% CI from -0.6 to 0.9, P = 0.6116), CM (-0.1; 95% CI from -0.9 to 0.7; P = 0.7315), FG (0.3; 95% CI from -0.4 to 1.1; P = 0.3844), XC (-0.6; 95% CI from -1.4 to 0.1; P = 0.0906). The sensitivity-per-protocol analysis did not yield substantially different results.

TABLE 3 RANDOMIZATION AND USE OF FLUORIDE GEL (FG). MCNEMAR: P = 0.0253. K = 0.52 (95% CI FROM 0.20 TO 0.84)

	Intake of FG		
	Intake of FG	No intake of FG	Total
Randomization			
FG prescribed	6 (55%)	5 (45%)	11
FG not prescribed	0 (0%)	9 (100%)	9

TABLE 4 RANDOMIZATION AND USE OF XYLITOL CHEWING-GUM (XC). MCNEMAR: P = 0.3173. K = 0.60 (95% CI FROM 0.26 TO 0.94)

	Intake of XC		
	Intake of XC	No intake of XC	Total
Randomization			
XC prescribed	9 (90%)	1 (10%)	10
XC not prescribed	3 (70%)	7 (70%)	10

TABLE 5 PATIENT SATISFACTION WITH THERAPY: GENERAL LINEAR MODEL

Randomization	Estimate	95%CI	P-value
FM	-0.4	-2.9; 2.2	0.7699
CM	-0.2	-2.7; 2.4	0.8980
FG	-1.0	-3.6; 1.5	0.3885
XC	0.6	-2.0; 3.2	0.6203

FM: fluoride mouthwash; CM: chlorhexidine mouthwash; FG: fluoride gel; XC: xylitol chewing-gum

TABLE 6 CHANGE IN SATISFACTION WITH ORAL HYGIENE FROM BASELINE TO ONE-MONTH FOLLOW-UP: GENERAL LINEAR MODEL USING SATISFACTION AT BASELINE AS A COVARIATE

Randomization	Estimate	95%CI	P-value
FM	0.2	-0.6; 0.9	0.6116
CM	-0.1	-0.9; 0.7	0.7315
FG	0.3	-0.4; 1.1	0.3844
XC	-0.6	-1.4; 0.1	0.0906

FM: fluoride mouthwash; CM: chlorhexidine mouthwash; FG: fluoride gel; XC: xylitol chewing-gum

DISCUSSION

The aim of this study was to estimate the percentage of adherence to caries-prevention therapy by patients classified as being at high risk of caries following the CAMBRA caries risk assessment[15]. CAMBRA risk predictors are markers indicative of a current or past carious processes, but they are not causative factors. The disease indicators of high risk of caries are clinical observation, or a recent history, of dental caries, i.e., visible cavities or radiographic penetration of the dentin, radiographic approximal enamel lesions, white spots on the smooth surface, and restorations during the last three years[15]. In a retrospective study these indicators were recognized as being highly predictive in terms of development of future lesions, and that the caries disease process would continue in the future[23].

In this study, adherence to caries-prevention therapy was low. Many participants (about 45%) were not adhering to the prescribed therapy after one month. Full adherence to therapy, including not taking non-prescribed treatments, was seen in only 30% of participants. Such a low adherence to the treatments considered could have important clinical and research implications.

Indeed, it is important for clinicians to consider that the prevention and therapy they prescribe may not be effective due to poor patient adherence. Often this problem is underestimated by dentists, who do not always take care to ensure that the patient is following their instructions. In one study, non-compliance with regular dental attendance, oral hygiene instruction, dietary advice and daily fluoride use was associated with the development of dental caries[19], and if our sample is any indication, this issue could be more impactful than clinicians might think.

Our findings may also have an important impact on research, as it is normally recommended to carry out an intention-to-treat analysis, i.e., based on randomization, without taking into account adherence[24]. This may not provide a full picture of the clinical reality. Many methodologists recommend always performing a sensitivity-per-protocol analysis, that is, one based on the treatment actually received by the patient, regardless of randomization. Carrying out both analyses would highlight any differences between prescription and treatment, and thereby shed light on the effect of adherence on the results of prevention or treatment.

In this study, the prescribed products were not provided free of charge to patients. This meant that patients had to find and purchase the products they were prescribed on their own. This situation mimics what normally happens in the clinic, while usually in research the products are provided free of charge to participants. This could be an important difference between clinical and research settings to bear in mind.

Also, adherence to the therapy likely depends on the product in question. It was decided to implement a randomized factorial design in this study to represent all the possible combinations of four treatments commonly prescribed to adult patients at risk of caries[15]. We observed that treatments such as chlorhexidine mouthwash and fluoride gel had a low adherence rate in the sense that only about 55% of patients used them as prescribed. Additionally, these products were not taken independently by patients if they had not been prescribed. In one study, daily fluoride gel use in custom-made trays was prescribed for 84 irradiated head and neck cancer patients[18]. Only 19% of patients continued to use the fluoride gel one year after the treatment was prescribed[18].

Conversely, fluoride mouthwashes and xylitol chewing-gum yielded greater adherence (70% and 90%, respectively). Furthermore, these products were often used by patients even if they had not been prescribed (this occurred in 30% of cases). This was the reason why agreement between assigned therapy and therapy undertaken was particularly low for fluoride mouthwash.

An important limitation of this study was the small sample size. In fact, the estimated number of patients was not reached because the operators decided to stop the study due to personal problems. In addition, the adherence of the patients to therapy was assessed over a short period of time: one month. Adherence to therapy probably decreases over time and a longer follow-up could have provided further information.

CONCLUSIONS

Adherence to therapy was low. Many patients (about 45%) did not adhere to the prescribed therapy after one month. Some treatments (xylitol chewing-gum and fluoride mouthwash) appear to have stimulated greater adherence than others (chlorhexidine mouthwash and fluoride gel).

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