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Radiotherapy-induced xerostomia: a randomised, double-blind, controlled trial of Visco-ease™ oral spray compared with placebo in patients with cancer of the head and neck

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Abstract

Radiotherapy-induced xerostomia (RIX) is a common and untreatable side effect of radiotherapy to the head and neck. Visco-ease™ mouth spray (Lamellar Biomedical Ltd), a new product that is made from lamellar body mimetics, reduces the viscosity of saliva ex vivo. The purpose of this study was to evaluate its safety and effectiveness in the treatment of RIX in 43 patients with cancer of the head and neck. They were randomised into the Visco-ease™ or placebo groups, and asked to complete the Groningen radiotherapy-induced xerostomia (GRIX) questionnaire each week. The primary endpoint was a change in GRIX score from baseline to end of treatment. There was no difference in scores between the two groups, and none of the patients had device-related serious adverse events. Visco-ease™ oral spray was safe and tolerable but no better than placebo in reducing RIX in this group of patients.

Keywords: Radiotherapy-induced xerostomia; Visco-ease™; LMS-611; GRIX; head and neck cancer

Introduction

Radiotherapy- induced xerostomia (RIX), the most commonly reported late and permanent side effect of radiotherapy for cancer of the head and neck,[1] impairs patients' quality of life (QoL),[2,3] and causes discomfort, altered taste, difficulties with speech and swallowing, and dental caries.[4] Despite advances in radiation technology, around 40% of patients have xerostomia 12 months after treatment.[5,6]

The epidemiology of head and neck cancer has changed with the rise in the incidence of human papilloma virus (HPV)-driven oropharyngeal cancer. Patients are often younger,[7] and the significant improvements in response to treatment and overall survival,[8,9] mean that they will live for longer with the consequences of treatment. [10,11]There is no effective treatment for RIX, and a Cochrane review concluded that "randomized controlled trials of topical interventions for dry mouth are required to provide evidence to guide clinical care".[12]

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Lamellar bodies have surface active properties and are an essential lubricant of the body's tissues. They prevent mucosal surfaces from sticking to each other, and sticky secretions (such as thick saliva) from congesting the hollow organs.

Visco-ease™ (Lamellar Biomedical Ltd), formerly known as LMS-611, is a multi-lipid mimetic of a naturally occurring lamellar body. Preclinical work has suggested that it may help to make the thick, sticky saliva seen after radiotherapy to the head and neck more fluid.[13]

The purpose of this study was to evaluate the safety and effectiveness of Visco-ease™ mouth spray for the treatment of RIX in patients with cancer of the head and neck. To our knowledge, this is the first study in humans. In line with published recommendations [14] we thought that reported outcomes were the most critical measures of its effectiveness, and we used the validated Groningen radiotherapy-induced xerostomia (GRIX) questionnaire [15] to evaluate patients' reports of RIX.

The primary endpoint was the change in GRIX score from baseline to the end of treatment. Secondary objectives were assessments of safety and frequency of use.

Material and methods

Participants

Patients with cancer of the head and neck who were planned to start radical primary radiotherapy or chemoradiotherapy, were recruited to this randomised, double-blind, placebo-controlled study.

Eligible patients were aged 18 years or older and were thought to be at high risk of RIX. Those with pre-existing xerostomia, or who had used any investigational drug or product within 30 days, and those who had had primary surgery for cancer of the head and neck or who had known allergies to egg, soya, or lanolin-based products, were excluded.

Randomisation and blinding

Patients were randomly assigned to be given Visco-ease™ or placebo (0.9% physiological saline) oral spray in a ratio of 2:1. Independent randomisation was done through an interactive web-response system at the Robertson Centre for Biostatistics. Neither the patient nor investigators were informed of the treatment allocated. All treatment and placebo kits were presented in an identical manner.

Procedures

In all cases, radical radiotherapy or chemoradiotherapy was delivered by volumetric modulated arc therapy (VMAT). Gross tumour and the all involved nodes were treated with doses of 65 Gy/30# over six weeks. The prophylactic dose to areas considered at high risk of occult disease was 54 Gy/30# over six weeks. Target volumes were selected and delineated according to international guidelines.[16] Cisplatin was delivered at 100 mg/m^2 on days 1 and 22 of treatment in those who had concurrent chemotherapy.

Patients were asked to use the oral spray (Visco-ease™ or placebo) as required, but to use at least one spray twice a day during the course of their treatment, beginning on day one. They were instructed to spray under the tongue then to move the fluid around the mouth. To enable us to assess the tolerability of the product independent of the subsequent symptoms, they began to use the spray before they developed RIX. They were assessed weekly during treatment, and adverse events were recorded. Patients' scores of RIX using the GRIX questionnaire were collected weekly, and patients were also asked to keep a daily diary to record when they used the spray.

Statistical analysis

Previous work has shown that changes in GRIX scores from baseline to week six of radiotherapy were normally distributed in untreated patients with a mean (SD) of 65.2 (22.3).[13]

To calculate the sample size we assumed a mean change of 65 in the placebo group and 35 in the treated group (SD 23 in both). Patients were allocated to the groups in a ratio of 2:1 (for each patient given placebo, two were given Visco-ease™). The sample size calculation was based on a comparison of the change in GRIX scores from baseline to week six of radiotherapy between the two groups using a two-sided two-sample *t* test, with a significance level of 0.05. The number required to achieve a power of 90% was 30 (20 in the Visco-ease™ group and 10 in the placebo group). The sample size calculation was done with the help of Proc Power in SAS™ software 9.3 (SAS Institute Inc). To allow for a dropout rate of 25%, 41 patients were required (27 randomised to the Visco-ease™ group and 14 to the placebo group).

Baseline characteristics were summarised overall and for each treatment group using mean (SD), range for continuous variables, and number (%) for categorical variables.

Statistical analysis of the effect of treatment on the primary was done using linear regression, with adjustments for baseline GRIX scores. Analysis of variance (ANOVA) was used to analyse the difference in mean clinic GRIX scores at each time point. Fisher's exact test was used to compare categorical variables at baseline between the placebo and Visco-ease™ groups, and also for the comparison of patients with adverse events during the study. Independent two-sample *t* tests were used to compare the mean of continuous variables at baseline.

All analyses were done with the help of the statistical software platform R.[17]

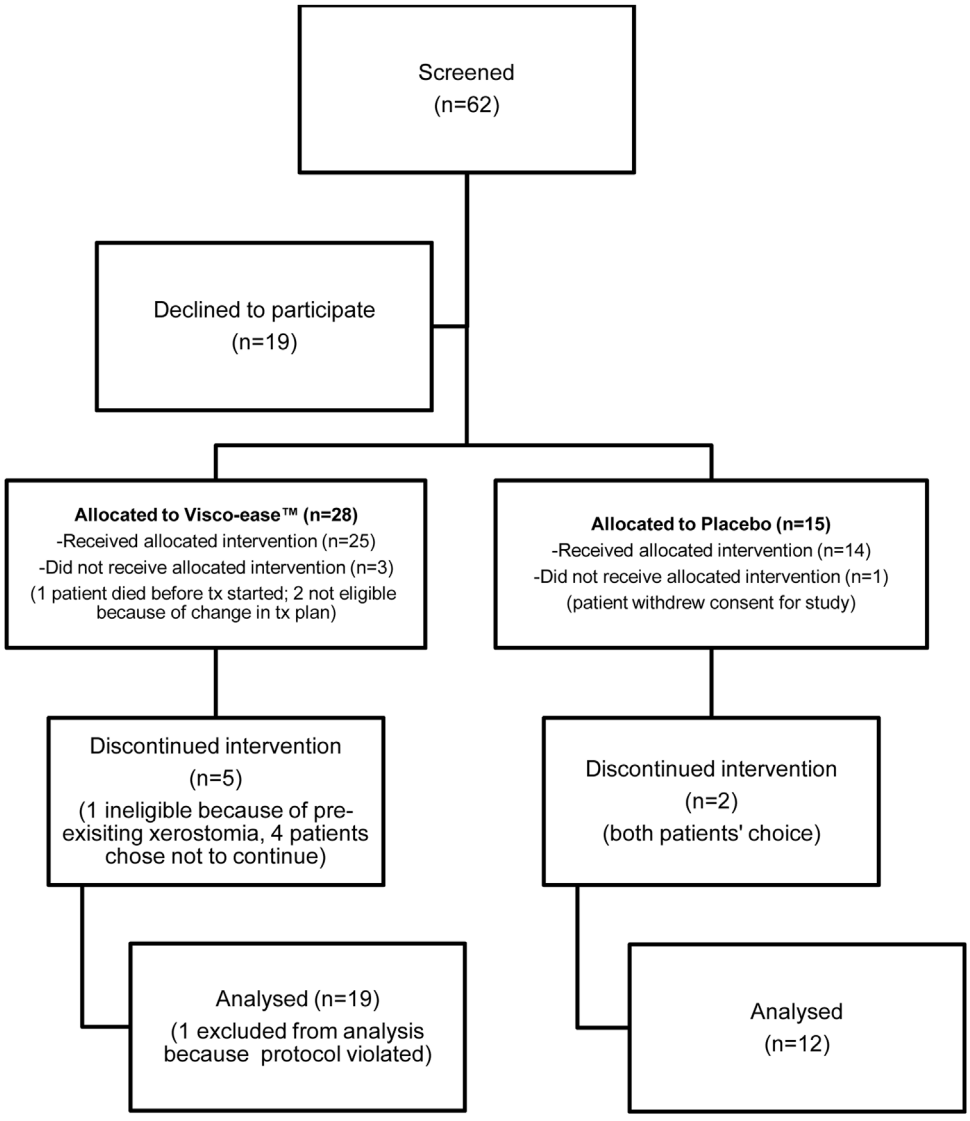

Fig. 1. Trial profile, CONSORT flow diagram.

Ethics approval and consent to participate

The protocol was approved by the Research Ethics Committee 4, (15/WS/0281) and MHRA (CI/2015/0053). Written informed consent was obtained from all participants. The study was sponsored by Lamellar Biomedical Limited and conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Results

Participants

A total of 43 patients (15 in the placebo group and 28 in the Visco-ease™ group) were recruited between March and December 2016 from 62 patients who were screened (Fig. 1). The intention-to-treat population reflected the number of patients actually recruited, which was slightly higher than planned, as the safety population (patients actually treated) was 25 in the Visco-ease™ arm and 14 in the placebo arm. The per protocol population (19 Visco-ease™, 12 placebo) reflected those who completed the study.

Baseline demographics

Table 1 shows the patients' details (mean (range) age 59 (41-78) years). The demographics seemed well balanced between the two groups. A total of 39 participants were male and all had squamous cell carcinoma (SCC). The oropharynx was the most common subsite, and 22 tumours (71%) were HPV-positive across both groups. The most notable imbalance between the groups was in tumour staging. In the Visco-ease™ group a higher proportion of patients had stage III or IV disease or higher T stages than in the placebo group. The greater use of concurrent chemoradiotherapy in the Visco-

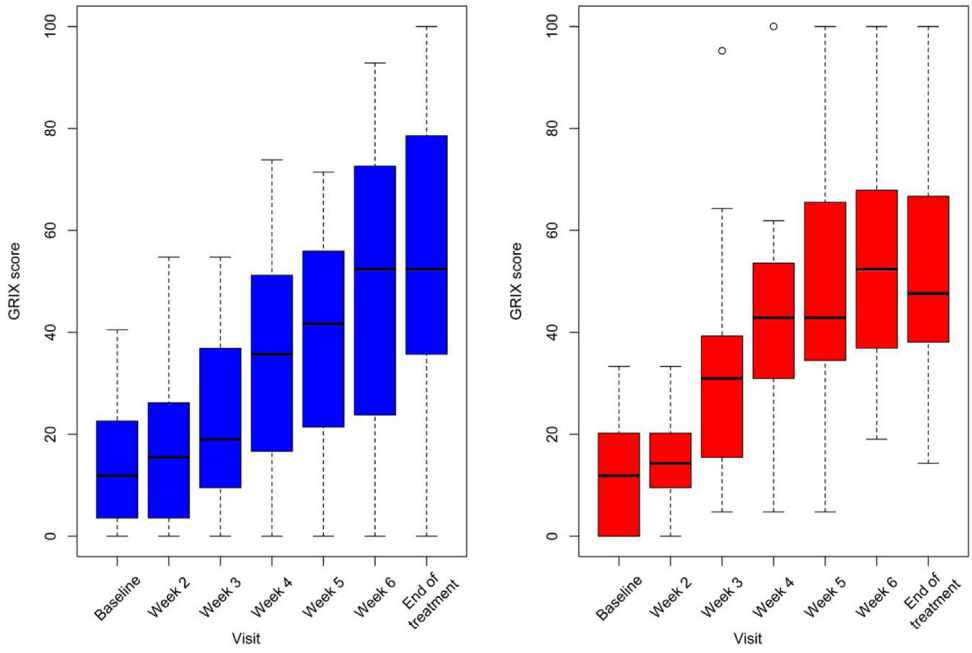

Fig. 2. Weekly GRIX clinic scores (blue = placebo, red = Visco-ease™).

Table 1
Baseline demographics for APT. Data are number unless otherwise stated.

	Placebo (n = 14)	Visco-ease™ (n = 25)	p value
Mean (range) age (years)	62 (51 – 78)	58 (41 – 70)	0.1513*
Sex:			
Male	13	22	1**
Female	1	3	
Subsite:			
Oropharynx	9	15	0.6735**
Larynx	3	5	
Hypopharynx	1	2	
Nasopharynx	1	0	
UKP	0	3	
Disease:			
SCC	14	25	1**
T classification:			
0–2	12	20	1**
3–4	2	5	
AJCC 7th edition			
I–II	4	3	0.2251**
III–IV	10	22	
Concurrent chemoradiotherapy			
Yes	7	17	0.3182**
No	7	8	

* 2-sample *t* test.
** Fisher's exact test.

ease™ group probably reflects this more advanced disease. The withdrawal of patients from both groups during the course of the study further increased this imbalance in disease stage.

Patient-reported xerostomia scores

Weekly GRIX scores are shown in Fig. 2 and Table 2. Patients reported an increase in xerostomia throughout radiotherapy. There was no significant difference (calculated using ANOVA) between each group for mean clinic GRIX score at any time point. Changes in scores from baseline to the end of treatment were compared between groups using linear regression adjusted for the baseline GRIX score. No relation was found (effect = −1.26, CI −21.77 to 19.24, p value = 0.90)

Table 2
Weekly Groningen radiotherapy-induced xerostomia (GRIX) scores. Data are mean (SD).

Variable	Placebo (n = 12)	Visco-ease™ (n = 19)	p value*
Baseline	13.5 (12.1)	11.5 (11.6)	0.6592
Week 3	23.2 (17.6)	31.6 (22.9)	0.2621
Week 4	34.7 (23.1)	44.4 (25.0)	0.2837
Week 5	38.3 (22.5)	50.8 (25.3)	0.1652
Week 6	49.8 (29.8)	53.6 (24.2)	0.7122
End of treatment	55.0 (30.8)	53.1 (24.0)	0.8631

* independent two-sample *t* tests between the groups.

Frequency of use of oral spray

The number of sprays used each day is shown in Fig. 3 for each group. The number increased initially during radiotherapy but decreased again towards the end of treatment.

Safety endpoints

Serious adverse events that were "at least possibly device-related" were monitored throughout the study. There were none in either group.

The number of participants with "at least one adverse event or serious adverse event" was compared between the groups as shown in Table 3. There was no significant difference between the groups in the percentage of participants affected.

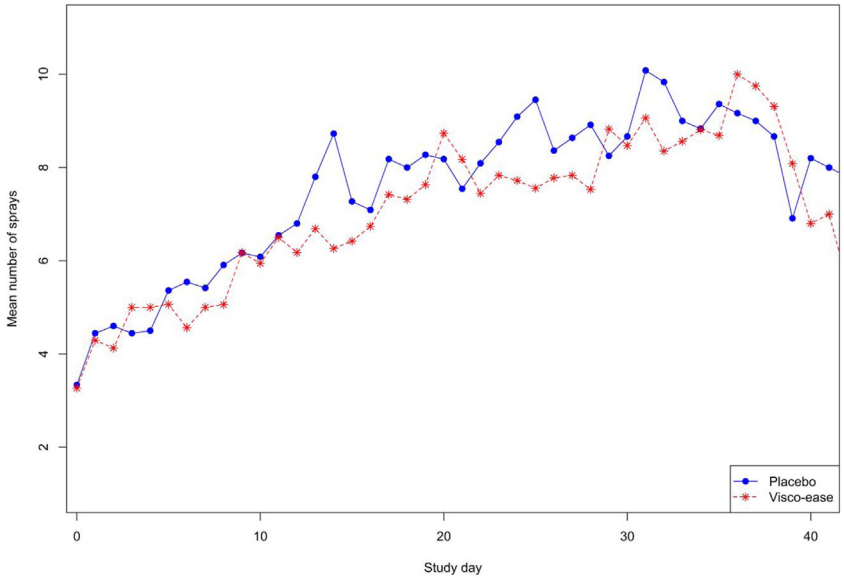

Fig. 3. Number of sprays used/day.

Table 3
Comparison between patients who had at least one adverse event (AE) or serious adverse event (SAE) (APT).

Event	Placebo (n = 14)	Visco-ease™ (n = 25)	p value
Non-serious AE	4	6	1.000
SAE	6	–	0.5145

The relative high incidence of both reflects the serious acute toxicity experienced by these patients, and was anticipated.

Discussion

The patients' characteristics were as expected for a group undergoing primary radiotherapy for cancer of the head and neck, and their xerostomia scores increased during treatment. Previous work has shown a mean increase in GRIX score of 65.2 during six weeks of radiotherapy,[13] but the mean increase was 41.6 in the Visco-ease™ group in our study. What was unexpected, however, was a similar increase in the scores in the placebo arm of only 41.5. Laboratory work has already shown no efficacy of the placebo (physiological saline) on the visco-adhesive properties of RIX saliva.[13] The smaller-than-expected increase in GRIX scores in the placebo group may be the result of the placebo effect, and the subjective symptom of RIX could have been genuinely improved with the use of oral saline spray compared with no intervention.

Our findings confirm the importance of including a placebo for comparison when investigating new treatments for RIX. Some previous studies that have assessed interventions for RIX have not included a placebo arm.[18,19] Had the placebo group not been included we could have assumed that the smaller increase in scores compared with the historical controls was clinically significant, as they were around 36% less than those recorded previously in the same setting (41.6 compared with 65.2).

Comparison of the GRIX scores in both groups failed to show a significant difference at any time point. In particular the primary efficacy endpoint of a 30-point reduction in the score with Visco-ease™ compared with placebo was not met. This was partly because scores in the placebo group were lower than anticipated and, as four patients (one in the Visco-ease™ and three in the placebo group) did not develop RIX (as defined by not reaching a GRIX score of 30 or more at any point during the study), it was impossible for their scores to meet the primary efficacy endpoint.

The number of sprays used increased during the course of radiotherapy and decreased over the final one to two weeks of treatment. However, as we did not evaluate compliance formally, it is unclear if the reported numbers showed true compliance or a failure to record use as time went on. Good compliance in the early weeks suggests good tolerability.

There was no difference in the frequency of adverse events or serious adverse events between the groups, and no adverse event was related to the device. This first-in-man study of Visco-ease™ therefore has shown a safe toxicity profile.

It is disappointing that the study did not meet the primary efficacy endpoint of a significant reduction in RIX, and our results show some of the difficulties involved in a study of a new intervention to treat it. It is widely accepted that patient-reported outcomes are the most important measure by which to judge the success of such an intervention[14] as physician-reported scores or measures such as salivary flow do not necessarily correlate with the symptom experienced by the patient.[1,20] Reports of RIX are therefore subjective,[14] making it a difficult metric to account for when designing a study such as this.

Our patients were currently being given radiotherapy for cancer of the head and neck. RIX is often considered to be a late or chronic side effect of the treatment, but can also occur as an acute side effect during treatment.[13,21] The acute group of patients were chosen from a safety perspective, as the device had not been tested in humans before and it was important to monitor its effects closely in those who were already attending hospital frequently. Patients who have completed radiotherapy generally attend monthly or less often as outpatients, and we thought that additional visits for safety monitoring would be an unjustified burden. Patients in the acute group are likely to have a considerably higher burden of symptoms (such as mucositis, dysphagia, skin reaction, pain, anorexia, weight loss, nausea, and vomiting) and a poorer QoL than those in the chronic group.[22] The modification of one acute symptom will probably make little difference to their QoL, as overall it will remain much poorer than it was at baseline. Now that we have shown the safety of Visco-ease™, further studies will be done in patients with established RIX after radiotherapy, as their symptoms are likely to be more stable. Its efficacy in those with chronic RIX will be the focus of future work.

During randomisation, the lack of stratification for any baseline characteristic (patients' characteristics, tumour, or treatment) resulted in a tendency for patients in the Visco-ease™ group to have stage III and IV cancer and for more to be treated by chemoradiotherapy. Unfortunately, given the nature of the withdrawals during the study, these imbalances were more pronounced at the end of treatment. Higher-stage disease will inevitably result in the treatment of larger volumes at higher doses and, compared with radiotherapy alone, concurrent chemoradiotherapy is well known to increase toxicity.[23,24] It seems likely therefore that the symptoms in the Visco-ease™ group will have been worse than those in the placebo group, which may have skewed the results. Stratification for all potentially confounding variables in this study (age, concomitant medication, smoking/alcohol history, tumour stage, treatment; and radiotherapy compared with chemoradiotherapy) would have meant that a larger sample size was required. We thought that this was inappropriate given that the study was the first to be done in humans.

Exploratory, post-hoc analyses were done after the initial results were examined and the difficulties described above were considered.

All patients who failed to reach a GRIX clinic score of 30 or more were excluded. Multivariate regression showed that tumour staging, concurrent chemoradiotherapy, use of morphine sulphate and study treatment had the greatest influence on the scores. When using the restricted population and after adjusting for the potentially confounding covariates, compared to placebo, Visco-ease™ seemed to have a positive effect in reducing GRIX scores. This supplementary data will be used only to inform the design of future clinical studies and not to make any claims about efficacy. It does, however, suggest that a signal may be detected with an appropriately designed study, and this is worth investigating. An alternative formulation of Visco-ease™ – for example, an oral rinse rather than a spray, is also being considered for future studies.

Ethics statement/confirmation of patients' permission

Ethics approval obtained. Patients' consent obtained.

Conflict of interest

A McLean, S Porteous, and S Clark, are employees and shareholders of Lamellar Biomedical Limited.

Availability of data and material

The authors vouch for the accuracy and completeness of the data and its analysis and for adherence to the study protocol. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The data was managed and analysed by the Robertson Centre of Biostatistics, University of Glasgow. Review of the data by the journal is welcome.

Throughout the study, monitoring visits by the sponsor were made to the study site to confirm compliance with the study requirements.

Authors' contributions

The study idea was conceived and designed by CP, BC, RJ, AMcL, SP, SC and MCT.

Statistical design and analysis was carried out by RY and CMM. Data management and analysis was overseen by SK. All authors contributed to acquisition of the data and interpreted the data. CP and MCT drafted the manuscript. All authors critically revised the manuscript.

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Clinical Trial Registration

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