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ORIGINAL ARTICLE

Randomised controlled trial of the efficacy of HybenX in the symptomatic treatment of recurrent aphthous stomatitis

SR Porter[1], K Al-Johani[1], S Fedele[1], DR Moles[2]

[1]*Oral Medicine and* [2]*Health Services Research, UCL Eastman Dental Institute, London, UK*

BACKGROUND: The treatment of recurrent aphthous stomatitis (RAS) is principally directed towards reducing the pain and duration of each episode of ulceration; however, there remain few agents for which there is definitive evidence of benefit.

AIMS: The aims of the present study were to determine the efficacy of HybenX (Epien Medical Inc., Minneapolis, MN, USA), *vs* another device used for the treatment of RAS (Salicept; Carrington Laboratories Inc., Irving, TX, USA) to reduce the symptoms and duration of RAS and determine the safety of HybenX for this clinical application.

MATERIAL AND METHODS: Sixty-three individuals (36 male, 27 female, group median age 25years, range 17.8–57.9years) were entered into a prospective randomised controlled trial of HybenX *vs* an occlusive covering device (Salicept oral patches; Carrington Laboratories).

RESULTS: Painful symptoms over a 5-day posttreatment period were reduced by both agents although HybenX was statistically more effective at day 2 than Salicept, and there was a trend for HybenX to cause greater pain reduction than Salicept over this 5-day period. Both agents gave rise to few adverse side effects – a total of nine adverse events in eight patients were recorded. All were unlikely to be related to the treatment devices. HybenX was only applied on one occasion to the HybenX group, while individuals in the Salicept group were able to self medicate as required. The mean number of Salicept patches used per day per subject was three (s.d. 3.3) on day 1 posttreatment, 3.4 (s.d. 3.1) on day 2 and 2.7 (s.d. 1.9) on day 3. Thereafter, the number of applications fell to a mean of 0.8 on day 7.

CONCLUSION: It is concluded that HybenX safely and effectively reduces the painful symptoms of RAS.

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Correspondence: Prof. Stephen Porter, Oral Medicine, UCL Eastman Dental Institute, 256 Grays Inn Road, London WC1X 8LD, UK. Tel: +44 (0) 20 7915 1142, Fax: +44 (0) 20 7915 2341, E-mail: s.porter@eastman.ucl.ac.uk
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Introduction

Recurrent oral ulceration [recurrent aphthous stomatitis (RAS), aphthous stomatitis, aphthae] is a common disorder characterised by superficial ulceration of the oral mucosa in otherwise healthy persons (Jurge *et al*, 2006; Scully, 2006; Scully and Porter, 2008). RAS can affect up to 25% of the general population (Scully, 2006), in women, people under the age of 40 years, non-smokers and those of high socio-economic status being more commonly affected (Jurge *et al*, 2006; Scully, 2006; Scully and Porter, 2008).

Recurrent aphthous stomatitis typically commences in childhood and is clinically characterised by recurrent oral mucosal ulceration in an otherwise healthy individual. The disease may be clinically characterised into three types (minor, major and herpetiform), of which the most common by far is minor aphthous ulceration. This presentation comprises approximately one to five ulcers of < 1 cm diameter that usually arise on the mobile, non-keratinised surfaces of the oral mucosa (Jurge *et al*, 2006).

The aetiology of recurrent oral ulceration remains unknown. A majority of patients do not have identifiable cause. Some do have a worsening of ulceration following trauma to the mouth (e.g. vigorous tooth cleaning or dental treatment). Others can suffer from an increase in RAS episodes caused by cessation of tobacco (McCullough *et al*, 2007) or psychological stress (Scully, 2006). Suggested aetiological factors include a family history of RAS, idiopathic haematinic deficiency and more rarely, food sensitivities, immune defects, menstrual cycle variations and perhaps infant feeding practices (McCullough *et al*, 2007).

At present, thalidomide is the only agent that successfully stops the recurrence of RAS (Jurge *et al*, 2006; Scully and Porter, 2008). However, the ulcers usually recur on cessation of therapy and the well known adverse side-effects of thalidomide, particularly the liability to teratogenicity and peripheral neuropathy limit its clinical application to specialist practice (Porter and Jorge, 2002). Thus, therapy is principally directed towards lessening the duration and pain of the ulceration. Typical therapies include chlorhexidine

gluconate (0.2%) mouth rinses, topical corticosteroids [e.g. triamcinolone acetonide (0.1%) in 1% carboxycellulose paste or betamethasone phosphate or prednisolone mouth rinses] and topical minocycline (Gorsky *et al*, 2007). A wide spectrum of other agents is available for the management of RAS, but the efficacy of these has rarely been formally assessed in appropriately designed studies (Porter and Scully, 2005).

Coagulation has been suggested to lessen and hasten healing of the ulceration of RAS (Rhodus and Bereuter, 1998), although there has been no widely available agent for self-administration by patients. The present study has examined the benefits of a commercially available product, HybenX, to lessen the painful symptoms of RAS. The primary aim of the present study was to determine the clinical benefits of a single application of HybenX device in lessening the painful symptoms of RAS by virtue of a randomised controlled comparison with another device (Salicept) approved for the treatment of such ulceration. Additionally, the study sought to determine the performance and safety of HybenX in the treatment of RAS.

Materials and methods

Ethical approval

Ethical approval for the study was obtained from the Joint Research and Ethics Committee of University College London (UCL) and University College London Hospitals NHS Foundation Trust (UCLHT).

Study groups

The study group comprised 53 otherwise healthy adults aged over 18 years with a history of RAS (Porter and Scully, 2005). Specifically, all subjects had a history of recurrent bouts of ulceration of the non-keratinised oral mucosa, this including two episodes in the past 12 months. None of the subjects had any local cause for the ulceration and history of infectious, haematological, gastrointestinal or dermatological disease likely to give rise to oral mucosal ulceration. None of the subjects received medication likely to precipitate oral mucosal ulceration (Scully *et al*, 2003). All subjects agreed to abstain from using other mouth ulcer treatments [i.e. topical or systemic anti-inflammatory or analgesic medications (e.g. aspirin, paracetamol or ibuprofen), corticosteroids, analgesics, mouthwashes containing alcohol or anaesthetic containing products] and tooth-bleaching agents during the course of the study. All female patients undertook a pregnancy test prior to entry to the study and females found to be pregnant did not enter the study.

Study protocol

At entry to the study, all subjects had at least one oral mucosal ulcer for < 48 h. At baseline, the size, location, colour and depth of each ulcer was estimated clinically and via photographs and the subjects were requested to estimate the intensity of the pain on a 100-mm visual analogue scale (VAS; the baseline unchallenged pain evaluation). Subjects then held 20 ml of natural orange juice over the area of ulceration for 5 s and then swallowed or expectorated the juice. A further VAS was then recorded (baseline challenged pain evaluation).

Each subject was then randomly assigned to the HybenX group or Salicept group. A single application of HybenX or Salicept was then undertaken by a clinician to the ulcers. This was immediately followed by a recording of an unchallenged VAS (immediate posttreatment unchallenged pain evaluation) and a challenged pain evaluation (with orange juice as with the baseline challenged pain evaluation). A further estimation of unchallenged and challenged VAS was obtained 20 min following application of the devices (20 min posttreatment unchallenged and challenged pain evaluations).

Subjects were then discharged. Subjects in the Salicept group were instructed on proper at-home self-administration of Salicept – these could be applied as often as the subject wished. Subjects in the HybenX group did not receive any additional devices. All subjects were instructed to complete a VAS of the highest estimated score for each day for the following 8 days – this was undertaken before they retired to bed. The Salicept group also recorded the number of Salicept applications undertaken each day. Each subject was contacted over the telephone by one of the study staff to remind him/her of these tasks. All subjects also recorded any potential adverse side effects of HybenX or Salicept.

At day 8 posttreatment, all subjects were examined by a clinician, masked to the treatment of the patient, to determine the size, site and subjectively the degree of healing of any areas of oral mucosal ulceration by comparison with baseline clinical notes and photographs. A day 8 posttreatment, unchallenged and challenged pain evaluation was undertaken. Additionally, patients completed a self-administered questionnaire on their satisfaction of the treatment provided by the device they had received.

Statistical analyses

Based on pain assessment of patients of a previous study of an agent allied to HybenX in which a mean change in baseline of 15–45 mm on VAS was observed for two active arms (Rhodus and Bereuter, 1998), a sample size of at least 22 in each treatment group was required to detect a 15-mm difference between the two groups with respect to pre and posttreatment pain scores. This assumed a two-sided test conducted at the 5% significance level with 80% power.

Pain reduction was compared between HybenX and Salicept by testing the changes from baseline in VAS pain score at all designated time points. Unchallenged and challenged pain scores were analysed separately. Pain scores as recorded on a 100-mm scale were treated as a continuous outcome. The differences in pain scores were compared between treatment groups by Student's *t*-test at each time point.

To assess the overall effect (including all time points) of treatment on unchallenged pain score, a repeated-

measurements regression model was fitted to pain scores for each patient at each time. The covariates included were an intercept, a HybenX treatment group indicator, time of assessment (value of 0–8), the treatment group by time of assessment interaction and the baseline pretreatment pain score.

The proportion of subjects with complete healing of all ulcers at day 8 as evaluated by the masked evaluator was compared between treatment groups using Fisher's exact test. The number of days to ulcer healing (subject perception) was compared between treatment groups by using a Cox Proportional Hazards Model. The model includes an indicator variable for HybenX treatment. A hazard ratio estimate > 1 indicates a faster perception of healing for HybenX patients.

The number of Salicept devices reapplied after challenged pain assessment was summarised by treatment group. Similarly, the daily diary information on the number of patches applied per day, patient ran out of patches, and reason for using less patches than the day before was summarised for the Salicept group.

A measure of change in general health was calculated for each patient as follows: For each body system assessed in the screening and day 8 physical examinations, a score of 0 (no change), 1 (new condition reported on day 8) or −1 (screening condition not reported on day 8) was assigned. The sum of scores was used as a measure of change in general health.

The total health score calculated for each patient was compared between treatment groups using a (non-parametric) two-sample Wilcoxon Rank Sum test as scores were not normally distributed.

In view of the small number of adverse events, no statistical analysis was performed to compare their incidence between the treatment groups. Instead, a complete listing of adverse events along with their full description is provided.

Results

Sixty-three patients were enrolled in the study. Thirty-two (19 male, group median age 23.1 years, range 18.3–57.9 years) were randomly assigned to the HybenX group while 31 (17 male, group median age 27 years, range 17.8–53.4 years) assigned to the Salicept group. Eight subjects of the HybenX group were ultimately excluded as they developed new ulcers in the course of the study, and thus were in violation of the study protocol and thus the final HybenX group comprised 24 patients (14 male, group median age 23.1years, range 20–47.6 years). Two subjects in the Salicept patients were likewise excluded as they developed new ulcers, while from the study, hence the final Salicept group comprised 29 subjects (17 male, group median age 27 years, range 17.8–53.4 years). There were no statistically significant differences in the baseline characteristics of the two groups (e.g. gender, age, medical histories, concurrent medication, pulse, blood pressure and respiratory rate) nor the number, size, colour or estimated depth of the ulcers (data not shown). Salicept application during study.

Pretreatment, immediate posttreatment and 20 min post-treatment pain scores

The unchallenged pain scores at pretreatment, immediately, 20 min and 8 days following treatment of the two groups were not statistically different (Table 1), although the subjects in the HybenX group had a trend for greater pain than the Salicept group. A pattern of increased scores following application of HybenX similar to that of Salicept was observed following orange juice challenge (Table 2), although of note the HybenX group had greater ($P = 0.025$) pretreatment challenge score than the Salicept group.

Day 1–8 unchallenged treatment pain scores

The reduction in pain scores as recorded by patients is detailed in Table 3 and Figure 1. The reduction in the mean pain score of the HybenX group pain was statistically greater than the Salcept group on days 1 ($P = 0.016$) and 2 ($P = 0.007$), as detailed clearly in Figure 1. It is interesting to note that HybenX caused an initial rise in pain (as denoted by the negative values), probably reflecting the initial stinging sensation following application. However, over the next two days HybenX is the more effective of the two agents in reducing pain.

Subjective assessment of ulcer healing

By day 8, 50% of the HybenX subjects and 44.4% of the Salicept subjects had had complete healing of all ulcers – this difference was not statistically significant. The mean closure of the largest ulcers also did not differ significantly between the two groups. Other than on day 4, HybenX had a higher cumulative percentage of patients

Table 1 Summary of unchallenged pain reduction[a] at pretreatment, immediate posttreatment, 20 min posttreatment and day 8 in subjects receiving HybenX or Salicept

	HybenX	*SaliCept*	P-*value*[b]
Pretreatment unchallenged pain score			
n	24	29	0.565
Mean (s.d.)	14.5 (18.7)	17.6 (20.3)	
Median	5.5	11.0	
Min, max	0.0, 62.0	0.0, 96.0	
Immediate posttreatment pain reduction			
n	24	29	0.056
Mean (s.d.)	−12.0 (22.8)	−1.2 (17.3)	
Median	−12.0	0.0	
Min, max	−64.0, 39.0	−50.0, 30.0	
20 min. posttreatment pain reduction			
n	24	29	0.437
Mean (s.d.)	5.0 (14.5)	8.1 (13.1)	
Median	1.0	3.0	
Min, max	−15.0, 51.0	−21.0, 48.0	
Day 8 pain reduction			
n	24	27	0.425
Mean (s.d.)	12.5 (17.6)	16.8 (20.5)	
Median	5.0	11.0	
Min, max	−4.0, 59.0	−6.0, 95.0	

[a]Pain reduction = (Pretreatment unchallenged pain score – designated time pain score).
[b]Two-sample *t*-test *P*-values.

Table 2 Summary of challenged pain reduction[a] at pretreatment, immediate posttreatment, 20 min posttreatment and day 8 in subjects receiving HybenX or Salicept

	HybenX	*SaliCept*	P-*value*[b]
Pretreatment challenged pain score			
n	24	29	0.025
Mean (s.d.)	22.7 (19.7)	37.5 (25.1)	
Median	18.0	39.0	
Min, max	2.0, 80.0	2.0, 99.0	
Immediate posttreatment pain reduction			
n	24	29	0.057
Mean (s.d.)	9.4 (16.6)	18.4 (16.1)	
Median	6.0	12.0	
Min, max	−13.0, 58.0	−3.0, 53.0	
20 min. posttreatment pain reduction			
n	24	29	0.392
Mean (s.d.)	13.1 (14.1)	17.7 (23.5)	
Median	8.0	12.0	
Min, max	−5.0, 59.0	−34.0, 79.0	
Day 8 pain reduction			
n	24	27	0.046
Mean (s.d.)	19.9 (18.0)	33.2 (27.7)	
Median	14.5	30.0	
Min, max	0.0, 67.0	−10.0, 98.0	

[a]Pain reduction = (Pretreatment challenged pain score – designated time pain score).
[b]Two-sample *t*-test *P*-values.

who perceived that their ulceration had healed, but the perceived healing was not statistically different between the two groups (Table 4).

Safety

Nine adverse events in eight patients were recorded. All were unlikely to be related to the treatment devices. The five adverse events in the HybenX group comprised probable common cold (two patients), sore throat (one patient), cough (one patient) and sprained ankle (one patient). The four adverse events of the Salicept group were indigestion and diarrhoea (cited as two events in one patient), traumatic lesion of lower lip (one patient) and 'hay fever' (one patient).

Acceptability

The mean number of Salicept patches used per day per subject was 3 (s.d. 3.3) on day 1 posttreatment, 3.4 (s.d. 3.1) on day 2 and 2.7 (s.d. 1.9) on day 3. Thereafter, the number of applications fell to a mean of 0.8 on day 7. The decreased use of Salicept was reported by subjects to principally reflect decreasing clinical need of the device, although other cited reasons included inconvenience of application, being 'too busy' or forgetting to apply the device.

Discussion

Recurrent aphthous stomatitis remains a difficult disorder to treat. As the precise aetiology remains unknown, there remains no specific, safe and effective means of causing cessation of the outbreaks of ulceration, hence almost all therapies are directed towards lessening the painful symptoms and duration of the ulcers (Porter and Scully, 2005). Patients may seek advice from a variety of sources as regards appropriate therapy and often self-medicate with a range of agents (Gill and Scully, 2007).

Table 3 Summary of posttreatment pain reduction[a] in subjects receiving HybenX or Salicept

	HybenX	*SaliCept*	P-*value*[b]
Day 1			
n	24	27	0.016
Mean (s.d.)	3.8 (16.3)	−9.2 (20.4)	
Median	−1.0	−8.0	
Min, max	−25.0, 51.0	−51.0, 24.0	
Day 2			
n	24	27	0.007
Mean (s.d.)	5.9 (15.1)	−9.4 (22.9)	
Median	2.0	−7.0	
Min, max	−9.0, 56.0	−61.0, 26.0	
Day 3			
n	24	27	0.182
Mean (s.d.)	5.3 (15.1)	−2.0 (22.5)	
Median	2.5	−1.0	
Min, max	−15.0, 57.0	−45.0, 59.0	
Day 4			
n	24	27	0.666
Mean (s.d.)	6.5 (17.2)	3.9 (23.9)	
Median	3.0	−1.0	
Min, max	−24.0, 58.0	−31.0, 89.0	
Day 5			
n	24	27	0.857
Mean (s.d.)	8.3 (18.2)	9.3 (22.5)	
Median	4.0	7.0	
Min, max	−25.0, 59.0	−20.0, 94.0	
Day 6			
n	24	27	0.616
Mean (s.d.)	9.4 (18.0)	12.2 (21.4)	
Median	4.0	9.0	
Min, max	−22.0, 58.0	−10.0, 95.0	
Day 7			
n	24	26	0.507
Mean (s.d.)	10.8 (18.4)	14.6 (21.4)	
Median	4.5	10.5	
Min, max	−22.0, 59.0	−14.0, 94.0	

[a]Pain reduction = (Pretreatment challenged pain score – designated time pain score).
[b]Two-sample *t*-test *P*-values.

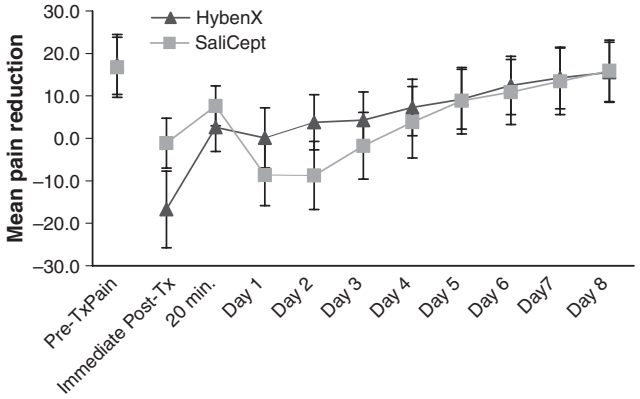

Figure 1 Unchallenged pain scores of subjects receiving HybenX or Salicept

Table 4 Cumulative number of subjects receiving HybenX or Salicept with perception of ulcer healing

	Day 2	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*
HybenX (n = 24)	3 (12.5%)	6 (25.0%)	10 (41.7%)	14 (58.3%)	16 (66.7%)	19 (79.2%)
SaliCept (n = 29)	2 (7.7%)	3 (12.0%)	9 (34.0%)	10 (38.5%)	13 (52.0%)	15 (62.5%)

Percentages are calculated out of number of patients responding on each study day within each group.

There remains no systematic review of the treatment of RAS and despite the wide range of agents that are purported to be of some benefit, the mainstays of therapy have been topical corticosteroids and antimicrobials such as chlorhexidine (Jurge *et al*, 2006; Scully, 2006; Scully and Porter, 2008). Nevertheless, there are little substantial data on the precise benefits of the former and the latter may give rise to an unpleasant bitter taste and extrinsic staining of the teeth. Newer agents include topical minocycline (Gorsky *et al*, 2007) and amlexanox. The latter has, in some but not all formulations, been found to lessen the clinical signs and symptoms of RAS, particularly when applied in the prodromal stage of ulcer development, but this agent is not available widely in all countries. Thus, as with herpes labialis, there is a therapeutic role for topical agents that can be easily applied by affected individuals to sites of painful orofacial disease that will safely reduce painful symptoms and be widely available to the general public.

It was previously observed that pain of RAS was significantly reduced 3 days after application of the chemical coagulation agent (Debacterol; Epien Medical Inc, St Paul, MN, USA) when compared with three times daily application of triamcinolone in an adhesive paste (Rhodus and Bereuter, 1998). In addition, the agent hastened healing of the ulcers such that by day 6, 80% of the ulcers treated with Debacterol had resolved, in comparison with only 30% of ulcers treated with topical corticosteroid. The results of this previous study suggested that chemical cauterisation or coagulation might be of clinical benefit in the treatment of RAS; however, it is unclear if any method of treatment randomisation was employed and the agent has never become commercially available. The present study examined the potential benefits of a commercially available device (HybenX) that conveniently releases a solution that chemically coagulates areas of ulceration. Approximately 0.2 ml of the cauterising solution is delivered from a hollow shaft of a cotton wool swab to the tip, which is then placed upon an ulcer for 10 s (Figure 2). The HybenX solution comprises a concentrated aqueous mixture of free sulphate and sulphonated aromatics, specifically hydroxybenzenesulphonic acid, hydroxymethoxybenzene suphonic acid and suphuric acid. The hydrozybenzenes are keratolytic, whereas the sulphonate groups and sulphuric acid are hygrposcopic and denaturing. The outcome of application to an area of ulceration is denaturation, precipitation and coagulation of the tissue debris on the ulcer surface and the creation of a protective layer of coagulated tissue debris over the surface of the ulcer that hence lessens local discomfort to painful stimuli. This protective surface debris is resorbed during healing (Rhodus and Bereuter, 1998).

The present study was a prospective, randomised trial of a suitable number of subjects to achieve the required statistical power. The two subject groups were of comparable age, gender and had comparable signs of RAS and associated pain symptoms at the commencement of the study. The results reveal that when compared with a device designed to protect areas of oral ulceration (Salicept), local application of HybenX significantly reduced the pain of RAS after 2 days. Both HybenX and the control device (Salicept) caused a reduction in unchallenged pain scores between days 1 and 4, but the reduction by HybenX was always greater than that of Salicept. The reduction in pain by both agents is of interest, as it perhaps confirms that the mode of action of HybenX may be similar to that of Salicept, in that it creates a physical barrier that lessens discomfort caused by local painful stimuli. The immediate treatment challenged and unchallenged pain of the HybenX groups were as expected greater than the Salicept group as the former agent is acidic, while the latter provides a bland covering and the presently observed benefits of HybenX would seem to outweigh the transient posttreatment increase in local pain.

Although not the primary objective of the study, the performance of both devices in aiding healing of ulceration was assessed. It has previously been reported that Debacterol induces more rapid early healing of RAS compared with topical corticosteroid paste or no treatment (Rhodus and Bereuter, 1998). In the present study, there was no difference in patient perception of ulcer healing over days 1–7 of the study period, and no difference in ulcer healing at day 8, as observed by a clinician masked to the test treatment. These contrasting results may reflect differences in the agents employed, as Debacterol has a higher content of sulphuric acid than HybenX, but it is doubtful that this is the mechanism of enhanced healing as this acid aids tissue necrosis. The contrasting results may reflect the control agents/devices that were employed in the two studies, but again it is difficult to appreciate how such variations would account for the different outcomes of healing. The effects of this agent upon nerve endings are not known; hence, it is unclear if HybenX, in some way, causes a reduction of pain as a consequence of a local neurological action. The present results reflect patient perceptions, whereas those of the earlier study were based on a more accurate examination by a clinician. It is thus possible that the present results underscore the effects of HybenX (and/or Salicept) upon ulcer healing. No correlations between time of onset on ulceration and commencement of therapy with either agent was

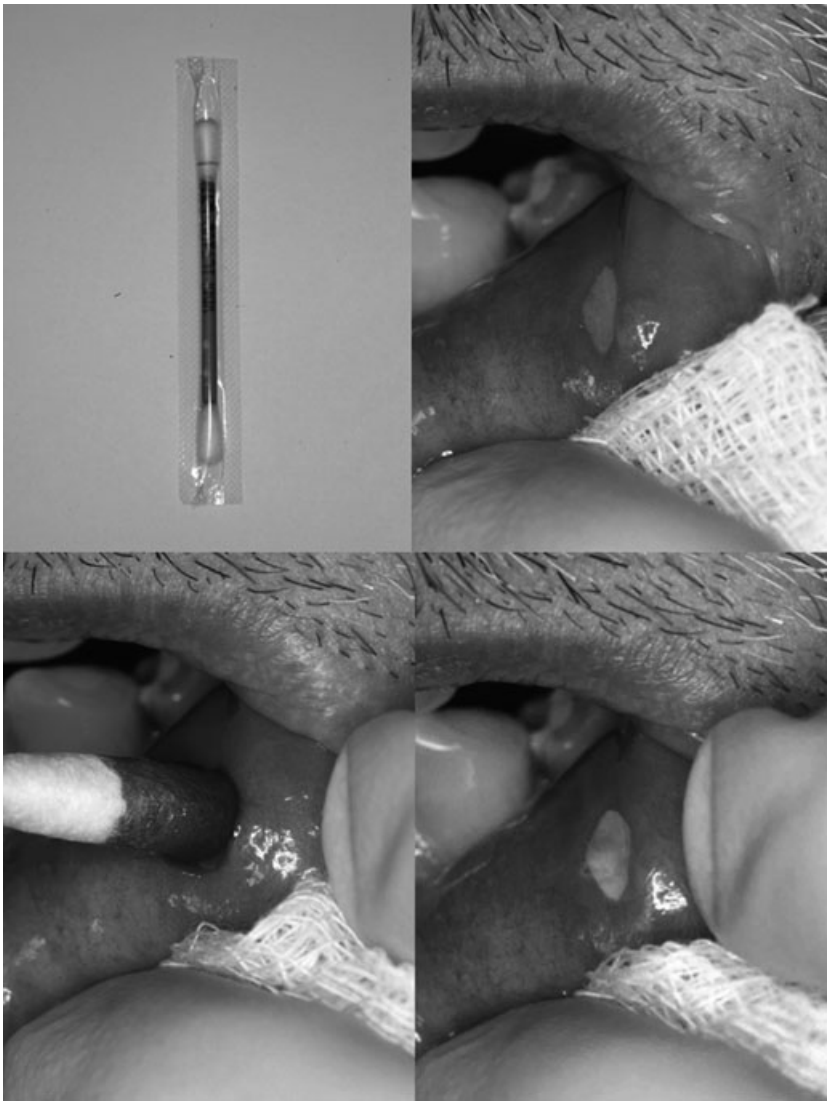

Figure 2 The cotton wool device contains the active solution that is delivered via placing the tip of the swab upon an ulcer for 10 s. The outcome of application of HybenX creates a protective layer of coagulated tissue debris over the surface of the ulcer

undertaken. However, it is probable that early application may hasten the reduction in pain associated with this type of ulceration.

Salicept had to be repeatedly applied to the ulcers over the 8-day study period; in contrast, HybenX was applied only once. Subjects receiving the Salicept gradually applied fewer patches as time progressed, this reflecting both clinical (i.e. ulcer healing) and social reasons (e.g busy lifestyle). It is thus evident that HybenX is more advantageous than Salicept in the treatment of RAS as it requires only single application, causes greater pain relief and is probably more convenient to use than the latter agent. Certainly both agents are safe as adverse events were uncommon and unlikely to be caused by their use.

The present data indicate that HybenX safely and conveniently reduces the pain of ulceration of RAS. This benefit extends over several days, although it is greatest at day 2 following application. HybenX is thus an acceptable agent for the management of the RAS symptoms and perhaps physical trauma, the two most common causes of oral ulceration. Although HybenX was applied by a clinician, patient-directed application should be easily possible with the present system. This agent will not cause cessation of RAS as its action is non-specific and not directed to any identifiable aetiological factor; nevertheless, it will provide symptomatic relief and unlike almost all agents available across the counter, it has now been definitively found by means of the present randomised controlled trial to lessen pain of one of the most common causes of ulceration of the mouth.

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Author contributions

SR Porter: design and instigation of study, data interpretation and writing of manuscript. K Al-Johani: design of study, data interpretation and writing of manuscript. S Fedele: design of

study, data interpretation and writing of manuscript. D. Moles: data interpretation.

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