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CLINICAL COMPARISON OF THREE POLYHEXANIDE-PRESERVED MULTI-PURPOSE CONTACT LENS SOLUTIONS

Lyndon Jones, Deborah Jones† and Mark Houlford‡*

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Abstract — *This study investigated the clinical differences between three commercially available polyhexanide (PHMB)-preserved disinfection systems containing varying percentages of PHMB, when used with FDA group II and group IV disposable contact lenses. After 1 month of wear the product with the highest concentration of PHMB ('All-in-One') was graded as being less comfortable on insertion ($P<0.03$), had lower overall satisfaction ($P<0.05$) and resulted in reduced lens comfort ($P<0.04$) when compared with the other two products. Corneal staining was also significantly higher with this product after both 14 days ($P<0.001$ with group II and $P<0.02$ with group IV) and 28 days ($P<0.00001$ with group II and $P<0.03$ with group IV).*

KEY WORDS: Disposable, polyhexanide, biguanide, corneal staining, solution reactions

Introduction

Although rare[1], *Acanthamoeba* keratitis is a devastating eye disease, often resulting in substantial vision loss, and recent studies have indicated that the incidence of such infections may be higher than initially thought.[2] Recent publicity in the UK, particularly on television and in the lay press, has resulted in many patients deciding to switch to care products which are perceived as being more efficacious in their ability to kill pathogenic micro-organisms. While it is a widely accepted principle that patients should not switch care products without first consulting their practitioner, few studies have shown that such an action will result in any untoward consequences. Furthermore, practitioners frequently interchange solution systems with similar chemical formulations believing them to be comparable — if not identical — in performance.

The purpose of this study was to investigate the clinical differences between three commercially available polyhexanide (polyhexamethylene biguanide, PHMB) preserved disinfection systems containing varying percentages of PHMB and in various formulations, when used with FDA group II and group IV frequent replacement contact lenses.

Materials

Ten male subjects were entered into the study. All subjects had ≤1.00D of astigmatism and had previously worn daily wear lenses without complications for at least 1 year. All subjects had previously used two-step hydrogen peroxide disinfection systems and none had prior exposure to either test lens. Subjects with eye disease, allergies, insufficient lacrimal secretions, pre-existing ocular infections and a history of problems with lens wear were all excluded. Before commencing the project all subjects were screened to ensure that they complied with the inclusion criteria. If suitable the aims of the study were explained and they were asked to sign an informed consent form. The demographic details are given in *Table 1.*

Table 1. *Demographic details*

	Mean ±SD	*Range*
Age	37 ± 12	22 −55
Sphere	−3.80 ± 1.12	−1.5 to −5.50
Cylinder	−0.23 ± 0.3	0 to −1.00
Flat keratometry reading	7.9 ± 0.3	8.35 −7.50
Steep keratometry reading	7.83 ± 0.3	8.30 −7.40

All subjects were fitted with the two test lenses, which were Bausch & Lomb 'Medalist 66' and Johnson & Johnson 'Surevue', details of which are given in *Table 2.* The subjects were trial fitted with each lens design to ensure that an adequate fit could be achieved with each type. In cases where it proved impossible to achieve a satisfactory fit with either design the subject was excluded from the study.

Table 2. *Lens parameters*

	Surevue	*Medalist*
Water content	58%	66%
Monomers	HEMA/MA	HEMA/VP
USAN	Etafilcon A	Alphafilcon A
FDA category	Group IV	Group II
ISO category	Filcon 1b	Filcon 4a
Manufacture	Moulded	Moulded
Back optic zone radius	8.40, 8.80	8.70
Total diameter	14.00	14.20
Centre thickness	0.105	0.110

HEMA = hydroxyethyl methacrylate; VP = vinyl pyrrolidone; MA = methacrylic acid.

The care regimes evaluated were Sauflon 'All-in-One', Allergan 'Complete' and Bausch & Lomb 'ReNu', whose details are given in *Table 3.* All solutions were used such that the lenses were rubbed, rinsed and stored in

* *BSc, FCOptom, DCLP, DOrth, FAAO.*
† *BSc, FCOptom, DCLP, FAAO.*
‡ *BSc, MCOptom.*

Table 3. *Solution details*

	Sauflon 'All-in-One'	*Allergan 'Complete'*	*B&L 'ReNu'*
Polyhexanide	0.0005%	0.0001%	0.00005%
EDTA	0.3%	0.05%	0.1%
Surfactant	poloxamine	tyloxapol	poloxamine

the solution overnight. All solutions were used with the cases provided by the manufacturers and each subject was given the instruction sheet provided by the manufacturer. No saline solutions, enzyme tablets or rewetting drops were used at any stage during the study and each care system was only taken from a single lot.

A clinical assistant randomly assigned the solutions and lenses for the study. The information regarding the lenses being worn in each eye was unknown to either the subjects or the investigator (double-masked paradigm) and the solution system being used at any time was unknown to the investigator (single-masked paradigm).

Each subject was issued with each of the three available disinfection systems in a randomised fashion. During the study the lenses were worn as a contralateral pair on a daily basis for 1-month periods, after which they were replaced. The right eye–left eye arrangement of the lenses remained the same throughout the period of the study, but the right eye–left eye combination was randomised such that each lens was worn an equal number of times in each eye.

Methods

Upon initial collection with each care regimen the clinical assistant inserted the first set of lenses to be worn. After an interval of at least 15min the investigator recorded the visual acuity and front surface wettability. If these factors were acceptable the subject was instructed on the recommended care regime by the clinical assistant, given all necessary solutions and dismissed for 2 weeks, the target date for the appointment being 14 (±2) days.

Upon return to the test centre visual acuity and wettability were measured. The lenses were then removed and a full slit-lamp examination undertaken to estimate the amount of corneal and conjunctival staining and palpebral lid appearance. Subjects were then dismissed for a further 2 weeks, with the final check-up with each care regime occurring after 28 (±3) days. At this appointment the same protocol as above was followed. After the slit-lamp examination the subjects' eyes were rinsed out with single-dose sterile saline, a new set of lenses inserted by the clinical assistant and the preliminary data taken once more. Subjects were then dismissed with the next combination of lenses and solutions and the above protocol followed with the remaining two care regimes.

Visual acuity was recorded as logMAR acuity at high (90%) and low (10%) contrast. Front surface wettability of the lenses was assessed with the Loveridge grid, a modified keratoscope in which the conventional mires are replaced with a grid.[3] The illumination system of the keratoscope is used to illuminate the cornea and the grid is viewed through the viewing system of the slit-lamp microscope at ×20. The time in seconds for the first break in the grid is noted and the median of three measurements is recorded as the pre-lens non-invasive break-up time (PLNIBUT).

Subjective satisfaction during the study was assessed via the use of two self-administered assessment forms, which used a conventional 10-point grading scale, with '1' representing the lowest score and '10' the highest. One form graded the lenses for visual quality, comfort and overall satisfaction and the other graded the solutions for comfort on insertion and overall satisfaction. These were completed by the subject at the end of the first full day of wear and every week thereafter. These were returned to the investigator at the end of each 4-week period.

The slit-lamp evaluations were graded using conventional severity and area scales, based on reports previously published.[4–9] When undertaking fluorescein assessments a Kodak Wratten No. 12 barrier filter was used to increase the contrast of the fluorescence.[10]

Data Analysis

Summary statistics were calculated for all variables. A one-way repeated measure ANOVA on ranks was used to compare results between solutions and the Wilcoxon signed rank test was used to compare the two materials. If the ANOVA proved significant then multiple comparison testing was conducted using the Student–Newman–Keuls test. In all cases a P value of <0.05 was taken as statistically significant.

Results

Visual Acuity

Both high and low contrast visual acuity remained consistent across the 4 weeks of wear, with no significant reduction across the wearing period (P=NS). There was no significant difference between lens types or solutions (P=NS).

Wettability (PLNIBUT)

Figure 1 reveals that there was no significant difference between materials or solutions at any visit (P=NS) but that wettability reduced equally with all combinations across the 4-week period and that this reduction was statistically significant ($P<0.05$).

Subjective Responses — Solution

Comfort *Figure 2* indicates that comfort on insertion reduced as the lenses aged with all solutions. This reduction was significant with All-in-One ($P<0.03$) but not with the other two products (P=NS). The comfort scores were not significantly different between solutions at the initial visit (P=NS) but were for the final visit ($P<0.03$), with the comfort of All-in-One being less than the other two products ($P<0.05$).

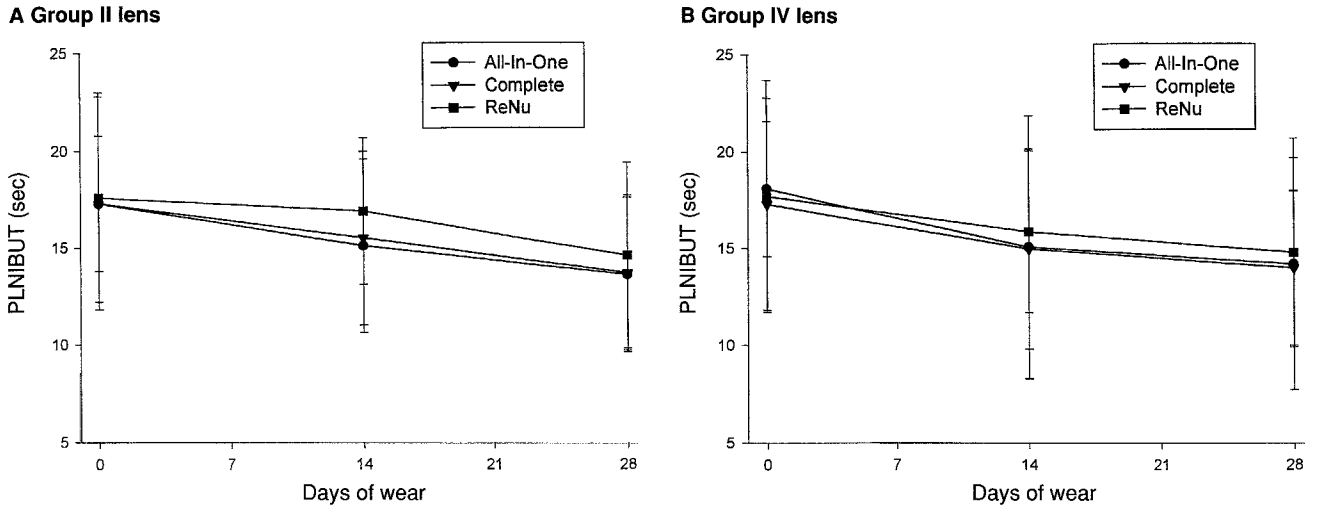

Figure 1. *Pre-lens non-invasive break-up time (PLNIBUT) in seconds (mean ± SD) of the group II lenses (A) and the group IV lenses (B) when used with all solutions, as assessed by the Loveridge grid. The time in seconds for the first break in the grid is noted and the median of three measurements is recorded as the PLNIBUT. This measurement provides an assessment of the front surface wettability of the lens material.*

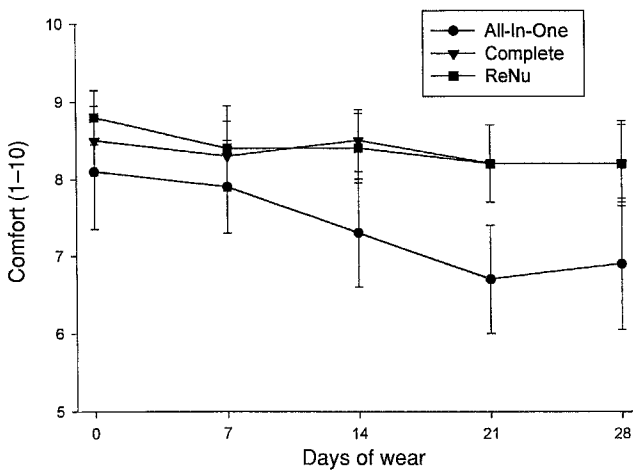

Figure 2. *Subjective comfort scores for all solutions following insertion (mean ± SD). Comfort was graded via the use of self-administered assessment forms, which used a conventional 10-point grading scale in which '1' represented the lowest score and '10' the highest.*

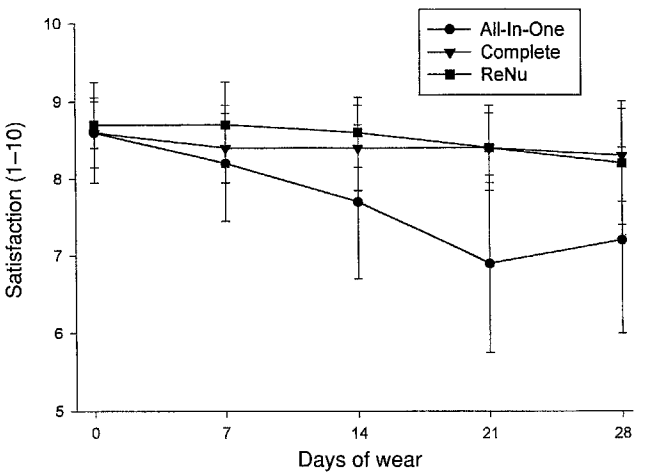

Figure 3. *Subjective overall satisfaction scores for all solutions (mean ± SD). Satisfaction was graded via the use of self-administered assessment forms, which used a conventional 10-point grading scale in which '1' represented the lowest score and '10' the highest.*

Overall Satisfaction *Figure 3* indicates that subjects became increasingly dissatisfied with all solutions as the study progressed. This reduction was significant only for All-in-One ($P<0.02$). While there was no significant difference between products at the beginning of the study (P=NS) there was at day 28 ($P<0.05$), with All-in-One resulting in lower satisfaction than the other two products ($P<0.05$).

Subjective Responses — Lenses

Visual Quality *Figure 4A and B* indicates that subjects felt that visual quality reduced during the study with all combinations of products. This reduction was only significant for All-in-One, for both the group II lens ($P<0.01$) and the group IV lens ($P<0.03$). There was no statistically significant difference between the three solutions at either collection or after 28 days (P=NS). There was no significant difference in subjective visual quality between the two lens types at any visit (P=NS).

Lens Comfort *Figure 5A and B* indicates that at all visits lenses were less comfortable with All-in-One and that there was a significant reduction in comfort across time with the All-in-One/group II combination ($P<0.01$). At day 28 both lens types were less comfortable with All-in-One than the other solutions ($P<0.04$). There was no significant difference in subjective comfort between the two lens types at any visit (P=NS).

Overall Satisfaction *Figure 6A and B* reveals that there was an obvious trend for subjects to be less happy with their lenses (regardless of type) when used with the All-in-One solution. While there was no difference in overall satisfaction upon collection, after 28 days both lenses demonstrated lower satisfaction scores

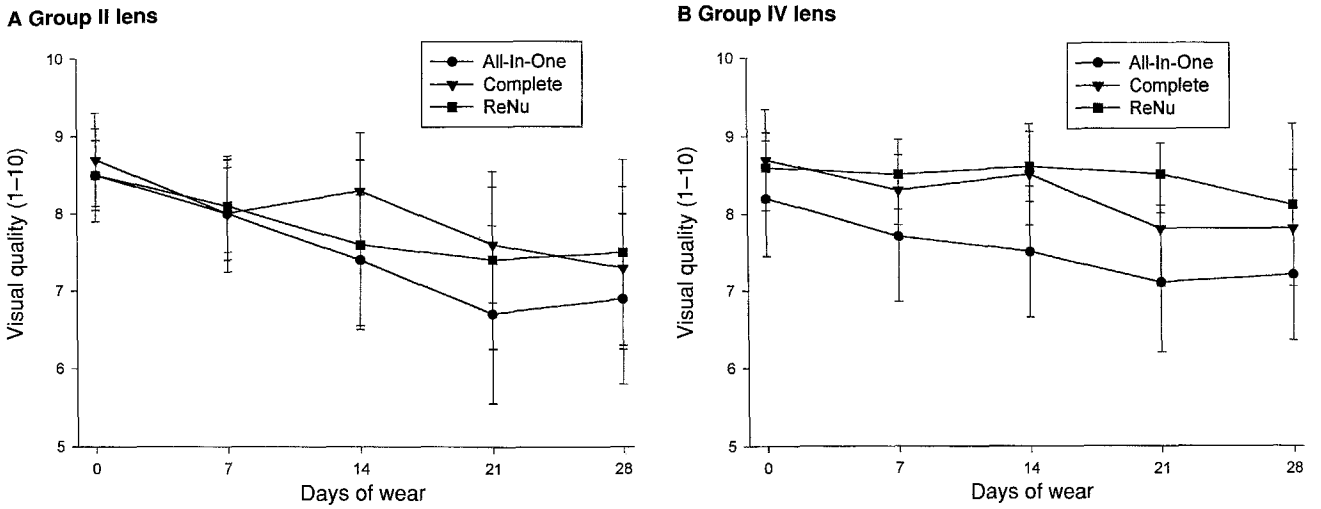

Figure 4. *Subjective visual quality scores for the group II lenses (A) and the group IV lenses (B) (mean ± SD). Visual quality was graded via the use of self-administered assessment forms, which used a conventional 10-point grading scale in which '1' represented the lowest score and '10' the highest.*

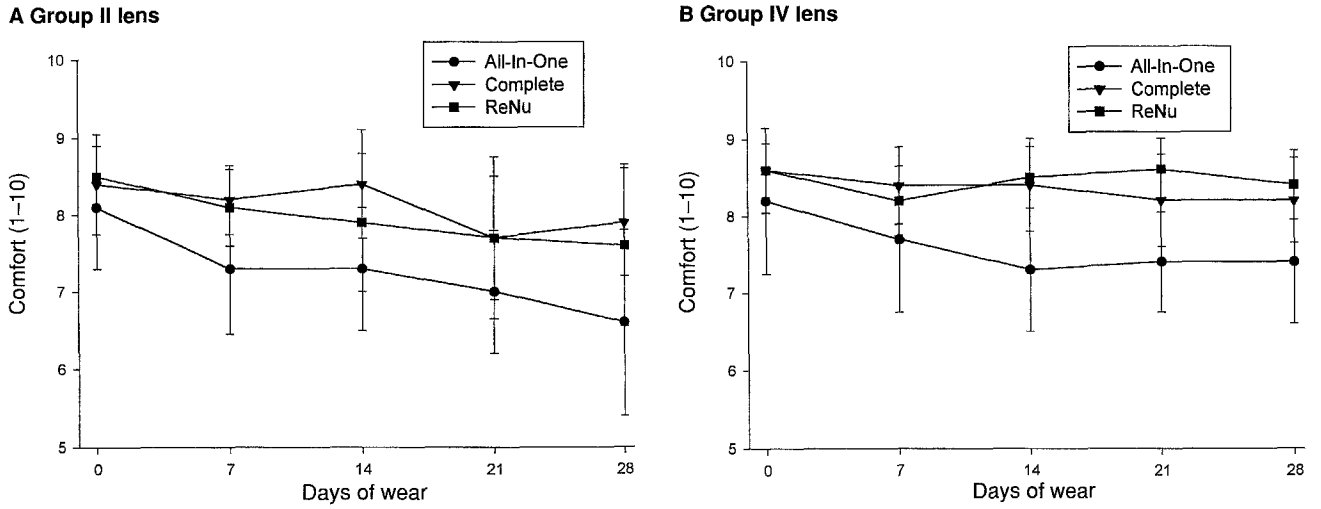

Figure 5. *Subjective comfort scores for the group II lenses (A) and group IV lenses (B) (mean ± SD). Comfort was graded via the use of self-administered assessment forms, which used a conventional 10-point grading scale in which '1' represented the lowest score and '10' the highest.*

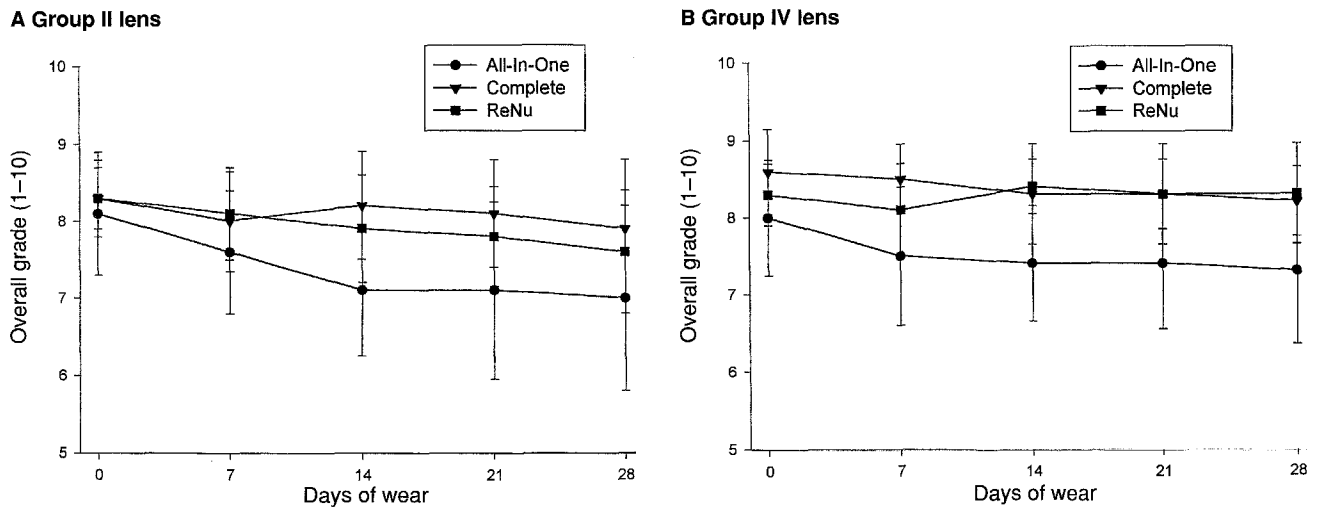

Figure 6. *Subjective overall satisfaction scores for the group II lenses (A) and group IV lenses (B) (mean ± SD). Satisfaction was graded via the use of self-administered assessment forms, which used a conventional 10-point grading scale in which '1' represented the lowest score and '10' the highest.*

when used with All-in-One ($P<0.05$). There was no significant difference in overall satisfaction between the two lens types at any visit (P=NS) and the reduction in satisfaction with all combinations was only significant for the All-in-One/group II combination ($P<0.04$).

Physiological Responses

Conjunctival Staining *Figure 7* indicates that while there was no difference between solutions (P=NS) or across time (P=NS), the group IV material produced more lens-edge staining on the conjunctiva than the group II material ($P<0.02$). None of the incidences of staining was considered clinically significant.

Corneal Staining *Figure 8* indicates that while there was no difference across time (P=NS), corneal staining

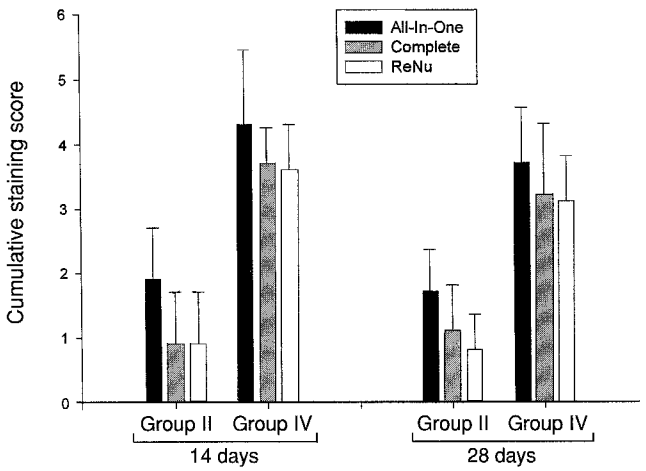

Figure 7. *Conjunctival staining score for all material and solution combinations (mean ± SD). The limbal/conjunctival region covered by the lenses was divided into four equal-sized sectors and the staining in each sector was ascribed an integer score between '0' (absent) and '4' (very severe). The cumulative staining score consisted of the sum of the scores from all four quadrants.*

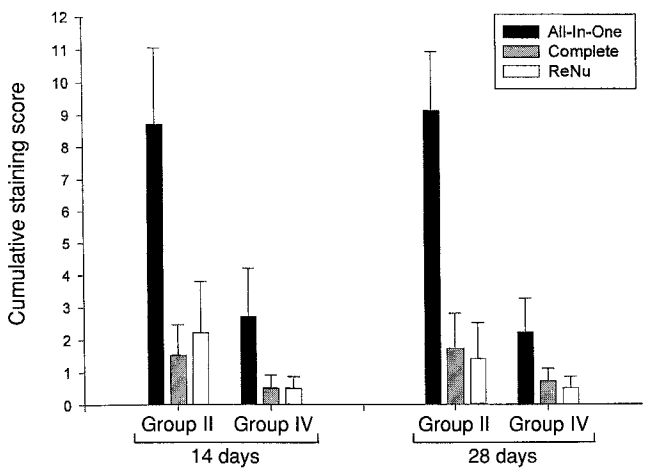

Figure 8. *Corneal staining score for all material and solution combinations (mean ± SD). The cornea was divided into five sections (central and four peripheral areas) and the staining in each sector was ascribed an integer score between '0' (absent) and '4' (very severe). The cumulative staining score consisted of the sum of the scores from all five quadrants.*

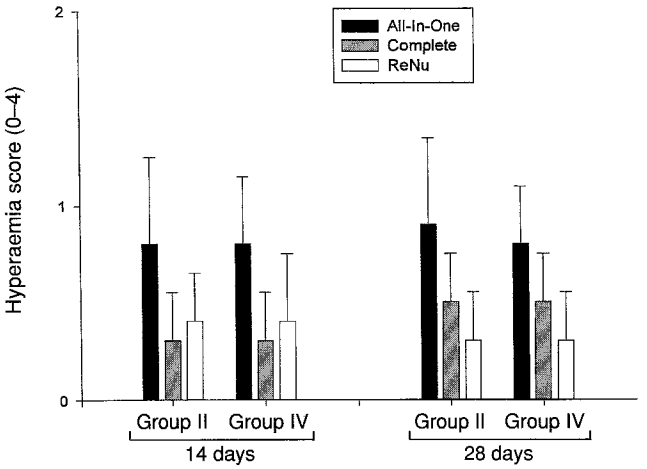

Figure 9. *Palpebral hyperaemia score (mean ± SD) for all material and solution combinations. The palpebral conjunctiva was graded for hyperaemia by ascribing it an integer score between '0' (absent) and '4' (very severe).*

was significantly higher with All-in-One after both 14 days ($P<0.001$ with group II and $P<0.02$ with group IV) and 28 days ($P<0.00001$ with group II and $P<0.03$ with group IV). Six subjects (60%) exhibited clinically unacceptable staining in the eye wearing the group II lens when using All-in-One after 28 days, compared with one subject (10%) wearing the group IV lens.

Palpebral Hyperaemia *Figure 9* indicates that there was no difference between material type or across time (P=NS), but that there was a tendency for increased palpebral hyperaemia with the All-in-One product with both materials. This difference was not statistically significant (P=NS).

Discussion

Widespread concern has arisen as a result of recent reports concerning the increasing incidence of bacterial and *Acanthamoeba* keratitis[11,12], particularly among wearers of frequent replacement lenses.[13,14] While several of these studies have merely confirmed previous reports that extended wear of soft lenses is a major risk factor for developing microbial keratitis[15,16], the increased incidence of such complications in the daily-wear population[17,18] has resulted in a call for practitioners to use care systems containing either hydrogen peroxide[19] or high concentrations of preservatives such as polyhexanide[20,21], in the hope that such systems will provide greater margins of safety. However, several studies have shown that both low concentration polyhexanide-containing solutions and 3% hydrogen peroxide systems are equally as ineffective against *Acanthamoeba* cysts if left to soak for the recommended soaking time.[22,23] Other work has demonstrated that the mere action of rubbing and rinsing alone is sufficient to remove such organisms[24,25] and that, if used in the manner in which the systems are licensed, that peroxide and polyhexanide-based systems are equally effective in dealing with *Acanthamoeba* attached to worn lenses.[26] It may therefore transpire

that a higher concentration of preservatives in the soaking solution is unnecessary and could potentially result in unwanted toxic or hypersensitivity reactions.[27,28]

Polyhexanide (PHMB) was originally developed by ICI and belongs to the same pharmaceutical family as chlorhexidine, although it has a much higher molecular weight. It is a cationic (positively charged) disinfectant at physiological pH. In contrast with the antibiotics (that act by disrupting cell walls), PHMB binds to the phospholipids found in the bacterial cell membrane and the hydrophobic portions of the molecule become associated with the internal core of the bilayer membrane, disrupting the cytoplasmic membrane and producing precipitation of cell contents and subsequent cellular lysis.[29] Ethylenediamine tetra-acetic acid (EDTA) is a chelating agent and works in a synergistic manner to enhance the effect of preservatives.

It has been estimated that between 5% and 35% of patients exhibit toxic and/or hypersensitivity reactions to 'older-technology' preserved contact-lens solutions, based on thiomersal and/or chlorhexidine.[30, 31] Newer products containing higher molecular weight disinfectants such as polyhexanide typically show a sensitivity reaction of less than 1%.[32–34] While increasing the concentration of preservatives may impart enhanced microbial activity to a care product, such solutions may exhibit increased solution-related complications such as corneal staining and reduced comfort. Previous work by Begley *et al.*[35] found that a solution of buffered saline containing the same concentration of PHMB as ReNu (0.00005%) did not cause high levels of epithelial toxicity, whereas increasing the concentration by 10–100 times resulted in significant epithelial damage. Further work[36] indicated that rigid gas-permeable contact lens solutions preserved with 0.0015% PHMB resulted in significant damage to the corneal epithelium in a human model. Such findings are corroborated by this study, with the All-in-One solution producing inferior results, both in terms of subjective response and physiological appearance. *Figures 2* and *3* indicate that solution comfort and overall satisfaction were clearly reduced by using a solution with a high concentration of preservatives. Furthermore, *Figures 4–6* indicate that subjective satisfaction with the lenses was also intimately linked with the solution type and resulted in reduced satisfaction with this solution. This has important implications when selecting an appropriate solution for a patient, particularly one who is new to lenses. Apparent discomfort in a new lens wearer may be incorrectly presumed to be due to the lens type, when it may actually be directly attributable to the chosen care system.

Figure 7 demonstrates that the group IV lens produced more conjunctival staining than the group II lens, which concurs with previous studies investigating the level of conjunctival staining with moulded Etafilcon lenses.[37] However, none of the incidences of staining were considered clinically significant. Of far greater concern is *Figures 8* and *9*, which clearly demonstrate the effect of the All-in-One product on the ocular tissues over a 4-week period. *Figure 9* indicates a clear trend, which, while not statistically significant, was considered clinically significant and indicates that palpebral hyperaemia was enhanced with the All-in-One product when compared with the other two multipurpose products. This is surprising given the short period of the study. *Figure 8* gives rise to clear concerns regarding the degree of corneal staining experienced with the All-in-One products, particularly when used with the group II material. The enhanced staining seen was statistically and clinically worse when compared with ReNu and Complete, with six subjects (60%) exhibiting clinically unacceptable staining in the eye wearing the group II lens when using All-in-One after 28 days and one subject (10%) when wearing the group IV lens. One of the patents relating to ReNu[38] demonstrated quite clearly that the degree of corneal staining increases with increasing concentrations of PHMB, with 5ppm producing 17% corneal staining and 55ppm producing 62%.

The subjective findings and slit-lamp results suggest that there was a specific interaction between the group II material and the All-in-One solution, which resulted in one or more chemical constituents in All-in-One being concentrated in or on the group II lenses to a toxic level. Recent work has shown that the accumulation of lipid on *N*-vinyl pyrrolidone (NVP)-containing group II materials progressively increases over a 4-week period, whereas lipid deposition plays only a minor role in non-NVP-containing group IV lenses.[39] It appears likely that one or both of the constituents in All-in-One that is present at a high concentration (polyhexanide or EDTA) progressively bound to the increasing levels of deposited lipid on the group II material to form a toxic complex, which then interacted with the corneal epithelium to result in a marked superficial punctate keratitis. Further work is necessary to investigate if the staining seen was due to a particular interaction with Medalist 66 or whether this can be extrapolated to other group II materials and whether the study findings were directly attributable to the increased concentration of preservatives or if it related to the overall formulation of All-in-One.

While this study demonstrated a clear preference against All-in-One, no difference could be found between the other two products. However, a recently published study[40] comparing ReNu and Complete demonstrated a bias towards ReNu, with fewer slit-lamp findings and greater patient preference. This further indicates that products of similar chemical formulation should only be interchanged with care.

Using pre-lens non-invasive break-up time (PLNIBUT) as an indicator of lens contamination Guillon and co-workers have shown that optimum replacement schedules are patient dependent.[41,42] This study lends further credence to this concept and clearly demonstrates the wide variation encountered in the wettability of contact lens materials by even a small sample of patients. *Figure 1* indicates that PLNIBUT reduces with wearing period, is patient dependent and

is independent of either material type or solution, which agrees with previous work investigating the performance of both rigid[43] and hydrogel materials.[44,45] *Figures 4–6* also demonstrate that subjective satisfaction reduced with all combinations of lenses and solutions over the 4-week period. The overriding conclusion is that, with the lens materials and solutions tested in this study, that optimum performance will only be achieved by replacing the lenses on a monthly replacement basis.

While avoiding corneal infection remains a crucial factor in contact lens wear, there is a fine balance between efficacy and safety. It is important to remember that avoidance of exposure to all pathogenic organisms remains the best approach to avoidance of keratitis. Failure to disinfect adequately is a significant factor in *Acanthamoeba* infection[19] and such organisms require bacteria to live on.[46,47] If patients use their solutions in the prescribed manner, always rub and rinse adequately, avoid tap water and replace their lens cases regularly[48,49] then the need for solutions with high concentrations of preservatives becomes unnecessary and toxicity reactions should remain at a low level.

Conclusions

Unacceptable levels of corneal staining were seen with a multipurpose solution preserved with 0.0005% polyhexanide (PHMB) and containing 0.3% EDTA, in particular when used with an FDA group II contact lens. Minimal staining was seen with similar products containing lower concentrations of polyhexanide and EDTA. In addition, reduced subjective comfort and satisfaction was obtained with the product with the highest concentration of preservatives. While products with increased concentrations of PHMB and EDTA will impart enhanced antimicrobial activity to multipurpose solutions, some subjects will notice reduced comfort and enhanced corneal staining may be seen, in particular with certain contact lens materials. Practitioners and patients alike should be advised that products with similar chemical constituents but differing formulations are not necessarily similar in action and should be interchanged with caution.

Address for Correspondence

Lyndon Jones, Collett and Jones, 103 Main Road, Sidcup, Kent DA14 6ND.

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