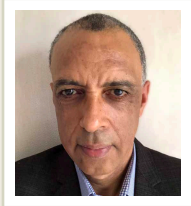


Contact Lens Update

CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Staining Wars Or ..How we came to understand SICS and love PHMB

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It's 2008. The Olympic Games are taking place in Beijing and the Spice Girls have reunited for one last tour (or actually not, as it turned out). Around the globe, people are struggling to come to terms with the most serious financial crisis since the Great Depression of the 1930s. Meanwhile, the contact lens world is also facing an event of seismic proportions; one that sets practitioner against practitioner, company against company and yes, even academics are at each other's throats. This is the 'Great Staining War'.

The first shots in this conflict were fired in 2002, when reports began to emerge of corneal staining associated with the use of silicone hydrogel lenses.^{1, 2} The key detail in this scenario was that these lenses were being worn on a daily basis and disinfected nightly in a multipurpose solution. It seemed that when that solution contained PHMB, many more wearers developed corneal staining than when a Polyquad-based system was used.² Additional reports of this phenomenon swiftly followed^{3, 4} and an interaction between PHMB and the silicone hydrogel material, which was relatively new at that time, was the suspected cause.

At this point, it is worth revisiting the characteristics of these staining events, as there are specific features that will be important for the discussion to come. The initial reports describe a superficial, diffuse, punctate appearance, covering either most of the corneal surface, or arranged in an annular pattern around the corneal periphery. Those affected were generally asymptomatic.^{1, 2} Subsequent work revealed an additional aspect, namely that the staining was transient, typically reaching peak intensity around 2-4 hours after lens insertion.⁵ Although various terms have been coined for this syndrome, we will refer to it here as 'solution induced corneal staining' (SICS).

As awareness of the phenomenon became more widespread, various groups began to study the effect of different materials and solution types and it quickly became apparent that there was a huge range of responses, across the spectrum of solution/lens material combinations. While some materials were relatively immune to the problem, others would produce extensive staining in a large percentage of wearers when used with certain solutions.⁶⁻⁸

This behavior precipitated the phenomenon of "Staining Grids".^{6, 8-10} These graphic cross tabulations of multiple lens and solution types, were arranged to show the degree of staining associated with each combination. Coloured shading was employed to highlight those permutations deemed more, or less, problematic. An example of one of the most extensive grids is shown in Figure 1.

Lens and Solution Combinations
Percentage of Average Corneal Staining Area at 2 Hours

		Unisol ¹ 4	Clear Care ⁴	Opti-free Express ¹	Opti-free Replenish ¹	Renu Moistureloc ³	Renu Multiplus ³	Walmart MPS (Renu MP)	Target MPS (Renu MP)	Complete Moisture Plus ²	Aquity ⁴
Hydrogel	Acuvue ⁵ 2	1%	1%	2%	5%	25%	1%	1%	1%	2%	1%
	Proclear ⁵	1%	1%	1%	2%	No Further Testing	57%	61%	54%	16%	12%
	Soflens ³ 66	1%	1%	1%	1%	No Further Testing	73%	66%	62%	53%	8%
Silicone Hydrogel	Acuvue Advance ⁵	1%	1%	1%	1%	No Further Testing	13%	16%	13%	20%	2%
	Acuvue Oasys ⁵	2%	1%	3%	5%	10%	9%	12%	8%	5%	3%
	Biofinity ⁵	2%	2%	3%	2%	No Further Testing	4%	4%	3%	6%	2%
	Purevision ³	2%	1%	4%	7%	6%	73%	71%	76%	48%	21%
	O2 Optix ⁴	2%	1%	2%	5%	7%	24%	41%	28%	18%	3%
	Focus Night & Day ⁴	2%	1%	2%	3%	No Further Testing	24%	36%	24%	16%	3%
Updated: May 27, 2007		Saline	H ₂ O ₂	POLYQUAD		Biguanides					

Figure 1: Screen shot of the Andrasko staining grid (www.staininggrid.com) taken in 2007. NB: this website is no longer functioning

Despite all this activity, the causes of the problem were still not understood. While there was a belief among some groups that PHMB was to blame, this view was strongly resisted by others, especially those with commercial interests in PHMB-based products. Given the long history of safe PHMB use prior to this time, this latter stance was not an unreasonable position. The prospect that a previously well tolerated preservative would suddenly be responsible for causing obvious epithelial disturbances was difficult to accept. These arguments were fueled by the emotive nature of the staining grid formats, particularly those using “traffic light” symbolism and so it is easy to see how heated the atmosphere became during this period. The “war” between products with PHMB and those without, was indeed in full swing.

All this confusion was intensified by the realization that long held beliefs about the nature of corneal staining had a very weak evidence base.¹¹ Researchers, clinicians and industry were therefore forced to concede that the details of what was actually happening at the ocular surface were uncertain. Not only was it unclear what mechanisms underpinned the staining events, but the nature of the changes to the tissue and their significance for corneal health, were also obscure. Evidently, significant new knowledge was going to be needed to fill this void and several groups responded by initiating research studies.

One substantial line of enquiry hypothesized that the observed appearance was not indicative of actual tissue damage at all but rather was a consequence of the fact that PHMB and fluorescein molecules can complex together. Subsequent attachment of these groups to the epithelial surface was proposed to mimic the appearance of staining.¹² This theory was developed along firm physico-chemical principles and was supported by *in-vitro* studies in which lipid bilayers were constructed to model the epithelial cell membrane.¹³ Although this model successfully accounted for differences in the behavior of PHMB and Polyquad, there were evident inconsistencies with respect to other clinical observations. For example, it was well known that the epithelial effects of solution use could be observed without using fluorescein, a phenomenon inaccurately, but commonly, referred to as “white light staining”.^{14, 15} Further, the model did not well explain the punctate appearance typical of affected corneas.¹⁵ Despite these problems and the lack of *in-vivo* confirmation, the idea that corneal staining associated with solution

use was nothing more than a pharmaco-kinetic artifact, became enthusiastically accepted in some quarters.¹⁶

That this view was somewhat premature, might have been suspected by considering work showing how the presence of staining was accompanied both by greater epithelial cell shedding,¹⁷ and an increased likelihood of inflammatory sequelae (in the form of corneal infiltrates).¹⁸ These findings suggested that SICS reflected real changes in epithelial cell physiology and evidence supporting this position has accumulated over the last few years. In particular, there have been three key studies, each of which have added important pieces of information to the understanding of the processes involved.

In the first of these, Bandamwar *et al.*, grew corneal epithelium cells in culture and subjected them to various kinds of stress, including from mechanical, osmotic and chemical sources.¹⁹ When fluorescein was subsequently introduced, normal, healthy cells exhibited a moderate level of fluorescence, but dead cells did not fluoresce at all. Conversely, cells that were stressed but still viable, significantly hyper-fluoresced, irrespective of the type of insult.

Again using cell culture, this time with multipurpose solutions as the challenge, Bakaar *et al.*,²⁰ confirmed Bandamwar *et al.*'s result and showed that the distribution of the hyperfluorescent cells on the culture plate replicated the punctate appearance of staining typical seen clinically. Furthermore, if these stressed cells were allowed to metabolise normally and recover, they were capable of eliminating the fluorescein from within their membranes, thus abolishing the hyperfluorescent appearance. Movements of fluorescein in and out of cells can thus be seen as active processes, which can be modified by the action of external influences, including a multipurpose solution.

Taken together, these two studies show that, without causing cell death, multipurpose solutions can alter cell behavior in respect of their uptake of fluorescein. When this occurs, the appearance of the affected cells mimics both the characteristic punctate appearance and transient nature of SICS.

The final piece needed to complete the puzzle was to identify which of the multipurpose solution components were responsible for producing these effects. An answer has been provided quite recently by the work of Khan *et al.*, a detailed review of which appears elsewhere in this issue of Contact Lens Update. In brief, these experiments demonstrated that the effect a multipurpose solution has on the active transport of fluorescein across the epithelial cell membrane is primarily mediated, not by its preservatives, but by its surfactants. In particular, the surfactant Tetronic 1107 was found to be highly influential.²¹

These results are very satisfying because they nicely draw the threads of the story together. We can now conclude that the observation of SICS does indeed signal that changes to epithelial cell physiology have taken place, in response to the multipurpose solution being used. These effects are mainly due to the surfactant Tectronic 1107, which alters the active transport of fluorescein across cell membranes in a direction that produces hyperfluorescence. The change is temporary, the cells remain viable and, under normal circumstances, the hyperfluorescence (and therefore the observed staining), dissipates within a short period of time.

The Great Staining War lasted for almost 20 years and became quite ugly at times. Looking back on it now, we can take comfort from the fact that the confusion it created has delivered a better understanding, not only of SICS, but also of the mechanisms of corneal staining. PHMB has finally been exonerated as the villain of the piece and attention can now turn to other components in the care system as levers for avoiding the problem. It will be very interesting to see how manufacturers and clinicians respond to this new knowledge, but for the momentVIVAT PACE!

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