· Original article ·

Benchmarking evaluation of five PHMB-based multi-purpose solutions and a silicone hydrogel contact lens

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国产5种PHMB多功能护理液搭配硅水凝胶隐形眼镜的基准评价

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摘要

目的:针对搭配市售硅水凝胶隐形眼镜使用的5种中国产含聚六亚甲基双胍(polyhexamethylene biguanide, PHMB)多功能护理液,通过护理液相关角膜染色、眼部反应(角膜染色、眼部充血)、角膜浸润、眼部舒适度来评估和比较其临床表现。

方法:前瞻性、开放、随机、平行对照临床试验。选取18岁以上受试者162名,并随机分为5组,分别使用5种中国产含PHMB多功能护理液:全能多功能护理液,海昌水感觉润护理液,保视宁护理液,卫康新视护理液及卫康2 000多功能护理液(分别缩写为C, H, B, W, 和W2)。所有受试者都配戴月抛型硅水凝胶隐形眼镜(博士伦纯视)3mo,并每日使用指定的多功能护理液。在配戴前,配戴后2wk,1和3mo进行随访。统计每百人每月护理液相关角膜染色及角膜浸润事件。眼部反应分0-4级,最小梯度为0.5(0=无反应,4=严重反应);眼部舒适度通过数字量表评定(分1-10级,最小梯度为1,1=差,10=优)。眼部舒适度和眼部反应采用线性混合模型进行分析。角膜浸润及护理液相关角膜点染通过Fisher确切概率法和logistic回归分析进行分析。

结果:有36名(22%)受试者中途退出试验。每组护理液相关角膜染色发生率为:H组26.3%, B组20.8%, W组19.4%, W2组13.4%, C组12.8%,其中H组的发生率分别与W2组(P= 0.012)、C组(P= 0.005)的差异有统计学意义。不同组间眼部反应、角膜浸润及眼部舒适度的差异均无统计学意义(P> 0.05)。存在护理液相关角膜染色的受试者在白天及结束时相比于不存在护理液相关角膜点染的受试者舒适度明显较低。

结论:对于不同的护理液,护理液相关角膜染色发生率存在差异,但角膜浸润、眼部反应及眼部舒适度不存在差异。PHMB多功能护理液引发的角膜染色与眼部舒适度相关。

关键词:角膜点染; 聚六亚甲基双胍; 角膜接触镜; 多功能护理液; 护理液相关角膜色染

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Abstract

• AIM: To evaluate and compare the clinical performance of 5 kinds of polyhexamethylene biguanide (PHMB) based multi-purpose solutions (MPS) manufactured in China when used with a commercially available silicone hydrogel contact lens in terms of solution-induced corneal staining (SICS), ocular response (corneal staining and ocular hyperemia), corneal infiltrative events (CIE) and ocular comfort.

• METHODS: This was a prospective, open label, randomized, parallel group clinical trial. Totally 162 participants who were at least 18y old were enrolled and randomized into 5 groups of PHMB-based MPS made in China: Complete® MPS, Hydron® Aqua-shining moist, Baoshining™, Weicon® Fresh, Weicon® 2000 MPS (abbreviated as C, H, B, W, and W2). All participants wore balafilcon A contact lenses with monthly disposal (Bausch & Lomb Purevision®) in conjunction with the designated MPS on a daily wear for 3mo. Clinical visits were at baseline, 2wk, 1 and 3mo. SICS and CIE were reported as first event incidence per 100 Px-months. Ocular response was graded on 0-4 scale in 0.5 steps (0=none, 4=severe) and ocular comfort was assessed *via* a numeric rating scale (1-10 in 1-point steps, 1=poor, 10=excellent). Ocular comfort and ocular response variables were analysed using linear mixed model. CIE and SICS were analysed using Fisher's exact test and logistic regression.

• RESULTS: There were 36 (22%) Pxs who dropped out. SICS incidence for each MPS were: H (26.3%), B (20.8%), W (19.4%), W2 (13.4%), C (12.8%). The SICS rate of H was significantly different to W2 (P = 0.012) and C (P = 0.005). There were no significant differences in ocular response, CIE incidence and ocular comfort between different MPSs (P>0.05). Pxs with SICS had significantly

lower comfort during the day and at the end of than those who did not have SICS.

• CONCLUSION: Differences in SICS incidence were found between MPSs but not for CIE incidence, ocular response or ocular comfort. SICS in PHMB-based MPS was found to be associated with ocular discomfort.

• KEYWORDS: staining; polyhexamethylene biguanide; contact lens; multi-purpose solutions; solution-induced corneal staining

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INTRODUCTION

Lens care products (LCP) used to clean, rinse, disinfect and store contact lenses are termed multipurpose solutions (MPS). A MPS should achieve a balance between consumer convenience, comfort and disinfection efficacy while minimizing interaction with the contact lens material[1]. Even though hydrogen peroxide-based LCP have advantages over MPS [including disinfection efficacy[2-3], reduced solution induced corneal staining[4] (SICS) and corneal infiltrative events[5] (CIEs)], MPS account for around 90% of all prescribed lens care systems[6]. The higher proportion of lens wearers using MPS is probably due to reduced cost and increased convenience compared to peroxide based systems[2].

Many studies have been done to determine the compatibility of various MPS and soft contact lenses around the world. As availability of lenses and MPS are different in various countries, similar studies need to be conducted in specific country, which in this case is China. MPS and soft contact lenses used in this study are all registered products of State Food and Drug Administration, P. R. China.

At the time of writing, we cannot find any published articles in English on the performance of various MPS that are locally made in China for either its effect on the ocular surface or ocular response when used with soft contact lenses.

Solution induced corneal staining is a characteristic sign of incompatibility between the lens care product, lens material and contact lens wearer. The clinical significance of this condition is controversial but recent studies showed its possible association to reduced contact lens comfort[7] and increased CIE incidence[8].

There is still controversy over the clinical significance of SICS. There are clinicians proposing the use of another model, preservative-associated transient hyperfluorescence[9] (PATH) to describe the solution induced corneal hyperfluorescence. In their theory, PATH is only benign interactions between the MPS preservative and the fluorescein molecules and is not "real staining". They suggest corneal staining which is associated with solution use (PATH), in general, is transient, superficial, asymptomatic and not related to contact lens associated infection. But recently reduced contact lens comfort[7] and increased CIE[8] incidence was found in patients with SICS and these two studies suggested SICS is a clinically relevant condition.

Typical symptoms of SICS[10] includes stinging on insertion, reduced contact lens discomfort during the day or at the end of wearing time, or maybe asymptomatic at all. Typical signs include two types of corneal staining, one is generalized punctate staining spreading all over the corneal and the second one is a doughnut shaped peripheral annular punctate staining. Furthermore, there might be hyperemia over the palpebral conjunctiva, bulbar conjunctiva, or limbus. One of the interesting phenomenon of SICS is that the level of staining changes over time. The mean staining extent staining score reach its peak at around 60min after CL insertion then gradually decrease[11-12]. This phenomenon indicates the etiology of SICS is related to the solution leaking from lens matrix.

The main objective of this trial is to evaluate and compare the clinical performance of 5 kinds of PHMB based multi-purpose solutions (MPS) manufactured in China when used with a commercially available silicone hydrogel contact lens in terms of solution-induced corneal staining (SICS), ocular redness, corneal infiltrative events (CIE) and ocular comfort. The secondary objective is to compare the comfort between Pxs with and without SICS in order to determine whether SICS caused by PHMB-based solution is clinically significant.

SUBJECTS AND METHODS

This was a prospective, open label, randomized, parallel group clinical trial. All participants wore the same contact lens type (balafilcon A, Bausch & Lomb Purevision®, Rochester USA) in conjunction with one of five randomly allocated PHMB-based MPS made in China: Complete® MPS (Abbott Medical Optics), Hydron® Aqua-shining moist (Hydron), Baoshining™ (Guangzhou Conmaster Eyeglass), Weicon® Fresh (Shanghai WEICON optics Eyeglass), Weicon® 2000 MPS (Shanghai WEICON optics Eyeglass). They are abbreviated as C, H, B, W, and W2 respectively.

The first and the last subjects were recruited in Jan. 2013 and Jan. 2014, respectively.

Inclusion criteria were:

-be at least 18y old, male or female;

-be myopic and correctable to at least 6/12 or better in each eye with contact lenses;

-have ocular health findings considered to be "normal" and which would not prevent the participant from safely wearing contact lenses;

-be experienced or inexperienced at wearing contact lenses;

-be able to insert and remove contact lenses, after tuition if required.

Exclusion criteria were:

-any pre-existing ocular condition that would preclude contact lens fitting and safe wearing of contact lenses;

-any systemic disease that adversely affects ocular health;
-use of or a need for any systemic medication or topical medication which may alter normal ocular findings;
-eye surgery within 12wk immediately prior to enrolment for this trial;
-previous corneal refractive surgery;
-known allergy or intolerance to ingredients in any of the clinical trial products;
-currently enrolled in another clinical trial;
-pregnancy (either at enrolment or during the course of the trial).

The study protocol was similar as has been described elsewhere[4-5]. Briefly, participants attended four scheduled visits at baseline, 2wk, 1 and 3mo. Participants were instructed to rub, rinse and soak lens with their MPS. All participants wore balafilcon A contact lenses with monthly disposal (Bausch & Lomb Purevision®) in conjunction with the designated MPS on a daily wear for 3mo. Clinical visits were at baseline, 2wk, 1 and 3mo and participants attended the visit wearing their allocated lenses except for the baseline visit.

If the participant attended baseline visit without a previous period of no-lens wear (washout) or contact lenses cannot be dispensed on the day of baseline visit, then they were required to return for a further dispensing visit, which may be scheduled within 10d of the baseline visit, at the discretion of the investigator or the participant.

Our primary endpoint was SICS and secondary endpoints included ocular response (conjunctival staining, limbal redness, bulbar redness, conjunctival palpebral redness and roughness), CIE and ocular comfort.

Same as previous studies done in Sydney, we defined SICS aspunctate fluorescein staining in at least 4/5 corneal sectors presenting as either diffuse (spread over the cornea) or as a peripheral/annual band around the limbus. SICS and CIE were reported as first event incidence per 100 Px-months.

Ocular redness was graded on 0-4 scale in 0.5 steps (0=none, 4=severe) and subjective rating (clarity of vision, comfort during the day, comfort at end of day, comfort on insertion, dryness at end of day, feelings of burning and stinging, overall vision) was assessed *via* a numeric rating scale (1-10 in 1-point steps, 1=poor, 10=excellent).

Ocular comfort and ocular response variables were analysed using linear mixed model. CIE and SICS were analysed using Fisher's exact test and logistic regression.

Data were collected at the Australia - China Centre for Optometry Research and Development at Guangzhou, China. All procedures met the tenets of the Declaration of Helsinki and were approved by the medical Ethics Committee of Zhongshan Ophthalmic Centre. Written consent was obtained from participants before participation.

RESULTS

Totally 162 participants were enrolled and there were 36 (22%) Pxs who dropped out and number of discontinuation of each MPS can be found (Figure 1). SICS incidence rate for each MPS were: H (26.3%), B (20.8%), W (19.4%), W2(13.4%), C(12.8%). Using the SICS rate of H as reference, it was significantly different from W2 (P=0.012) and C(P=0.005) (Figure 2). The SICS incidence for all five MPS combined was 18.5%.

There were two CIE during the course of study, one asymptomatic infiltrates event for C and one asymptomatic infiltrative keratitis for W. There were no significant differences between five MPSs in CIE incidence (Table 1).

There were also no significant differences in ocular response, and ocular comfort between MPSs (P>0.05).

Among the subjective ratings, Pxs with SICS showed a statistically significant decrease in comfort during day (6.7±1.5 *vs* 7.3±1.7, P=0.035) and comfort at end of day (6.7±1.8 *vs* 7.2±1.8, P=0.034) when compared with Pxs without SICS.

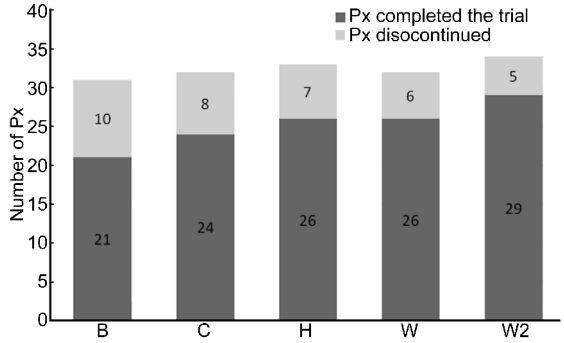

Figure 1 Distribution of discontinuation among 5 MPS groups B: Baoshining™; C: Complete®; H: Hydron® Aqua-shining moist; W: Weicon® Fresh; W2: Weicon® 2000.

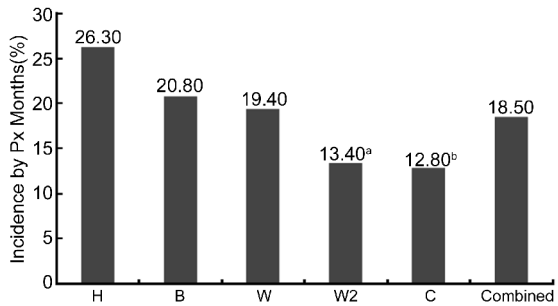

Figure 2 SICS incidence of 5 MPS groups H: Hydron® Aqua-shining moist; B: Baoshining™; W: Weicon® Fresh; W2: Weicon® 2000; C: Complete®; [a]Compared with H, P=0.012; [b] Compared with H, P=0.005.

Table 1 CIE incidence of 5 MPS groups

Solutions	Total No.	No. of events	Incidence by Px (%)	P
Baoshining™	31	0	0	
Complete®	32	1	3.1	
Hydron® Aqua-lshining moist	33	0	0	0.541
Weicon® Fresh	32	1	3.1	
Weicon® 2000	34	0	0	
Combined	162	2	1.2	0.541

DISCUSSION

Reported SICS rate with Purevision® when used with MPS made in other countries ranged from 11.3% to 23.2%[5]. This range is similar with the one we found in our study (12.8% to 26.3%). Interestingly, Complete® MPS (Abbott Medical Optics), which is originated from western countries but manufactured in China, has the lowest SICS incidence.

Result of current study reminds practitioner, especially the one in China, not all solutions are the same and they perform differently, at least in terms of corneal staining. With the approach of evidence based optometry, practitioner should make a sensible recommendation based on existing clinical evidence. Mainly there are two different systems/series of studies assessing the corneal staining-specific clinical performance and they are the BHVI Matrix studies[1] and the Andrasko Staining Grid[13]. Practitioners should bear in mind the fundamental differences between them[14]. In BHVI Matrix studies, we determined the percentage of patients who had SICS per month during the first three months of wear for each lens/solution combination while the Andrasko Staining Grid were derived from the average percentage area of the cornea exhibiting staining for the worst eye after an overnight soak and 2-hour wear of each lens/solution combination.

Although different SICS rates were observed, reason behind is hard to find as the formulation is complicated and many ingredients are involved. It is almost impossible to just change the concentration of a particular chemical to study its biocompatibility in clinical environment. What makes the situation even worse is that although ingredient list can be found, occasionally the concentration is not clearly shown by the manufactures.

Based on currently available information, both Hydron® and Complete® solution contain PHMB, but SICS rate was significantly higher with Hydron®. It is possibly due to the different PHMB concentrations between two MPS (Hydron®: 0.00018%; Complete®: 0.0001%). PHMB act as a preservative in MPS. And as PHMB is a kind of polymer, the molecular size is variable and we are not sure whether the PHMB in different MPS are of same molecular size. This difference, if exist, may have crucial effect on preservative uptake and release from lens matrix which will affect the cytotoxicity of solution.

It was also observed that Complete® had the lowest SICS rate, one unique characteristic of Complete® is that it doesn't contain the surfactant poloxamer which all four other solution have. As poloxamer was found to have effect of increasing drug transport across corneal membrane and ocular retention time[15], it was proposed poloxamer may amplifies preservative toxicity[15] and data from our study add supportive evidence to this theory.

But when investigating cytotoxicity we have to be cautious corneal cytotoxicity is not exactly equivalent to corneal staining. For example, using the same lens Purevision®, laboratory study showed that for the cell alteration, Opti-free express perform worse than Renu[16] but for corneal staining Opti-free express perform much better than Renu[13]. Furthermore, toxicity is not limited at corneal region and other region such as palpebral and bulbar conjunctiva might also be affected[17-18].

While SICS incidence can be a parameter for evaluating the clinical performance of a specific MPS, CIE rate is also another parameter we need to consider. Previous studies found that different types of lens care solution (Polyquad, PHMB and Peroxide solution) leaded to different CIE rates[19]. For PHMB solution, even different formulations exhibited different CIE rates[5]. But in our study, there was no such relation found, possibly due to the smaller sample size used in this study.

Regarding the possible relationship between SICS and CIE, a retrospective study[8] showed that CIE were 3 times more likely to occur in eyes experienced SICS but there were also studies showing that corneal staining was not associated to CIE in both daily wear[20] and continuous wear[21] of silicone hydrogel contact lenses. It is logical to infer that with an increased level of corneal staining, the intactness of corneal external surface is compromised and there should be a higher chance of CIE due to the weakening of the cornea's natural defences against microbial, lens related and environmental challenges. Although the relationship between corneal staining/SICS and CIE is still controversial, from the clinical perspective SICS should be avoided in order to minimize any chance of having a CIE.

Despite of previous research[7] showing patients with SICS had significantly lower contact lens comfort, there was no statistically significant difference found in ocular comfort between MPS in this study. This could be attributed to relatively small sample size and high dropout rate. The best way to look at the effect of SICS on discomfort is to analyse the symptom score between SICS and non-SICS participants but it was not done to the small sample size. We could only conclude these 5 MPS had no difference in ocular comfort when used with Purevision®.

It has been proposed that "The PATH theory could explain all or some of the observed SICS"[22] while clinically it is rather difficult[23] for clinician to differentiate PATH from SICS if such model is applied. Based on our result and from a clinical aspect, when a clinician noticed typical pattern of solution induced corneal hyperfluorescence/"staining" after the use of PHMB based MPS, these staining should be minimized (whether it is a PATH or not) due to its effect on subjective comfort during the day and at the end of the day. While the relationship between CIEs and SICS in PHMB-based MPS has not been reported yet, if such relationship exists then it is more important to minimize SICS in all solution, no matter it is PHMB-based or not.

Although SICS does not appear to be associated with long-term damage, based on the finding of previous studies[7-8] in which showed possible clinical significance of SICS, we recommend SICS should be minimized. Management includes

changing lens/solution combination, changing into hydrogen peroxide solution or single-use contact lenses.

To the best of our knowledge this study is the first ever published articles in English regarding the performance of solution in China. One may say daily disposable lenses will finally take over all the contact lens market, but clearly there is still a long journey for that to happen in China. Considering the increasing number of contact lens user in China[24], more research on MPS biocompatibility should be done in China.

Differences in SICS incidence were observed between MPS but not for CIE incidence, ocular response or ocular comfort. SICS in PHMB-based MPS was found to be associated with ocular discomfort. More MPS/lens combinations should be studied in the future.

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