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Therapeutic outcomes of oral cefcapene in meibomitis-related keratoconjunctivitis: A Propensity-matched cohort study

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Abstract:

PURPOSE: The purpose of the study was to evaluate the clinical characteristics and therapeutic response in patients with meibomitis-related keratoconjunctivitis (MRKC) who were treated with oral cefcapene pivoxil hydrochloride hydrate, and to determine factors associated with favorable outcomes.

MATERIALS AND METHODS: A retrospective analysis was conducted on 62 patients with MRKC, including 31 patients who received a 14-day course of oral cefcapene (100 mg three times daily) in combination with standard warm compression and lid hygiene. These patients were 1:1 propensity score–matched with 31 controls who underwent warm compression and lid hygiene, based on age, sex, meibomian gland expressibility, and meibum quality. Baseline characteristics and posttreatment outcomes – including corneal staining score (CSS) and ocular surface disease index (OSDI) – were compared between the groups.

RESULTS: One month after treatment, mean CSS was significantly lower in the cefcapene group (0.55 ± 0.65) compared with controls (0.86 ± 0.44, $P = 0.032$*). The cefcapene group also showed higher rates of complete corneal staining resolution (CSS = 0) and greater OSDI improvement, although these outcomes did not reach statistical significance.

CONCLUSION: Adjunctive use of short-term oral cefcapene therapy alongside standard eyelid hygiene measures resulted in a significant reduction in CSSs in patients with MRKC. However, this reduction was not accompanied by a statistically significant improvement in subjective symptoms.

Keywords:

Antibiotic therapy, cefcapene, lid margin inflammation, meibomian gland dysfunction, meibomitis-related keratoconjunctivitis, ocular surface disease

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Introduction

Meibomitis-related keratoconjunctivitis (MRKC) is a chronic ocular surface inflammatory disorder characterized by meibomian gland dysfunction (MGD) and concurrent keratoconjunctival involvement. First described by Suzuki *et al.*, MRKC is regarded as a distinct subtype of blepharokeratoconjunctivitis (BKC) that occurs predominantly in younger-aged patients and typically lacks dermatologic features such as rosacea.[1]

Clinically, MRKC presents with persistent ocular discomfort, photophobia, conjunctival hyperemia, and recurrent episodes of keratitis. Two phenotypic variants have been described: A "phlyctenular type" characterized by nodular cellular infiltration on the cornea with superficial neovascularization, and a "nonphlyctenular type" exhibiting diffuse superficial punctate keratopathy (SPK) without cellular infiltrates. Slit-lamp examination commonly reveals lid margin telangiectasia, anterior migration of the mucocutaneous junction (MCJ), thickened lid margins, plugging of

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meibomian gland orifices, and turbid or absent meibum expression.[2-4] In advanced cases, corneal scarring, thinning, or neovascularization may occur. Diagnosis is based on the constellation of clinical signs, often supplemented by meibography and tear film evaluation.[5]

Conventional treatment includes warm compresses, eyelid hygiene, preservative-free artificial tears, and topical anti-inflammatory agents such as corticosteroids or cyclosporine. In some cases, systemic antibiotics – most commonly tetracyclines such as minocycline or doxycycline – are employed for their anti-inflammatory and lipid-modifying properties.[6-13] However, in phlyctenular-type MRKC, where corneal infiltration and superficial neovascularization may be more prominent, anti-inflammatory strategies alone, such as sub-antimicrobial dosing of tetracyclines or macrolides, are insufficient to fully suppress disease activity.[14-16]

Cefcapene pivoxil hydrochloride hydrate (Flomox®), a third-generation cephem antibiotic, acts by inhibiting bacterial cell wall synthesis and is broadly used in respiratory, urinary, and skin infections.[17] In clinical practice, cefcapene has been prescribed for MRKC patients with severe lid margin inflammation, particularly in cases refractory to conventional therapies.[1,2] Clinical observations suggest that cefcapene may be effective in a subset of patients with severe lid margin inflammation, potentially by reducing bacterial load and associated inflammatory responses.

Notably, Suzuki previously suggested the potential utility of systemic antibiotics in MRKC, but to date, no formal clinical studies had validated this approach.[1-4] Although anecdotal evidence supports its efficacy in reducing ocular surface inflammation, objective data regarding its clinical effectiveness and the patient profiles most likely to benefit remain sparse. Thus, a scientific gap exists regarding the therapeutic efficacy and patient selection criteria for systemic antibiotic use in MRKC.

In this study, we aimed to evaluate the therapeutic efficacy of short-term oral cefcapene therapy in MRKC patients by comparing posttreatment ocular surface outcomes with those of matched controls. Using a propensity score-matched design, we investigated whether cefcapene was associated with greater improvement in objective signs of inflammation, such as corneal staining score (CSS), and explored patient characteristics associated with treatment response.

Materials and Methods

Study design and patient selection

This retrospective, propensity score-matched cohort study was approved by the Institutional Review Board (IRB) of the Public Institutional Bioethics Committee (IRB Approval Number: P01-202309-01-035) and conducted under the tenets outlined in the Declaration of Helsinki. Requirement for informed consent was waived by the IRB owing to the retrospective nature of the study. This study included patients diagnosed with MRKC at Share Bright Vision Eye Clinic between September 2023 and August 2024. Inclusion criteria were: (1) clinical diagnosis of MRKC, defined by the presence of lid margin inflammation with MGD and keratoconjunctival staining; and (2) completion of 14 days of oral cefcapene (Flomox® 100 mg three times daily) treatment combined with standard lid hygiene (10-min warm compress and lid scrubbing twice a day). Exclusion criteria included active ocular infection, prior ocular surgery within 6 months, or systemic immunosuppressive therapy. As no prior studies have established a standardized treatment protocol for oral cefcapene in ocular surface disease, we included 31 patients who received oral cefcapene, based on the conventional statistical rationale that a minimum of 30 subjects is typically required to ensure stability of parameter estimates in exploratory analyses. To establish a matched control group, 1:1 propensity score matching without replacement was performed using logistic regression. Propensity scores were calculated based on clinically relevant baseline variables: age, sex, meibomian gland expressibility (MGE), meibum quality (MQ), tear meniscus height (TMH), CSS, and presence of Demodex blepharitis. Demodex blepharitis was identified clinically by the presence of cylindrical dandruff and confirmed by the epilation of eyelashes when blepharitis was suspected. The cefcapene group ($n = 31$) was treated as the reference (treated) group, and each patient was matched to a control subject with the closest estimated propensity score. Propensity score matching was performed using a 1:1 nearest-neighbor algorithm without replacement, utilizing a caliper width of 0.2 standard deviations of the logit of the propensity score, and matching proceeded in random order of the treated subjects.

As a result, a total of 62 patients (31 in each group) were included in the final analysis. The balance of covariates was assessed using the standardized mean difference (SMD). SMDs were calculated for each covariate before and after matching, based on the entire unmatched cohort and the matched pairs, respectively. After matching, most covariates showed excellent balance (SMD < 0.1), including age, sex, MGE, MQ, TMH, CSS, and female proportion. While a few variables remained mildly unbalanced (TMH: 0.17, anterior shift of MCJ: 0.13, Demodex blepharitis: 0.19), all SMDs were within the clinically acceptable limit of < 0.20.

Ophthalmic examinations and outcome measures

All patients underwent baseline and posttreatment ophthalmic evaluation, including slit-lamp examination

of MGE, MQ, TMH, and CSS. Subjective symptoms were recorded using the Ocular Surface Disease Index (OSDI) questionnaire. CSS and OSDI were reassessed 1 month after treatment.

Primary outcomes and response criteria

The primary outcome was improvement in CSS, defined both by absolute reduction and the proportion of patients achieving a CSS score of zero. Secondary outcomes included changes in OSDI and the proportion of patients reaching minimal symptom levels (OSDI <13).

Statistical analysis

Statistical analysis was performed using Python version 3.13 with the SciPy module. The Shapiro–Wilk test was used to assess the normality of continuous variable distributions, and the Levene test was used for homogeneity of variance. Continuous variables were compared using an independent *t*-test or Mann–Whitney *U*-test, depending on distribution normality. CSS, a semi-quantitative scale, was treated as a continuous variable for the *t*-test comparisons, consistent with previous ophthalmic literature using CSS means to assess treatment effect size in clinical trials. Categorical variables were compared using the Chi-square or Fisher's exact test. A $P < 0.05$ was considered statistically significant. Raw mean differences and risk differences with 95% confidence intervals (CIs) were reported. Effect sizes were reported as mean differences for continuous outcomes (CSS and OSDI), and risk differences for binary outcomes (CSS = 0, OSDI <13). Corresponding 95% CIs were calculated to estimate the precision of the effect estimates. Given the exploratory nature of this study and the relatively small sample size, we did not perform a correction for multiple comparisons. Consequently, the findings should be interpreted with caution, given the potential for type I error. No patient data were excluded or imputed; all included patients had complete baseline and 1-month posttreatment data.

Results

Baseline characteristics after matching

There were no significant differences in baseline demographics or ocular surface parameters between the two groups [Table 1]. The mean age was 54.73 ± 12.12 years in the control group and 55.87 ± 11.17 years in the cefcapene group (P = 0.702). Female sex was similarly distributed (67.7% vs. 71.0%, P = 1.000). Baseline OSDI, MGE, MQ, TMH, and CSS prevalence were also comparable.

Posttreatment clinical outcomes

At 1-month posttreatment, the cefcapene group demonstrated significantly greater improvement in conjunctival staining compared to controls [Table 2 and Figure 1]. The mean CSS after treatment was significantly lower in the cefcapene group (0.55 ± 0.65) than in the control group (0.86 ± 0.44). The mean difference was −0.30 (95% CI: −0.581 ~ −0.019, P = 0.032*). Moreover, the proportion of patients achieving a CSS score of 0 was higher in the cefcapene group (65%) versus the control group (42%), indicating a greater resolution of corneal staining. The risk difference was +0.10 (95% CI: −0.143 ~ +0.343, P = 0.127).

Table 1: Baseline demographic and ocular surface characteristics of meibomitis-related keratoconjunctivitis patients

Variable	Control (*n*=31)	Cefcapene (*n*=31)	*P*
Age (years)	54.73±12.12	55.87±11.17	0.702
Female, *n* (%)	21 (67.7)	22 (71.0)	1.000
OSDI	22.35±11.22	22.75±10.65	0.886
MGE	2.12±0.83	2.08±1.12	0.874
MQ	1.87±1.01	1.79±1.17	0.774
TMH (μm)	215.26±24.32	211.29±22.00	0.503
CSS	1.15±0.42	1.13±0.34	0.837
Anterior shift of MCJ, *n* (%)	10 (32.3)	12 (38.7)	0.791
Demodex blepharitis, *n* (%)	9 (29.0)	11 (38.7)	0.786

CSS=Corneal staining score, MGE=Meibomian gland expressibility, MQ=Meibum quality, TMH=Tear meniscus height, MCJ=Mucocutaneous junction, OSDI=Ocular surface disease index

Table 2: 1-month clinical outcomes of oral cefcapene treatment

Variable	Control (*n*=31)	Cefcapene (*n*=31)	*P*
CSS after treatment	0.86±0.44	0.55±0.65	0.032*
CSS improvement (CSS=0) (%)	42	65	0.127
OSDI after treatment	20.45±12.11	17.33±11.28	0.298
OSDI response (OSDI <13) (%)	16	35	0.147

CSS=Corneal staining score, OSDI=Ocular surface disease index. *p<0.05

In terms of subjective symptom relief, the cefcapene group showed a reduction in OSDI scores (17.33 ± 11.28) compared to controls (20.45 ± 12.11), although the difference did not reach statistical significance (P = 0.298). The mean difference was 2.92 (95% CI: −8.898 ~ +3.058). Similarly, the proportion of patients with minimal symptoms (OSDI under 13) was higher in the cefcapene group (35%) than in the control group (16%), but this difference was also not statistically significant (P = 0.147). The risk difference was + 0.20 (95% CI: −0.010 ~ +0.410).

Discussion

This propensity score-matched cohort study is, to our knowledge, the first study to investigate the clinical outcomes of short-term oral cefcapene pivoxil hydrochloride hydrate (Flomox®) therapy in patients diagnosed with MRKC, with a particular focus on objective and subjective treatment responses. Although Suzuki *et al*. previously highlighted the theoretical

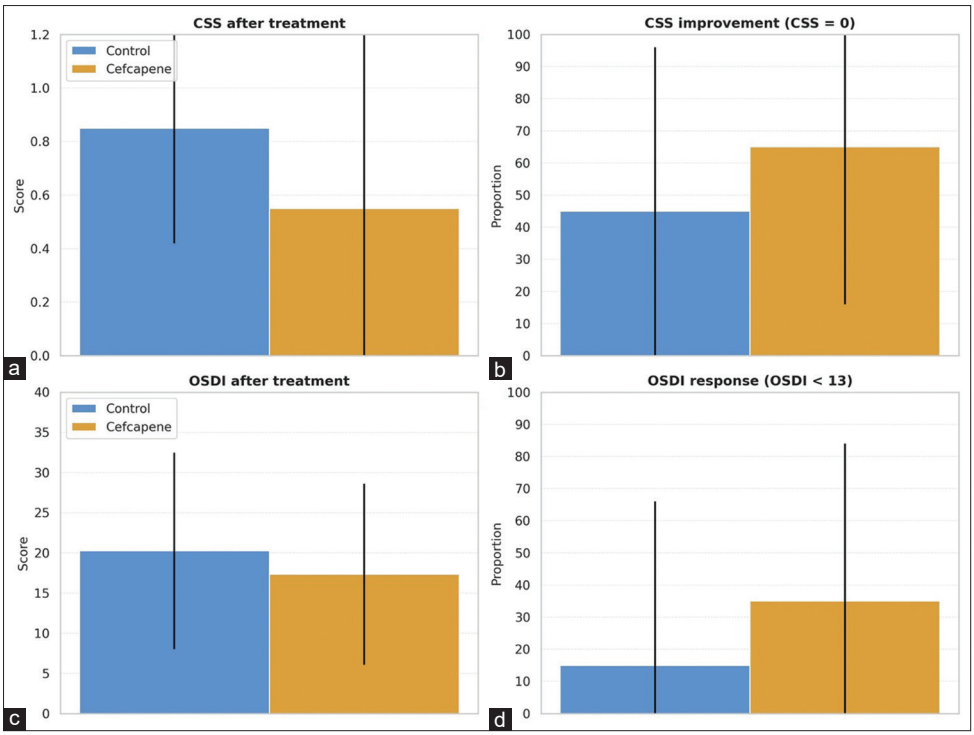

Figure 1: Corneal staining score and symptom response after oral cefcapene treatment in meibomitis-related keratoconjunctivitis. Bar plots compare outcomes between the control group and the cefcapene-treated group. (a) Mean corneal staining scores (CSS) after treatment were significantly lower in the cefcapene group than in controls. (b) The proportion of patients achieving full CSS resolution (CSS = 0) was higher in the cefcapene group. (c) Mean ocular surface disease index (OSDI) scores showed a trend toward reduction in the cefcapene group but did not reach statistical significance. (d) The proportion of patients achieving symptomatic resolution (OSDI < 13) was higher in the cefcapene group, but this difference was not statistically significant. CSS = Corneal staining score, OSDI = Ocular surface disease index

value of oral cefcapene therapy in patients with MRKC, no formal interventional study had been conducted to assess the clinical outcomes of such therapy until now.[1,2] By comparing a cohort receiving systemic cefcapene in conjunction with standard lid hygiene to matched controls undergoing standard treatment alone, we were able to isolate the additive therapeutic benefit of short-term oral antibiotic administration.

Our findings demonstrate that patients who received oral cefcapene therapy in addition to standard eyelid hygiene exhibited significantly greater improvements in CSS compared to controls, with a higher – though not statistically significant – proportion achieving complete resolution (CSS = 0). Given that corneal staining reflects epithelial compromise and inflammation, the improvement observed in our study suggests that cefcapene may play a meaningful role in mitigating the early inflammatory cascade of MRKC, and that targeted systemic antibiotic therapy can suppress this pathogenic axis. This objective improvement supports the hypothesis that systemic cefcapene may reduce bacterial burden and associated inflammatory responses at the lid margin and ocular surface.

Interestingly, while improvements in subjective symptoms (OSDI) also trended in favor of the cefcapene group, statistical significance was not reached. The statistically significant reduction in CSS with a lack of parallel improvement in OSDI may reflect the known dissociation between objective ocular surface healing and symptom resolution. In fact, this discrepancy between clinical signs and patient-reported symptoms has been commonly observed in studies on ocular surface disease and underscores the importance of including both domains in therapeutic assessment.[18] Objective improvement without parallel subjective benefit may suggest that objective signs of inflammation may respond more readily or earlier to systemic antibiotic treatment than subjective symptoms. Nevertheless, improvements in objective findings suggest disease modification. The lack of a significant difference in subjective improvement may also reflect the therapeutic contribution of standard lid hygiene, which was administered in both groups. Eyelid hygiene is known to reduce bacterial load on the lid margin, restore meibomian gland function, and mitigate local inflammation – mechanisms that can meaningfully improve symptoms even in the absence of systemic antibiotics.[19] The pharmacological mechanism of cefcapene differs meaningfully from that of tetracyclines and macrolides, which are widely used in ocular surface disease. Tetracyclines such as doxycycline are bacteriostatic – inhibiting bacterial growth rather than directly killing bacteria – and exert both antimicrobial and anti-inflammatory effects by suppressing matrix metalloproteinases (MMPs) and

modulating pro-inflammatory cytokine production.[20,21] Several studies have examined the efficacy of systemic tetracyclines in MGD and BKC-related ocular surface disease. For instance, minocycline has demonstrated significant improvement in both objective signs, such as gland expressibility and lid margin findings, and subjective symptoms after 1 and 2 months of treatment.[6-8] Doxycycline has similarly shown improvement in lid margin abnormalities and subjective symptoms, presumably via controlling inflammation through MMP suppression and cytokine modulation, after treatment lasting over 4 weeks.[20,21] The anti-inflammatory and lipase-inhibitory actions of doxycycline may be more appropriate for chronic management or rosacea-associated MGD.[14-16] Tetracycline therapies often require prolonged administration lasting from 1 to 2 months and are limited by gastrointestinal side effects.

Cefcapene, by contrast, is a third-generation cephem antibiotic that exerts a bactericidal effect via cell wall synthesis inhibition, with activity against a wide range of Gram-negative and Gram-positive organisms.[17] Bactericidal antibiotics may potentially offer a more effective therapeutic strategy in MRKC cases where bacterial overgrowth contributes to ongoing epithelial inflammation and corneal damage. This mechanism may be critical in cases where anti-inflammatory strategies alone, such as sub-antimicrobial dosing of doxycycline, are insufficient to fully suppress disease activity. In East Asian populations – where phlyctenular-type MRKC is more common and patients frequently exhibit corneal nodules and inflammatory neovascularization – short-term bactericidal therapy may offer a practical and rapid-acting solution. The relatively rapid bactericidal activity of cefcapene may help explain the favorable short-term response observed in this study, particularly in terms of objective corneal staining improvement. Accordingly, this study expands the therapeutic landscape beyond traditional anti-inflammatory strategies, positioning cefcapene as a hypothesis-generating option for cases with active infection–driven lid margin inflammation.

Due to differences in study design, treatment duration, and outcome measures, however, direct cross-study comparisons with tetracyclines or macrolides could not be made. The observed improvements in CSS in our cohort may reflect cefcapene's pharmacodynamic properties; however, these findings should be interpreted as preliminary rather than confirmatory. Future head-to-head studies are warranted to establish relative efficacy.

Clinically, MRKC can be distinguished from typical cases of MGD by its unique presentation. As originally described by Suzuki, MRKC typically presents in a younger patient demographic, lacks associated dermatologic conditions such as rosacea, and features pronounced ocular surface inflammation involving both the lid margin and cornea.[1,2] Characteristic findings include corneal inflammatory cellular infiltration (corneal nodules), superficial corneal neovascularization, SPK, and conjunctival injection associated with meibomitis.[3,4] Unlike classic MGD, MRKC often demonstrates more extensive epithelial involvement and a higher degree of inflammatory stigmata, and is frequently refractory to conventional lid hygiene and topical anti-inflammatory treatments alone.

In this context, cefcapene may be particularly effective in MRKC cases demonstrating significant active lid margin inflammation and early-stage corneal epithelial damage. Given its bactericidal mechanism of action and known efficacy against *Propionibacterium acnes*, cefcapene is likely to reduce bacterial burden rapidly, which may in turn alleviate epithelial toxicity and inflammation. Our findings suggest that patients without confounding comorbidities such as demodex infestation or rosacea, and those with mild to moderate corneal staining at baseline, are more likely to exhibit objective improvement following short-term cefcapene therapy.

While our study did not include a predefined subgroup analysis of patients with documented treatment failure prior to cefcapene administration, we have observed in clinical practice that patients who do not respond adequately to conventional management – including warm compresses, lid hygiene, and topical anti-inflammatory agents – may experience meaningful improvement with short-term cefcapene therapy, particularly when lid margin inflammation remains pronounced. However, this anecdotal observation lies outside the scope of the present analysis and is not statistically validated by the current data, as the dataset did not stratify patients by prior treatment failure. Accordingly, this statement should be interpreted as a hypothesis-generating clinical insight that warrants further studies validating the role of cefcapene in patients with refractory disease through targeted subgroup analysis or prospective trial design.

Clinicians should consider the use of cefcapene in MRKC patients who exhibit: prominent lid margin inflammation, early conjunctival or corneal staining, suboptimal response to lid hygiene and topical therapy, and no evidence of coexisting conditions like ocular rosacea or Demodex blepharitis. In such patients, short-term cefcapene may offer a targeted and microbiologically justified intervention, especially during the active inflammatory phase of MRKC when bacterial proliferation is a dominant factor in disease progression. While cefcapene demonstrates clinical

benefits in this study, systemic cephalosporins carry known risks, including gastrointestinal disturbance, hypersensitivity reactions, and potential contribution to antibiotic resistance. Given the growing global concern regarding antimicrobial stewardship, prescribing systemic agents such as cefcapene should be reserved for cases where the benefits are expected to outweigh these risks.

This study has several limitations. First, its retrospective nature introduces the potential for selection bias, despite the use of propensity score matching. Residual confounding variables also remain possible. Second, although the matched design improved comparability, the sample size remains limited, and subgroup analysis was not feasible due to sample size limitations. The lack of statistical significance in OSDI does not rule out a potentially clinically relevant effect, as the small sample size may have underpowered significant differences in subjective outcomes. To guide future studies, we conducted a *post hoc* power calculation based on our observed effect size in CSS change. Assuming an α of 0.05 and a power of 80%, we estimate that at least 53 patients per group would be required to detect a difference similar to that observed in this study. Third, we did not perform microbiological cultures or standardized Demodex quantification, which could have provided deeper insights into pathogen-specific responses. Fourth, long-term outcomes beyond 1 month were not assessed. All findings, particularly those approaching but not reaching statistical significance, should be interpreted within the context of the unadjusted, exploratory analysis. Future studies incorporating microbiological or cytokine-based endpoints and long-term follow-up could help clarify the role of cefcapene in chronic ocular surface disease management and potentially broaden its indications. Furthermore, this study did not include a tetracycline treatment arm or historical control data for systemic doxycycline or minocycline. As such, the relative efficacy of cefcapene versus more widely used systemic antibiotics remains unknown. Future studies should incorporate head-to-head comparisons between bacteriostatic agents (e.g., doxycycline) and bactericidal agents (e.g. cefcapene) to clarify the optimal systemic approach based on MRKC phenotype and inflammatory burden.

Short-term oral cefcapene, when added to standard eyelid hygiene, significantly improved CSSs in MRKC patients. The objective anti-inflammatory effect supports the use of systemic antibiotics in carefully selected patients. Early treatment in cases with moderate conjunctival involvement and absence of confounding lid margin pathology may yield optimal outcomes. Further prospective trials incorporating microbiological, immunological, and lid margin parameters are needed to define optimal treatment protocols.

Conclusion

This study contributes novel evidence supporting the use of oral cefcapene in MRKC, a previously under-investigated area in ophthalmic care. Our findings emphasize the importance of tailored therapy based on disease phenotype and severity and provide a foundation for future prospective studies evaluating systemic antibiotics in meibomian gland–associated ocular surface disease.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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