KX Cheong[1] and CSH Tan[1,2]

[1]National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Singapore
[2]Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore, Singapore
E-mail: Colintan_eye@yahoo.com.sg

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Sir,
Effect of cooling proparacaine 0.5% eye drops on patient's comfort during instillation

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Proparacaine is commonly used for topical ophthalmic anaesthesia. However, it causes stinging when instilled into the eye. Studies have suggested that cooling tetracaine eye drops may be helpful in reducing the patient's discomfort during instillation.[1,2]

We aimed to study if there is any difference in pain score and duration between cooled proparacaine eye drops and room temperature proparacaine eye drops by measuring the difference in the mean pain scores and duration using a previously validated visual analogue scale (VAS).[3]

Healthy study subjects were recruited from our adult clinic staff. The exclusion criteria were personnels with any pre-existing ocular disease, history of corneal surgery, current pregnancy, or eye drop usage. All volunteers received both anaesthetics in a prospective, randomised, double-masked protocol. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Each subject received one drop of refrigerated (at 4 °C/39.2 °F) proparacaine hydrochloride 0.5% in one eye and one drop of proparacaine hydrochloride 0.5% at room temperature (at 23–25 °C/73.4–77 °F) in the other eye in a randomised manner using a computer-generated randomisation table. Both the subject and the observer evaluating the pain score were blinded to the temperature of the drops. The proparacaine used in this study was Alcaine 0.5%, manufactured by Alcon (Singapore), containing proparacaine hydrochloride 0.5%. Each subject was asked to indicate on the VAS the amount of pain they felt after each drop and to report when the pain resolved completely. A timer was started immediately by the first observer after instillation of the eye drop and stopped when the subject reported no further pain. Immediately, after the administration of the first drop, the second observer who was blinded to the temperature of the administered drop evaluated the pain score using the VAS. The procedure was repeated for the other eye. After the administration of both the eye drops, subjects were then asked to indicate which eye drop they felt was the cooler one. The VAS score and pain duration were then analysed using Student's *t*-test on SPSS version 21 (IBM Corp, Singapore).

Twenty-five subjects consisting of 18 females and 7 males were enrolled into the study. The mean age of participants was 31 years (SD 10.1, range 22–56 years). Thirteen received cooled proparacaine first, and 12 received room temperature proparacaine first. The difference in mean pain scores between cooled proparacaine (13.16 ± 9.96 mm, (95% confidence interval (CI), 9.05–17.27 mm)) and room temperature proparacaine (14.22 ± 10.31 mm, (95% CI, 9.97–18.48 mm)) was not statistically significant ($P = 0.549$). The mean duration of stinging for cooled proparacaine was 10.68 (SD 7.14, (95% CI, 7.67–13.70)) seconds compared with room temperature proparacaine 12.79 (SD 8.60, (95% CI, 9.16–16.43)) seconds. Cooling proparacaine reduced the duration of pain associated with instillation only by a mean of 3 s ($P = 0.036$). Forty per cent ($n = 10$) of the subjects were able to guess the cooled eye drops correctly.

In our study, we found that cooling proparacaine eye drops reduces the duration of pain associated with instillation but not the severity. In contrast to tetracaine studies,[1,2] our study did not show a significant difference in pain severity. This might be because proparacaine induces less pain on instillation compared with tetracaine,[4] and so any reduction in pain due to cooling might be difficult to detect by our study participants. However, our study showed that cooling proparacaine reduced the duration of stinging sensation.

There are several limitations to our study. We enrolled healthy volunteers, not patients. Hence, our findings may not be generalisable to the patient population. Subjects were not blinded to the objective of the study, as we were required by our institutional review board to inform our subjects that we are comparing cold and room temperature proparacaine. There is a possibility that the study subjects are able to tell the temperature of the eye drops used, which may lead to subject bias in the reporting of pain scores. Our findings may be especially relevant in the pediatric patient population. Proparacaine eye drops are often used before cycloplegic eye drop instillation for cycloplegic refraction in our centre. This is because instilling cycloplegic eye drops can be especially uncomfortable.[5] As the cooperation of the child is dependent on their comfort, any measure that reduces pain associated with eye drop usage may be helpful. However, further studies are needed to ascertain the usefulness of cooling proparacaine eye drops in this population.

In conclusion, we found that cooling proparacaine had an effect in reducing the duration but not the severity of discomfort associated with instillation.

Conflict of interest

The authors declare no conflict of interest.

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J Hu Youwei and B Chang

Department of Ophthalmology, Khoo Teck Puat Hospital, Singapore, Singapore
E-mail: jeremy.hu@mohh.com.sg

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Sir,

Patterns of ranibizumab and aflibercept treatment of central retinal vein occlusion in routine clinical practice in the USA

In their retrospective study, Lotery and Regnier[1] comprehensively assessed the real world usage of intravitreal ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA) and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) in the treatment of central retinal vein occlusion (CRVO) in the USA. The authors evaluated for the first time the treatment patterns of both drugs in a US claims database for treatment-naive patients with at least a 12-month follow-up. The mean number of injections received by patients treated with ranibizumab and aflibercept was 4.4 ± 2.8 and 4.7 ± 2.9 ($P = 0.38$), respectively, and the mean interval between injections was 55.1 days and 54.2 days ($P = 0.44$), respectively.

The level 1 evidence of clinical trials[2–4] recommended an aggressive therapy in the first year of treatment, that is, ranibizumab and aflibercept should be given monthly for the first 6 months, with a subsequent 6 months dosing as required (pro re nata (PRN)). The Lotery and Regnier results[1] exhibited that in routine clinical practice in the USA, the number of injections was too small (approximately half of the standard claimed by the clinical trials),[2–4] and the interval between injections was too long. For this reason, we concluded that in the real world, CRVO patients had been insufficiently treated in a period of time in which the amount of vascular endothelial growth factor had been upregulated, which adversely influenced the final restoration of visual function. With such treatment patterns, maximal treatment benefit could not be achieved. We wonder if the data extracted from the US claims database, indeed, reflect the real world results of CRVO patients treated with ranibizumab and aflibercept.

In conclusion, during the first 12 months of treatment, CRVO associated with macular edema should be aggressively treated and the therapy should be applied as soon as possible after CRVO onset. The sooner the treatment is started, the sooner the patient is likely to have gains in visual functions.[5] Of note, PRN treatment undertaken after the first 12 months of aggressive treatment does not prevent the delayed occurrence of deterioration in visual acuity and foveal thickness, which has been reported by all the clinical trials.[2–4]

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Both authors (DC and MC) were involved in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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D Călugăru and M Călugăru

Department of Ophthalmology, University of Medicine, Cluj-Napoca, Romania
E-mail: mihai.calugaru@mail.dntcj.ro

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Sir,

Response to 'Patterns of ranibizumab and aflibercept treatment of central retinal vein occlusion in routine clinical practice in the USA'

We are grateful that Dan and Mihai Călugăru[1] took interest in our article and opened the debate on the optimal level of anti-VEGF in the treatment of central retinal vein occlusion. Our analysis aimed at understanding the real-world treatment patterns of aflibercept and ranibizumab in the United States. We agree with Dan and Mihai Călugăru that the observed treatment patterns in our analysis should not be interpreted as the optimal treatment frequency. In fact, in our conclusions, we recommend conducting further studies to link our findings to visual outcomes that were not available in the claims database at our disposal. The analysis of electronic medical records, similar to the study conducted by the UK Age-Related Macular Degeneration EMR Users