Codeine Plus Acetaminophen for Pain After Photorefractive Keratectomy: A Randomized, Double-Blind, Placebo-Controlled Add-On Trial

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Background: Pain after photorefractive keratectomy (PRK) is significant, and the analgesic efficacy and safety of oral opioids in combination with acetaminophen has not been fully investigated in PRK trials.

Purpose: To assess the efficacy and safety of the combination of codeine plus acetaminophen (paracetamol) versus placebo as an add-on therapy for pain control after PRK.

Study design: Randomized, double-blind, placebo-controlled trial.

Setting: Single tertiary center.

Methods: One eye was randomly allocated to the intervention, whereas the fellow eye was treated with a placebo. Eyes were operated 2 weeks apart. The participants were adults older than 20 years with refractive stability for ≥1 year, who underwent PRK for correction of myopia or myopic astigmatism. Codeine (30 mg) plus acetaminophen (500 mg) was given orally 4 times per day for 4 days after PRK. The follow-up duration was 4 months. The study outcomes included pain scores at 1 to 72 hours, as measured by the visual analog scale, McGill Pain Questionnaire, and Brief Pain Inventory, as well as adverse events and corneal wound healing.

Results: Of the initial 82 eyes, 80 completed the trial (40 intervention, 40 placebo). Median (interquartile range) pain scores as measured by the visual analog scale were statistically and clinically lower during treatment with codeine/acetaminophen compared with the placebo: 1 hour: 4 (2–4) versus 6 (3–6), $P < 0.001$; 24 hours: 4 (3–6) versus 7 (6–9), $P < 0.001$; 48 hours: 1 (0–2) versus 3 (2–5), $P < 0.001$; and 72 hours: 0 (0–0) versus 0 (0–2), $P = 0.001$. Virtually identical results were obtained by the McGill Pain Questionnaire and Brief Pain Inventory scales. The most common adverse events with codeine/acetaminophen were drowsiness (42%), nausea (18%), and constipation (5%). No case of delayed epithelial healing was observed in both treatment arms.

Conclusions: When added to the usual care therapy, the oral combination of codeine/acetaminophen was safe and significantly superior to the placebo for pain control after PRK.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02625753.

Key Words: opioids, photorefractive keratectomy, visual analog scale, pain, paracetamol, acetaminophen, codeine

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Photorefractive keratectomy (PRK) has been extensively used to correct refractive errors. Although there is an ongoing debate as to whether PRK and other techniques, such as laser-assisted in situ keratomileusis, are comparable in terms of efficacy and safety, compelling evidence supports the notion that PRK is safe, technically simple, and highly effective for the correction of low-to-moderate degrees of myopia, hyperopia, and astigmatism.[1]

PRK is typically associated with moderate-to-severe pain within the first 48 hours after surgery. The current "usual care" after PRK varies depending on the surgeon. However, it typically involves prescription of contact lenses until complete reepithelialization is achieved along with a multicomponent pharmacological management protocol, which may involve antibiotics, nonsteroidal antiinflammatory drugs, and corticosteroids.[2] Although many analgesic and antiinflammatory drugs are available to be used in the PRK postoperative period, empirical evidence suggests that pain control after PRK is still suboptimal.[3]

Despite intensive investigation in this area and the long-standing benefits of opioids in the management of pain in other medical specialties, the safety and efficacy of opioid analgesics as pharmacological adjuncts for pain management after PRK have not been fully investigated. Previous investigations highlighted the efficacy and safety of topical morphine for post-PRK pain management,[4] but there is a scarcity of evidence on potential harms and benefits of systemic opioid analgesics for PRK patients.[2] In addition, acetaminophen (paracetamol) is one of the most popular and widely used analgesics for treatment of general pain. In postoperative pain management trials from medical specialties other than ophthalmology, there has been

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a tendency toward combining codeine with acetaminophen. Although cumulative evidence suggests that codeine–acetaminophen preparations are safe and superior to acetaminophen alone for postoperative pain in adults,[5] there is no study specifically designed to address the effects of this combination on pain levels and corneal healing after PRK.

Therefore, the objective of this randomized, placebo-controlled trial was to investigate whether a combination of codeine plus acetaminophen added to the usual care therapy is safe and provides greater pain control after PRK compared with the standard treatment alone.

METHODS

Trial Design

This is a single tertiary center, double-blind, placebo-controlled, add-on, paired-eye trial with allocation ratio 1:1. The trial took place at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

The eye was the unity of analysis. Specifically, one eye was randomly allocated to the intervention, whereas the fellow eye was assigned to the placebo arm. Eyes were treated 2 weeks apart. Both outcome assessors and participants were masked to treatment allocation. The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki. Informed consent was also obtained from all patients. We have adhered to the CONSORT statement (http://www.consort-statement.org/) in reporting the results of this study.[6] The protocol was registered at ClinicalTrials.gov (NCT02625753).

Eligibility Criteria for Participants

Eligible participants were all adults aged 20 years or above, scheduled for myopic excimer laser PRK. Eyes had to have a spherical component between −1.00 and −5.00 diopters (D) with or without astigmatism; cylindrical component ≤1.5 D; spherical anisometropia ≤0.75 D, cylindrical anisometropia ≤0.5 D, and documented refractive stability over the previous year. Exclusion criteria were as follows: the presence of active allergic disease; inflammatory or infectious conditions, a history of ocular disease or trauma; best-corrected visual acuity ≤20/25; autoimmune diseases or immunosuppression, diabetes mellitus; and pregnancy or lactation.

Photorefractive Keratectomy

All patients were assigned to morning (9–10 AM) surgeries. Briefly, the corneal epithelium was marked with a ring of 9-mm diameter, followed by instillation of 20% ethanol into the ring. After 30 seconds, ethanol was removed using a dry and sterile cellulose sponge, followed by irrigation performed with balanced salt solution to remove excess alcohol. Finally, the epithelium was removed with a centripetal blunt spatula. Immediately, the stromal bed was dried with a dry sponge, and stromal photoablation was performed with the NIDEK EC-5000 CXIII excimer laser system (NIDEK Co Ltd, Gamagori, Japan). Corneal epithelial debridement performed with alcohol is fast and results in a stromal bed without irregularities and epithelial islands.[7] Patients were scheduled for surgery on 2 separate occasions (one eye at a time), 2 weeks apart. The same surgeon performed all procedures between November 2014 and June 2015.

Usual Care

All patients in both intervention and control groups received the same basic postoperative regimen for pain control, hereafter named "usual care." Briefly, 1 hour before the PRK procedure, patients were instructed to take celecoxib 200 mg (twice/d) for 4 days. Immediately after surgery, all participants received a commercially available ophthalmic solution containing moxifloxacin 0.5% and 0.1% dexamethasone. One drop was instilled a single time. After instillation, all operated eyes received a therapeutic contact lens (Acuvue II; Johnson & Johnson, New Brunswick, NJ). Finally, all participants were instructed to use moxifloxacin 0.5% and 0.1% dexamethasone ophthalmic drops (every 4 h) for 7 days, nepafenac ophthalmic suspension 1 mg/mL (every 6 h) for 3 days, and artificial tears as needed. One week after surgery, patients received fluorometholone 1 mg/mL eye drops (every 8 h) for 7 days, with increasing dosing intervals: every 12 hours in the third week and once per day in the fourth week. No concurrent medications were allowed during the 72-hour period after PRK.

Intervention

Eyes allocated to the intervention group received usual care therapy plus codeine/acetaminophen given orally. Participants were given a vial containing 16 custom-made, unlabeled capsules containing the active principles. Each capsule contained 30 mg of codeine and 500 mg of acetaminophen (acetaminophen). These doses were chosen on the basis of previous trials on the management of moderate/severe postoperative pain.[2,5] One hour before the PRK procedure, patients were instructed to take 1 capsule every 6 hours for 4 days.

Placebo

Eyes in the placebo group received the same usual care therapy and followed the same therapeutic protocol, except that they were given a matching placebo.

Outcomes

The primary outcome was the difference in pain intensity between the codeine/acetaminophen-treated eyes and placebo-treated eyes as measured on a 0-to-10 pain visual analog scale (VAS) obtained 24 hours after surgery. Secondary outcomes included 1) VAS scores at 1, 48, and 72 hours, 2) pain as assessed using the McGill Pain Questionnaire (MPQ) at 1, 24, 48, and 72 hours, and the Brief Pain Inventory (BPI) scale at 24, 48, and 72 hours, and 3) adverse events (AEs) and clinical assessment of corneal wound healing. Validated Brazilian–Portuguese versions MPQ and

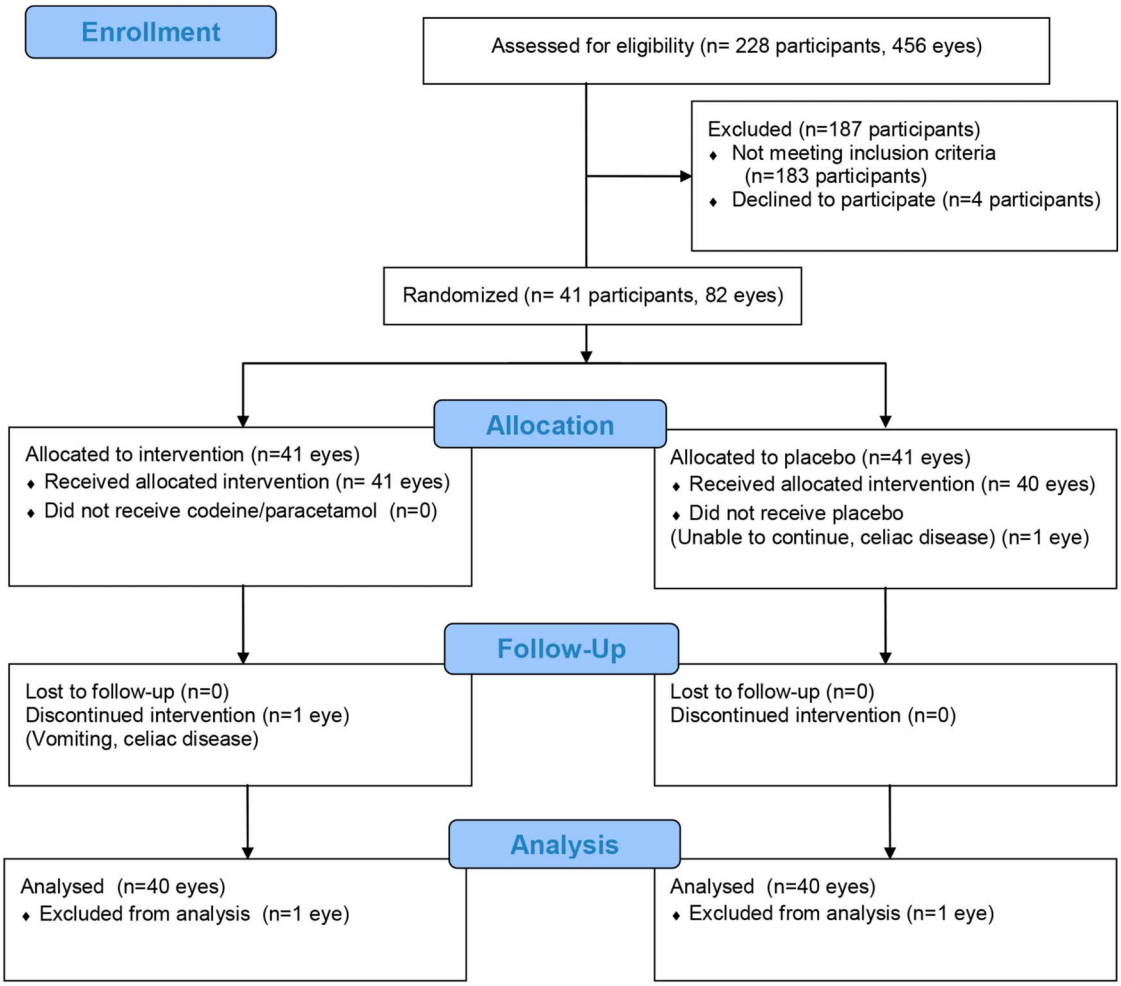

FIGURE 1. Consort flowchart.

BPI scales were used.[8,9] Based on recent reports on the most common harms associated with opiates in ocular surgery,[10] AEs were captured through the McGill scale using the list accompanying symptoms (none, nausea, headache, dizziness, drowsiness, constipation, and diarrhea).

The treating physician closely monitored the patients with a focus on epithelial healing and corneal haze. Ophthalmology visits were performed daily for 4 days after PRK and periodically thereafter: weekly for 4 weeks and then monthly for 3 months. Patients were instructed to immediately call the attending ophthalmologist in the case of any complications or side effects putatively associated with surgery. Any complications or AEs were fully documented.

Sample Size

Thirty-eight patients (or 76 eyes) would provide 90% statistical power (at $\alpha = 5\%$) for the detection of a predefined minimal clinically important difference (Δ) of 1.5 units in the VAS scores at 24 hours. Calculations assumed a "paired-eye design" and the use of the Student *t* test for paired samples. We also assumed a correlation of 0.5 and a common population SD of 2.85, which was sourced from previous studies in similar populations.[11,12]

Randomization

Participants were randomized with respect to which eye received the intervention and the order of treatment that was applied. Simple randomization was implemented in advance by an independent pharmacist not involved in patient enrollment or treatment (central allocation), using computer-generated random numbers (MS Excel 1997; Microsoft, Seattle, WA).

Allocation Concealment Mechanism

Participants who gave consent for participation were first pseudoanonymized through the use code identifiers. Before each surgical procedure, patients were given a medical prescription along with their code identifiers within sequentially numbered, opaque, sealed envelopes, which were opened only at the time of medication dispensing by the independent pharmacist. The randomization sequence was concealed from all participants and research investigators at all times.

Statistical Analysis

Data are presented as mean (SD), mean (95% confidence intervals), median (interquartile range), or counts (percentage). Differences in baseline characteristics were tested by paired *t* tests. The efficacy was estimated by the variable Δ, in which $\Delta = \text{mean}_{\text{intervention}} - \text{mean}_{\text{placebo}}$. For each postoperative time point, multiple linear regression models were built. These models explicitly incorporated the paired-eye design using a robust estimator of the variance, which takes into account the correlation between pairs of eyes.[13] *P* values were adjusted for multiple comparisons by the Holm–Šidák method. Multinomial logistic regression models were constructed to test the safety of the intervention when compared with the placebo. Relative risks and 95% confidence intervals were calculated as described in detail elsewhere.[14] All analyses were performed using Stata (version 14.0; Stata Corp, College Station, TX). All *P* values are 2 tailed with statistical significance claimed for $P < 0.05$.

RESULTS

Participant and Eyes Characteristics

Recruitment began in November 2014, and the trial was completed in June 2015. Of the first 282 participants assessed for eligibility, 41 met the inclusion criteria, resulting in a total of 82 randomized eyes (Fig. 1). Visual acuity of both groups was similar (Table 1). Of the 82 eyes included at baseline, 80 (98%) had complete assessment. Two eyes (from 1 participant) were excluded from analysis because the patient presented with recurrent vomiting after the first surgery. The patient was later found to have celiac disease. This information was not disclosed by the patient during the screening phase. Hence, a total of 40 eyes were successfully allocated to the intervention arm, and 40 eyes were assigned to the placebo arm. Randomization resulted in 34 eyes receiving the intervention first and 46 eyes receiving the placebo first. There was no case of significant refractive disparity. Baseline mean spherical equivalent scores were very similar between the intervention and placebo groups: −2.15 (0.68) versus −2.15 (0.60), respectively, $P > 0.99$. A summary of patient demographics and ocular characteristics is presented in Table 1.

Efficacy

Mean pain scores as measured by the VAS were significantly lower in the intervention arm than in the placebo arm throughout the intervention period (Table 2). For example, at 24 hours after PRK, the median percentage reduction in pain with codeine/acetaminophen versus placebo was 38%, and half of the participants achieved pain reductions between 13% and 57%. Findings based on the MPQ and BPI led to very similar conclusions. Using the criterion of pain relief of at least 50%,[15] results based on the VAS revealed that 35%, 42%, 80%, and 40% of the participants achieved a clinically meaningful improvement in pain at 1, 24, 48, and 72 hours, respectively. For the MPQ, the correspondent estimates were 32%, 30%, 45%, and 42%, respectively, whereas for the BPI (total) scale, they were 32%, 50%, and 42% at time points 24, 48, and 72 hours after PRK, respectively. For the BPI scale, both pain intensity and interference were significantly lower in the intervention arm than in the placebo arm (Table 2). The magnitude of the treatment effect as measured by the VAS, MPQ, and BPI scales was not influenced by the spherical equivalent refractive error, sex, age, race, or order of treatment at any time point (data not shown).

TABLE 1. Patient Demographics and Clinical Characteristics of the Eyes

Age, yr, mean (range)	30 (22–52)
Women, n (%)	27 (67)
Race, n (%)	
White	23 (57)
Mixed	16 (40)
Black	1 (3)
Spherical equivalent, mean (SD)	
Right eye	−2.18 (0.66)
Left eye	−2.16 (0.63)

Safety

Based on clinical assessment, no case of delayed epithelial healing was observed in both arms. All eyes were clinically healed by day 5, and contact lenses were removed. Clinical evaluation of corneal reepithelialization up to 4 months indicated that the combination of codeine plus acetaminophen is safe. Neither short-term nor later complications were reported by either group regarding corneal wound healing. No corneal haze developed during the 4-month follow-up period.

With respect to adverse drug reactions, except for the patient diagnosed with celiac disease after the first surgical procedure and that was later excluded because of severe vomiting, no serious AEs were reported in both groups. One patient developed grade 1 rash, which subsided spontaneously within 72 hours and did not require discontinuation of the intervention. The most common complaint was drowsiness. Patients were significantly more likely to report drowsiness when receiving codeine with acetaminophen than when taking the placebo. Furthermore, although not statistically significant, more patients reported nausea and constipation on the codeine/acetaminophen regimen than on placebo throughout the 72-hour period. Dizziness and diarrhea were relatively rare events and not statistically different between groups (Table 3).

DISCUSSION

Main Findings

The principal finding of our study is that the oral combination of codeine with acetaminophen at doses of 30 and 500 mg, respectively, is safe and efficacious add-on therapy for management of pain after PRK. Clinically important treatment effects are achieved within 1 hour after commencing treatment and persist for 48 hours. We found that treatment with codeine/acetaminophen had no effects on epithelial healing and haze, whereas most commonly reported AEs were usually mild (grade 1 according to the Common Terminology Criteria for Adverse Events).[16]

TABLE 2. Results for VAS, MPQ, and BPI Scales

Pain Scale	Intervention (n = 40)	Placebo (n = 40)	Δ (95% CI)	*P*
VAS				
1 h	4 (2–4)	6 (3–6)	−1.60 (−2.45 to −0.75)	<0.001
24 h	4 (3–6)	7 (6–9)	−2.55 (−3.29 to −1.81)	<0.001
48 h	1 (0–2)	3 (2–5)	−2.27 (−2.94 to −1.61)	<0.001
72 h	0 (0–0)	0 (0–2)	−0.60 (−0.95 to −0.24)	0.001
MPQ total				
1 h	5 (3–7)	8 (5–11)	−2.47 (−3.58 to −1.37)	<0.001
24 h	6.5 (4–10)	10 (6–13)	−2.80 (−3.98 to −1.61)	<0.001
48 h	2 (1–4)	4.5 (3–6)	−2.00 (−2.99 to −1.00)	<0.001
72 h	1 (0–2)	2 (1–3)	−0.55 (−1.00 to −0.09)	0.02
BPI total				
24 h	36 (25–44)	56 (42–76)	−19.2 (−25.6 to −12.7)	<0.001
48 h	19 (13–24)	40 (26–48)	−16.9 (−21.6 to −12.1)	<0.001
72 h	10.5 (6–16)	22 (13–28)	−10.6 (−13.9 to −7.30)	<0.001
BPI intensity				
24 h	11.5 (6–15)	21.5 (17–27)	−8.4 (−10.6 to −6.2)	<0.001
48 h	5 (4–7)	12.5 (7–16)	−6.7 (−8.33 to −5.01)	<0.001
72 h	2 (0–3)	4.5 (3–6)	−3.0 (−4.19 to −1.91)	<0.001
BPI interference				
24 h	23 (16–30)	35.5 (24–49)	−10.8 (−15.3 to −6.27)	<0.001
48 h	13 (8–18)	24 (17–33)	−10.2 (−13.7 to −6.68)	<0.001
72 h	7.5 (5–12)	15.5 (10–23)	−7.5 (−10.2 to −4.93)	<0.001

Δ, the mean difference between codeine/paracetamol-treated eyes and placebo-treated eyes is shown with 95% confidence intervals (CIs). All remaining estimates are given as median (interquartile range).

BPI intensity (min–max: 0–40); BPI interference (min–max: 0–70).

BPI, Brief Pain Inventory total (min–max, 0–130); MPQ, McGill Pain Questionnaire total (min–max, 0–20); VAS, visual analog scale (min–max, 0–10).

Comparison to Previous Investigations

A myriad of pharmacological alternatives for pain control in the immediate postoperative period after PRK are currently available.[3,17] However, randomized trials have mostly focused on the safety and efficacy of anticonvulsants,[18] anesthetics,[19] and nonsteroidal antiinflammatory drugs.[20] Nonpharmacological interventions such as corneal cooling and bandage contact lenses are also valuable therapeutic adjuncts that ameliorate patient discomfort and promote healing. Thus, multimodal therapeutic approaches have been suggested as the most robust strategy for satisfactory pain control after PRK.[17] Nonetheless, based on our own[11,12] and others' experience,[17,21] despite substantial advances in the field of refractive surgery over the past decades, post-PRK pain continues to represent a major clinical management challenge for ophthalmologists. By applying the BPI and exploring different aspects of pain (eg, pain intensity and interference), in this study, we show that the combination of codeine with acetaminophen might display a robust and favorable impact not only on the pain intensity but also on the ability of patients to perform activities of daily living. These results are in line with recent clinical management trends that put forward the notion that quality of life and well-being should also be evaluated and set as main targets during pain management after PRK.[11,12]

Morphine-like drugs are historically known as the most effective drugs for pain relief,[22] and acetaminophen is one of the most commonly used drugs worldwide. Although both empirical[17] and evidence-based[4] reports support their routine use after PRK, to date, no randomized trial has specifically determined the safety and efficacy of codeine plus acetaminophen for the management of post-PRK pain. Although topical morphine was demonstrated to be safe and efficacious in controlling pain in patients who underwent PRK,[4] the use of codeine/acetaminophen after PRK has been studied only as an indicator of efficacy of other drugs.[18,23] Thus, our study helps to fill a gap in the medical literature by showing that systemic opioid analgesics, such as codeine, might be safe and valuable tools for pain management after PRK.

Regarding safety, we found that nervous system symptoms, such as nausea and drowsiness, may be common in post-PRK patients under codeine/acetaminophen treatment. These results agree with those from previous observations regarding the use of opioids in clinical practice.[10,22] However, similar to previous clinical trials in ophthalmology,[24] opioid-related symptoms reported by participants were mild, self-limiting, and could be promptly addressed and well managed. Taken together, our results increase the body of evidence that the combination of codeine with acetaminophen may be safe and efficacious in reducing postoperative pain in different medical specialties.[25]

Epithelial healing is essential for corneal regeneration after PRK affecting patient comfort and visual recovery. In this regard, postoperative interventions that interfere with epithelial healing might increase the risk of subepithelial haze

TABLE 3. Common AEs

	Postoperative Time											
	24 h						48 h					
	Intervention (n = 40)		Placebo (n = 40)		RR		Intervention (n = 40)		Placebo (n = 40)		RR	
Symptoms	No.	%	No.	%	(95% CI)	*P*	No.	%	No.	%	(95% CI)	*P*
None	7	18	14	35	0.50 (0.28–0.90)	0.014	7	18	14	35	0.5 (0.25–0.99)	0.03
Nausea	7	18	3	8	2.33 (0.59–9.20)	0.194	7	18	2	5	3.5 (0.72–17.1)	0.09
Headache	6	15	17	42	0.35 (0.15–0.84)	0.007	1	2	19	47	0.05 (0.01–0.37)	<0.001
Dizziness	1	2	2	5	0.50 (0.05–5.29)	0.573	0	0	0	0	—	—
Drowsiness	17	42	2	5	8.50 (1.96–36.8)	<0.001	21	52	3	8	7 (2.25–21.8)	<0.001
Constipation	2	5	1	2	2.00 (0.17–23.2)	0.565	3	8	1	2	3 (0.30–30.0)	0.313
Diarrhea	0	0	1	2	—	—	1	2	1	2	1 (0.06–16.9)	>0.999

	Postoperative Time					
	72 h					
	Intervention (n = 40)		Placebo (n = 40)		RR	
Symptoms	No.	%	No.	%	(95% CI)	*P*
None	27	67	32	80	0.84 (0.65–1.09)	0.186
Nausea	2	5	1	2	2 (0.17–23.2)	0.555
Headache	1	2	5	13	0.20 (0.02–1.76)	0.094
Dizziness	0	0	0	0	—	—
Drowsiness	10	25	1	2	10 (1.24–80)	0.003
Constipation	0	0	1	2	—	—
Diarrhea	0	0	0	0	—	—

RR, relative risk; 95% CI, 95% confidence intervals.

formation, which, in turn, reduces corneal transparency and visual acuity.[26] On this basis, in this study, we show that the combination of codeine plus acetaminophen did not affect corneal reepithelialization, reinforcing the assumption that this combination can be regarded as a safe therapeutic option during the PRK postoperative period.

Study Limitations, Implications for Clinicians, and Directions for Future Research

Our trial possesses a number of limitations that must be acknowledged. First, although sufficiently powered to detect differences in pain-related outcomes, our study may be underpowered to detect rare AEs and/or the effect of the intervention on specific domains in the MPQ. Hence, a more thorough evaluation of the safety profile of the combination of codeine and acetaminophen is warranted in large observational studies, whereas well-designed assessments regarding its influence on qualitative aspects of pain perception may be desirable.[11] Second, we examined 3 distinct pain scales and performed a relatively large number of statistical tests. Our aim was to further substantiate findings from the 1-dimensional VAS, which is focused primarily on the pain intensity. Nevertheless, the use of different scales may be highly recommended in our study, since, as mentioned above, recent investigations point toward the importance of multidimensional assessments of pain in ophthalmology. In fact, there is a growing body of evidence indicating that the longitudinal perception of pain after PRK might depend not only on the pain intensity but also on qualitative aspects such as negative emotions and past experience with pain.[11] Finally, corneal wound healing was examined clinically but not by more objective assessments such as fluorescein staining,[7] slit-lamp biomicroscopy,[27] or in vivo confocal microscopy.[28] As a result, the hypothesis that the add-on treatment with codeine plus acetaminophen might cause minor delays in corneal reepithelialization cannot be entirely excluded. Based on our findings, however, any putative detrimental effects of codeine/acetaminophen therapy on the corneal healing process is unlikely to be of clinical significance.

Acknowledging the caveats mentioned above, this randomized placebo-controlled add-on trial demonstrated that the combination of codeine (30 mg) and acetaminophen (500 mg) given orally 4 times per day is safe and efficacious for relieving pain after PRK. Our findings provide further support for the proposition that opioid analgesics are pivotal for an optimal pain management protocol[29] and that this class of drugs might be considered a valuable component of pain management after PRK.[17]

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