Narrative Review

Opioids for Ocular Pain – A Narrative Review

Vinicius BP Pereira, MD, Renato Garcia, MD, André AM Torricelli, MD, and Samir J. Bechara, MD

From: São Paulo University Medical School, Ophthalmology Department, Refractive Surgery Service, Brazil

Address Correspondence:
Vinicius B. P. Pereira, MD
São Paulo University Medical School
Ophthalmology Department
Refractive Surgery Service
Avenida Dr. Enéas de Carvalho Aguiar 255
6o Andar, Cerqueira César
São Paulo/SP, Brazil, CEP: 05403-000.
E-mail:
viniciusbppereira@hotmail.com

Background: Refractive surgery is a common procedure, but may be associated with severe post-operative pain.

Objectives: To describe studies addressing the use of opioids for control of pain after ocular surgery, with an emphasis on refractive surgery.

Study Design: This is a narrative review of relevant articles on the physiology of corneal pain and the use of opioids for its treatment after surgery.

Setting: Single tertiary center.

Methods: A PubMed search was conducted for studies published from January 1985 to May 2015 on the physiopathology of corneal pain and opioid treatment of post-refractive surgical pain. Reviews, meta-analyses, and randomized clinical trials were included. Inclusion criteria focused on photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK).

Results: Authors found 109 articles through the search strategies. A total of 75 articles were included based on the inclusion criteria.

Discussion: Pain after ocular surgery is likely to be a multifactorial phenomenon. A combination of topical and systemic analgesics is used to treat post-operative pain after refractive surgery. Pain may be severe during the first 72 to 96 hours, depending on the surgical procedure. No studies were found that directly analyze the benefits of opioids after PRK, although they are routinely prescribed in some centers.

Limitations: This is a narrative review in contrast to a systematic review and did not include studies indexed in databases other than PubMed.

Conclusions: Although opioids are used for the short-term treatment of post-operative pain in refractive surgery, their benefits and risks should be properly evaluated in randomized clinical trials before their use can be safely advised.

Key words: Photorefractive keratectomy, in situ keratomileusis, pain, analgesia, opioid, codeine, review

The management of pain represents a major challenge in ophthalmology. It is an important symptom of inflammatory or traumatic disorders affecting the anterior segment of the eye, which includes the cornea, sclera, conjunctiva, and uveal structures (1).

Several types of surgery directly damage the ocular sensory nerves at different points in their path (2). Photorefractive keratectomy (PRK) is a common procedure performed to efficiently and safely correct refractive errors (3-5). The number of patients who undergo PRK, however, remains lower than those who undergo

laser in situ keratomileusis (LASIK), even though LASIK carries a risk of flap-related complications (6,7). The 2 primary reasons for the preference of LASIK over PRK are reduced post-operative pain and faster visual recovery.

The aim of this work is to review the literature regarding the mechanisms of pain after corneal refractive surgery and the use of opioids in this setting.

METHODS

Data Extraction and Synthesis

Data pertaining to pain in ophthalmologic procedures were extracted from reviews, meta-analyses, and randomized trials, and they were described through text or in tables according to the type of procedure, number of patients, type of pain measurement, and outcome results.

Literature Search Strategy

A search of literature published from January 1985 to May 2015 on the pathophysiology of eye pain, opioid use in general and in ophthalmology, and PRK was conducted using PubMed. The following search strategies were used:

1. (((((((("physiopathology"[MeSH Subheading]) AND "cornea"[MeSH Terms] OR "cornea/surgery"[MeSH Terms]))) AND photorefractive keratectomy) OR laser in situ keratomileusis)) AND ((("2000"[Date - Entrez] : "3000"[Date - Entrez])) AND english[Language])) AND review[Publication Type]).

2. ((((((((((("ophthalmology"[MeSH Major Topic]) OR "ophthalmologic surgical procedures"[MeSH Terms]) OR "ophthalmology"[MeSH Terms])) AND (((("analgesia"[MeSH Terms]) OR "pain"[MeSH Terms]) OR "analgesia"[MeSH Major Topic]) OR "pain"[MeSH Major Topic])) AND (((("opiate alkaloids"[MeSH Terms]) OR "opioid peptides"[MeSH Terms]) OR "opiate alkaloids"[MeSH Major Topic]) OR "opioid peptides"[MeSH Major Topic])) AND Clinical Trial[ptyp] AND Humans[Mesh])) OR (((((((((eye AND (((("analgesia"[MeSH Terms]) OR "pain"[MeSH Terms]) OR "analgesia"[MeSH Major Topic]) OR "pain"[MeSH Major Topic])) AND (((("opiate alkaloids"[MeSH Terms]) OR "opioid peptides"[MeSH Terms]) OR "opiate alkaloids"[MeSH Major Topic]) OR "opioid peptides"[MeSH Major Topic]))) AND ((pain)

OR analgesia)) AND ((opioid) OR opiate))) AND Clinical Trial[ptyp] AND Humans[Mesh])))) AND ("1985"[Date - Entrez] : "3000"[Date - Entrez]).

RESULTS

One hundred and nine articles were found through both searches. Forty-nine articles were excluded, whereas 15 additional articles were found through the analysis of references and related articles in PubMed. A total of 75 articles were included based on the inclusion criteria.

DISCUSSION

Pathophysiology

Empirical evidence indicates that corneal sensitivity might be reduced after PRK, suggesting that pain and dysesthesias after refractive surgeries might involve not only functional, but also important molecular changes that follow neural injury (8). Indeed, after peripheral axotomy, both morphological aspects and functional properties of corneal nerve fibers change considerably. Specifically, when the central stumps of the cut axons form microneuromas and start to regenerate; they produce sprouts, which grow and intersect the scar tissue to infiltrate into the denervated area (9). As soon as the nerve signal is triggered, pain perception occurs in the somatosensory cortex of the brain (10). However, the somatosensory cortex is not the only area responsible for pain perception in humans. Indeed, many other brain areas are thought to be involved, particularly emotion-related areas, such as the thalamus, cerebellum, and cingulate gyrus (11).

Different surgical approaches, such as PRK, LASIK, and laser-assisted subepithelial keratectomy (LASEK) have been employed to correct refractive errors. All of these procedures cause functional and morphological alterations in stromal and epithelial corneal nerves, varying with the extent of the lesion. In all conditions, nonetheless, the recovering cornea is re-invervated by sprouting from pre-existing, undamaged neurons, which, weeks later, is followed by the regeneration of axons in the damaged nerves (12-14).

A myriad of factors are thought to be involved in the mechanism of pain after PRK (15). The inflammatory cascade initiated after the surgery generates inflammatory mediators that stimulate the nerves sensitive to chemical stimulation and also lower the sensitivity threshold of other types of nerve fibers (16,17), thereby impacting post-surgery pain and discomfort. Indeed,

stimulation of nerve endings in inflammatory conditions tends to produce more pain than in non-inflammatory environments (18).

While the exact mechanisms for this phenomenon are not completely understood, experimental evidence supports the notion that damaged keratocytes release pro-inflammatory cytokines, which stimulate the migration of both resident ocular cells and activated leukocytes into the cornea. In addition, there is a direct and indirect stimulation of nerve fibers. (17,19). Direct stimulation involves the binding of inflammatory mediators to the voltage-gated ion channels on the nerve fibers, thereby inciting Ca2+influx , ultimately leading to neuronal firing (20).

Inflammatory mediators also bind to the transient receptor potential (TRP) family of cation channels, so-called transducers. Once activated, transducers evoke pain through voltage-gated ion channels in the nerve membranes (21). The magnitude of stimuli needed to activate transducers during the early post-operative period after PRK (<48 hrs.) is typically smaller than the correspondent intensity in undamaged corneas.

Successful penetration of the injured corneal tissue is only achieved by a portion of the regenerated stromal nerves, which is typically accomplished through the edge of the flap, as in LASIK (22), or via the corneal transplant (23). Experiments based on confocal microscopy have shown that the time for complete morphological recovery of corneal nerve fibers after both PRK and LASIK may be longer than one year (9,24,25). As a result, patients may still have some level of sensory impairment even after 12 months (26,27).

In a study comparing LASIK and PRK, patients submitted to PRK displayed corneal mechanical thresholds with a decreased sensitivity in the center of the cornea. The sensitivity threshold began to rise 7 days after surgery and increased slowly to reach values close to normal about 3 months later. However, incomplete recovery was still observed in some patients between 6 months and one year after surgery (28).

Both conventional histological techniques and "in vivo" confocal microscopy experiments provide evidence for a negative correlation between sensitivity and reduction in innervation density following photorefractive surgery (9,24,25). By the same token, there seems to be a positive correlation between the regeneration of corneal nerves and corneal sensation (25).

Following refractive surgery, there is a possibility of spontaneous acute and chronic pain sensations, although the degree of pain is difficult to predict and may be highly heterogeneous from patient to patient. While peak discomfort after PRK occurs at 3 hours and may persist at moderate or low levels for at least 7 days, pain is typically noticeable within a short window of 30 to 60 minutes after PRK, reaching severe intensity between the 4th and 6th post-operative hour (29). Evidence indicates that pain following PRK may remain at severe levels for the first 24 hours, but can continue for up to 4 days until the early phase of the corneal wound healing process is accomplished by the re-establishment of the first epithelial barrier in the previously exposed area. Although of a lower intensity compared to PRK, pain is also reported after LASIK for a period of up to 3 days (30).

Up to 40% of patients experience significant levels of ocular discomfort after LASIK or PRK, including foreign body sensation, dry eyes, and intense pain. However, the discomfort after PRK appears to be not only more frequent and intense, but also longer in duration compared to LASIK (31).

Opioid Use for Pain Treatment

Opioids have been used to treat pain since early history (32). These compounds mimic endogenous analgesics (endorphins) and interact with endogenous receptors (mu, kappa, delta, and sigma), which are distributed in specific areas of the brain (32,33). Opioids are considered potent and appropriate analgesics for moderate to severe acute and chronic pain (34).

The so-called pure opioid agonists, the most potent analgesics, such as morphine, hydromorphone, and fentanyl, bind more avidly to mu receptors and display a higher intrinsic activity at the cellular level compared to partial opioid agonists (e.g., buprenorphine and pentazocine). Unfortunately, the high rate of adverse events limits their use in practice, especially for regimens consisting of augmented doses (32).

Among the currently available arsenal of opioids for pain control, we have codeine, oxycodone, hydromorphone, buprenorphine, tramadol, fentanyl, remifentanil, pethidine, meperidine, and methadone (35).

All of them, with a few differences, present a range of both adverse events and side effects related to their mechanism of action. Nausea, constipation, sedation, addiction, and respiratory depression, among other reactions, are common and can be quite severe (32,36) depending on the dose and half-life. Addiction is of great concern because of inapropriate prescriptions, especially for patients at risk (37). Tolerance, the lowering of analgesic effects over time for the same

dose, is one of the mechanisms related to addiction, and it can develop after acute and chronic administration of opioids (32).

Codeine was first isolated in 1832, and it is considered the prototype of weak opioid analgesics, with approximately 50% of the analgesic potency of morphine (38). Codeine derives its analgesic properties through its conversion into morphine (39), as 5 – 10% of oral doses are o-demethylated to morphine by cytochrome P450 2D6 (CYP2D6), an enzyme whose gene is highly polymorphic in humans. Polymorphisms in the CYP2D6 may cause important interindividual differences not only on the metabolism and clinical efficacy of codeine, but also of tramadol (40). Empirical evidence demonstrates that doses of codeine may be increased up to 90mg, although the largest proportion of studies have employed 60 mg, as shown by a systematic review of studies of single dose codeine for acute postoperative pain in adults (41). Typically associated with other non-opioid analgesic drugs, such as acetaminophen (paracetamol), aspirin or ibuprofen, codeine is found in a wide range of different preparations and over-the-counter medicines for pain control (42). Besides its utilization in pain relief, codeine has also been widely used as the active ingredient in cough suppressants and anti-diarrhoeal mixtures (43,44). Most published studies using codeine and other opioids originate from areas such as dentistry (45), oncology (46), and orthopedics (42).

In a recent umbrella review (47) of single dose oral analgesics for post-operative pain, codeine 60 mg demonstrated the highest number necessary to treat (NNT) of all the studied drugs, which improved considerably if it was associated with NSAIDs such as paracetamol (from 12 to 3.9). Compared to placebo, the relative risk for a clinical benefit, defined as the achievement of least 50% pain relief over 4 – 6 hours, was 2.6 for codeine 30 mg plus paracetamol 600/650 mg, and 6.3 for codeine 60 mg plus paracetamol 1000/800 mg.

A recent survey of prescribing habits of maxillofacial surgeons in the United States and Canada showed that codeine was the most prescribed opioid drug in Canada, while hydrocodone was preferred in the US (48).

Opioids are routinely used in orthopedics, particularly in the treatment of chronic back pain, where it may be effective for short-term relief (49). Other uses in this therapeutic area include pain control after arthroscopic surgery, with good results, as described in a study of tramadol/acetaminophen (paracetamol) use

versus placebo (50). In contrast, a review of 2 different studies has shown that celecoxib may be superior to a combination of hydrocodone/acetaminophen for these patients (51).

Opioid use is extremely common for the treatment of cancer pain (46), which is typically a chronic condition. A Cochrane meta-analysis of 15 studies showed that codeine is effective for cancer pain control compared to placebo, but with higher risks of adverse events (46), similar to studies with other opioids, such as morphine (52), oxycodone (53), hydromorphone (54), methadone (55), and tramadol (56). In this population, morphine, oxycodone, and hydromorphone seem to have similar efficacy and tolerability (57).

For the control of break-through pain (i.e., exacerbation of pain in a patient already taking analgesics) in cancer patients, several formulations can be used. A systematic review of this subject found that transmucosal fentanyl produced a greater level of pain relief in a shorter time frame than oral morphine (58).

Use of Opioids in Ophthalmology

Studies about the effects of opioids in ophthalmic surgery date back at least 6 decades (59). Fentanyl and morphine have been evaluated as adjuncts to anesthesia in randomized studies on post-operative pain and have been found to have varying efficacy. Table 1 lists all the articles retrieved from PubMed and those found in a search of the references that evaluated post-operative pain in relation to opioid use (60-69).

Three studies assessed the use of fentanyl versus sub-Tenon's block with local anesthetics in children. The use of IV fentanyl was similar to sub-Tenon's block for pain control 2 hours after squint surgery in the study of Ramachandran et al (60).

In a retrospective case series, fentanyl, given by patient-controlled analgesia (PCA), was compared to IV ketorolac in patients submitted to enucleation or evisceration (61). The mean pain score on day 0 was significantly lower in the fentanyl group, but there were no differences in the following 2 days. Fentanyl's analgesic effect was significantly stronger in the enucleated patients than in the eviscerated group.

In children undergoing strabismus surgery, the use of IV morphine was evaluated in 2 studies. No difference in the pain assessment until discharge was found in comparison to IV ketorolac or rectal diclofenac (61,62).

Peribulbar lignocaine alone was compared to peribulbar lignocaine plus morphine for pterygium surgery in adults (63). While pain scores at 24 hours post-

Table 1. *List of studies evaluating opioid treatment in ophthalmic surgery post-operative period.*

Author Year	N	Pain Scale/ Outcome	Topical/Local	Systemic	Outcome
Ramachandran 2014 (60)	67	CHEOPS	Sub-Tenon block	Fentanyl	No difference
Ghai 2009 (64)	114	Number of patients	Sub-Tenon block	Fentanyl	Fewer pts in the sub-Tenon block required rescue analgesia
Chhabra 2009 (65)	200	AIIMS	Sub-Tenon block	Fentanyl	Higher pain score in the fentanyl group
Kim 2013 (69)	82	VAS	na	Fentanyl vs Ketorolac	Fentanyl more effective on day zero***
Munro 1994 (61)	42	nd	na	Morphine vs Ketorolac	No difference
Wennström 2002(62)	50	FACES	na	Morphine vs diclofenac	No difference
Wishaw 2000 (63)	20	VAS	Peribulbar lignocaine vs peribulbar morphine	na	Lower pain scores in morphine group at 24 hours
Hemmerling 2000 (66)	36	NRS	Retrobulbar morphine, saline	SC morphine, saline	Both morphine groups required less rescue pain medication during the first 3 hours
Kaufmann 2004 (67)	35	AUC	na	CRO vs tramadol/ metamizol	Higher AUC in CRO group
Ko 2009 (68)	29	VAS	na	Tramadol vs placebo	No difference

CHEOPS – Children's Hospital of Eastern Ontario Pain Scale; AIIMS – All India Institute of Medical Science Pain Scale; VAS – Visual Analog Scale; FACES – Wong and Baker Pain Rating Scale; NRS – Numeric Rating Scale; CRO – controlled-release tramadol; AUC – area under the curve for quality of analgesia; na - not applicable; nd - not described. *** retrospective study

operatively were significantly lower in the morphine group, both interventions resulted in similar sedation levels as well as the proportions of patients experiencing side-effects.

In a study by Ghai et al (64), IV fentanyl use resulted in a larger number of patients requiring analgesia for the 24 hours following cataract surgery. Chhabra et al (65) found the same result for vitreoretinal surgery.

The efficacy of retrobulbar or subcutaneous morphine was also studied in adult patients who had undergone antiglaucomatous cyclodestructive or vitreoretinal surgery (66). Both groups received less local anesthetic (mepivacaine) than the saline group for the 12 hours following surgery.

Opioids, such as oxycodone and tramadol, have been studied in adults in the post-operative setting of retinal surgery (67). Controlled release oxycodone significantly outperformed IV tramadol/metamizol in adult patients during the first 24 hours after surgery, with fewer side effects and an overall greater patient satisfaction. In another study, the authors failed to demonstrate any benefits of tramadol compared to placebo in diabetic patients undergoing panretinal photocoagulation, most likely because of the small sample size of the study (68).

Commonly Reported Adverse Effects of Opioids in Ocular Surgery

Adverse events were not reported consistently in the reviewed studies (Table 2). As expected, the most important reported adverse events included nausea and vomiting (32). Overall, approximately 50% (95% confidence interval = 31% to 69%) of patients under opioid therapy reported either nausea or vomiting. Among the evaluated studies, severe vomiting and nausea were managed with anti-emetics. No serious or fatal adverse events related to the use of opioid medications were reported. No study reported incidence of opioid-induced hyperalgesia, sleep disturbances, constipation, dry mouth, somnolence, or dysgeusia. However, Ghai et al (64) pointed out that hypoapnea or apnea requiring intraoperative ventilatory support was observed in 18 (32%) children in the fentanyl group compared to none in the sub-Tenon block group.

One study reported itching in one out of 10 patients treated with morphine (63), whereas mild sedation (4 hrs. post-surgery) was observed in 3 out of 19 patients (16%) that received tramadol (67). One study reported lack of adverse events due to morphine (66). Finally, no information on side effects was described in the trial by Ko et al (68) that inves-

Table 2. *Commonly reported complications and adverse effects of opioids for pain control after ocular surgery*.*

Opioid	Chemical class	Reported adverse events	Reference
Morphine	Phenanthrenes	Vomiting and nausea Severe vomiting† Postoperative itching	(61,62,63)
Fentanyl	Phenylpiperidines	Intraoperative hypoapnea or apnea. Vomiting. Severe vomiting† Severe nausea requiring antiemetics.	(60,64,65,69)
Oxycodone	Phenanthrenes	Vomiting and nausea	(67)
Tramadol‡	Phenylpropyl Amines	Vomiting and nausea. Severe vomiting† Sedation 4h after surgery	(67)

* Adverse effects of specific opioids (such as codeine and meperidine/pethidine) not investigated in the reviewed studies are described in detail elsewhere (32).
† Defines as >1 episodes of vomiting.
‡In combination with metamizol.

tigated the analgesic properties of tramadol during panretinal photocoagulation.

Use of Systemic Opioids in Refractive Surgery

Although several methods have been used to provide pain relief after PRK, including bandage contact lenses (16), topical non-steroidal anti-inflammatory drugs (NSAIDs) (70), dilute topical anesthetics (71), and gabapentinoids (gabapentin and pregabalin) (72,73), refractive surgeons are still searching for the best combination of analgesics to treat post-operative pain. Few studies in the ophthalmology literature addressed the use of systemic opioids for pain treatment after refractive surgery (74).

In a study by Saleh and Almasri (75), the dominant eyes of 14 patients were either randomized to PRK or LASIK, using topical anesthetics, a benzodiazepine, and codeine associated with paracetamol for post-operative pain. The study was not designed to evaluate the effect of the analgesic association and concluded that patients reported less pain at 2 hours post-surgery, but there was no difference at 12, 24, and 48 hours.

Magone et al (76) treated 60 patients, with one eye randomly receiving epi-LASIK with flap amputation and the other eye receiving automatic epithelial brush treatment. Similar to the previous study, the main objective of the trial was to compare surgical techniques, not the effect of drug treatments to manage pain. The patients received 800 mg ibuprofen orally twice a day,

one tablet of oxycodone – a semisynthetic opioid – every 4 hours as needed, and no more than one drop of nonpreserved tetracaine HCl (0.5%) every 2 hours as needed. The conclusion was that the flap group showed a statistically, but not clinically significant advantage in the pain scores, however there was no difference in the epithelial healing times between the 2 groups.

Conclusion

In conclusion, the paucity of studies in the literature focusing on the use of opioids for pain treatment after refractive surgery is concerning because, as these studies suggest, these drugs may be commonly used in some centers (74) without confirmed evidence of their effectiveness.

Opioid use is common in some other specialties, but it carries risks of severe adverse reactions (32) and addiction (33). Serious adverse reactions include death, respiratory depression, severe vomiting, and bowel obstruction (35). Other, less severe reactions, include nausea, immunologic effects, hormonal changes, hyperalgesia, sedation, sleep disturbances, psychomotor alterations, bladder dysfunction, and cardiac effects, among others. (32)

Although they are used for the short-term treatment of post-operative pain in refractive surgery, their benefits and risks must be properly evaluated in randomized clinical trials before their indication can be safely advised.

REFERENCES

1. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: Structure, contents and function. *Exp Eye Res* 2003; 76:521-542.

2. Rózsa AJ, Guss RB, Beuerman RW. Neural remodeling following experimental surgery of the rabbit cornea. *Invest Ophthalmol Vis Sci* 1983; 24:1033-1051.

3. Wilson SE. Clinical practice. Use of lasers for vision correction of nearsightedness and farsightedness. *N Engl J Med* 2004; 351:470-475.

4. Stanley PF, Tanzer DJ, Schallhorn SC. Laser refractive surgery in the United States Navy. *Curr Opin Ophthalmol* 2008; 19:321-324.

5. Trattler WB, Barnes SD. Current trends in advanced surface ablation. *Curr Opin Ophthalmol* 2008; 19:330-334.

6. Waring GO, Durrie DS. Emerging trends for procedure selection in contemporary refractive surgery: Consecutive review of 200 cases from a single center. *J Refract Surg* 2008; 24:S419-S423.

7. Lin RT, Maloney RK. Flap complications associated with lamellar refractive surgery. *Am J Ophthalmol* 1999; 127:129-136.

8. Benitez-del-Castillo JM, del RT, Iradier T, Hernández JL, Castillo A, Garcia-Sanchez J. Decrease in tear secretion and corneal sensitivity after laser in situ keratomileusis. *Cornea* 2001; 20:30-32.

9. Linna TU, Vesaluoma MH, Pérez-Santonja JJ, Petroll WM, Alió JL, Tervo TM. Effect of myopic LASIK on corneal sensitivity and morphology of subbasal nerves. *Invest Ophthalmol Vis Sci* 2000; 41:393-397.

10. Basbaum AI, Jessel TM. The perception of pain. Eds: Kandel ER, Schwartz JH, Jessell TM. In: *Principles of Neuroscience.* McGraw-Hill; New York; 2000. pp. 472-491.

11. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005; 9:463-484.

12. Felipe CD, Belmonte C. c-Jun expression after axotomy of corneal trigeminal ganglion neurons is dependent on the site of injury. *Eur J Neurosci* 1999; 11:899-906.

13. Linna T, Tervo T. Real-time confocal microscopic observations on human corneal nerves and wound healing after excimer laser photorefractive keratectomy. *Curr Eye Res* 1997; 16:640-649.

14, Tervo T, Moilanen JA. In vivo confocal microscopy for evaluation of wound healing following corneal refractive surgery. *Prog Retin Eye Res* 2003; 22:339-358.

15. Belmonte,C, Tervo,T. Pain in and around the eyes. Ed: Mcmahon,S, Koltzenburg,M, In: *Wall & Melzack's Textbook of Pain.* Elsevier Churchill Livingstone, Philadelphia; 2006. pp. 887-891.

16. Cherry PM. The treatment of pain following excimer laser photorefractive keratectomy: Additive effect of local anesthetic drops, topical diclofenac, and bandage soft contact. *Ophthalmic Surg Lasers* 1996; 27:S477-S480.

17. Netto MV, Mohan RR, Ambrosio R Jr., Hutcheon AE, Zieske JD, Wilson SE. Wound healing in the cornea: A review of refractive surgery complications and new prospects for therapy. *Cornea* 2005; 24:509-522.

18. Gallar J, Acosta MC, Gutierrez AR, Belmonte C. Impulse activity in corneal sensory nerve fibers after photorefractive keratectomy. *Invest Ophthalmol Vis Sci* 2007; 48:4033-4037.

19. Fagerholm P. Wound healing after photorefractive keratectomy. *J Cataract Refract Surg* 2000; 26:432-447.

20. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009; 139:267-284.

21. Materazzi S, Nassini R, Andrè E, Campi B, Amadesi S, Trevisani M, Bunnett NW, Patacchini R, Geppetti P. Cox-dependent fatty acid metabolites cause pain through activation of the irritant receptor TRPA1. *Proc Natl Acad Sci U S A* 2008; 105:12045-12050.

22. Vesaluoma MH, Petroll WM, Pérez-Santonja JJ, Valle TU, Alió JL, Tervo TM. Laser in situ keratomileusis flap margin: Wound healing and complications imaged by in vivo confocal microscopy. *Am J Ophthalmol* 2000; 130:564-573.

23. Tervo T, Vannas A, Tervo K, Holden BA. Histochemical evidence of limited reinnervation of human corneal grafts. *Acta Ophthalmol (Copenh)* 1985; 63:207-214.

24. Lee BH, McLaren JW, Erie JC, Hodge DO, Bourne WM. Reinnervation in the cornea after LASIK. *Invest Ophthalmol Vis Sci* 2002; 43:3660-3664.

25. Moilanen JA, Vesaluoma MH, Muller LJ, Tervo TM. Long-term corneal morphology after PRK by in vivo confocal microscopy. *Invest Ophthalmol Vis Sci* 2003; 44:1064-1069.

26. Erie JC, Patel SV, Bourne WM. Aberrant corneal nerve regeneration after PRK. *Cornea* 2003; 22:684-686.

27. Gallar J, Acosta MC, Moilanen JA, Holopainen JM, Belmonte C, Tervo TM. Recovery of corneal sensitivity to mechanical and chemical stimulation after laser in situ keratomileusis. *J Refract Surg* 2004; 20:229-235.

28. Kanellopoulos AJ, Pallikaris IG, Donnenfeld ED, Detorakis S, Koufala K, Perry HD. Comparison of corneal sensation following photorefractive keratectomy and laser in situ keratomileusis. *J Cataract Refract Surg* 1997; 23:34-38.

29. Epstein RL, Laurence EP. Effect of topical diclofenac solution on discomfort after radial keratotomy. *J Cataract Refract Surg* 1994; 20:378-380.

30. Autrata R, Rehurek J. Laser-assisted subepithelial keratectomy for myopia: Two-year follow-up. *J Cataract Refract Surg* 2003; 29:661-668.

31. Alió JL, Peréz-Santonja JJ, Tervo T, Tabbara KF, Vesaluoma M, Smith RJ, Maddox B, Maloney RK. Postoperative inflammation, microbial complications, and wound healing following laser in situ keratomileusis. *J Refract Surg* 2000; 16:523-538.

32. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. *Pain Physician* 2008; 11:S105-S120.

33. Han W, Ide S, Sora I, Yamamoto H, Ikeda K. A possible genetic mechanism underlying individual and interstrain differences in opioid actions: Focus on the mu opioid receptor gene. *Ann N Y Acad Sci* 2004; 1025:370-375.

34. Sachs CJ. Oral analgesics for acute nonspecific pain. *Am Fam Physician* 2005; 71:913-918.

35. Smith MT, Goh WH. Opioid Analgesics. Ed: Racz,GB, Noe,CE. In: *Pain Management - Current Issues and Opinions.* InTech;Rijeka, Croatia; 2011. pp. 287-306.

36. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL. Side effects of commonly prescribed analgesic medications. *Phys Med Rehabil Clin N Am* 2014; 25:457-470.

37. Gordon A, Cone EJ, DePriest AZ, Axford-Gatley RA, Passik SD. Prescribing opioids for chronic noncancer pain in primary care: Risk assessment. *Postgrad Med* 2014; 126:159-166.

38. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician* 2008; 11:S133-S153.

39. Kadiev E, Patel V, Rad P, Thankachan L, Tram A, Weinlein M, Woodfin K, Raffa RB, Nagar S. Role of pharmacogenetics in variable response to drugs: Focus on opioids. *Expert Opin Drug Metab Toxicol* 2008; 4:77-91.

40. Yiannakopoulou E. Pharmacogenomics and Opioid Analgesics: Clinical Implications. *Int J Genomics* 2015; 2015:368979.

41. Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2010; CD008099.

42. Moore PA. Pain management in dental practice: Tramadol vs. codeine combinations. *J Am Dent Assoc* 1999; 130:1075-1079.

43. Wee B. Chronic cough. *Curr Opin Support Palliat Care* 2008; 2:105-109.

44. Schiller LR. Review article: Anti-diarrhoeal pharmacology and therapeutics. *Aliment Pharmacol Ther* 1995; 9:87-106.

45. Roberts M, Brodribb W, Mitchell G. Reducing the pain: A systematic review of postdischarge analgesia following elective orthopedic surgery. *Pain Med* 2012; 13:711-727.

46. Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, Straube S. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. *Cochrane Database Syst Rev* 2014;CD006601.

47. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - An overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015;CD008659.

48. Pynn BR, Laskin DM. Comparison of narcotic prescribing habits and other methods of pain control by oral and maxillofacial surgeons in the United States and Canada. *J Oral Maxillofac Surg* 2014; 72:2402-2404.

49. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146:116-127.

50. Bourne MH, Rosenthal NR, Xiang J, Jordan D, Kamin M. Tramadol/acetaminophen tablets in the treatment of postsurgical orthopedic pain. *Am J Orthop (Belle Mead NJ)* 2005; 34:592-597.

51. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Ther* 2001; 23:228-241.

52. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2013;CD003868.

53. Wang YM, Liu ZW, Liu JL, Zhang L. Efficacy and tolerability of oxycodone in moderate-severe cancer-related pain: A meta-analysis of randomized controlled trials. *Exp Ther Med* 2012; 4:249-254.

54. Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: A systematic review. *Palliat Med* 2011; 25:471-477.

55. Nicholson AB. Methadone for cancer pain. *Cochrane Database Syst Rev* 2007; CD003971.

56. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. *Pharmacol Rep* 2009; 61:978-992.

57. Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliat Med* 2011; 25:402-409.

58. Zeppetella G, Davies AN, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. *J Pain Symptom Manage* 2014; 47:772-785.

59. Jensen CD, Haffly GN, Sarro LJ. The use of intravenous morphine in ocular surgery. *Am J Ophthalmol* 1950; 33:98-106.

60. Ramachandran R, Rewari V, Chandralekha C, Sinha R, Trikha A, Sharma P. Sub-Tenon block does not provide superior postoperative analgesia vs intravenous fentanyl in pediatric squint surgery. *Eur J Ophthalmol* 2014; 24:643-649.

61. Munro HM, Riegger LQ, Reynolds PI, Wilton NC, Lewis IH. Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. *Br J Anaesth* 1994; 72:624-628.

62. Wennström B, Reinsfelt B. Rectally administered diclofenac (Voltaren) reduces vomiting compared with opioid (morphine) after strabismus surgery in children. *Acta Anaesthesiol Scand* 2002; 46:430-434.

63. Wishaw K, Billington D, O'Brien D, Davies P. The use of orbital morphine for postoperative analgesia in pterygium surgery. *Anaesth Intensive Care* 2000; 28:43-45.

64. Ghai B, Ram J, Makkar JK, Wig J, Kaushik S. Subtenon block compared to intravenous fentanyl for perioperative analgesia in pediatric cataract surgery. *Anesth Analg* 2009; 108:1132-1138.

65. Chhabra A, Sinha R, Subramaniam R, Chandra P, Narang D, Garg SP. Comparison of sub-Tenon's block with i.v. fentanyl for paediatric vitreoretinal surgery. *Br J Anaesth* 2009; 103:739-743.

66. Hemmerling TM, Budde WM, Koppert W, Jonas JB. Retrobulbar versus systemic application of morphine during titratable regional anesthesia via retrobulbar catheter in intraocular surgery. *Anesth Analg* 2000; 91:585-588.

67. Kaufmann J, Yesiloglu S, Patermann B, Krombach JW, Kiencke P, Kampe S. Controlled-release oxycodone is better tolerated than intravenous tramadol/metamizol for postoperative analgesia after retinal-surgery. *Curr Eye Res* 2004; 28:271-275.

68. Ko BW, Shim JH, Lee BR, Cho HY. Analgesic effects of tramadol during panretinal photocoagulation. *Korean J Ophthalmol* 2009; 23:273-276.

69. Kim JH, Jang SY, Kim MJ, Lee SY, Yoon JS. Comparison of pain-relieving effects of fentanyl versus ketorolac after eye amputation surgery. *Korean J Ophthalmol* 2013; 27:229-234.

70. Assouline M, Renard G, Arne JL, David T, Lasmolles C, Malecaze F, Pouliquen YJ. A prospective randomized trial of topical soluble 0.1% indomethacin versus 0.1% diclofenac versus placebo for the control of pain following excimer laser photorefractive keratectomy. *Ophthalmic Surg Lasers* 1998; 29:365-374.

71. Brilakis HS, Deutsch TA. Topical tetracaine with bandage soft contact lens pain control after photorefractive keratectomy. *J Refract Surg* 2000; 16:444-447.

72. Kuhnle MD, Ryan DS, Coe CD, Eaddy J, Kuzmowych C, Edwards J, Howard RS, Bower KS. Oral gabapentin for photorefractive keratectomy pain. *J Cataract Refract Surg* 2011; 37:364-369.

73. Pakravan M, Roshani M, Yazdani S, Faramazi A, Yaseri M. Pregabalin and gabapentin for post-photorefractive keratectomy pain: A randomized controlled trial. *Eur J Ophthalmol* 2012; 22:S106-S113.

74. Faktorovich EG, Melwani K. Efficacy and safety of pain relief medications after photorefractive keratectomy: Review of prospective randomized trials. *J Cataract Refract Surg* 2014; 40:1716-1730.

75. Saleh TA, Almasri MA. A comparative study of post-operative pain in laser epithelial keratomileusis versus photorefractive keratectomy. *Surgeon* 2003; 1:229-232.

76. Magone MT, Engle AT, Easter TH, Stanley PF, Howells J, Pasternak JF. Flap-off epi-LASIK versus automated epithelial brush in PRK: A prospective comparison study of pain and reepithelialization times. *J Refract Surg* 2012; 28:682-689.