Original Article

Comparison of the Analgesic Effect of Nepafenac 0.1%, Ketorolac 0.5%, and Diclofenac 0.1% Ophthalmic Solution during Intravitreal Injection

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Background: Pain during intravitreal injection (IVT) is inevitable and might reduce the patient's compliance. Topical anesthetic eye drop usually is administered to reduce pain during IVT. However, severe ocular pain has been reported in some patients. The most effective anesthesia for IVT is still controversy.

Objective: To evaluate the analgesic effect of three topical non-steroidal anti-inflammatory drugs (NSAIDs) eye drop, nepafenac 0.1%, ketorolac 0.5%, and diclofenac 0.1%, during IVT.

Materials and Methods: The present study was a prospective randomized, double-blinded, placebo-controlled study. Patients undergoing intravitreal bevacizumab injections were randomly divided into four groups. Group 1, group 2, group 3, and group 4 received topical nepafenac 0.1%, topical ketorolac 0.5%, diclofenac 0.1%, and artificial tear (placebo), respectively. One hour after receiving the eye drops, all patients underwent IVT with topical anesthetic eye drop. Pain assessment was performed immediately after IVT using the Thai version of Short-Form McGill Pain Questionnaire (SF-MPQ). The SF-MPQ consists of the main component of the SF-MPQ, the visual analogue scale (VAS), and the present pain intensity (PPI).

Results: Eighty patients voluntarily enrolled in the present study. Median of VAS scores were 1.5 (0.8 to 4.6), 2.3 (1.5 to 4.6), 1.5 (1 to 3.2), and 2.4 (1.4 to 3.6) in nepafenac group, ketorolac group, diclofenac group, and placebo group, respectively (p=0.159). Median of the main component of the SF-MPQ scores were 4 (1.25 to 5.75), 5 (2.25 to 11.5), 5 (1.25 to 9.5), and 5 (3 to 13), in nepafenac group, ketorolac group, diclofenac group and placebo group, respectively (p=0.409). Median of the PPI scores were 1 (1 to 1.75), 1 (1 to 2), 1 (1 to 1), and 1 (1 to 2), in nepafenac group, ketorolac group, diclofenac group, and placebo group, respectively (p=0.529).

Conclusion: There were no significant differences in analgesic effect during IVT between topical NSAIDs, nepafenac 0.1%, ketorolac 0.5%, diclofenac 0.1%, and placebo.

Keywords: Intravitreal injection; Analgesic effect; Topical NSAIDs eye drop; SF-MPQ

Received 22 February 2021 | Revised 21 April 2021 | Accepted 21 April 2021

J Med Assoc Thai 2021;104(6):982-8

Website: http://www.jmatonline.com

Nowadays, intravitreal injection (IVT) is a mainstay of treatment in ophthalmology. This procedure will deliver various therapeutic agents to the posterior segment of the eye with minimal systemic effect. Intravitreal anti-vascular endothelial growth factor (VEGF) injection provides better treatment results than the previous conventional treatment for many retinal diseases such as diabetic macular edema (DME), macular edema in retinal vein occlusion (RVO), and exudative age-related macular degeneration (AMD)[1]. Since the introduction of anti-VEGF agents in 2006, intravitreal anti-VEGF injection has become much more common and increased every year[2]. However, repeated IVTs are often needed because of the half-life of anti-VEGF agents and the chronicity of the diseases. Although IVTs are safe and severe complications are very rare[3], the procedures are invasive. Pain and discomfort during the procedures are inevitable and might reduce the patient's compliance. Before the procedure, topical anesthesia usually is administered to reduce pain. However, some patients still report severe pain during injections.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in ophthalmic

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How to cite this article:

Wongchaikanakorn N, Dangprapai Y. Comparison of the Analgesic Effect of Nepafenac 0.1%, Ketorolac 0.5%, and Diclofenac 0.1% Ophthalmic Solution during Intravitreal Injection. J Med Assoc Thai 2021;104:982-8.

doi.org/10.35755/jmedassocthai.2021.06.12592

procedures including prevention of intraoperative miosis, treatment for cystoid macular edema, and reducing ocular pain from cataract and refractive surgery[4,5]. The mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX) in arachidonic acid cascade to prevent the production of prostaglandins, which are the potent mediators of pain and inflammatory process[6]. Some publications have reported the efficacy of topical NSAIDs in reducing pain from IVT[7-12]. The aim of the present study was to evaluate the analgesic effect of topical NSAIDs available in Thailand, which are nepafenac 0.1%, ketorolac 0.5%, and diclofenac 0.1%, during IVT.

Materials and Methods

The present study was a prospective randomized, double-blinded, placebo-controlled study. Eighty patients were recruited at the Department of Ophthalmology, Taksin Hospital between November 2019 and October 2020.The study had been approved for the ethics from the Bangkok Metropolitan Administration Ethic Committee for Human Research, the Certificate of Approval No. S006h/62. All patients provided informed consent.

Diagnosed patients of AMD, DME, and RVO scheduled for intravitreal bevacizumab (Avastin) injection were eligible to the present study. To decrease anxiety from first-time IVT, all patients had received at least one prior injection before entering the present study. Only one eye per patient was included in the present study. Exclusion criteria were a history of previous eye surgery other than phacoemulsification such as pterygium excision, trabeculectomy, strabismus surgery, pars plana vitrectomy, or scleral buckling procedure, glaucoma, uveitis, bullous keratopathy, herpetic eye disease, bilateral IVTs, a history of allergy to NSAIDs, and any use of sedative medications, opioid, acetaminophen or NSAIDs within seven days. Uncooperative, impaired communication, pregnant, and breastfeeding patients were also excluded.

Eighty patients were enrolled to the study and randomized by statistician with block randomization method to four groups to receive one drop of nepafenac 0.1% (Nevanac, Alcon Laboratories, Inc., Fort Worth, Tx, USA), ketorolac 0.5% (Acular, Allergan Pharmaceuticals Ireland, Westport, Ireland), diclofenac 0.1% (Voltaren, Seng Thai Company, Bangkok, Thailand), or artificial tear (Tears Naturale II, Alcon Laboratories, Inc., Fort Worth, TX, USA) as placebo by assigned nurse, one hour before IVT. All bottles of study medication eye drop were blinded by aluminum foil paper. Investigators, patients, and nurses were masked to the instilled eye drop.

Intravitreal injection technique

Before IVT, one drop of topical anesthetic eye drop, which was tetracaine hydrochloride 0.5%, was instilled every five minutes for three times. Then one drop of 10% povidone iodine was applied to inferior conjunctival fornix. The eyelids and eyelashes were applied with 10% povidone iodine and draped in a sterile fashion. A sterile eyelid speculum was placed. The location of injection was marked as 3.5 mm from limbus, in an inferotemporal quadrant, then 10% povidone iodine was placed to sterile the injection site for 15 seconds. Bevacizumab, at 1.25 mg per 0.05 mL, was injected with a 30-gauge needle perpendicular to the sclera by the straight technique[13]. A Q-tip was applied immediately at injection site after removal of the needle. One drop of tobramycin 0.3% was instilled after the procedure. All IVTs were performed by the same surgeon (Wongchaikanakorn N).

Pain assessment

After IVT, the patient was asked immediately about the pain during the procedure by the trained technician. The pain was assessed using the Thai version of Short-Form McGill Pain Questionnaire (SF-MPQ)[14]. The SF-MPQ is a multidimensional tool for evaluating both qualitative and quantitative characteristics of pain. The SF-MPQ consists of main component of the SF-MPQ, visual analogue scale (VAS) and present pain intensity (PPI).

Main component of the SF-MPQ: The main component of the SF-MPQ consists of 15 questions of pain descriptors with 11 sensory scores and four affective scores. Pain intensity of each descriptor was graded as 0 for no pain, 1 for mild, 2 for moderate, and 3 for severe. The total scores are 45. A higher score means more pain experienced.

Visual analogue scale: VAS is a self-rated pain score in a 10 cm long horizontal line with anchor statements on the left as no pain, and on the right as the worst possible pain. The patient is asked to mark the level of pain on the line. The examiner scores the VAS from 0 to 10 by measure the distance from the "no pain" anchor point to the patient's mark point.

Present pain intensity: A measure of the magnitude of the overall pain experienced by a numerical verbal rating scale included six levels as 0 for none, 1 for mild, 2 for discomforting, 3 for distressing, 4 for horrible, and 5 for excruciating.

Table 1. Baseline characteristics of patients

Characteristic	Nepafenac (n=20); n (%)	Ketorolac (n=20); n (%)	Diclofenac (n=20); n (%)	Placebo (artificial tear) (n=20); n (%)	p-value
Age (years); mean±SD	62.45±9.64	61.30±7.83	68.25±13.98	62.95±14.67	0.265§
Sex					0.801†
Female	12 (60)	14 (70)	11 (55)	12 (60)	
Male	8 (40)	6 (30)	9 (45)	8 (40)	
Study eye					0.572†
Right	12 (60)	8 (40)	11 (55)	9 (45)	
Left	8 (40)	12 (60)	9 (45)	11 (55)	
Diagnosis					0.898†
AMD	5 (25)	7 (35)	8 (40)	7 (35)	
DME	12 (60)	11 (55)	8 (40)	10 (50)	
RVO	3 (15)	2 (10)	4 (20)	3 (15)	
No. of previous injection; median (range)	3 (1 to 5.75)	1 (1 to 3)	2 (1 to 3.75)	2 (1 to 3)	0.483π

AMD=age-related macular degeneration; DME=diabetic macular edema; RVO=retinal vein occlusion; SD=standard deviation

§ One-way analysis of variance, † Chi-square tests, π Kruskal-Wallis test

Table 2. The SF-MPQ pain scores during intravitreal injection in 4 groups

SF-MPQ	Nepafenac; median (range)	Ketorolac; median (range)	Diclofenac; median (range)	Placebo (artificial tear); median (range)	p-value
Visual analogue scale	1.5 (0.8 to 4.6)	2.3 (1.5 to 4.6)	1.5 (1 to 3.2)	2.4 (1.4 to 3.6)	0.159*
Main component of the SF-MPQ	4 (1.25 to 5.75)	5 (2.25 to 11.5)	5 (1.25 to 9.5)	5 (3 to 13)	0.409*
Present pain intensity	1 (1 to 1.75)	1 (1 to 2)	1 (1 to 1)	1 (1 to 2)	0.529*

SF-MPQ=Short-Form McGill Pain Questionnaire

* Kruskal-Wallis test

Statistical analysis

The sample size calculation was based on previous literature[8,11,12] with 90% power of analysis and type I error level at 0.05. From the calculation, the sample size required was 18 patients in each study group. Considering a drop-out rate at 10%, the sample size required was 80, which was 20 patients per group. The baseline characteristics including gender, study eye, diagnosis, of the four groups were examined by chi-square tests. ANOVA was used for the distribution of age across groups. Kruskal-Wallis test was applied to compare the SF-MPQ pain scores, which was the main component of the SF-MPQ, VAS, and PPI, in the four groups. Mann-Whitney U test was used for comparison of VAS between male and female. All statistical analyses in the present study were performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA) and considered statistically significant at p-value less than 0.05.

Results

Eighty patients were enrolled in the present study between November 2019 and October 2020. There were 49 females and 31 males. DME was the most common reason for IVT with 41 patients, followed by AMD with 27 patients, and RVO with 12 patients. No differences of baseline characteristics among the four groups were detected (Table 1).

The SF-MPQ pain scores from all groups using VAS, main component of the SF-MPQ, and PPI, during IVT were not statistically significant (Table 2). However, the pain scores from the main component of the SF-MPQ in nepafenac group were lower than the other groups. The distribution of the SF-MPQ pain scores are indicated in Figure 1.

VAS score was significantly higher in female than male with female at 2.4 (1.35 to 4.90) versus male at 1.4 (1 to 2.4) (p=0.009), using the Mann-Whitney U test.

Eleven patients with mild localized subconjunctival hemorrhage were detected. One case had mild subconjunctival bleb of vitreous reflux after IVT. No severe complications such as endophthalmitis, retinal detachment, massive ocular hemorrhage, traumatic lens injury, intraocular inflammation or

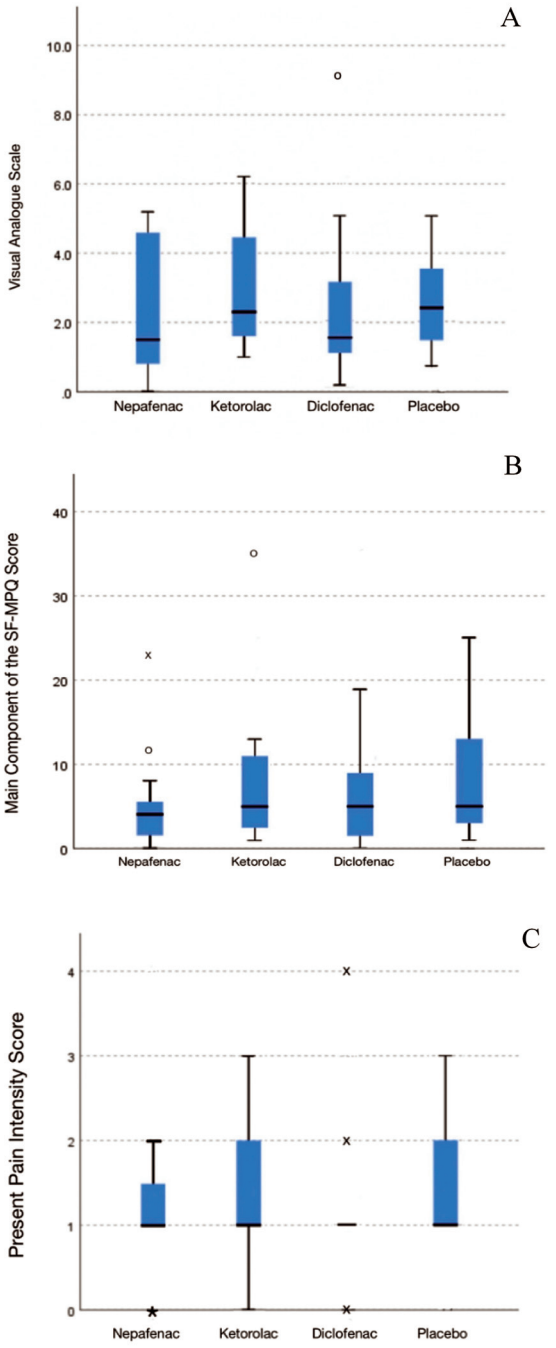

Figure 1. The box plots of the SF-MPQ pain scores during IVT in each group were shown. (A) VAS score, (B) Main components of the SF-MPQ score, (C) Present pain intensity score. Black horizontal lines were median. The boxes represented the 25th to 75th percentile of data. The circles, crosses and stars indicated the outliers (the extreme values).

thromboembolic events were encountered in the present study.

Eighteen in 20 patients (90%) in diclofenac group reported transient burning and stinging sensation on instillation. These undesirable effects were also reported by six patients (30%) in the ketorolac group, but none in the nepafenac and the placebo group. No serious adverse events from topical NSAIDs such as keratitis, corneal thinning, corneal perforation, or abnormal ocular bleeding, were detected in the present study.

Discussion

IVTs have become the most common intraocular procedure and are rising every year. Repeated injections are necessary for patients to treat chronic eye conditions such as AMD, DME, and RVO. IVTs are often associated with pain. Reducing pain and discomfort during IVT may promote compliance in patients. From the Euretina Expert Consensus on IVTs in 2018, only topical anesthesia is recommended[15].

The instillation of tetracaine 0.5% eye drop is routinely performed before IVT for analgesic effect because it is convenient and safe. However, some patients still reported severe pain during IVT. The other anesthetic methods such as subconjunctival anesthesia or topical anesthetic gel such as lidocaine gel can be performed to decrease pain and discomfort. However, complications from these procedures have been reported. Subconjunctival anesthesia may cause chemosis and subconjunctival hemorrhage[16]. Topical anesthetic gel may cause keratitis and increase risk of endophthalmitis from interfering with the antiseptic action of povidone iodine[17].

Although topical NSAIDs showed trend toward reducing pain associated with IVT in some studies[7-12], Sanabria et al reported that topical diclofenac did not reduce pain score after IVT[18]. However, there were differences among these studies concerning types of topical NSAIDs, types of administration such as pre or post IVT, and methods of pain assessment.

In the present study, the authors evaluated the analgesic effect during IVT of three topical NSAIDs, nepafenac 0.1%, ketorolac 0.5%, and diclofenac 0.1%, which are available in Thailand and compared them with a placebo, artificial tear, by instillation before IVT. The authors found no statistically significant differences among these topical NSAIDs and the placebo. Analgesic effect of topical NSAIDs was approved for reduction of ocular pain associated with cataract and corneal refractive surgery[5]. Topical NSAIDs for analgesic effect during IVT is practically off-label use. No analgesic effect of three topical NSAIDs were detected during IVT in the present

study. However, topical nepafenac showed the lowest pain scores in main component of SF-MPQ among these eye drops.

Diclofenac, ketorolac, nepafenac are in the group of aryl acetic acid derivatives, which are the potent COX-inhibitors. Unlike the other topical NSAIDs, nepafenac is the first prodrug NSAID formulation. Nepafenac is the prodrug of amfenac, which is converted by intraocular enzymatic hydrolysis[19]. Nepafenac showed significantly greater ocular bioavailability than other conventional NSAIDs[20]. After one drop of instillation, nepafenac rapidly penetrate the ocular tissue and distribute to the vascularized tissues of the eye where it was converted to amfenac, the potent COX-inhibitor. From the study, nepafenac inhibited the prostaglandin synthesis in iris, ciliary body including the retinochoroidal tissue, which diclofenac had the minimal effect[21]. Recently, Ogurel et al published that topical nepafenac demonstrated the additive analgesic effect when combined with topical anesthesia in intravitreal Ozurdex injection[22]. Although, the authors found that topical nepafenac had the lowest pain scores of the main component of SF-MPQ, it was not statistically significant compared with the placebo and the other NSAIDs. Further studies are needed to confirm this. In addition, topical nepafenac had a better ocular tolerability than the other two topical NSAIDs in the present study.

Topical NSAIDs may cause corneal epithelial breakdown, corneal melting, or corneal perforation for long term administration, especially its concurrent use with topical corticosteroid[23,24]. A case report by Yaşar et al stated that allergic urticaria had occurred after topical nepafenac instillation[25]. Systemic NSAIDs as well as topical ophthalmic NSAIDs have been associated with asthma exacerbation, gastrointestinal erosions, and bleeding disorder[26-28]. Nonetheless, instillation of one drop of topical NSAIDs before IVT for analgesic effect is safe for most patients.

Several factors associated with pain during IVT have been reported. Although higher number of previous injections, older age, and female had lower pain scores during IVT[10], Shin et al reported that female were more prone to perceive pain than male[29], which was similar to the present study. There was no correlation between pain score and gender, age, or underlying disease in the study by Ogurel et al[22]. Karimi found that the superonasal quadrant was associated with a lower pain score than other quadrants for IVT[30]. The small diameter of needle was associated with lower pain score and low risk of vitreous reflux[13]. Therefore, 30-gauge or thinner needles are recommended[15].

Perception of pain is subjective and can be highly variable among individuals. The SF-MPQ is a multidimensional tool for pain evaluation although it has not been specifically developed for ocular pain. However, it contains VAS pain score, which is a generally accepted tool for evaluating ocular pain.

The most common complication of IVT in the present study is mild localized subconjunctival hemorrhage at injection site as seen in 11 of 80 patients (13.75%,). One case had mild subconjunctival bleb of vitreous reflux. The straight technique of the present study injection may cause the vitreous reflux. Rodrigues et al reported that the severity of pain and risk of vitreous reflux were not different between the straight and beveled technique in small diameter needles of 29 or 30-gauge needles[13]. Although the straight technique may cause the vitreous reflux, the beveled technique is not convenient and may enhance risk of retinal tears, retinal detachments, or lens injuries, particularly in uncooperative patients. Furthermore, the subconjunctival bleb of vitreous reflux had a very low amount of the injected therapeutic agent[31].

However, the present study has some limitations including small sample sizes, the yellow appearance of nepafenac 0.1% eye drop, which is different from the other eye drops, thus, could not be fully blinded to the assigned nurse who were not involved in the present study, and the SF-MPQ is not designed particularly for ocular pain assessment.

Conclusion

Topical nepafenac 0.1%, ketorolac 0.5%, and diclofenac 0.1% eye drops did not show significant analgesic effect during IVT in the present study.

What is already known on this topic?

Topical NSAIDs eye drop was approved for reduction of ocular pain in cataract and refractive surgery. The analgesic effect during IVT of topical NSAIDs is still questionable.

What this study adds?

There were no significant differences in analgesic effect during IVT among topical NSAIDs, nepafenac 0.1%, ketorolac 0.5%, and diclofenac 0.1%, and the placebo.

Acknowledgment

The authors gratefully acknowledge all staffs in

the Department of Ophthalmology, Taksin Hospital and Dr. Saowalak Hunnangkul for the advice on statistical analyses. This study was supported by the Taksin Hospital Research Fund.

Conflicts of interest

The authors declare no conflict of interest.

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