



## Effect of Intravenous Administration of Ketorolac As Preventive Analgesia To Pupil In Eye Surgery With General Anesthesia

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### ABSTRACT

**Background:** NSAID (Non steroid anti inflammatory drug ) inhibit cyclooxygenase enzyme and also inhibition of proinflammation prostaglandin (PG). Ketorolac has recommended for a short time use on post operation, not longer than 2 days intravenous administration. So this drugs is good for acute analgesia. The research useful for looking an effect of ketorolac administration as a preventive analgesia concern to pupil in prevent myosis in eye's surgery within general anesthesia.

**Methods:** it was a quasi experimental study done in Sumatera Eye Centre Hospital, Medan, Indonesia during January to June 2012. Sampling was taken using total sampling method with 44 patients.

**Results:** There is no significant difference in myosis for patient with ketorolac as preventive analgesia in eye surgery

**Keywords:** ketorolac, preventive, analgesia, eye surgery, general anesthesia

### INTRODUCTION

Broadly speaking the eye surgery is divided into intraocular and extraocular eye surgery. Intraocular eye surgery includes surgery of the cornea, iris, anterior chamber, cataract, trabeculectomy, vitreous and retina. Meanwhile, extraocular eye surgery include eyelid surgery, conjunctiva, cornea surface, lacrimal system, and strabismus. In deviation prevention intraocular surgical IOP (Intra Ocular Pressure), immobilization of the eye (akinesia), and the maximum pupil dilation will provide optimal surgical conditions, while in the extraocular surgical

anesthesia attention is directed to the prevention and treatment of oculocardiac reflexes <sup>1,2,3</sup>

Most anesthetics can decrease or have no effect on intraocular pressure. Inhalation anesthetics reduce intraocular pressure proportionally along with it the level of anesthesia. Intravenous anesthesia drugs also lower the intraocular pressure. The exception is ketamine, which usually increases in arterial blood pressure and relaxes the extraocular muscles. NSAIDs (Non-steroidal Anti-Inflammatory Drug) inhibit the enzyme siklogenase and also blocking pro-inflammatory prostaglandin (PG).

Prostaglandins synthesized by the ciliary body and iris in response to the mouth of the surgery that causes miosis, pain and inflammation.<sup>1,3</sup> Some prospective studies, which are random has demonstrated efficacy of topical NSAID that inhibits miosis, reduced postoperative pain and inflammation, prevent edema makuler sistoid. As well as improving the recovery of vision in cataract surgery but, no research the latest regarding the potential benefits of topical NSAIDs in vitreoretinal surgery, this study is a prospective, randomized placebo-controlled double-blind trial is designed and indicated for evaluating topical ketorolac 0.4% in midriasis and intraoperative pain, inflammation, thickening of the retina, and vision restoration surgery vitreoretinal settings.<sup>2,4,5,6</sup>

PG inhibit biosynthesis inhibition of intraoperative miosis during cataract surgery, reduces the permeability of blood vessels eye, and modify inflamation. NSAID inhibit the enzyme cyclooxygenase, thus inhibiting the biosynthesis of PG but not LTs (leukotrienes).<sup>7,8</sup> Topical ophthalmic NSAIDs have been proven effective in treating a variety of conditions in which prostaglandins are believed to play a causative role, including surgically induced miosis, postoperative inflammation, treatment and prevention of cystoid macular edema (CME), and controlling pain in refractive surgery. NSAID ketorolac tromethamine has shown efficacy in the prevention of surgically induced miosis, in the treatment of postoperative pain eye, in the treatment of chronic aphakic and pseudophakic CME and in the prevention and suppression of ocular inflammation following cataract surgery.<sup>3,9</sup>

Ketorolac, 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, is a rare mix. Anti-inflammatory activity of drugs levorotatory isomer (l) doubled compared dextrorotatory isomer (d). These drugs can be found on the market, known as tromethamine salt (0.5%, wt / vol) that has a solubility in water higher than ketorolac. Ketorolac is applied topically on the handling of conjunctivitis, seasonal allergies, used post surgery to deal with ocular pain and inflammation. The use of ketorolac tromethamine

solution associated with the incidence of ocular irritation, especially burning and get stabbed.<sup>5,10,11</sup> To reduce the incidence of these side effects, the use of ketorolac tromethamine (0.4% wt / vol) low doses have been considered.

Based on the research of Robert Stewart et al Multicenter, double-blind, randomized, parallel study comparing the safety profile and efficacy ketorolac tromethamine ophthalmic solution 0.5% normal saline in the maintenance of mydriasis pupil during catharact surgery.as much as 176 adult patients scheduled to undergo extracapsular cataract extraction unilateral and intraocular lens implantation in the posterior chamber received ketorolac tromethamine 0.5% (n = 89) or normal saline (n = 87), starting 2 hours before surgery. One drop of the study drug was given every 30 minutes for a total of 4 drops. Epinefrin not used in intraoperative irrigation solution. Pupil diameter was measured with calipers at three time points during operation. no significant differences between groups were observed in changes in pupil diameter between the end of surgery and the postoperative administration of semiotic agent, security variable, or the occurrence of side effects.<sup>8,9,10,11,12</sup> In this study, the drug ketorolac tromethamine 0.5% ophthalmic provide effective inhibition and well tolerated surgery inhibiting induced miosis during cataract surgery.<sup>3,13</sup>

M.Suleiman study by Yusuf et al, Department of Ophthalmology Al Assad Hospital, Tishreen University, Syria (2010), which aims to compare the efficacy and safety of topical prednisolone acetate 1% and topical ketorolac tromethamine 0.5% in the maintenance of mydriasis pupil during catharact surgery.Declare that topical ketorolac tromethamine 0.5% and prednisolone acetate 1% were equally well tolerated without side effects related, but ketorolac better in preventing surgically induced miosis.<sup>14,15</sup>

Another study by Richards Atanis, et al, International Eye Institute St Lukes Medical Centre in Quezon city, Philippines (2011), which aims to compare the effectiveness of topical prophylactic administration of ketorolac tromethamine 0.5% and

0.1% nepafenac to the maintenance of mydriasis during phacoemulsification. conclude that Nepafenac topical has proved a more effective inhibitor against miosis during phacoemulsification and provide a more stable midriatic effect during surgical procedures compared with topical ketorolac and placebo.<sup>16,17</sup>

While other studies using topical ketorolac for retinal surgery by Stephen J.Kim et al, Ophthalmology department of Emory University, Georgia, USA (2008), which aims to evaluate the effect of topical ketorolac in patients undergoing surgery vitreoretinal. declare topical ketorolac was well tolerated and safe, postoperative pain and inflammation reduced and a better visual recovery in this study with a double-blind manner.<sup>10,13,15</sup>

NSAID drugs have been popular as analgesia. These medications are helpful in reducing opioid analgesic requirement. Besides NSAIDs facilitate the healing process by reducing the side effects of opioids. NSAIDs on the other hand also cause unwanted effects, such as gastrointestinal mucosal disorders and renal blood flow. The Agency for Health Care Policy and Research of the Department of Health and Human Services United States published a practical guide to the management of acute pain, which if not obtained contra indications, pharmacological therapy for post-surgical pain mild to moderate should start with the nonsteroidal anti-inflammatory drugs.<sup>6,7,10</sup>

While the drug inhibiting the activity of COX-1 and COX-2 are frequently used ketorolac, ketorolac is recommended for short-term use in post-surgical does not exceed 2 days of intravenous administration so that both acute analgesia used as medicine. Ketorolac can through the placental barrier. Transfer of ketorolac into milk has been known and declared safe for use in nursing mothers. Ketorolac is a drug that works by blocking the enzyme COX-1 and COX-2 so that in addition to the relief of pain and inflammation but also have side effects such as gastric mucosal disorders, kidney and blood clotting processes.<sup>5,9,10</sup>

## AIM & OBJECTIVES

In the laboratory study, providing analgesic before their acute pain stimulus is more effective in minimizing changes in the dorsal horn due to central sensitization as compared to the same analgesics administered after pain states happen. This raises the hypothesis that pain management prior to surgery can relieve post-surgical pain better this so-called 'pre-emptive analgesia' written by Wall, 1988. the latter definition of refined by Kissin (2005) on the grounds that the process of central sensitization caused not only by the skin incision, but also by tissue damage in the whole procedure of intraoperative and post-surgical inflammation, then the focus has shifted from the timing of a single intervention to the concept of "preventive analgesia".<sup>9,10</sup>

## MATERIAL & METHODS

### Design

This research is a quasi experimental study with pretest and posttest design.

### Place

*Sumatera Eye Centre Hospital, Medan, Indonesia*

### Time

January 2012 until June 2012

### Population

Patient undergoing eye surgery with general anesthesia at *Sumatera Eye Centre Hospital, Medan, Indonesia*

### Sample

All the population that meets inclusive and exclusive criteria.

### Inclusion Criteria

1. Intraocular surgery
2. PS ASA 1-2
3. Duration of surgery  $\leq$  3 hours
4. Bleeding Time within normal limits
5. Ideal body weight and BMI
6. Obtaining Parental consent / Families Participant in study.

### Exclusion Criteria

1. Abnormal Liver Function Test
2. History of Allergic Reaction against the studied drug.

3. History of ulcer Pepticum
4. History of trauma pupil
5. History of eye infection
6. Usage of topical or systemic steroid and NSAID 14 days before surgery.

#### Drop-out criteria

1. Experienced a threatening complication as a result of the given treatment
2. Patient / Family who withdraw from study

#### Total Sampling

The technique of sampling with *consecutive sampling* while total sampling was calculated with Hypothesis test sample rule to an average of two population paired as follow :

$$n = \left[ \frac{(z_{\alpha} + z_{\beta}) \times sd}{d} \right]^2$$

Note :

n = minimal total sampling

$z_{\alpha}$  = Normal standard deviation value  $\alpha$  5% = 1,96

$z_{\beta}$  = Normal standard deviation value  $\beta$  10% = 1,282

sd = Standard deviation of the difference between the diameter of pupil (mm) = 0,41 mm ( the result of the initial survey)

d = The average difference in pupil size diameter (mm) = 0,20 mm ( the result of the initial survey)

Minimal total sampling = 44 persons

#### Methods

After obtaining informed consent and ethnics committee approved all the sample will undergo surgery included in the inclusive and exclusive criteria.

On the research day, drug prepared by volunteers who will conduct the research. Preparation with the previous way of volunteers administrated and given intravenous infusion of ringer lactate preload as much 10 ml/kg for the replacement of fasting and then all of volunteers get tropicanamid topically to the eye to be operated one hour before surgery and then measured the size of pupil of the eye to be operated by caliper kastroviego, and the next :

- a. Volunteers got ketorolac ( ketopain/soho) 30 mg i.v 30 minutes after induction and intubation and then premedication.
- b. After volunteers entered the operating room assembled the tool (monitoring ) to the body.
- c. After volunteers got the same drugs, both for intravenous anesthesia induction intubation and inhalation anesthesia as maintenance.
- d. After Intubation has been done, remeasured the pupil size with caliper kastroviego.
- e. It determined having on effect on the pupil when mydriasis pupil can be maintained as its size before anesthesia.

#### Independent Variable:

1. Ketorolac 30 mg IV

#### Dependent Variable:

1. Pupil size is measured with Kaliper Kastroviejo

#### Data analysis plan

Data Analysis:

1. Univariate Analysis, to explain / describe the characteristics of each variable studied and to view the pupil size data normality was used Kolmogorov – smirnov test.
2. Bivariate Analysis, to see the difference in pupil size after intravenous ketorolac. If the test data normality pupil size in normal distribution to see the difference use dependent T Test and if the test results are normal distribution used Wilcoxon test.

Significance limit set : 5%

Confidential intervals were used : 95%

#### Operational defenition

Preventive analgesia is the administration of analgesia prior to surgery and after surgery so as to prevent sensitization of pain thoroughly either injury or traumatic inflammation. Ketorolac are NSAIDs that shows potent analgesia but only has moderate anti-inflammatory activity when given by im or iv. This drug is used as a post- surgical analgesia either as a single drug ( less pain in outpatients) and supplement with opioids. Onset

start 15-30 minutes. Adult dose < 65 years 60 mg single dose of i.m, 30 mg single dose.

Normally, location of pupil is in the middle of iris (slightly tend to nasal). Congenital eccentric (coreoptopia) is rarely happened. Pupil size varies between 4 to 4 mm depend on the intensity of the light. Pupil size can be changed abnormally become small (myosis) or large (midriasis).

Kaliper Kastroviejo is a divider instrument. On one arm of this tool is a measurement scale which is used to change the scale. Used to measure squint, ptosis, retinal detachment and pars plana vitrectomy surgery. It also can be used to measure cornea diameter and measure horizontal diameter of iris that visible.

### Ethical Issues

Before under Anesthesia and research process has started, the prepared emergency instrument (*oro/nasofaringeal airway, ambu bag, oxygen source, laryngoscope, endotracheal tube* suitable to patient, *suction*), monitor (*pulse oxymetri, blood pressure, ECG and HR*), emergency drug (adrenaline, sulfas atropin, lidokain, aminofilin, deksametason).

If emergency in airway, cardio, lung and brain appears during anesthesia and this process of study, then always conduct the management of therapy according to the standard technic, instrument and drug. Patient and family are being informed about aim, usage and risk of the study. Then they being asked to fill the form of consent as a participant of the study. (inform consent)

This under study drug has a side effect which could be anticipated. This research is safe conducts to human, because this drug has been used for a long time as post surgery analgesia and proven safe if there is no contraindication to the patient.

In this research the dosage of drug that used is therapeutic dose. Moreover research with the same drug has already done on the others education centers.

## CONCLUSION AND SUGGESTION

### CONCLUSION

Gender population with the most eye intraocular surgery with general anesthesia is a male sex.

The type of action most intraocular surgery performed under general anesthesia is vitrectomy, phaco, SOR-OD and SOR-OS. From statistical test pupil diameter before and after intravenous administration of preventive analgesia ketorolac not significantly different

### SUGGESTION

There is need for further studies to determines the most effective dose ketorolac in preventing eye miosis. There is need for further research to determine the type of drugs known as NSAIDS are most effective in preventing eye miosis. Preventive analgesia techniques ketorolac intravenous therapy protocol can be used to prevent miosis in the intraocular eye surgery with general anesthesia.

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