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Differences in pain and inflammation between Diclofenac 0.1% and Nepafenac 0.1% after cataract surgery

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双氯芬酸与奈帕芬胺在白内障术后抗炎疗效比较

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摘要

目的:比较白内障患者术前局部应用 0.1%双氯芬酸与 0.1%奈帕芬胺的疼痛度和抗炎疗效。

方法:该前瞻性随机临床试验于 2017/06-08 在 Dr. Yap 眼科医院进行。共 56 例患者诊断为老年性白内障并接受超声乳化术,未出现并发症。受试者按术前应用滴眼剂分为两组(双氯芬酸组和奈帕芬胺组)。炎症特征(第 1,7 和 14d 随访)如疼痛度、结膜充血、眼睑痉挛、房水闪辉和细胞水平为主要结果,而角膜内皮细胞密度和形态为次要观察结果。

结果:术后 1d(分别为 $P=0.284$, 效应量=0.29, 95% $CI=-0.09\sim0.31$; $P=0.254$, 效应量=0.31, 95% $CI=-0.13\sim0.49$)和 7d($P=1.000$ 和 $P=0.556$, 效应量=0.18, 95% $CI=-0.08\sim0.16$),两组间结膜充血和眼睑痉挛水平无统计学差异。奈帕芬胺组疼痛指数(术中及术后 1、4d)显著低于双氯芬酸组(分别为 $P=0.006$, 效应量=0.77, 95% $CI=0.24\sim1.34$; $P=0.045$, 效应量=0.39, 95% $CI=-0.10\sim0.62$; $P=0.014$, 效应量=0.69, 95% $CI=-0.06\sim0.50$)。术后 1d 奈帕芬胺组房水闪辉和细胞水平较低($P=0.029$, 效应量=0.59, 95% $CI=0.02\sim0.36$)。两组间角膜内皮密度降低无统计学差异,而术后 7d 奈帕芬胺组六角形细胞比例减少较多($P=0.042$, 效应量=-0.55, 95% $CI=-2.33\sim-0.03$)。

结论:与双氯芬酸组相比,奈帕芬胺组疼痛度和房水闪辉细胞值较低。

关键词:超声乳化术;老年性白内障;房水闪光细胞;双氯芬酸;奈帕芬胺

Abstract

• AIM: To compare pain level and inflammation between preoperative topical Diclofenac 0.1% and Nepafenac 0.1% in patients undergoing cataract surgery.

• METHODS: This research was designed as prospective randomized clinical trial and conducted in June to August 2017 at Dr. Yap Eye Hospital. There were 56 subjects underwent phacoemulsification operation (single operator) and diagnosed as senile cataract and no adverse events were found. Subjects were divided into 2 groups according to preoperative eye drop medication, namely Diclofenac group and Nepafenac group. Participants and phaco-surgeon were blind regarding to the treatment. Inflammation parameters (at 1, 7 and 14d follow up) such as pain, conjunctiva hyperemic, blepharospasm, flare and cell in anterior chamber level as the primary outcome, whereas density and morphology of corneal endothelial cells as the secondary outcome.

• RESULTS: There were no statistically difference in conjunctiva hyperemic and blepharospasm level between 2 groups at 1d ($P=0.284$, effect size=0.29, 95% $CI=-0.09$ to 0.31; $P=0.254$, effect size=0.31, 95% $CI=-0.13$ to 0.49, respectively) and 7d ($P=1.000$ and $P=0.556$, effect size=0.18, 95% $CI=-0.08$ to 0.16, respectively) postoperatively. The pain scores (during surgery, 1d and 14d postoperative) in Nepafenac group was statistically lower than Diclofenac group ($P=0.006$, effect size=0.77, 95% $CI=0.24$ to 1.34; $P=0.045$, effect size=0.39, 95% $CI=-0.10$ to 0.62; and $P=0.014$, effect size=0.69, 95% $CI=-0.06$ to 0.50, respectively). The degree of flare and cell in Nepafenac group was lower at the 1d after phacoemulsification ($P=0.029$, effect size=0.59, 95% $CI=0.02$ to 0.36). Reduction of corneal endothelial density

between 2 groups were not statistically significant, however the reduction of hexagonal cell percentage at 7d after phacoemulsification was lower than Nepafenac group (P = 0.042, effect size = -0.55, 95% CI = -2.33 to -0.03).

• CONCLUSION: The pain and flare-cell levels in Nepafenac group was lower when compared with Diclofenac group.

• KEYWORDS: phacoemulsification; senile cataract; flare and cell; Diclofenac; Nepafenac
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INTRODUCTION

The use of anti-inflammatory eye drop for cataract surgery has become a standard procedure to prevent postoperative intraocular inflammation and reduce pain level[1-4]. Hence, it increases patients comfort and accelerate the recovery of visual acuity[5]. Postoperative inflammation might cause pain, photophobia and increase of intraocular pressure as well as associated with posterior capsule opacity (PCO) and cystoid macular edema[2]. Previously, steroid was mostly used agent, however, it might lengthen corneal recovery, increase intraocular pressure and risk of infection[6]. Recently, nonsteroidal anti-inflammation drugs (NSAID) has been found having similar effectivity as steroid in order to control inflammation reaction postoperatively[7]. Administrations of Diclofenac before or after cataract surgery has been shown equal effectivity as steroid in reducing inflammation[3-4]. Most recently, Nepafenac, a more neutral and a prodrug, is able to penetrate cornea 6x faster than Diclofenac group[8].

This study was aimed to compare pain and inflammation level between Diclofenac 0.1% and Nepafenac 0.1% as preoperative medications for phacoemulsification cataract surgery. Primary outcomes (as inflammation signs) were pain score, blepharospasm, conjunctival hyperemia, and flare-cells in anterior chamber. Furthermore, endothelial cells are prone to injury that is caused by either mechanical injury (surgical techniques and manipulation) or intracellular injury (inflammation). Furthermore, the examination of corneal endothelial cells parameters might help to determine the level of endothelial trauma and injury caused by phacoemulsification[1]. Therefore, secondary outcomes of this study were corneal endothelial cells counts, coefficient of variance, hexagonal cells percentage and central corneal thickness.

SUBJECTS AND METHODS

Study Design and Patients Enrollment This study was a prospective randomized controlled trial design (RCT). The sample size was calculated based on the hypothetical test formula of two unpaired means for flare mean calculation: $n_1 = n_2 = 2[(Z\alpha+Z\beta)S/(X_1-X_2)]^2$, n = estimated sample size, $Z\alpha$ = critical value of the normal distribution at α = 0.05 (1.96); $Z\beta$ = critical value of the normal distribution at β = 0.2 (0.84), standard deviation (SD) = 1.52[2], X_1-X_2 = the minimum mean difference is considered significant = 1.2[2]. The calculation was then added by estimated sample drop out (10%) and became 28 samples. The inclusion criteria were patients (aged 40-80 years old) with senile cataract (Burrato grade II-III), and willing to provide and sign the informed consent form prior to examination and surgical procedure. Exclusion criteria for this research were patients with previous other ophthalmic disease (*i.e.* history of glaucoma, uveitis, lens luxation and exfoliation syndrome), diabetes mellitus, surgical complications (posterior capsule rupture or vitreous prolapse), preoperative corneal endothelial cell count < 1500 cell/mm^2, surgery duration > 15min, ultrasound (US) time > 2min. The drop out criteria for this research were patients not presented at postoperative monitoring, emergence of complications such as endophthalmitis, persistent corneal edema, and not compliance of postoperative medication. The study followed the tenets of the Declaration of Helsinki. The Ethics Committee of the Faculty of Medicine Universitas Gadjah Mada/Dr. Sardjito General Hospital (Indonesia) has approved the study protocol.

Study Protocol This study was conducted at Dr. Yap Eye Hospital Yogyakarta, Indonesia, from June 2017 until August 2017. Subjects were divided equally into 2 groups (Diclofenac *vs* Nepafenac groups). Surgical procedure was performed by a single operator using a single surgical technique. Patients and operator were kept blind regarding the interventions. Preoperative examinations included uncorrected and best-corrected visual acuity (Snellen's chart), anterior segment biomicroscopy and cataract morphology examination, tonometry (Shin-nippon non-contact Tonometry), ultrasonography, and biometry (IOL calculation). Cataract morphology and grading was done by a single observer.

Surgical Technique Eyes were anaesthetized with topical anesthesia [Pantocaine 0.5% (Cendo®)] on a maximally dilated eye. Eyes were then irrigated with povidone-iodine 5%, eye lids and area around the eye were done aseptic and antiseptic procedures with povidone-iodine 10%. Cornea were incised with a keratome, followed by intracameral injection of 0.5 mL preservative-free (PF) lidocaine hydrochloride 1%, hydroxypropil methylcellulose (HPMC) OVDs were injected into anterior chamber followed by capsulotomy using the continuous curvilinear capsulorhexis (CCC) technique, cataract lens was hydrodissected. Centurion® Vision System was applied for phacoemulsification with the vertical chop technique, residual cortex were irrigated and aspirated until clean, implantation foldable acrylic hydrophilic intraocular lens (Rohto neo eye®) in the bag. Intracameral injections were then administered [0.1 mL dexamethasone (4 mg/mL) and 0.1 mL solution containing 0.5 mg 0.5% levofloxacin].

Table 1 Subject characteristics

Variables	Diclofenac (n=28)	Nepafenac (n=28)	P
Age, a	62.64±8.19	63.00±7.72	0.867
Sex (n, %)			
M	15 (53.6%)	13 (46.4%)	0.601
F	13 (46.4%)	15 (53.6%)	
Lensdensity (n, %)			
Grade 2	9 (32.2%)	11 (39.3%)	0.548
Grade 3	19 (67.8%)	17 (60.7%)	
Surgery duration (s)	390.92±71.57	378.32±127.8	0.321
Phacoemulsification duration (s)	32.30±16.51	33.97±14.58	0.687
Irrigation fluid volume (mL)	57.17±10.01	53.42±13.83	0.250
CDE	10.61±3.85	9.03±4.18	0.119
IOP (mmHg)			
Initial	14.46±2.42	14.93±2.76	0.680
1d	16.07±5.56	16.28±3.82	0.864
7d	13.14±2.64	14.92±3.52	0.077
14d	12.46±2.87	13.42±2.91	0.218
Visual acuity (LogMar)			
Initial	1.41±0.54	1.38±0.48	0.94
1d	0.56±0.35	0.38±0.35	0.243
7d	0.28±0.21	0.15±0.21	0.063
14d	0.19±0.19	0.10±0.11	0.059

Parameters are in Mean±SD (except: sex and lens density); CDE: Cumulative dissipated energy; IOP: Intraocular pressure.

EPT (effective phaco time) was calculated by multiplying US (ultrasound) time with US average power /100.

Outcomes Measures The primary outcomes were the inflammation variables, such as: pain score based on Visual Analogue Score[9], blepharospasm based on the Jankovic *et al*[10], conjunctival hyperemia based on the Cornea and Contact Lens Research Unit (CCLRU)[11], flare and cell in the front chamber of the eye using the grading system from Standardization of Uveitis Nomenclature (SUN) Working Group[12]. Follow-up was done on the 1, 7 and 14d postoperative. The secondary outcomes were the measurement of corneal endothelial density, morphology, and corneal thickness (Topcon SP-3000®). The operator who measured and examined the outcome was kept blind regarding the treatment groups.

Statistical Analysis Statistical analysis was performed using the SPSS 22.0 for Windows software. Continuous data were expressed as the mean±SD and range, normality was first confirmed by the Kolmogorov-Smirnov test. For subject characteristics, categorical data was analyzed using Chi square test and independent samples t-test for numerical data if normally distributed (Mann-Whitney test if not normally distributed). Inflammation variable is analyzed using the Chi square test. Difference in density and corneal endothelial cell morphology between the two groups is analyzed using independent samples t-test followed by comparison between the follow-up days.

RESULTS

Fifty-six eyes (56 patients) were enrolled in this study (no loss of follow-up subject and no adverse events were found during and after the administration of treatment to the participants). There were no statistically significant differences in subject characteristics between diclofenac and nepafenac group (Table 1).

There were no significant differences between Diclofenac and Nepafenac in conjunctival hyperemia and blepharospasm both groups at 1d (P=0.284, effect size=0.29, 95% CI=-0.09 to 0.31; P=0.254, effect size=0.31, 95% CI=-0.13 to 0.49, respectively), and 7d (P=1.000 and P=0.556, effect size=0.18, 95% CI=-0.08 to 0.16, respectively) postoperatively. In pain score, Nepafenac group was found significantly lower during surgery (P=0.006, effect size=0.77, 95% CI=0.24 to 1.34), 1d postoperative (P=0.045, effect size=0.39, 95% CI=-0.10 to 0.62) and 7d postoperative (P=0.014, effect size=0.69, 95% CI=-0.06 to 0.50). In flare-cell score, Nepafenac group was also found significantly lower at 1d postoperative (P=0.029, effect size=0.59, 95% CI=0.02 to 0.36) (Table 2).

Table 3 shows the corneal endothelial parameters at 7d and 14d postoperative. The decrease in hexagonal cell percentage was found lower in Nepafenac group at 7d postoperative (P=0.042, effect size: -0.55, 95% CI=-2.33 to -0.03). There were no significant correlations between phacoemulsification duration and loss of endothelial cell counts (7d and 14d) in Diclofenac (7d: r=-0.167, P=0.424; 14d: r=-158, P=0.452) as well as in Nepafenac group (7d: r=0.125, P=0.543; 14d: r=0.039, P=0.850). Therefore, the endothelial loss in this study was not dependent of the duration of phacoemulsification.

Table 2 Primary outcomes: inflammations parameters Mean±SD

Variables	Diclofenac (n=28)	Nepafenac (n=28)	Effect size (95%*CI*)	*P*
Conjunctival Hyperemia				
1d	1.21±0.42	1.10±0.32	0.29 (-0.09-0.31)	0.284
7d	1.00±0.00	1.00±0.00		1.000
Blepharospasm				
1d	0.75±0.58	0.57±0.57	0.31 (-0.13-0.49)	0.254
7d	0.07±0.26	0.03±0.18	0.18 (-0.08-0.16)	0.556
Pain score				
During surgery	2.32±1.12	1.53±0.92	0.77 (0.24-1.34)	0.006
Posoperative				
1d	0.89±0.68	0.63±0.67	0.39 (-0.10-0.62)	0.045
7d	0.39±0.48	0.11±0.32	0.69 (-0.06-0.50)	0.014
Flare score				
1d	1.03±0.69	0.65±0.59	0.59 (0.04-0.72)	0.043
7d	0.11±0.31	0.07±0.26	0.14 (-0.11-0.19)	0.642
Cell score				
1d	0.58±0.33	0.39±0.31	0.59 (0.02-0.36)	0.029
7d	0.13±0.25	0.05±0.16	0.38 (-0.03-0.19)	0.263

Table 3 Secondary outcomes: corneal endothelial parameters

Variables	Diclofenac (n=28)	Nepafenac (n=28)	Effect size (95%*CI*)	*P*
Corneal endothelial cell (cell/mm^2)				
Preoperative	2469.90±228.12	2501.44±224.16	-0.14 (-152.72-89.64)	0.604
Postoperative EC loss				
7d	177.36±94.37	163.75±55.82	0.18 (-27.93-55.15)	0.514
14d	244.10±125.58	223.63±73.18	0.20 (-34.60-75.54)	0.491
Coefficient of variance (%)				
Preoperative	37.05±9.32	41.50±8.61	-0.50 (-9.26-0.36)	0.069
Postoperative ΔCV				
7d	1.53±1.63	1.46±1.22	0.05 (-0.70-0.84)	0.600
14d	3.63±4.32	2.29±1.56	0.41 (-0.40-3.08)	0.310
Hexagonal cell (%)				
Preoperative	50.92±10.28	50.07±8.93	0.09 (-4.31-6.01)	0.740
Postoperative ΔHexagonal cell				
7d	-3.07±2.05	-1.89±2.23	-0.55 (-2.33--0.03)	0.042
14d	-4.07±2.81	-4.85±8.21	0.13 (-2.51-4.07)	0.249
Central corneal thickness (μm)				
Preoperative	528.00±25.79	535.03±25.25	-0.28 (-20.71-6.65)	0.113
Postoperative ΔCCT				
7d	10.39±4.81	13.89±7.14	-0.57 (-6.76--0.24)	0.050
14d	5.53±4.37	6.32±6.37	-0.14 (-3.72-2.14)	0.248

CV: Coefficient of variance; CCT: Central corneal thickness.

DISCUSSION

Recently, preoperative medication using NSAIDs (for instances: Diclofenac or Nepafenac) is important to reduce metabolic stress and inflammation caused by phacoemulsification cataract surgery. In this RCT study, the administration of Nepafenac eye drop prior to surgery was found effective in reducing post-operative pain and inflammation. The pain (during surgery, 1d and 7d postoperative) and flare-cell score (1d postoperative) were found lower in Nepafenac group.

The results of the present study, might be caused by greater ability of Nepafenac to penetrate cornea and convert into its active substance, amfenac[13-15]. It has been known to have 6x faster corneal penetration (with longer duration of action) than Diclofenac[16]. The results of this study was in line with a study by Nardi *et al*[15] that found subjects who receiving Nepafenac had milder pain sensation if compared to subjects receiving Ketorolac and Diclofenac. Similarly, Lane *et al*[2] has found that Nepafenac administration 3d prior to phacoemulsification was more effective to reduce postoperative

flare-cell than other NSAIDs. No statistically significant difference of flare-cell score at 7d might be caused by the administration of topical steroid therapy. The surgical methods in this study produced very mild degree of hyperemic and blepharospasm that result in no difference between 2 groups. Previous surgical methods, such as: the application of retrobulbar or peribulbar anesthesia and peritomy of the conjunctiva were prone to produce more hyperemic and conjunctival edema[13].

In severe inflammation condition, inflammation cells are able to replace normal endothelial cells that cause sloughing of the endothelial cells into aqueous humor[17-18]. In the present study, there were no statistically significant difference between 2 groups in the corneal endothelial cells parameters (corneal endothelial cells counts, coefficient of variance and central corneal thickness). It could be assumed that corneal endothelial cells parameters changes were not dependent of NSAIDs administration but rather than the surgical manipulation itself[19]. However, the decrease of hexagonal cell was lower in Nepafenac at 7d but not at 14d, that showed morphology plasticity of endothelial cells[20]. In the present study, the similarity of type and cataract turbidity would standardize the use of phacoemulsification energy.

In conclusion, pain level and flare-cell score at the first day after phacoemulsification in Nepafenac group was lower than Diclofenac group. Reduction of hexagonal cell percentage at the seventh day after phacoemulsification was lower for Nepafenac group than Diclofenac group. The limitation of this study was the short period of follow-up, therefore, for future researches, follow up time could be conducted in longer period to assess the occurrence of cystoid macular edema post phacoemulsification.

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