

Aqueous Humor *Transforming Growth Factor*- β 2 Level in Patients with and without Posterior Capsule Opacity After Congenital Cataract Surgery

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ABSTRACT

Although microscopic operation technique improves pediatric cataract surgery results, posterior capsule opacification (PCO) remains the most common complication after congenital cataract surgery. Histology of PCO has been known, but the underlying cellular mechanisms remain unclear. Recently the role of cytokines present in the anterior segment after cataract surgery was investigated, such as TGF- β 2. TGF- β controls the differentiation of various types of cells. TGF- β also induces cataractogenesis. Laboratory studies showed that in high level of TGF- β 2, PCO occur more easily. The aim of this study is to determine the differences of aqueous humor TGF- β 2 level in patients with and without posterior capsule opacity after congenital cataract surgery. The design of study was cross-sectional, and population target is all congenital cataracts that were underwent cataract surgery by using intraocular lens (IOL) in the bag, and without primary posterior curvilinear capsulorexis (PPCC) in Sarjito Hospital Yogyakarta and Dr Yap Eye Hospital Yogyakarta. This study revealed mean TGF- β 2 level in the group with PCO was 259.91 (\pm 63.45) pg/ml and in the group without PCO was 225.81 (\pm 121.26) pg/ml. The difference of TGF β 2 level in the group with PCO and without PCO is not significant.

Key words: congenital cataract, PCO, TGF- β 2

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INTRODUCTION

Congenital cataract is opacities of the lens that occur and be seen immediately after birth or before 3 months after birth. Pediatric cataract represents the commonest treatable cause of childhood blindness and is thereby an important component of the World Health Organisation's program to eliminate avoidable blindness by 2020, accounting for a 1/10 th of worldwide childhood blindness and having an incidence of 2.5–3.0/10,000 live births in a global context pediatric.¹

Progression of microoperation technique improves the outcome of cataract surgery and intraocular lens implantation. But posterior capsule opacification (PCO) remains the most common long-term complications after

cataract surgery. Estimation of PCO is up to 50% of cases and the latest clinical survey stated that the incidence did not diminish despite the progression of the technique of surgery.² In the recent study incidence of PCO after congenital cataract surgery was 87.2%.³

Histology of PCO has been known, but the underlying cellular mechanisms remain unclear. Recently the role of cytokines in the anterior segment of the eye after cataract surgery was investigated, among them is TGF- β 2.⁴ TGF- β controls the differentiation of various cell types and play role in embryogenesis, as indicated by the high levels in the area of rapid morphogenesis, as demonstrated in experiments using rat lens, in which TGF- β induces cataractogenesis. Several laboratory studies showed that in the high levels of TGF- β 2, PCO occurs more easily.⁵

The aims of this study is to determine whether there are differences of TGF-β2 levels in the group of patients with and without PCO after congenital cataract surgery.

MATERIAL AND METHOD

The design of this research was cross-sectional, with population target were children with congenital cataracts that underwent cataract surgery with in the bag IOL implantation, and without PCCC in the Sarjito Hospital and Dr Yap Eye Hospital Yogyakarta. Some confounding variables were identified: the ages of patients (less than 14 years old), the place of IOLs insertion (in the bag IOL implantation), the materials of IOL (one piece PMMA IOLs), all without anterior vitrectomi, and uveitis after surgery, was treated by topical and oral steroid.

In this study, TGF-β2 referred to the level of aqueous humor transforming growth factor-beta 2 (TGF-β2), was examined by ELISA, pg/ml. Definition of PCO was the presence or absence of posterior capsule opacification after cataract surgery, observed for 2 months after surgery. PCO (+) when there was opacity in the posterior capsule and PCO (-) if the inspection found no opacity in the posterior capsule. Evaluation of PCO was done by slit lamp and direct ophthalmoscope.

Patients who met inclusion and exclusion criteria underwent research procedures: alloanamnesis about age, gender, address. Eye examination, including routine inspection, direct ophthalmoscope, and slit lamp examination. The patient was underwent cataract surgery, and the sample of aqueous humor as much as 0.2 ml is taking prior to cataract extraction to examine TGF-β2 level.

RESULT AND DISCUSSION

This research was conducted at Dr. Sardjito Hospital and Dr Yap Eye Hospital Yogyakarta. Patients who participated in this study were all patients who underwent cataract surgery in both hospitals.

During the study period, after the inclusion and exclusion criteria, this study obtained 30 eyes, consisting of 15 (50.00%) female patients and 15 (50.00%) male patients. Age range in this study was 4 months to 158 months with the average age, mean ± SD 56,27 (± 39.04) months. Characteristics of all subjects that describes the distribution of age and sex were shown in table 1.

This study found no significant differences between the two groups for age distribution ($p = 0.224$), gender ($p = 0.961$), and history of rubella infection (0.094). Frequencies of male: female patients was 1:1. Rubella was found in 2 patients with PCO. This mean that the distribution of age, gender, and history of rubella infection among groups of PCO and without PCO was not homogeneous.

Table 1. The characteristics of subjects

| Characteristics | PCO (+) (n = 13) | PCO (-) (n = 17) | P value |
|-----------------------|---------------------|---------------------|------------|
| Age | | | |
| Mean (months) ± SD | 60,61(± 40,94) | 52,94 (± 38,44) | 0.224 |
| Sex | | | |
| Male | | | |
| Patients (%) | 6 (46,15%) | 9 (52,94%) | 0.961 |
| Female | | | |
| Patients (%) | 7 (53,85%) | 8 (47,06%) | |
| Rubella | | | |
| Rubella (+) | | | |
| Eyes (%) | 2 (18,00%) | 0 (0,00%) | 0,094 |
| Rubella (-) | | | |
| Eyes (%) | 11 (82,00%) | 17 (94,74%) | |
| Operator | | | |
| Senior | | | |
| Eyes (%) | 5 (62,5%) | 14 (82,35%) | 0,023 |
| Resident | | | |
| Eyes (%) | 8 (37,5%) | 3 (17,65%) | |

Incidence of PCO is varies greatly. A metaanalysis study in 1998 stated that the incidence of PCO in senile cataract was 11.8% (9.3–14.3%) in the first 1 year after surgery, 20.7% (16.6–24.9%) in the first 3 year after surgery and 28.4% (18.4–38.4%) in the first 5 years after surgery.⁶ Other research stated that the incidence was 87.2% and no mention of gender distribution.³ The age is the most important factor for the formation of PCO. PCO often occurs in cataract surgery and IOL in children.³ Children younger than 1 year have a tendency to become posterior capsule opacities.⁷ Other diseases that associated with the changes of aqueous blood barrier lead to be higher levels of PCO. The relationship between PCO and systemic disease is still unclear.⁸

The mean levels of TGF-β2 in the group with PCO and without PCO were not significantly different, as shown in table 2.

Table 2. The mean TGF-β2 levels between the group of PCO and without PCO

| Levels of TGF-β2 | PCO (+) | PCO (-) | P Value |
|-----------------------|----------------|-----------------|------------|
| Means ± SD (pg/ml) | 257.71 ± 86.65 | 223.48 ± 115.73 | |
| Median (pg/ml) | 247.11 | 229.80 | 0.392 |
| Range (pg/ml) | 88.31–402.94 | 19.52–373.50 | |

In this study the mean TGF- β 2 level in PCO group was 257.71 (\pm 86.65) pg/ml and the mean TGF- β 2 level in the group without PCO was 223.48 (\pm 115.73) pg/ml. With *Mann Whitney* test the difference of mean TGF- β 2 levels in the group with PCO and without PCO was not significant with p values $>$ 0.05. In the PCO group the median value of TGF- β 2 level was 247.11 pg/ml with the lowest level 88.31 pg/ml and the highest 402.94 pg/ml. In the group without PCO the median value of TGF- β 2 229.80 pg/ml with the lowest levels 19.52 pg/ml and the highest 373.50 pg/ml.

The result of this study was not consistent with some previous studies. Until now the role of TGF- β 2 and other growth factors in PCO is not yet clear. Several studies of the human eye lens and animals concluded that the provision of TGF- β 2 would cause turbidity of the capsule.⁹⁻¹² These studies cultured epithelial cells of the lens until the lens capsule and commonly used culture medium with serum. In study that culture in pure ocular tissue culture medium and no serum added showed that aqueous humor in which there was some TGF- β 2 inhibited cell proliferation of lens epithelial cells, induced apoptosis of epithelial cells of the lens, and prevented PCO. Epithelial cells of the lens begins to apoptosis in the first week and have a total apoptosis in the fifth week. Kurosaka added with 10% aqueous humor and anti-TGF- β 2 in the culture medium to determine their effects on proliferation of epithelial cells of the lens and the result showed that the proliferation of cells in cultures without antibodies against TGF beta 2 was more constrained and lower than the concentration of normal TGF- β 2 in aqueous humor.¹³ Meacock suspected that TGF- β 2 inhibit the proliferation of epithelial cells through G1 phase elongation of cell cycle.⁴

The different operators affect this research. Operating factor such as hydrodissection stage to clean the cortex is the most important.¹⁴ The duration of operation and number of manipulations during the operation was also an important operating factor. This will cause the different level of inflammatory reaction and have different effects to the PCO. The children respond to surgery with intraocular inflammation intensely, so difficult to handle.^{15,16} Atraumatic operation is the key to prevent PCO.¹⁴

In this study PCO inspection technique was not carry out uniformly, especially in infants. Examination of the baby was not done by slitlamp. So, the PCO assessment is not uniform. This limitation condition affected the result.

Another factor affected the result of this study was the inflammatory reaction after cataract surgery. In this study we did not examine the inflammatory status. Severe inflammation reaction will increase the occurrence of PCO. The existing inflammatory reaction should be examined with flare cell meter, so the status of post operative inflammation can be evaluated.

The correlation between TGF- β 2 level and age of patients was shown in Table 3.

Table 3. The correlation between TGF- β 2 level and age of patients

| Correlation | Result of correlation test |
|----------------------|----------------------------|
| TGF- β 2 - age | P: 0.071 (r: -0.334) |

In this study with Spearman test, we obtained a significance value of 0.071 indicating that the correlation between the age and the TGF- β 2 level was not significant, with correlation values -0.334. Until now no study mentioned about TGF- β 2 level in the groups of age and their correlation.

TGF- β 2 levels based on gender was shown in Table 4.

Table 4. TGF- β 2 levels based on gender

| TGF- β 2 level | Male | Female | |
|-------------------------|--------------------|---------------------|----------|
| Means \pm SD pg/ml | 219.82 \pm 92.61 | 254.48 \pm 113.30 | P: 0.262 |

Table 4 showed that there was no significant difference between the average levels of TGF- β 2 of the male and female patients. The result was consistent with previous research that gender did not affect the levels of TGF- β 2.¹⁷

CONCLUSION

There is no significantly difference of TGF- β 2 level in the group with PCO and in the group without PCO. Further research is recommended to conduct research with one operator, similar PCO examination, and to examine the status of post operative inflammation with flare cell meter.

REFERENCES

- Rahi JS and Dezateux C. Congenital and infantile cataract in the United Kingdom: underlying or associated factors. *British Congenital Cataract Interest Group Organization. Invest Ophthalmol Vis Sci* 2000, 41: 2108–2114.
- Apple D.J., Peng Q., and Vissessook N. Eradication of Posterior Capsule Opacification. *Ophthalmology*. 2001. 108 (3): 505–518.
- Wilson, Jr., M.E.; Trivedi, Rupal H.; Pandey, and Suresh K. *Pediatric Cataract Surgery: Techniques, Complications, and Management*. Lippincott Williams & Wilkins (LWW). 2005.
- Meacock W.R., Spalton D.J., and Stanford M.R. Role of Cytokines in the Pathogenesis of Posterior capsule Opacification. *Br. J. Ophthalmol*. 2000. 84: 332–336.
- Gordon-Thompson C. Differential Cataractogenic Potency of TGF- β 1, 2, 3 and Their Expression in the Postnatal Rat Eye. *IOVS*. 1998. 39: 1399–1409.
- Schaumberg D.A., Dana M.R., Christen W.G., and Glynn R.J. A Systematic Overview of The Incidence of Posterior Capsule Opacification. *Ophthalmology*. 1998. 105 (7): 1213–21.

7. Kim KH, Ahn K, Chung E, and Chung TY. **Clinical Outcomes of Surgical Techniques in Congenital Cataracts.** *Korean J Ophthalmol.* 2008. 22 (2): 87–91.
8. Bertelman E. and Kojetinsky C. Posterior Capsule Opacification and Anterior Capsule Opacification. *Curr Opin Ophthalmol.* 2000. 12: 35–40.
9. Norihito G., Nikole R.P., Hiroyuki M., Helene S., Qi Yan, and Clark I.J. An In Vitro Model of Posterior Capsular Opacity: SPARC and TGF-Beta 2 Minimize Epithelial-to-Mesenchymal Transition in Lens Epithelium *Invest Ophthalmol Vis Sci.* 2007; 48: 4679–4687.
10. Lovicu F.J., Schulz M.W., and Hales A.M. TGF-beta Induced Morphological and Molecular Change Similar to Human Anterior Subcapsular Cataract. *Br. J. Ophthalmol.* 2002. 86: 220–226.
11. Saika S., Miyamoto T., and Ishida I. TGF-Beta Smad Signaling in Post Operative Human Lens Epithelial Cells. *Br. J. Ophthalmol.* 2002. 86: 1428–1433.
12. Wormstone I.M., Tamiya S., and Anderson I. TGF-Beta 2 Induced Matrix Modification and Cell Transdifferentiation in the Human Lens Capsular Bag. *IOVS.* 2002. 43: 7.
13. Kurosaka K and Nagamoto T. Inhibitory effect of TGF-beta2 in human aqueous humor on bovine lens epithelial cell proliferation. *Invest Ophthalmol Vis Sci.* 1994. 35: 3408–3412.
14. Apple D.J., Peng Q., and Vissessook N., Surgical Prevention of Posterior Capsule Opacification. *J Cataract Refract Surg.* 2000. Feb; 26 (2): 180–7.
15. Cavallaro B.E., Madingan W.P., Ohara M.A., Kreimer K.K., and Bauman W.C. Posterior Chamber Intraocular Lens Use in Children. *J Pediatr Ophthalmol Strabismus.* 1998. 35: 254–256.
16. Wilson M.E., Pandey M.K., and Charleston M.D. Managing paediatric Cataract. *Rev Ophthalmology.* 2002. 9: 5.
17. Ochiaie Y and Ochiaie L. Higher concentration of transforming growth factor beta in aqueous humor of glaucomatous eye and diabetic eye. *Japan J Ophthalmol.* 2002. 46, 249–253.