LITERATURE REVIEW

PROPHYLAXIS PHARMACOLOGICAL MANAGEMENT FOR PATIENTS WITH INTRAOPERATIVE FLOPPY IRIS SYNDROME RISK DUE TO α1-ADRENERGIC RECEPTOR ANTAGONISTS USE

Brigitta Marcia Budihardja[1], Ade Ajeng Cempakadewi[2]
[1]Faculty of Medicine, Udayana University, Bali, Indonesia
[2]Faculty of Medicine, Trisakti University, Jakarta, Indonesia
Email: marciabudihardja@gmail.com

ABSTRACT

Introduction: *Intraoperative floppy iris syndrome (IFIS) remains a challenge that increases the risk of complications in patients undergoing cataract surgery who use α1-adrenergic receptor antagonists. To date, no definite consensus on a preventive strategy for IFIS is available. The aim of this review is to assess various pharmacological managements to prevent IFIS in high-risk patients.*
Methods: *This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic search using PubMed, Science Direct, Cochrane Library, and WorldCat database was performed. Quality of each study was evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0), Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I), or Newcastle-Ottawa Scale (NOS).*
Results: *The search identified 1589 articles of which 7 met the eligibility criteria. Experimental and observational studies between 2010 and 2018 were included. Pharmacological managements included in this review are administered in varying routes. Phenylephrine, lidocaine, a combination of lidocaine and epinephrine are given intracamerally. Other pharmacological managements included are sub-tenon injection of lidocaine, topical atropine, a combination of topical atropine with intracameral epinephrine, combined irrigation solution of phenylephrine and ketorolac, and mydriatic cocktail-soaked wick sponges.*
Conclusion: *Various pharmacological managements for IFIS prophylaxis have shown promising potential. However, studies that evaluate the efficacy of each agent and comparison between these strategies are still limited. Further research is needed to determine the best prophylaxis strategy to reduce the incidence of IFIS.*

Keywords: *alpha-1 adrenergic receptor antagonists, pharmacological prophylaxis, intraoperative floppy iris syndrome*

INTRODUCTION

Cataract surgery is the most common procedure performed by ophthalmic surgeons worldwide. The key to success in cataract surgery is adequate pupillary dilation and the stability of the iris. Intraoperative floppy iris syndrome (IFIS), first described by Chang and Campbell in 2005, is defined as a triad of intraoperative signs, including billowing of a floppy iris stroma under normal fluidics in the anterior chamber, propensity for iris prolapse through surgical incisions, and progressive intraoperative miosis despite adequate use of mydriatics.[1] If IFIS occurs, complications including loss of corneal endothelial cells, iris trauma, macular

edema, vitreous loss, hyphema, and postoperative ocular inflammation are significantly increased.[2,3]

A variety of risk factors, including age, gender, hypertension, the axial length of the eye, angiotensin II blockers, 5α-reductase inhibitors, α1-adrenergic receptor antagonists (α1-ARAs), antipsychotics, and neuromodulators have been connected with IFIS. Selective α1-ARAs were found to be strongly associated with IFIS.[3] Tamsulosin has a long half-life and its blocking effect on the receptor is irreversible. It can cause pathological changes within the iris arterioles, induce permanent iris atrophy, and cause disturbance of blood supply.[2,3] This may explain why the discontinuation of drugs with a causative relationship to IFIS such as tamsulosin does not seem to fully eliminate the risk of developing IFIS.[3,4]

This paper aims to review the current evidence and various usage of prophylaxis management on high-risk patients to reduce incidents of IFIS in cataract surgery while reassessing the quality of evidence and suggesting the necessary measurements for future research.

MATERIAL AND METHODS

Protocol

This review was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[5]

Eligibility criteria

We included studies that meet the following criteria: 1. The study population included patients using alpha-1 adrenergic receptor antagonists undergoing cataract surgery. 2. The study used prophylaxis medication including atropine, NSAID, epinephrine, phenylephrine, local anesthetics agents, or combinations of these agents. 3. Written in English. 4. Published from 2010 - 2021. Our exclusion criteria were: 1. Studies on animals 2. Full publication unavailable. 3. Case reports and expert reviews.

Literature searches

Two reviewers conducted a systematic search using PubMed, Science Direct, and Cochrane Library databases. A systematic search using a gray literature database was also performed using WorldCat database. The keywords in our search strategy include “adrenergic alpha-1 receptor antagonists” (Mesh term), “atropine” (Mesh term), “non-steroidal anti-inflammatory agents” (Mesh term), “epinephrine” (Mesh term), “local anesthetics” (Mesh

term), “intraoperative floppy iris syndrome”, and “intraoperative miosis”. We adapted the search terms to fit the requirements of each database. The search was not restricted by the date of publications or language filters. An additional search was also performed by hand-searching bibliographies of relevant studies.

Selection process and data extraction

After retrieving studies from each database, duplicates were removed using Mendeley Reference Manager and manually. We scanned the titles and abstracts of the search results. Studies that clearly do not meet the criteria were excluded. If the title or abstract appeared to meet the criteria for this review, we retrieved the full text to review the study further. Studies that meet the eligibility criteria were included in this review. Data were extracted from the selected studies using a predesigned table. Extracted data includes study design, intervention groups, number of patients, and outcomes. Study selection and data extraction were performed by two reviewers. Disagreements regarding study selection and data extraction were resolved by consensus. A meta-analysis was not conducted because of the heterogeneity in study design and population, measurement and outcomes.

Risk of bias and quality assessment

Randomized studies were assessed with the Cochrane Risk of Bias Tool 2.0 (RoB 2.0).[6] Non-randomized studies were assessed with The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[7] Risk of bias of each study was presented in Figure 2 and 3 using the robvis tool.[8] Disagreements in determining the risk of bias were resolved by discussion between 2 reviewers. We also included observational studies that we assessed using the Newcastle-Ottawa Scale (NOS) as presented in Table 2.[9]

RESULTS

Study selection

A total of 1589 abstracts and titles were obtained through database searching and hand-searching. After duplicate removal, 1456 articles were screened. A total of 1444 records were excluded as they were irrelevant to our review. The remaining 12 articles were assessed for eligibility and 5 articles were excluded (3 were case reports-expert review; 2 full-text articles were not available). There were 7 studies that met our criteria and were included in this review.

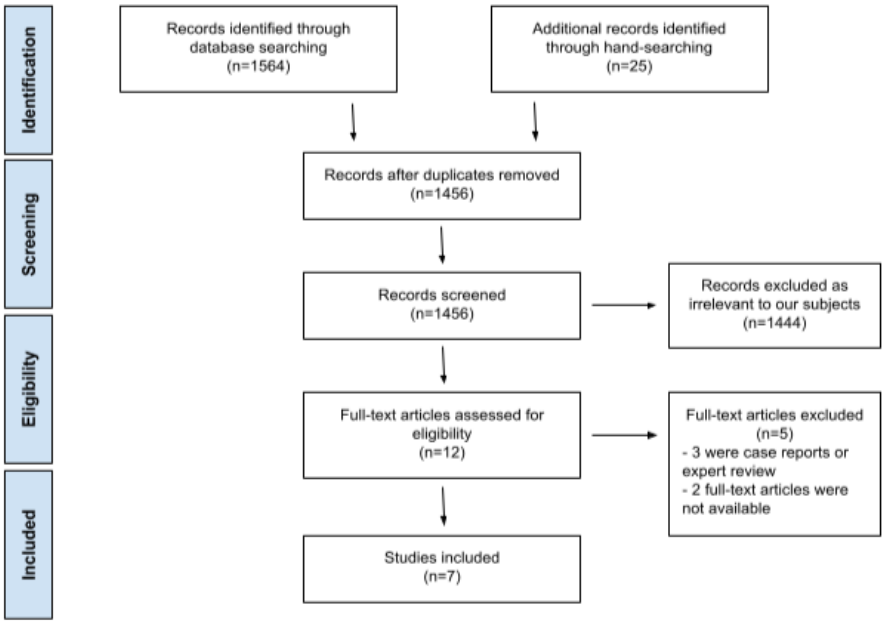

Figure 1. PRISMA Flowchart of the process of article selection

Study characteristics

Data was extracted from 7 studies that met our criteria, including 4 randomized controlled trials, one non-randomized controlled trial, and 2 observational studies. Studies were published from 2010 and 2018; 4 European, 2 from the United States and 1 from Asia. The total number of samples is 416 patients (497 eyes). The table below summarises the characteristics of the included studies and their outcomes (Table 1).

Synthesis of results

Due to the wide variation of interventions given in each of the studies, meta-analysis was not conducted for this review

Table 1. Summary of studies

Study; Setting; Design	α1-ARAs use	Number of patients	Intervention groups	IFIS in treatment group	Results
Chen et al.[10] ; 2010, USA; Cohort retrospective	Only tamsulosin	59 patients, 81 eyes divided into two groups (group 1= 26 eyes, group 2= 55 eyes)	1. Intracameral combination of lidocaine 2% and epinephrine (1:1000) after paracentesis construction 2. No additional intervention	38.5%	Use of prophylactic intracameral lidocaine–epinephrine did not reduce the incidence of IFIS (p=0.174).
Lorente et al.[11]; 2012, Spain; Randomized controlled trial (RCT), paired-eye study	Only tamsulosin, no discontinuation (Duration of use between 5-180 months)	42 patients 84 eyes, divided into two groups (group 1= 42 eyes; group 2= 42 fellow eyes)	1. Intracameral phenylephrine 1,5% 2. Injection of Balanced saline solution (BSS)	0.0%	The incidence of IFIS was significantly higher in group 2 (**p<0.001**) compared with group 1. No signs of IFIS were noted in group 1, whereas 88,09% in group 2 showed some sign of IFIS.
Hargitai et al.[12]; 2013, Denmark; RCT	Only tamsulosin	89 patients, divided into three groups (group 1=30; group 2=28; group 3=31). Third group who did not take any α1-ARAs was not included in this review.	1. 4 mm x 5 mm of mydriatic cocktail-soaked wick sponges (oxybuprocaine 0,4%, cocaine 4%, tropicamide 1%, phenylephrine 10%, diclofenac 0,1%, chloramphenicol 0,5% in 1:1:1:1:1:1 ratio) for 30 minutes 2. Conventional eye drops regimen repeated 3 times with 10 minutes interval	63.3% for iris billowing; 23.3% for iris prolapse	No significant differences between the two groups in miosis **(p=0.073)** No significant difference of IFIS signs between group 1 and group 2 (p= 0,583 incidence of iris billowing, p= 1,000 incidence of iris prolapse)
Klysik et al.[13]; 2014, Poland; RCT	Tamsulosin, doxazosin, alfuzosin, terazosin; At least 1 year prior to surgery, no discontinuation	71 patients divided into two groups (group 1= 34; group 2= 37)	1. 2% sub-tenon lidocaine injection 2. Topical analgesia (2% proparcaine) + 1% intracameral lidocaine injection	8.8%	Injection of 2.5 ml of 2% lidocaine into the sub-tenon space has reduced significantly the incidence of all three features of IFIS, compared with 1% intra cameral lidocaine (**p=0,0002**)

Silverstein et al.[14]; 2018, USA; RCT	Only tamsulosin. Current or previous usage	50 patients divided into two groups (group 1= 25; group 2= 25)	1. Combination irrigation solution of phenylephrine 1,0% and ketorolac 0,3% 2. Basic saline irrigation solution	4.0% for severe iris billowing; 12.0% for iris prolapse	The treatment group irrigating solution led to significantly better prevention of miosis, less pupil billowing, and a reduced incidence of iris prolapse. The iris billowing was significantly less severe in the treatment group (**p<0,01**). More eyes in the control group had iris prolapse than in the treatment group (**p<0,01**).
Esen et al.[15]; 2018, Turkey; Cohort retrospective	Tamsulosin, doxazosin, alfuzosin. Discontinuation of alpha-adrenergic antagonist (at least 10 days)	72 eyes of 55 patients divided into three groups (group 1= 22; group 2= 29; group 3= 21)	1. No further prophylactic medication 2. Topical atropine (1%) 3. Combination of topical atropine (1%) with intracameral injection bisulfite-containing epinephrine (1:16.000)	9.5% in combined prophylaxis group; 17.2% in atropine only group	Development of IFIS was significantly reduced in Group AE (**p<0,0001**) and Group A (**p=0,0002**) when compared against Group NP.
Nuzzi et al.[16]; 2018, Italy; Non-randomized clinical trial	Tamsulosin for at least 1 year	81 patients divided into two groups (group 1 = 43; group 2= 38)	1. Instillation of atropine sulfate 1% 2. Combination of intracameral lidocaine 2%-epinephrine 1:3000-balanced salt solution (BSS plus)	86.05% in atropine group; 60.53% in intracameral lidocaine-epinephrine group	The mydriatic intracameral solution containing epinephrine was more effective than atropine in preventing IFIS in its mild form, but not in severe forms in which anatomical changes have occurred. Group B showed a statistically significant difference (**p=0,0115**) of IFIS (60,53%) when compared with Group A (86,05%).

Risk of bias within studies

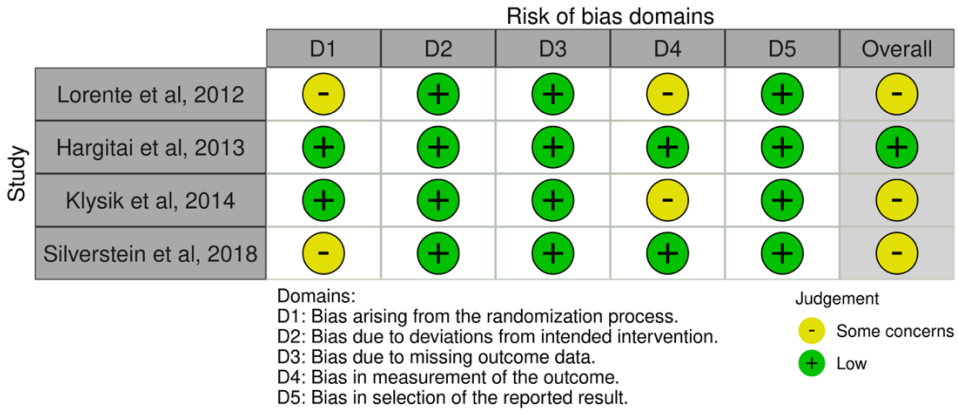

Figure 2. Risk of bias assessment for RCT on ROB 2.0

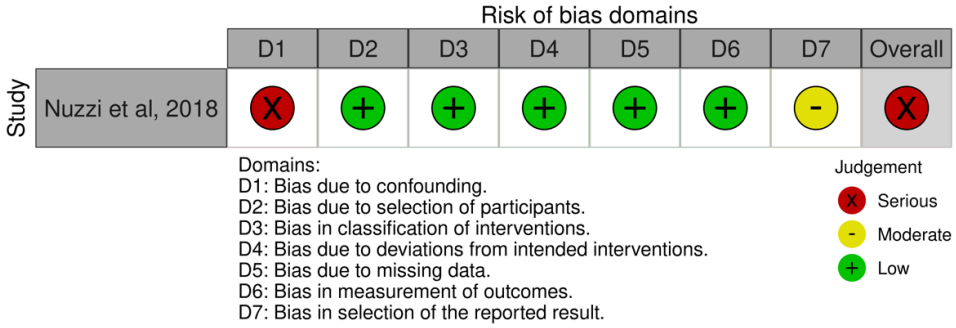

Figure 3. Risk of bias assessment for non-RCT on ROBINS-I

Table 2. Quality assessment for observational study with NOS[9]

Author	Selection				Comparability	Outcome			Overall Quality
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough	Adequacy of follow up cohorts	
Chen et al, 2010	★	★	★	★	-	★	★	★	Poor Quality*
Esen et al, 2018	★	★	★	★	-	★	★	★	Poor Quality*

*Both studies were poor quality because they scored 0 for the comparability domain.

DISCUSSION

Summary of evidence

This review summarizes findings in the literature regarding the pharmacological management to prevent IFIS in patients receiving α1-ARA prior to cataract surgery. The studies included in this review evaluate various types of pharmacological management, including eye drops, sub-tenon injection, intracameral injection, cocktail-soaked wick sponges, and irrigation

solution. Overall, most of the pharmacological interventions in this review had shown effectiveness in reducing IFIS incidence.

There were seven studies included in this review with 5 of them being interventional studies (four RCTs and one non-randomized study). Lorente et al found that the incidence of IFIS was significantly lower in the intracameral phenylephrine group. This finding showed the efficacy of intracameral phenylephrine for IFIS prevention and its ability to reverse IFIS. Phenylephrine is an α1-adrenergic receptor agonist that works by inducing pupil dilatation and restoring iris rigidity by increasing dilator smooth muscle tone.[11] Shams et al addressed the potential cardiovascular hazard of intracameral phenylephrine and recommended close cardiovascular monitoring for patients with risk factors.[17] But, Myers responded that the use of intracameral phenylephrine 1.5% should have a lower risk for systemic complications than topical phenylephrine 2.5%[18], which has been proven to be safe.[19] Further study might be needed to establish the safety profile of intracameral phenylephrine use.

Hargitai et al reported no significant difference of miosis and IFIS signs (iris billowing or iris prolapse) between the group receiving mydriatic wick sponges and the control group. The patients dilated with mydriatic wick sponges had greater preoperative mydriasis, but the difference was not statistically significant and disappeared at later stages of surgery. This method offers the benefit of considerable saving of nursing resources along with medicine expenses, but is only as effective, not superior, as the conventional eye-drop methods. This study found no adverse effect related to the use of a mydriatic sponge.[12]

Klysik et al found that sub-Tenon lidocaine significantly reduces the incidence of IFIS compared to intracameral lidocaine. No severe IFIS was found in the sub-Tenon group. Lidocaine causes mydriasis with multiple mechanisms that are not mediated by sympathetic or parasympathetic receptors. It works by blocking the initiation and propagation of the action potential, preventing the voltage-dependent increase in sodium conductance via a direct action on the sodium channel, and also by stabilizing membranes. This might be beneficial in cases where standard receptor-mediated mydriasis is compromised, such as in patients who have been receiving α1-ARA. Sub-Tenon injection gives a longer-lasting mydriatic effect than intracameral injection where only a small volume of lidocaine is injected to the anterior chamber and quickly washed away with viscoelastics. Compared to other local injection techniques such as the peri-bulbar or retrobulbar technique, sub-Tenon injection is considered safer.[13] Several studies have explained the side effects of lidocaine as a local anesthetic agent, not specifically as a mydriatic agent. Changes in electroretinogram showed retinal toxicity following the exposure to intracameral lidocaine. But, these changes are dose-dependent and

transient.[20] Mohammadpour et al also reported transient visual loss related to damaged posterior capsule after intracameral lidocaine injection during cataract surgery.[21]

Silverstein et al found that the use of phenylephrine 1.0% - ketorolac 0.3% injection combination added to the irrigating solution resulted in significantly better prevention of miosis, less pupil billowing, and iris prolapse.[14] Phenylephrine induces pupil dilation by α-adrenergic stimulation of iris dilator muscle.[22] Ketorolac as a nonsteroidal anti-inflammatory drug that inhibits cyclooxygenase enzymes, both COX-1 and COX-2, also plays a role in mydriasis by inhibiting prostaglandin synthesis that is induced by surgical insult.[23]

Nuzzi et al reported that intracameral lidocaine-epinephrine was more effective in preventing IFIS than topical atropine. IFIS reduction was significant, especially for mild forms.[16] Epinephrine has dual effects to contract the dilator musculature by its α-receptor actions and relax the sphincter by a β effect, resulting in mydriasis.[24] Epinephrine works directly by displacing tamsulosin, while atropine acts indirectly by inhibition of iris constrictor muscle activity. This may explain the lower efficacy of atropine compared to epinephrine. [16]

There were only 2 observational studies that are included in this review. Chen et al reported that intracameral lidocaine-epinephrine did not reduce IFIS incidence significantly. It was proved by a higher incidence of IFIS with lidocaine-epinephrine injection, rather than with standard regimen. But this result could have been biased by the confounding effect of preoperative dilated pupil size. Lidocaine-epinephrine was injected in 66.7% of eyes with preoperative dilated pupil diameter ≤ 7.0 mm and 13.3% of eyes with a diameter > 7.0 mm. Since smaller preoperative pupil diameter is associated with IFIS, this may explain the higher incidence of IFIS in the intracameral lidocaine-epinephrine group.[10]

Esen et al found the incidence of IFIS was significantly reduced with topical atropine and a combination of topical atropine with intracameral epinephrine, compared to the control group. Atropine sulfate works by blocking the muscarinic cholinergic receptors in the iris sphincter muscle better than other pupiloplegics. Meanwhile, injection of intracameral epinephrine can improve stabilisation of pupil size during the surgery by stimulating the weakened iris dilator. But this study found no significant difference of IFIS incidence between the epinephrine-atropine combination group compared to the atropine group.[15]

In summary, most of the pharmacological strategies included in this review have shown effectiveness in reducing IFIS incidence. Because of the different baseline sample characteristics and control group in each study, this review could not compare the effectiveness of each strategy. All the studies have their own limitations and strengths that should also be taken into consideration.

Other prophylaxis treatment options

Other than pharmacological management, there are other strategies in preventing IFIS in high-risk patients. A modified surgical method of anterior corneal incision has been suggested as a strategy to reduce the risk of IFIS in high-risk patients. This method offers several advantages, including no additional expensive devices needed, no exposure to additional pharmaceuticals, and does not limit the surgeon to one strategy. But, the incidence of IFIS was still rather high and this new method will require the surgeon to learn a new skill. This method also potentially increases the risk for surgically induced astigmatism or endophthalmitis.[25] Although many surgeons tend to stop the use of α1-ARA drugs prior to surgery, there is no strong evidence that withdrawal can help reduce the incidence of IFIS. Pupil expansion devices can also be used as a preventive measure. Mechanical devices such as iris Malyugin pupil expansion devices are effective but they increase the cost, time, and risk of surgery.[26]

Preoperative examination

Thorough preoperative evaluation is essential in preventing complications associated with IFIS. To date, there is still no consensus on a risk stratification system. Therefore, every ophthalmologist needs to stratify the risk and decide on the best preventive strategy for each patient.[2,3]

Strengths and Limitations

This review has several limitations. Due to the subjective nature of IFIS assessment, especially iris billowing sign, measurement of outcome is less ideal compared to quantitative evaluation. Based on the critical appraisal, the quality of studies included in this review was limited in general. Most studies had a risk of bias due to confounding factors, lack of detail in the concealment process, and inability to mask intervention in some studies. Furthermore, owing to the great degree of heterogeneity across studies, including study design, intervention, and control group, a comparison of each study could not be performed and a definitive conclusion could not be drawn.

However, this systematic review used a well-designed methodology. We included several databases, including gray literature to expand our data result. To the best of our knowledge, studies included in this review are the most updated studies about IFIS prophylaxis. Critical appraisal was done according to the design of each study. Data in this review were

reported narratively to minimize the risk of drawing inaccurate conclusions despite the wide heterogeneity of the studies.

CONCLUSION

Various pharmacological managements have shown promising potential to prevent IFIS incidence in patients using α1-ARA. However, studies that evaluate the efficacy and safety profile of each agent and comparison between these strategies are still limited. Further research is needed to determine the best prophylaxis strategy to reduce the incidence of IFIS in high-risk patients.

FUNDING

No funding was received for this review.

CONFLICTS OF INTEREST

The authors affirm no conflict of interest in this study.

DISCLOSURE

The scientific poster for this review was presented at the Perdami Virtual Scientific Meeting 2021.

CONCLUSION

The primary advantage to perform a two-step surgery on an open globe injury case is its performed on a “quite” eye condition; providing better visualization of the cataract and lowering the occurrence of complication intraoperatively. At the event where the anterior capsule ruptures and the lens material touches endothelium, surgery needs to be performed immediately to prevent further damage in corneal endothelium. Calculation of the IOL power could be more accurate if measurement was taken biometrically on the operative eye. Hence, IOL Implantation is best performed on the second phase of the surgery.

REFERENCES

1. Li X, Zarbin MA, Bhagat N. Pediatric open globe injury: A review of the literature. J Emerg Trauma Shock 2015; 8(4): 216-223.
2. Gogate P, Sahasrabudhe M, Shah M, Patil S, Kulkarni A. Causes, epidemiology, and long-term outcome of traumatic cataracts in children in rural India. Ind J of Ophthalmol 2012; 60(5): 481-6
3. Reddy AK, Ray R, Yen KG. Surgical intervention for traumatic cataracts in children: Epidemiology, complications, and outcomes. J AAPOS 2009; 13: 170-174

4. Shah M, Shan S, Agrawal J, Khanna R, Rathod C. Controversies of traumatic cataract in children. EC Pediatrics 2018; 35-47.
5. Tabatabaei SA, Rajabi MB, Tabatabaei SM, Soleimani M, Rahimi F, Yaseri M. Early versus late traumatic cataract surgery and intraocular lens implantation. Eye 2017;1-6
6. Sen P. Shah C, Sen A, Jain E, Mohan A. Primary versus secondary intraocular lens implantation in traumatic cataract after open-globe injury in pediatric patients. J Cataract Refract Surg 2018; 44(12): 1446-1453.
7. Ciloglu E, Unal F. Surgical approach to pediatric traumatic cataract. EC Ophthalmology 2018; 9 (3): 143-147.
8. Salvin JH. Systematic approach to pediatric ocular trauma. Curr Opin Ophthalmol 2007; 18:366-372
9. Kinori M, Tomkins-Netzer O, Wygnanski-Jaffe T, Ben-Zion I. Traumatic pediatric cataract in southern Ethiopia- results of 49 cases. J AAPOS 2013; 17: 512-515.
10. Burgos-Elias VY, Marroquin-Sarti J, Zimmermann-Paiz MA, Rivaz AM,Quezada-del NC. Traumatic cataract surgery in pediatric patients. Experince in a site. Arch Argent Pediatr 2018; 116(3): 216-223.
11. Xu YN, Huang YS, Xie LX. Pediatric traumatic cataract and surgery outcomes in eastern China: a hospital-based study. Int J Ophthalmol 2013; 6(2): 160-164.
12. Shah MA, Shah SM, Appleware AH, Patel KD, Rheman RM, Shikhange KA. Visual outcome of traumatic cataract in pediatric age group. Eur J Ophthalmol 2012; 22(6): 956-963.
13. Yardley A, Ali A, Najm-Tehrani N, Mireskandari K. Refractive and visual outcomes after surgery for pediatric traumatic cataract. J Cataract Refract Surg 2018; 44: 85-90.
14. Kuhn F. Ocular traumatology.Berlin. Springer. 2008. Hal 245- 268
15. Steinert RF. Cataract Surgery. Techniques and principle of surgical management for the traumatic cataract. Edisi ke-3. California. Elsevier Saunders 2011. Hal 351-68
16. Adhikari S, Shrestha UD. Pediatric cataract surgery ith hydrophilic acrylic intraocular lens implantation in Nepalse children. Clinical ophthalmology 2018; 12: 7-11.
17. Ram J, Sukhija J. Pediatric cataract surgery: current concepts. JIMSA 2010; 23(3): 132-137.