

# Effect of low molecular weight heparin (enoxaparin) on congenital cataract surgery

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## Abstract

• **AIM:** To assess the efficacy of intracameral enoxaparin (a low-molecular-weight heparin) infusion, in variable doses on postoperative inflammatory response in congenital cataract surgery.

• **METHODS:** It is a prospective, randomized controlled trial. Eighty eyes of 53 children with congenital cataract were enrolled in this study. Every eye had primary posterior capsulorrhexis and intraocular lens (IOL) implantation after lens aspiration. The eyes were divided into 4 equal groups. In group 1 balanced salt solution (BSS) without enoxaparin was used as an irrigation solution. Whereas in group 2, 3 and 4, 40mg, 20mg and 10mg enoxaparin in 500mL BSS was used respectively. The inflammatory response in the anterior chamber was compared among the groups with slit-lamp biomicroscopy.

• **RESULTS:** The mean follow-up period was (17.75±3.95) months in group 1, (18.00±5.15) months in group 2, (19.20±5.47) months in group 3 and (18.65±5.16) months in group 4. Mean number of inflammatory cells in the anterior chamber in group 1 was significantly higher than that of group 2, 3, 4 ( $P<0.001$ ). There was fibrin formation in the anterior chambers of 3 eyes in group 1 and one eye in group 4. There was synechia formation in 3 eyes of group 1 and one eye of group 4. There was no significant difference among the groups by means of fibrin or synechia formation ( $P>0.05$ ). There were IOL precipitates in 4 eyes of group 1 and 2 eyes of group 4. IOL precipitate formation was significantly higher in group 1 than that of group 2 and 3 in which there was no IOL precipitate ( $P=0.048$ ). There was IOL subluxation in only one eye of group 1, 3 and 4 while no subluxation was observed in group 2 ( $P>0.05$ ). There was no statistically significant difference detected about IOL subluxation occurrence in all 4 groups ( $P>0.05$ ).

• **CONCLUSION:** Complications of cataract surgery in congenital cataract patients associated with postoperative inflammatory response found to be decreased with the use of enoxaparin in intraocular infusion solutions. Furthermore according to our results the anti-inflammatory effect of enoxaparin was dose dependant.

• **KEYWORDS:** congenital cataract; enoxaparin; inflammatory response

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## INTRODUCTION

In pediatric cataract surgery an intense inflammatory reaction may be observed associated with weak trabecular meshwork with decreased fibrinolytic activity and breakdown of the immature blood-aqueous barrier. Dense inflammatory membranes, thickened and opacified anterior hyaloid and proliferated lens epithelial cells may block the papillary area<sup>[1]</sup>.

It is previously reported that heparin surface-modified intraocular lens (IOL) has been claimed to reduce the incidence of inflammatory precipitates on its surface<sup>[2]</sup>. Johnson *et al*<sup>[3]</sup> reported that heparin injection into anterior chamber decreases fibrin clot formation in a rabbit model, but it had no effect on bleeding time. Anterior chamber flare and cells after cataract surgery with heparin were found to be lower than that of without heparin and no postoperative adverse effects were noted<sup>[4,5]</sup>. Primary posterior capsulorrhexis and optic capture with a heparin-coated intraocular lens was shown to be a safe and effective method to decrease secondary visual axis opacification in pediatric cataract surgery<sup>[6]</sup>. However, the heparin-coated IOLs are not widely used because of their cost<sup>[7]</sup>.

Heparin has several therapeutic and also side effects on coagulation cascade like inhibition of thrombin and prothrombinase complex. The use of a low molecular weight variant in pediatric cataract surgery to reduce the postoperative inflammatory response<sup>[5,6,8]</sup>.

In this present study, we aimed to evaluate the efficacy of intracameral enoxaparin infusion, in variable doses on postoperative inflammatory response in congenital cataract surgery.

## SUBJECTS AND METHODS

**Subjects** Eighty consecutive eyes of 53 patients who admitted to Department of Pediatric Ophthalmology, Medical Faculty, the Dicle University between June 2007 and June 2009 with the diagnosis of congenital cataract were included in this prospective study. The study was approved by the ethics committee of the Dicle University Faculty of Medicine and conducted according to the tenets of the Declaration of Helsinki. All patients had informed consent form for the surgical procedure, data collection and establishment of database signed by their parents or caregivers. Exclusion criteria were traumatic cataract, infection, steroid-induced cataract, congenital glaucoma, uveitis, optic nerve or other fundus abnormalities and a postoperative follow-up period of less than 12 months. Bilateral cases were operated under separate sessions with an interval of 15 days.

**Methods** The children underwent cataract surgery with lens aspiration by the same surgeon (IC). The eyes were divided into 4 equal groups according to the irrigation fluid used. In group 1, balanced salt solution (BSS Plus; Alcon Laboratories, Inc., Fort Worth, TX, USA) without enoxaparin was used. In group 2, 3, and 4, enoxaparin was used with the dose of 40, 20, and 10mg (Clexane; Aventis Pharma, Surrey, England, United Kingdom) in 500mL BSS respectively.

Cyclopentolate 1% and phenylephrine 10% eye drops were instilled to dilate the pupils every hour during 6 hours' period before surgery. Eyes and surrounding adnexa were cleansed using 5% and 10% povidone-iodine solution respectively. Coaxial cataract surgery was performed through a 3.2mm clear corneal tunnel incision, centered on the 12-o'clock position. The anterior chamber was filled with sodium hyaluronate 1.6% (Amvisc<sup>®</sup>), and anterior continuous curvilinear capsulorhexis of between 5.0mm and 5.5mm was accomplished using a capsulorhexis forceps. Nucleus and cortex were removed using a manual irrigation/aspiration device. Posterior capsulotomy was performed and then enlarged to 4.0mm and 4.5mm with an anterior vitrectomy probe. An anterior vitrectomy was performed through this posterior capsulotomy site. Sodium hyaluronate was injected into the anterior chamber again. Then a posterior chamber intraocular lens (AcrySof MA30BA Alcon) in the capsular bag was implanted. Viscoelastic material was removed by irrigation/aspiration canule. Cornea was sutured with 10-0 monofilament nylon sutures. Subconjunctival corticosteroid and antibiotic were then injected. Topical corticosteroid eye drops (dexamethasone

0.1%, Maxidex) were used every hour during the first week, 8 times a day during the second week, and 6 times a day for the following 4 weeks postoperatively. Antibiotic eye drops (ciprofloxacin 0.3%, Ciloxan) were applied 5 times a day for 1 month, continued postoperatively. Mydriatic eye drops were added when there were more than 10 cells in the anterior chamber. Patching for amblyopia was instituted by adhesive eye patches when indicated within 2 weeks after surgery.

The patients were examined daily in the first 3 postoperative days, weekly during the first month, monthly during the 6 month and 2-monthly thereafter. The children underwent a complete slit-lamp biomicroscopic evaluation of the anterior and posterior segment without pupil dilation and dilated fundus examination with indirect ophthalmoscope. The inflammatory response in the anterior chamber was compared among the 4 groups with slit-lamp biomicroscopy (SM-70N Takagi, Japan). Portable Slit Lamp (Reichert) was used in patients with poor cooperation. The degree of postoperative inflammation was graded according to the number of cells present in the anterior chamber at high magnification (x1.6) with an oblique intense beam as previously described<sup>[9]</sup>. Cells were counted at least 3 times in each examination. The results were reported as the average grading.

**Statistical Analysis** Age and follow-up were compared by one-way ANOVA test. The least square difference (LSD) test was used in Post-hoc analysis. Gender, anterior chamber cell, synechiae, IOL precipitate and IOL subluxation was analyzed by Chi-square test.

## RESULTS

Table 1 shows demographic features of the patients. Mean age was (37.30±11.63) months (ranged 20-62 months) in group 1, (37.65±11.37) months (ranged 22-60 months) in group 2, (39.45±12.52) months (ranged 22-66 months) in group 3, and (37.50±12.36) months (ranged 22-60 months) in group 4. Follow-up period was (17.75±3.95) months (ranged 13-25 months) in group 1, (18.00±5.15) months (ranged 12-27 months) in group 2, (19.20±5.47) months (ranged 14-29 months) in group 3 and (18.65±5.16) months (ranged 12-30 months) in group 4. There was no significant difference among the groups in terms of age, gender, and mean follow-up period ( $P>0.05$ , Table 1).

Table 2 shows biomicroscopic signs and distribution of the complications after congenital cataract surgery. Presence of inflammatory cells in the anterior chamber was significantly higher in group 1 than that of group 2, 3, and 4 ( $P<0.001$ ). There was fibrin formation in the anterior chamber of 3 eyes in group 1 and only one eye in group 4 but none of the eyes in group 2 or 3. Any statistically significant difference was not detected about fibrin formation in all 4 groups ( $P>0.05$ ). Synechiae formation was observed in 3 eyes of group 1, one

**Table 1 Demographic features of the patients**

|                      | Group 1     | Group 2     | Group 3     | Group 4     | P     |
|----------------------|-------------|-------------|-------------|-------------|-------|
| Age (months)         | 37.30±11.63 | 37.65±11.37 | 39.45±12.52 | 37.50±12.36 | >0.05 |
| Gender (Male/Female) | 6/6         | 8/6         | 8/7         | 7/5         | >0.05 |
| Follow-up (months)   | 17.75±3.95  | 18.00±5.15  | 19.20±5.47  | 18.65±5.16  | >0.05 |

**Table 2 Biomicroscopic signs and distribution of the complications after congenital cataract surgery (n=20)**

|                           | Group 1 | Group 2 | Group 3 | Group 4 | P      |
|---------------------------|---------|---------|---------|---------|--------|
| Cells in anterior chamber |         |         |         |         |        |
| <10                       | 4       | 17      | 15      | 14      | <0.001 |
| >10                       | 16      | 3       | 5       | 6       |        |
| Anterior chamber fibrin   | 3       | 0       | 0       | 1       | >0.05  |
| Synechiae                 | 3       | 0       | 0       | 1       | >0.05  |
| IOL precipitates          | 4       | 0       | 0       | 2       | =0.048 |
| IOL subluxation           | 1       | 0       | 1       | 1       | >0.05  |

IOL: Intraocular lens.

eye of group 4, but none of the eyes in group 2 or 3. There was no statistically significant difference about synechiae formation in all 4 groups ( $P > 0.05$ ). IOL precipitates observed in 4 eyes of group 1, 2 eyes of group 4 but none of the eyes in group 2 or 3. IOL precipitate formation was significantly higher in group 1 than that of group 2 and 3 ( $P = 0.048$ ). There was IOL subluxation in one eye of group 1, 3, and 4 but none of the eyes in group 2. There was no statistically significant difference about IOL subluxation occurrence in all 4 groups ( $P > 0.05$ , Table 2). Hyphema, endophthalmitis and corneal decompensation was not observed in any group.

**DISCUSSION**

Postoperative complications are common in pediatric cataract surgery due to increased inflammation and glaucoma rate.<sup>[5]</sup> Heparin has anti-inflammatory, antiproliferative effects and also anticoagulant function.<sup>[4]</sup> It inhibits fibrin formation as well as fibroblast activity after intraocular surgery<sup>[10]</sup>. Zaturinsky *et al*<sup>[11]</sup> reported that the addition of heparin into the irrigating solution during cataract surgery in rabbit eyes, results in less disturbance of the blood-aqueous barrier. Previous studies reported that heparin inhibits inflammation via induction of apoptosis in human peripheral blood neutrophils, inhibition of the complement activation and lymphocyte migration. It also inhibits L- and p-selectin adhesion-molecules that support the initial attachment of leukocytes to the vessel wall at the inflammation site, neutrophil chemotaxis, and generation of reactive oxygen species by mononuclear and polymorphonuclear leukocytes<sup>[5,12]</sup>. Heparin is also used for the prevention of membrane formation over the IOL optic<sup>[13]</sup>. Dada *et al*<sup>[6]</sup> claimed that routine use of heparin in the irrigation fluid augments the effects of heparin coated IOL and primary posterior capsulorrhexis in preventing secondary visual axis opacification. While the use of heparin

alone without any primary opening in the posterior capsule, may not prevent secondary posterior capsule opacification sufficiently<sup>[6]</sup>. Bayramlar *et al*<sup>[12]</sup> reported that use of heparin sodium in the irrigating solution decreased the postoperative inflammatory and fibrinoid reactions and related complications such as synechia, pupil irregularity, and IOL decentration in pediatric cataract surgery.

Enoxaparin is composed of heparin fragments in different lengths<sup>[14]</sup>. Iverson *et al*<sup>[15]</sup> reported that less postoperative inflammation was noted in eyes irrigated with low-molecular-weight heparin in lensectomy, vitrectomy, and retinotomy rabbit models.

Metha *et al*<sup>[16]</sup> reported that the use of postoperative intracameral injection of tissue plasminogen activator was safe and effective in the treatment of postoperative intense anterior chamber inflammation. However, this treatment is not always convenient, as it is not cost-effective, and also not practical in children<sup>[5]</sup>.

Portoles *et al*<sup>[17]</sup> reported that heparin could have an effect to diminish adherence of the bacteria by either coating the surface or coating the bacteria. Gills JP indicated that the use of heparin in antibiotic/BSS solution with a concentration of 1.6 IU/mL is effective in preventing endophthalmitis in his series of 27 000 cases<sup>[18]</sup>. However, Manners *et al*<sup>[19]</sup> reported that there was no difference in bacterial contamination between the groups who received or not received low molecular weight heparin at a concentration of 5 IU/mL. They couldn't establish any direct antibacterial effect of heparin.

Both heparin and low molecular-weight heparin are effective to reduce postoperative inflammatory reactions. On the other hand, hyphema can be seen during surgery due to heparin irrigation. This can be prevented by using low molecular weight heparin. It is explained with a less side effect on platelet function<sup>[15]</sup>. As a result, the use of a low molecular

weight variant is preferable instead of crude heparin [6]. Bayramlar *et al* [12] also reported hyphema after the intraocular use of heparin sodium during a pediatric secondary IOL implantation. They also reported need for a second surgery to remove the hyphema and vitrectomy for intravitreal hemorrhage, because all eyes of their patients with uveitis and diabetes mellitus developed severe hyphema. They suggest that heparin is contraindicated in eyes with a defective blood aqueous barrier such as severe uveitis and diabetes mellitus [20]. Low-molecular-weight heparin was developed to decrease the risks of active bleeding during major surgeries [21]. Iverson *et al* [15] reported an increased incidence of haemorrhage in vitrectomy with heparinised intraocular infusions, although animal studies using low molecular weight heparin suggest no significant effect on intraocular bleeding. Rumelt *et al* [5] suggested that the degree of postoperative vitreous hemorrhage didn't change with or without low-molecular weight heparin irrigation, besides, corneal clarity was better in the group with low-molecular-weight heparin. However, adverse reactions weren't observed in animal models [3,15] or humans [4,19,22] in the studies that used heparin and low-molecular-weight heparin.

To the best of our knowledge, this study has the widest series on congenital cataract surgery in which enoxaparin is used with different concentrations. We detect the least surgical inflammation and related complications in the eyes that received 40mg enoxaparin in 500mL BSS. Besides, in this study we did not see any toxic side effects like corneal edema or hyphema with any dose of intracameral enoxaparin.

In conclusion, intraocular enoxaparin, a low-molecular-weight heparin, infusion is an effective, reliable, and non-toxic treatment; while it reduces postoperative complications related inflammatory response in congenital cataract surgery, IOL implantation as shown in this study. Furthermore according to our results the anti-inflammatory effect of enoxaparin was dose dependant.

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