A RANDOMIZED CLINICAL TRIAL ON THE ANTI-INFLAMMATORY EFFECT OF INTRACAMERAL LOW MOLECULAR WE HEPARIN (ENOXAPAIN) IN DIABETIC CATARACT SURGERY

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ABSTRACT: AIM: To study the effect intracameral low molecular weight on postoperative inflammation after cataract surgery in diabetic patients. SETTING: Department of Ophthalmology J. N. Medical College. Belgaum. DESIGN: Randomized control trial. MATERIAL AND METHODS: Forty patients with diabetes undergoing small incision cataract surgery with posterior chamber intraocular lens (IOL) implantation were randomly assigned to two groups, group A and group B. All patients in group A received low molecular weight heparin (enoxaparin) in the concentration of 40 IU in 500ml in the irrigating solution and patients in group B received irrigating solution without low molecular weight heparin. In all patients polymethyl methacrylate (PMMA) IOLs were implanted. The patients were examined postoperatively on day 1, day 7, day 30 and day 60 for anterior chamber cells and flare and iris pigments on cell by slit lamp biomicroscopy. RESULTS: A statistically significant reduction in postoperative cells, flare and intraocular lens surface pigments was noted in group with addition of low molecular weight heparin (enoxaparin) at day 1(p<0.001) and 1 week (p<0.001). At 4 weeks and 8 weeks no statistically significant reduction in post-operative cells and flare was seen between the two groups but there was a significant reduction in the intraocular lens pigments in the group with addition of low molecular weight heparin (enoxaparin). CONCLUSION: Intraoperative use of low molecular weight heparin (enoxaparin) reduced disturbance in the blood-aqueous barrier in the early post-operative period evidenced by lower postoperative anterior chamber cells and flare, and also reduced iris pigments on the intraocular lens. At 8 weeks cells and flare in both the groups did not show significant difference. KEYWORDS: low molecular weight heparin, irrigating solution, post op inflammation, cataract surgery.

INTRODUCTION: In diabetics with or without evidence of diabetic retinopathy the blood aqueous barrier is impaired and also surgical trauma during cataract surgery causes breakdown of the blood- aqueous barrier, leading to augmented protein leakage and cellular reaction in the aqueous humor resulting in an increased risk of post-operative inflammation.¹ Postoperative anterior chamber reaction is significant as it may lead to increased intraocular pressure (IOP), corneal edema, endothelial injury, fibrin formation on intraocular lens (IOL) surface, posterior synechia, posterior capsular opacity (PCO), cystoid macular edema and chronic anterior uveitis.
Heparin has anti-inflammatory and anti-proliferative effects in addition to its anticoagulant function, inhibits fibrin formation after intraocular surgery, and has also been shown to inhibit fibroblast activity.\textsuperscript{2,3} These unique properties of heparin lead researchers to use heparin in surface modified IOLs. But its use is limited due to high cost.

In this prospective study, we evaluated the postoperative inflammation and cellular reaction after adding low molecular weight heparin (Enoxaparin) in the irrigating solution during cataract surgery in diabetic patients.

METHODS: In this prospective randomized study, 40 diabetic patients were enrolled. Informed consent was obtained from all patients. Ethical clearance from the institution ethical committee is taken. Inclusion criteria were presence of a cataract sufficient to cause visual symptoms in patients 45 years or older with diabetes mellitus requiring medical control. Exclusion criteria included patients with bleeding disorders, on anti-coagulant therapy, traumatic cataract, and complicated cataract.

Patients were randomly assigned to one of two groups; group A and group B each having 20 patients each. During surgery 40 mg of low molecular weight heparin (Enoxaparin) was added to the 500ml irrigating solution of ringer lactate in patients assigned to Group A. Patients in group B received only ringer lactate as irrigating solution. All patients underwent manual small incision cataract surgery. One experienced surgeon performed all the cases using same techniques. Surgery was done under peribulbar anesthesia. After making a 6 to 6.5mm scleral incision which was 1.5 to 2mm away from the limbus was taken. Corneo-sclera tunnel was made. The anterior chamber was entered with the help of 3.2mm keratome and a 5 to 5.5mm capsulotomy was done. Hydro dissection was performed with hydro dissection cannula. Cataractous lens was prolapsed into anterior chamber and removed by sandwich technique. Cortical wash was given by bimanual irrigation aspiration cannula. In all patients posterior chamber intraocular lens (IOL) implantation was done. At the completion of surgery, the eye was patched after subconjunctival injection of steroid and antibiotic.

Next day the patch was removed and the patients received corticosteroid eye drops (Prednisolone acetate 1%) hourly for one week and tapered over 6 weeks, antibiotic eye drops (moxifloxacin 0.4%) 6 hourly and mydriatic eye drops once daily. Each patient had a complete eye examination including slit lamp, retinal examinations and measurement of the intraocular pressure preoperatively and at 1st, 7th, 30th and 60 day post operatively. The postoperative inflammation was assessed at all visits with slit lamp biomicroscopy and the degree of postoperative inflammation was graded according to the number of cells present in the anterior chamber and the degree of flare according to Hogan’s criteria at high magnification (1.6) with an oblique intense beam.

STATISTICAL ANALYSIS: Statistical analysis was performed using SPSS software. The baseline characteristics of the patients were expressed as means for continuous variables. For univariate analysis, the student t test was used for continuous variables. Postoperative cells and flare was assessed using fisher exact test and p value of 0.05 or less was considered significant.
RESULTS: The two groups were comparable in age, distribution of sex. The median age of the patients was 64.2±9.98 years in group A and 58.9±7.94 years in group B. 40 eyes had intraocular infusion of enoxaparin (group-A) and 40 eyes were operated without intraocular enoxaparin (Group-B). There were no significant differences between the two groups at baseline. A statistically significant reduction in postoperative cells and flare was noted in group with addition of low molecular weight heparin (Enoxaparin) at days 1(p<0.001) and 1 week (p<0.001). Iris pigments on lens showed statistically significant reduction in patients in group A compared to patients in group B at day 1 and day 7. At 4 weeks and 8 weeks no statistically significant reduction in post-operative cells and flare was seen but there was a significant reduction in the intraocular lens pigments. All patients in group A had no postoperative inflammation related complications such as precipitates over IOL surface, posterior synechiae and optic capture. Of the patients in group B five (25%) of 20 eyes had precipitates over IOL surface. Papillary membrane, posterior synechiae and optic capture were not noted in any of the patients. We did not observe intraoperative or postoperative complications related to heparin supplementation. Hyphema was not noted in any of the patients

DISCUSSION: The major challenge in case of diabetic cataract surgery is severe postoperative inflammation with subsequent fibrin formation that is responsible for postoperative complications which can worsen the final visual outcome.\textsuperscript{4} Therefore new therapeutic approaches are being invented to prevent postoperative complications. Two factors which exacerbate ocular inflammation include surgical trauma and foreign body reaction to the intraocular lens.\textsuperscript{5,6} Surgical trauma causes breakdown of blood aqueous barrier leading to augmented protein leakage and cellular reaction in the aqueous humor. We minimized surgical trauma by avoiding excessive handling of the iris. The mean operating time in both the groups was identical. Early use of systemic and frequent instillation of topical corticosteroid also decreased postoperative inflammation but they were used in both the groups in a similar manner. One surgeon performed all the surgeries using the same surgical technique and same type of PMMA intraocular lens. Thus the effect of two factors that could have resulted in trauma and induced inflammation was minimized.

Heparin has anti-inflammatory and anti-proliferative effects in addition to its anticoagulant function, inhibits fibrin formation after intraocular surgery, and has also been shown to inhibit fibroblast activity. Heparin of molecular weight (MW) of 15,000 Daltons (Da) and its derivative, LMWH (MW < 7,000 Da) have been used successfully in vitreoretinal surgery to prevent fibrin formation. Due to its antithrombin effect, heparin inhibits fibrin formation by accelerating the control mechanisms for thrombin and activated X-factor. LMWH has been used in animal and human models (clinical trials) at different concentrations.

Previous studies elucidate several mechanisms through which heparin may inhibit inflammation including induction of apoptosis in human peripheral blood neutrophils, inhibition of the complement activation and lymphocyte migration, \textit{l-} and \textit{p-selectin}, adhesion-molecule support of the initial attachment of leukocytes to the vessel wall at the inflammation site, neutrophil chemotaxis, and generation of refractive oxygen species by mononuclear and polymorphonuclear leukocytes.\textsuperscript{7} Another useful adjunct for the prevention of membrane formation over the IOL optic is the use of a heparin-coated IOL.
In our study of cataract surgery in diabetic patients, addition of low molecular weight heparin (Enoxaparin) to the irrigating solution reduced early post-operative inflammation and thereby prevented postoperative inflammatory complications. We did not note any adverse effect that could be attributed to the use of enoxaparin. In 2 studies by Kruger and Sharan both noted postoperative hyphema after use of low molecular weight heparin.8,9 However, in our study hyphema was not noted in any of the patients.

In conclusion, the results of our prospective randomized clinical trial show that addition of low molecular weight heparin to the irrigating solution is an effective, safe and cheaper method to reduce the postoperative inflammation in patients with diabetes without any complications related to the drug.

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|        | Day 1 | Day 7 | Day 30 | Day 60 |
|--------|-------|-------|--------|--------|
| Grade 0 | 0     | 17(85)| 20(100)| 20(100)|
| Grade 1 | 17(85)| 3(15) | 0      | 0      |
| Grade 2 | 3(15) | 0     | 0      | 0      |
| Grade 3 | 0     | 0     | 0      | 0      |
| Grade 4 | 0     | 0     | 0      | 0      |

Anterior chamber cells in group A
### Anterior Chamber Cells in Group B

| Grade | Day 1 | Day 7 | Day 30 | Day 60 |
|-------|-------|-------|--------|--------|
| 0     | 0     | 4(20) | 19(95) | 20(100) |
| 1     | 5(25) | 15(75)| 1(5)   | 0      |
| 2     | 12(60)| 1(5)  | 0      | 0      |
| 3     | 3(15) | 0     | 0      | 0      |
| 4     | 0     | 0     | 0      | 0      |

### Anterior Chamber Flare in Group A

| Grade | Day 1 | Day 7 | Day 30 | Day 60 |
|-------|-------|-------|--------|--------|
| 0     | 2(10) | 20(100)| 20(100)| 20(100)|
| 1     | 18(90)| 0     | 0      | 0      |
| 2     | 0     | 0     | 0      | 0      |
| 3     | 0     | 0     | 0      | 0      |
| 4     | 0     | 0     | 0      | 0      |

### Anterior Chamber Flare in Group B

| Grade | Day 1 | Day 7 | Day 30 | Day 60 |
|-------|-------|-------|--------|--------|
| 0     | 2(10) | 13(65)| 20(100)| 20(100)|
| 1     | 8(40) | 7(35) | 0      | 0      |
| 2     | 10(50)| 0     | 0      | 0      |
| 3     | 0     | 0     | 0      | 0      |
| 4     | 0     | 0     | 0      | 0      |
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