Low molecular weight heparin in intraocular infusion in high risk group cataract surgery - minimizes inflammatory reaction and prevents posterior capsular opacification

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Abstract
Aim: To evaluate the influence of heparin infusion with square edge IOL on postoperative inflammatory response and posterior capsular opacification.

Methods: This randomized prospective study included 60 patients with high risk i.e. congenital traumatic, complicated, diabetic cataract and lens induced glaucoma. All cases had small incision cataract surgery with square edge IOL implantation. The cases were divided in two groups- Group A (study group), Group B (control group). Heparinized (40mg/500ml) infusion was used in 31 cases (group A). 29 cases (group B) were done without heparin infusion.

The degree of postoperative inflammation was compared between two groups with slit lamp biomicroscopy. PCO was assessed subjectively at slit lamp with fully dilated pupil.

Result: Group A revealed 0 to +1 anterior chamber reaction and mild to moderate surface deposition during early postoperative days. Groups B revealed +2 to +4 anterior chamber reaction and moderate to severe surface deposition during early postoperative days.

The regenerating PCO was significantly higher in group B than group A. This reveals that use of heparin infusion during cataract surgery in high risk cases significantly reduces the anterior chamber reaction and postoperative inflammation related complications.

Conclusion: In high risk cases heparin infusion with square edge IOL implantation has the advantage of being safe and is effective means of reducing postoperative inflammation and decreases PCO formation without significant side effects.

Introduction
Cataract surgery in the modern era of hi-tech innovations, has undergone major evolution. Use of viscoelastics, high end phaco machines with quality and design of intra-ocular lenses have improved the visual results drastically. Surgery has a higher incidence and more pronounced postoperative inflammatory reaction in high risk cases such as Congenital, Traumatic, Complicated cataract, Diabetic patients and in Lens induced glaucoma, that an ophthalmologist has to face.
Intraocular inflammation is manifested as increased cells and flare, inflammatory precipitates over the IOL surface, formation of synechiae and inflammatory cyclitic membranes. The increased post operative inflammation may contribute to the formation of posterior capsular opacity.

In an attempt to reduce the occurrence of postoperative inflammation and PCO formation, there have been experimental and clinical trials using TPA (Tissue Plasminogen Activator), Anexin V (a calcium binding protein having anticoagulant property) and low molecular weight heparin.

The use of heparin surface modified intraocular lenses may decrease inflammatory reaction and PCO without significant side effects but did not gain wide popularity because of their cost. In our prospective study we evaluated the degree of postoperative inflammation and PCO formation in high risk groups with or without a low-molecular weight heparin added to the anterior chamber infusion bottle.

**Aim**

To evaluate the effect of low molecular weight heparin sodium in irrigating solution on postoperative inflammation and PCO in high risk cases

**The advantages of LMWHs over UFHs are**

1. No need for monitoring aPTT and other coagulation parameters
2. Decreased risk of corneal toxicity
3. Smaller bleeding
4. Greater bioavailability and longer half life than crude heparin

**Material and Method**

The present study was carried out in our Department of Ophthalmology, Shyam Shah Medical College and Hospital, Rewa (M.P.) from February 2009 to February 2010.

**Inclusion Criteria**

1. Congenital cataract
2. Traumatic cataract
3. Complicated cataract
4. Diabetic cataract
5. Lens induced glaucoma

**Exclusion Criteria**

1. Senile cataract
2. Patients having any other ocular pathology with cataract
3. Patients with bleeding tendencies or on anticoagulant drugs
4. Patients with intraoperative complications such as iris trauma, posterior capsular rent etc.
5. Patients on systemic anti-inflammatory drugs

**Data collection** - We conducted this study in 80 eyes of high risk groups, ranging in age from 2 years to 80 years, who underwent manual small incision cataract extraction with posterior chamber intraocular lens implantation at our institution (Deptt of Ophthalmology, SSMH, Rewa) from February 2009 to February 2010. All patients had complete preoperative medical checkup including documenting evidence of prior bleeding tendencies and were routinely instructed to avoid preoperative and postoperative use of aspirin and aspirin containing medications.

Patients were randomly assigned to one of the two groups; during surgery 40mg of low molecular weight heparin sodium was added to the 500 ml irrigating solution of fortified balanced salt solution (BSS plus) in 40 eyes (Group A). The control group (Group B) received only fortified balanced salt solution as the intra ocular irrigating infusion in 40 eyes.

Same surgical technique (SICS) was used for all patients by single surgeon. Each patient had a complete eye examination including slit lamp, retinal examinations and measurement of the intraocular pressure preoperatively and at 1st, 3rd and 7th day, 4th week, 3rd month and 1 year postoperatively. 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 (0 to +4) according to Hogan’s criteria at high magnification (x1.6) with an oblique intense beam.

Early and late postoperative intraocular reaction were recorded and compared. Posterior capsular opacification was graded from 0 to 4 according to “snellman and Lindstorm”.

**Results**

Two groups were comparable with age distribution and types of high risk group cataract (Table-1). The median age of the patients was 40 years.

**Table No. 1** Distribution of Type of Cataract in Study (Group-A) and Control Group (Group-B)

| Age in years | Congenital cataract | Traumatic cataract | Complicated cataract | Diabetic cataract | Lens induced glaucoma | Total no of patients |
|--------------|---------------------|--------------------|----------------------|-------------------|-----------------------|----------------------|
| 70-79        | -                   | -                  | -                    | 6                 | 4                     | 10                   |
| 60-69        | -                   | 3                  | -                    | 8                 | 2                     | 13                   |
| 50-59        | -                   | 2                  | -                    | 4                 | 6                     | 12                   |
| 40-49        | -                   | 3                  | -                    | 3                 | -                     | 7                    |
| 30-39        | -                   | 11                 | 4                    | -                 | -                     | 15                   |
| 20-29        | -                   | 4                  | -                    | -                 | -                     | 4                    |
| 10-19        | 4                   | 8                  | -                    | -                 | -                     | 12                   |
| 5-9          | 3                   | -                  | -                    | -                 | 3                     | 4                    |
| 2-4          | 4                   | -                  | -                    | -                 | -                     | 4                    |
| **Total**    | **11**              | **31**             | **5**                | **21**            | **12**                | **80**               |

80 eyes of 76 patients were included in this study. Forty eyes that had intraocular infusion of enoxaparin (group-A) and 40 eyes were operated without intraocular enoxaparin (group-B).

**Table No. 2** Distribution of Type of Cataract in Study and Control Group

| Type of Cataract | Group A (with heparin) (40 eyes) | Group B (without heparin) (40 eyes) |
|------------------|----------------------------------|-------------------------------------|
| Congenital Cataract | 6                               | 5                                   |
| Traumatic Cataract | 15                              | 16                                  |
| Complicated Cataract | 2                               | 3                                   |
| Diabetic Patients | 10                              | 11                                  |
| Lens Induced Glaucoma | 7                               | 5                                   |
| **Total**        | **40**                          | **40**                              |

Both of the groups were having high risk cases like congenital, traumatic, complicated cataract; lens induced glaucoma and diabetic patients (Table-2).

**Table No.3** Grading of anterior chamber cells and flare after surgery in study group

| GRADE OF CELLS | D-1 | D-7 | D-28 | 8th Week |
|----------------|-----|-----|------|----------|
| ±              | 22  | 20  | 17   | 21       |
| + 1            | 14  | 12  | 8    | 0        |
| + 2            | 4   | 4   | 0    | 0        |
| + 3            | 0   | 0   | 0    | 0        |
| + 4            | 0   | 0   | 0    | 0        |
| N              | 40  | 36  | 25   | 21       |

| GRADE OF FLARE | D-1 | D-7 | D-28 | 8th Week | 3rd month |
|----------------|-----|-----|------|----------|-----------|
| 0              | 24  | 18  | 18   | 21       | 18        |
| + 1            | 13  | 13  | 7    | 0        | 0         |
| + 2            | 3   | 5   | 0    | 0        | 0         |
| + 3            | 0   | 0   | 0    | 0        | 0         |
| + 4            | 0   | 0   | 0    | 0        | 0         |
| N              | 40  | 36  | 25   | 21       | 18        |
On day 1 only 10% patients were having graded +2 cells. Not even a single patient was having graded +4 cells at any occasion. Similarly flare values were also not significant in study group.

Table No.4 Grading of anterior chamber cells and flare after surgery in control group

| GRADE OF CELLS | D-1 | D-7 | D-28 | 8th Week |
|----------------|-----|-----|------|----------|
| ±              | 0   | 0   | 2    | 8        |
| + 1            | 2   | 4   | 10   | 8        |
| + 2            | 12  | 10  | 11   | 4        |
| + 3            | 24  | 19  | 5    | 0        |
| + 4            | 2   | 1   | 0    | 0        |
| N              | 40  | 34  | 28   | 20       |

| FLARE         | D-1 | D-7 | D-28 | 8th Week | 3rd month |
|---------------|-----|-----|------|----------|-----------|
| 0             | 0   | 0   | 3    | 9        | 5         |
| + 1           | 3   | 6   | 9    | 8        | 7         |
| + 2           | 12  | 11  | 13   | 3        | 4         |
| + 3           | 23  | 16  | 3    | 0        | 0         |
| + 4           | 2   | 1   | 0    | 0        | 0         |
| N             | 40  | 34  | 28   | 20       | 16        |

N – number of patients, D - day

Follow up of patients was 100% at 1st postoperative day and 75% at 3rd month. On days 1, 3 and 7, cell values were significantly lower in eyes with heparin infusion group (p<0.004) and were very similar to the flare values. Flare values were raised on 1st, 3rd and 7th postoperative days in control group (P<0.003). None of the eyes of group A was having +4 cells and +4 flare postoperative, while 2 (5%) eyes of group B were having +4 cells and flare on 1st postoperative day. Flare values in both groups peaked at 1st postoperative day with a subsequent decrease thereafter. Similar re-establishment of the blood-aqueous-barrier (BAB) between groups was found.

Table No. 5 Early and Late Postoperative Complications

| Complications            | Group A (With Heparin) | Group B (Without Heparin) |
|--------------------------|------------------------|---------------------------|
| Early                    | (40 eyes)              | (40 eyes)                 |
| Fibrin in anterior chamber | 4                     | 8                         |
| Mild                     | 4                      | 8                         |
| Moderate                 | 1                      | 7                         |
| Severe                   | 2                      | 4                         |
| Intraocular lens precipitates | 0                   | 2                         |
| Late                     |                        |                           |
| Pupillary Membrane       | 0                      | 4                         |
| Posterior Synechia       | 0                      | 3                         |
| Optic capture            | 0                      | 3                         |

Some patients had more than one complications. Group A had mild to moderate fibrinoid reaction in 7 (17.5%) eyes on 1st postoperative day while 19 (49.75%) eyes of group B were having mild to severe fibrinoid reaction. All eyes with heparin infusion had no postoperative inflammation related complications such as precipitates over IOL surface, posterior synechia and optic capture. Seven (17.5%) of 40 eyes that underwent surgery without heparin had precipitates over IOL surface, pupillary membrane, posterior synechia and optic capture related to postoperative complication. None of the patients of either group developed cyclitic membrane. We did not observe intraoperative or postoperative complications attributed to heparin supplementation. All corneas in study and control group remained clear for the entire follow up period. We also did not observe adverse effects that may be attributed to heparin such as hyphema (Table-4).
Table no. 6 Grades of PCO in study group and control group at 1 month, 3 month, 6 month and 1 year

| Grade PCO | 1 month | 3 month | 6 month | 1 year |
|-----------|---------|---------|---------|--------|
|           | Group A | Group B | Group A | Group B | Group A | Group B | Group A | Group B |
| Grade 0   | 36      | 6       | 28      | 2       | 20      | 1       | 20      | 1       |
| Grade 1   | 4       | 8       | 5       | 5       | 6       | 1       | 6       | 1       |
| Grade 2   | -       | 6       | 3       | 5       | 4       | 3       | 4       | 3       |
| Grade 3   | -       | 8       | -       | 9       | -       | 10      | -       | 9       |
| Grade 4   | -       | 12      | -       | 15      | -       | 15      | -       | 15      |
| Total     | 40      | 40      | 36      | 36      | 30      | 30      | 29      | 29      |

The posterior capsule was examined with direct ophthalmoscope and graded with fully dilated pupil according to “snellman and lindstorm” slit lamp grading of PCO. At 1st month 36 (90%) patients in group A were having grade 0 PCO and no one was having grade 4 while in group B 12(30%) patients were having grade 4 PCO. Similarly at 1 year not even a single patient was having grade 4 PCO in group A while in group B, 15 (30%) patients were having the same (Table no. 5).

Postoperative Slit Lamp Photographs of Non-Heparinised Group

Aqueous Cells and Flare on D-1

Keratic Precipitates On D-7

Postoperative Slit Lamp Photographs of Heparinised Group

Aqueous Cells and Flare on D-1

IOL Deposits and Optic Capture
Discussion
The major challenge in case of high risk cataract surgery is severe postoperative inflammation with subsequent fibrin formation that is responsible for postoperative complications which can worsen the final visual outcome. Therefore new therapeutic approaches are being invented to prevent postoperative complications of high risk cases. Two factors which exacerbate ocular inflammation includes surgical trauma and foreign body reaction to the intraocular lens.\textsuperscript{2,3,10} Surgical trauma during surgery causes breakdown of blood aqueous barrier leading to augmented protein leakage and cellular reaction in the aqueous humor.\textsuperscript{1}

We minimized surgical trauma by avoiding touching the intraocular structures. Early use of systemic and topical corticosteroid and frequent instillation also decreased postoperative inflammation but they were used in both the groups in a similar manner. One skillfull surgeon performed all the surgeries using the same surgical technique and same type of PMMA (round edge) intraocular lenses. Thus the effect of two factors that could have resulted in trauma and induced inflammation were minimized.

Heparin is known to have anti-inflammatory effect. The use of heparin in ophthalmic surgery was first described by Johnson and co-authors.\textsuperscript{11} Iverson and coauthors demonstrated that an infusion of low molecular weight heparin inhibits the development of fibrin after lensectomy, vitrectomy and retinotomy in rabbits.\textsuperscript{13} Heparin has been shown to induce apoptosis in human peripheral neutrophils which may help in explaining its anti-inflammatory effect.\textsuperscript{14} Heparin also inhibits reactive oxygen species generation by mononuclear and polymorphonuclear leucocytes.\textsuperscript{15} In addition, heparin posseses anti-inflammatory properties through its ability to inhibit activation of the complement system.\textsuperscript{16-17} Enoxaparin was added to the infusion solution which has a potential to reduce the severity of postoperative fibrin formation after cataract surgery in the eyes prone to postoperative inflammation.

In our study the postoperative inflammatory response in high risk group was statistically milder, when enoxaparin was infused into the anterior chamber during surgery (group-A) until 7\textsuperscript{th} postoperative day. On day 1, 7 and 28 both cells and flare values were significantly lower in eyes with heparin infusion group (p<0.004) and were very similar to the flare values. Flare values were raised on 1\textsuperscript{st}, 3\textsuperscript{rd} and 7\textsuperscript{th} postoperative days in control group (P<0.003). Kruger A, Amon M et al
Investigated the influence of heparin sodium in irrigation fluid on postoperative inflammation. On day 1, 3 and 7 the flare values were significantly lower in patients who had received a heparin sodium infusion (p< .05), however there was no statistically significant difference between cell values in the 2 groups at any time.

Rumelt S, Stolovich C et al (2006) showed in their study that addition of LMW heparin in irrigating solution (40 mg/500ml) in paediatric cataract surgery results in decreased number of cells and degree of flare. 79% patients in their control group showed +2 to +3 grade cells and flare in comparison of 12% of study group.

In our study we found pigment and cell deposition along with fibrin in anterior chamber in 51.75% patients who were not heparinised while 17.5 % only in cases who were heparinised. Similarly Zetterstrom (1993) implanted conventional PMMA IOL and HSM IOL after extracapsular cataract extraction in 40 human eyes with exfoliation syndrome. Three months after surgery, they observed that pigment and cell deposits along with fibrin in AC were present in 43% patients with PMMA while only 16% in patients with HSM IOLS.

Bayramlar H, Totan Y et al (2004) demonstrated the effect of adding heparin sodium to the irrigating solution to prevent fibrinoid reaction and related long term complication after paediatric cataract surgery and they found that postoperative fibrinoid reaction and related complications such as synechiae, pupil irregularities and IOL decentration were present in 56% cases of control group while 12% cases of study group. Very similarly in our study 17.5 % patients of study group suffered from these complications in comparison of 68 % of control group.

Our finding agrees with those of Kohnen et al, who observed reduced inflammation in early postoperative days.

Heparin inhibits leucocyte migration and pigment deposition. Inflammatory cells originate from the uveal tissue enter the anterior chamber and are frequently found over IOL surface. We found that at 1st postoperative day group-A had no IOL precipitates over the anterior surface (p < .001) (Table-3). This may also explain decrease in late postoperative complications such as fibrin over the IOL, posterior synechiae, pupillary membrane and optic capture. Indeed in our study, these complications were absent in group-A treated with intraoperative heparin infusion while common in group-B without heparin infusion.

We also did not observe the side effects that may attribute to enoxaparin such as development of postoperative corneal opacity or hyphema. Rumelt S, Stolovich C also did not find any postoperative heparin related complications such as hyphema or decreased endothelial cell count.

Kruger A, Amon M et al in their study concluded that heparin sodium added to the standard irrigating solution reduces disturbances of blood-aqueous barrier in the early postoperative period but there seemed to be no long-term effect specially on PCO formation.

The anticoagulant effect of enoxaparin has long been known. Enoxaparin is composed of heparin fragments in different lengths. Heparin acts indirectly at multiple sites in both the intrinsic and extrinsic blood clotting systems. Heparin binds to antithrombin III to form heparin-AT complex. This inactivates a number of coagulation enzymes including thrombin factor IIa and IXa, Xa. Of these thrombin II a and factor Xa are most responsible for the result. As such it may decrease the postoperative intraocular inflammatory response by coagulation pathway and inhibit formation of a fibrin scaffold.

In addition to its anti-coagulant properties, heparin is known to have antiproliferative effects. It stabilizes the dividing lens epithelial cells at equators and prevents them to move onto the posterior capsule.

Kruger A, Amon M et al concluded in their study that there seemed to be no long-term effect specially on PCO formation with heparin. while Zaturinsky et al described reduced secondary
cataract formation following ECCE with heparin infusion solution, which was in concordance of our study. This effect of heparin may be due to it’s stabilizing effect on equatorial cells. None of our patients had grade 3 and 4 PCO in heparin infusion group. Our study agrees with Knorr et al\textsuperscript{5} who demonstrated antiproliferative effect in cultured bovine lens epithelial cells. Cataract surgery in high risk groups is associated with intense postoperative intraocular inflammation which can lead to sight-threatening complications.\textsuperscript{21} Early significant posterior capsular opacification is also a common occurrence in high risk cases. Both of these factors i.e. postoperative inflammation and PCO formation can compromise with visual acuity even after successful cataract surgery. In recent studies, it has been found that because of its antiinflammatory and antiproliferative action, use of heparin in irrigating solution during cataract surgery significantly reduces both early postoperative fibrinoid reaction as well as PCO.

Although the safety of cataract surgery has dramatically improved in past years, high risk cases are predisposed to an enhanced postoperative inflammatory response. Adding heparin sodium to the irrigating solution might help in controlling early postoperative inflammation after cataract surgery. In addition it is safe, economical, non-toxic, easily available and easy to use.

\textbf{Summary and Conclusion}

The results of study were as follows –

- The median age of the patients was 40 years with the highest number of patients in age group 30 – 39 yrs.
- Postoperative aqueous cell values were significantly lower in eyes with heparin infusion group (p<0.004) and were very similar to the flare values.
- Study group (A) had mild to moderate fibrinoid reaction in 17.5% eyes on 1\textsuperscript{st} postoperative day while 49.75% eyes of control group (B) were having mild to severe fibrinoid reaction which was statistically significant (p< 0.05).
- 17.5% eyes of control group had precipitates over IOL surface, pupillary membrane; posterior synechiae and optic capture as postoperative complications while study group was free from these inflammation related complications ( p < 0.04)
- We did not observe intraoperative or postoperative complications attributed to heparin supplementation in either group.
- At 6\textsuperscript{th} month, in group A no one was having grade 4 PCO while in group B 43% patients were having grade 4 PCO ( p < 0.003).

This study shows that infusion of low molecular weight heparin in irrigating solution (40 mg/500ml) is effective in minimizing postoperative inflammatory reactions, related complications and posterior capsular opacification after cataract surgery in high risk cases such as congenital, traumatic, complicated, diabetic cataracts and lens induced glaucoma without any significant side effects.

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