

ORIGINAL ARTICLE

EFFECT OF LOW-MOLECULAR-WEIGHT HEPARIN ON POSTOPERATIVE INFLAMMATION IN PHACOMORPHIC GLAUCOMA

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Background – Low-molecular-weight heparin (LMWH) has been shown to reduce the severity of postoperative inflammatory response. We decided to evaluate the specific effect of intraoperative LMWH in reducing the severity of postoperative inflammatory response after standard extracapsular cataract extraction and posterior chamber intraocular lens implantation in cases of phacomorphic glaucoma.

Methods – In a randomized, double-blind, clinical trial, 46 eyes (23 case eyes and 23 control eyes) were operated on by a single surgeon. In the first group, 5 IU/mL LMWH (Fragmin) was added to the irrigating fluid. Intraoperative and postoperative hemorrhage, degree of postoperative inflammation, fibrin and posterior synechiae formation, pigment deposits on the intraocular lens surface, visual acuity and intraocular pressure (IOP) were evaluated. The control group underwent a routine conventional surgery.

Results – The mean age was 68 years (standard deviation, 8.1; range, 63 – 79 yr). No statistically significant difference in age, sex, duration of operation and hospitalization, preoperative IOP, concurrent ocular and systemic illness, or smoking was found between the cases and controls. There was a statistically significant difference between the two groups in terms of density of cell and flare in anterior chamber, fibrin formation, pigment deposition over intraocular structure, and severity of postoperative inflammation. There was also a statistically significant difference in postoperative visual acuity between cases and controls (20/50 vs 20/125, respectively; $p = 0.001$). The incidences of intra- and postoperative hemorrhage were similar between the two groups ($p = 1.0$).

Conclusion – LMWH can be used safely in patients with phacomorphic glaucoma. In this study, it was positively correlated with reduced postoperative inflammation and fibrin formation, and gave rise to better visual acuity.

Keywords • glaucoma • low-molecular-weight heparin • phacomorphic
• postoperative inflammation

Introduction

Despite the progress in small incision cataract surgery and foldable intraocular lenses (IOLs), phacomorphic glaucoma is still a major problem in developing countries. In India, 3.91% of the patients undergoing cataract surgery present with this condition.¹ Even in developed countries, a significant number of patients have less than 20/200 vision

when operated on for cataract.²

This is mainly due to the general misbelief that cataract should be mature at the time of surgery to avoid complications.³ Lack of need for better vision, long hospital waiting lists for cataract surgery during economically difficult times, concurrent systemic disease and old age are among other reasons for patients not receiving treatment. Cataract surgery is the final treatment for phacomorphic glaucoma⁴ and has more complications compared to other conditions associated with cataract.⁵ One of the most common postoperative complications of phacomorphic cataract surgery is fibrinous uveitis.² Fibrin is an

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irregular semitranslucent mass which usually forms across the pupil, occluding it and cause blurred vision and reduction of the red reflex.⁵

The pathogenesis of postoperative fibrinoid inflammation is unknown. Any defect in the blood-aqueous barrier, possibly due to intraocular inflammation, preoperative high intraocular pressure (IOP), or excessive eye manipulation during surgery may lead to a disturbance in coagulation and fibrinolytic pathway.⁶ Heparin of molecular weight (MW) of 15,000 Daltons⁷ (Da) and its derivative, LMWH (MW < 7,000 Da)⁸ 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.⁵ LMWH has been used in animal and human models (clinical trials) at different concentrations.⁷ In this study, we investigated the antifibrin formation effect of LMWH in phacomorphic glaucoma, a condition associated with severe eye inflammation at high risk of fibrin formation after cataract surgery.

Patients and Methods

During a 6-month period (23 July 2000 to 23 January 2001), 56 patients with phacomorphic glaucoma were referred to our emergency ward. This group comprised 8.3% of admitted patients in the emergency ward and 1.7% of patients who underwent cataract surgery.

After providing informed consent, the patients were selected according to the following inclusion criteria: 1) diagnosis of intumescent lens glaucoma; 2) IOP > 21 mmHg; 3) shallow anterior chamber; 4) closed chamber angle; and 5) lack of any previous surgical or laser intervention. Vitreous loss during surgery qualified patients for exclusion from the study. Using a random numbers table, the 56 patients were assigned either to group A (active therapy) or group B (control). Fifty-six were drawn from the random numbers table and recorded consecutively. The first number belonged to the first patient, the second number to the second patient and so on, in the same order in which patients were admitted. If the number was an odd one, the patient would belong to group A. The even-numbered patients were assigned to group B and received placebo.

All patients were evaluated according to their age, sex, history of smoking, visual acuity of both

eyes, duration of corneal edema, ocular congestion, IOP on arrival, and any associated systemic or ocular illness. All patients were given mannitol (1g/kg), oral acetazolamide 500 mg initially, and 250 mg every 6 hours thereafter for maintenance; atropine (1% eyedrops) four times a day; betamethasone (0.1% eye drops) every 2 hours; and timolol 0.5% twice a day.

One hour prior to surgery, the pupil was dilated with mydriatic solutions (mydriacil and phenylephrin) and, according to the random seed table, the patients were randomly assigned to either the treatment group or the control group.

For the treatment-group patients, 5 IU/mL of LMWH (Fragmin™, Farmacia INC, Sweden) was added to the irrigation fluid. Control-group patients received only balanced salt solution (BSS). One surgeon performed all of the operations for both groups using the standard method: extracapsular cataract extraction (ECCE) plus posterior chamber intraocular lens (PCIOL) implantation.

Intraocular lenses used were all from Opsia, Saphir (Chauvin Opsia SA, Labege Cedex, France). Postoperatively, the patients received chloramphenicol eye drops every 6 hours for one week and betamethasone eye drops every 2 hours for at least 3 weeks. In patients who developed a fibrinoid reaction, homatropine eye drops 2% was also added to the regimen (the dosage and the duration of therapy were decided by the surgeon; one drop every 8 hours for about 7 days).

Preoperative intraocular hemorrhage, duration of the operation, and any extensive manipulations (sphincterectomy, sector peripheral iridectomy) were all recorded. After surgery, the extent of fibrin formation was observed and graded as 1⁺ if one quadrant was involved in a 5-mm dilated pupil; 2⁺ for two quadrants, 3⁺ for three quadrants, and 4⁺ for involvement of all four quadrants. During a mean follow-up of 2 months, the duration of symptoms and use of homatropine 2%, visual acuity, pigment deposits on the IOL, and synechiae of the iris to the IOL were recorded.

Data were analyzed by SPSS 9 (SPSS Inc, Chicago, Illinois, USA) and tested by Fisher's exact test. The two groups were compared for intraocular inflammation and postoperative hemorrhage according to the severity of fibrin formation and size of blood clot. Heparin-surfaced IOLs have been used successfully in patients with uveitis and cataract by different investigator.

Table 1. Comparison of fibrinous reaction between the low-molecular-weight heparin and control groups after surgery for phacomorphic glaucoma.

Group	Fibrin formation grade					Total
	0	1	2	3	4	
Heparin group, no. (%)	18 (78.3)	4 (17.4)	1 (4.4)	0	0	23
Control group, no. (%)	0	4 (17.4)	10 (43.5)	8 (34.8)	1 (4.3)	23
Total, no. (%)	18 (39.1)	8 (17.4)	11 (23.9)	8 (17.4)	1 (2.2)	46 (100)

Results

The mean age of the patients in the LMWH group was 70 years (\pm standard deviation [SD] 8.3 yr) and in the control group was 67.3 years (\pm 7.9 yr). Thirty percent of patients in the first group and 33% in the second group were males. The mean duration of hospitalization before the surgery was 6.6-hours for the LMWH group and 8.6-hours for the control group. Forty-two percent of the LMWH group and 57.1% of controls were smokers. Nine patients (16%) were operated on using local anesthesia, three among the LMWH group and six in the control group.

Two patients were one-eyed. Visual acuity in the involved eye was light perception in 69.6% and hand motion in 30.4% of cases. In 54.3% of cases, the right eye was involved.

Initial symptoms had started 8.08 days before surgery in the LMWH group and 5.43 days before in the control group. The mean IOP before medical treatment and surgery was 43.3 and 17.8 mmHg for the cases and 45.2 and 18 mmHg for the control group. Before the operation, corneal edema was significantly more severe in the control group, $p = 0.01$. Hyphema was nearly equal in both groups, during and after the operation.

Regarding fibrin formation (Table 1), 78.3% of the patients in the LMWH group had no fibrinoid reaction, and the remainder had grades 1⁺ to 2⁺. In all patients in the control group, fibrin formation was significant ($p = 0.0005$).

The amount of cells in the anterior chamber was, on average, 1 – 3⁺ in the LMWH group and 2 – 4⁺ in the control group ($p = 0.003$; Table 2).

Table 2. Comparison of cells in anterior chamber (AC) between heparin and control groups after surgery in phacomorphic glaucomatous patients.

Cell in AC / groups	Anterior chamber cell grading				Total
	1	2	3	4	
Heparin group, no. (%)	15 (65.2)	7 (30.40)	1 (4.3)	0	23
Control group, no. (%)	2 (8.7)	10 (43.5)	9 (39.1)	2 (8.70)	23
Total, no. (%)	17 (37)	17 (37)	10 (21.7)	2 (4.3)	46 (100)

Regarding the presence of flare in the anterior chamber (Table 3), among those in the LMWH group, there was less corneal edema ($p = 0.03$).

Two weeks after surgery, corneal edema had disappeared in all patients. Hyphema was equally formed in both groups (3 in the LMWH group; 2 in the control group).

On average, posterior synechiae were present at 7.8° in the LMWH and at 63° in the second group ($p = 0.01$).

A patient with long-standing (> 3 wk) phacomorphic glaucoma developed extensive peripheral anterior synechiae and high IOP postoperatively, who was successfully controlled by medications.

The intraocular inflammation (fibrin, flare and cells) subsided within a week in 95.7% of the heparin and 26.1% of the control group ($p = 0.0005$).

Homatropine 2% drops was used in 8.7% of the LMWH and 78.3% of the control-group patients ($p = 0.0005$). In the control group, homatropine was used for a longer period and more frequently (Table 4).

Discussion

LMWH at a concentration of 5 IU/mL has beneficial effects in the surgery of phacomorphic glaucomatous patients by inhibiting fibrin formation and reducing ocular inflammation. The rate of fibrin formation, postoperative cells and flare in the anterior chamber, pigment deposits on the IOL, and posterior synechiae were all reduced in LMWH-group patients, and there was no

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Table 3. Comparison of flare at the anterior chamber between low-molecular-weight heparin (LMWH) and control -group patients after surgery for phacomorphic glaucoma.

	Flare-plus grade				Total
	0	1	2	3	
Heparin group, no. (%)	7 (34.4)	15 (65.2)	1(4.3)	0	23
Control group, no. (%)	0	5 (21.7)	10 (43.5)	8 (34.8)	23
Total, no. (%)	7 (15.2)	20 (43.5)	11(23.9)	8 (17.4)	46 (100)

increase in the rate of pre- and postoperative bleeding. Postoperative visual acuity has been better in the LMWH group. Because there was a lower rate of postoperative inflammation in LMWH group, homatropine eye drops were used less frequently, but the two groups were similar for postoperative corneal edema. In a similar study by Iverson et al concerning the effect of LMWH on corneal edema,⁸ there was also no significant difference between their LMWH and control groups. Johnson et al have been successful in controlling fibrin formation in patients with advanced proliferative vitreoretinopathy who had undergone deep vitrectomy. In their study, ordinary heparin at 10 IU/mL was used, which led to more frequent intraocular hemorrhage.⁷ However, at the lower concentration of 5 IU/mL, there was no more hemorrhage than in the control group.⁷

Xin et al in China used 25 IU/mL of ordinary heparin for cataract surgery and observed less fibrin and pigment deposits on the lens, and the patients had better final vision.⁹ The group observed two hyphemas among 25 surgical patients who received heparin. It seems that the type and concentration of heparin are responsible for the occurrence of pre- and postoperative intraocular hemorrhage. The anticoagulant activity of LMWH is higher than ordinary heparin and, consequently, less hemorrhage occurs.⁵ This has been well demonstrated in patients with deep vein thrombosis who receive heparin.⁵

Iverson et al suggest that Fragmin at a

concentration of 5 IU/mL lowers the risk of hemorrhage during vitreoretinal and lensectomy surgeries.⁸ It has been shown that LMWH 2 IU/mL is not effective in preventing fibrin formation.⁵ Fibrin is more easily formed in diabetic patients undergoing surgery, and in deep vitrectomy, iris surgery, existence of silicone in the eye, glaucoma, uveitis and pseudoexfoliation.⁶

Phacomorphic glaucoma patients can obtain good vision, if operated on in time. The mean vision of 93 surgical patients in India has been reported at 5/10,¹⁰ and there is even a report on a controlled capsulorhexis and phacoemulsification with insertion of PCIOL in the bag, in Rao and Padmanabhan's patients.¹¹ Therefore, it is advised to use LMWH of 5 IU/mL concentration to prevent fibrin formation and complications such as IOL luxation, pupillary block glaucoma, low vision, photophobia, dysfunction of the iris, cornea and iridocorneal angle, and for long-term use of corticosteroids and mydriatics.⁶

The reason for intense fibrin formation in our control group (Table 1) might be the shorter interval between the appearance of symptoms and the surgery (mean duration, 7.6 hr). In other studies, this interval has been longer.² In McKibbin et al's study, among patients who were operated after a mean duration of 6 days, fibrinoid reaction was observed in 40% of cases.²

IOP was controlled in all of our patients, after surgery, except for one patient who needed postoperative medical treatment.

Prajna and Ramakrishnan showed that, if vision

Table 4. Postoperative findings.

Finding	Treated group	Control	p Value
Flare	$69.6\% \leq 1^+$	$67.4\% \geq 2^+$	0.0005
Visual acuity postoperative	20/50	20/125	0.01
No. of pigment deposits on IOL	3.2	15	0.01
Mean postoperative intraocular pressure	14.2 ± 3	13.2 ± 1.7	0.082
Need to use homatropine	8.7%	7.8%	0.0005

IOL: Intraocular lens

is certain.¹⁰

Regarding the relatively high incidence of phacomorphic glaucoma lasts more than 5 days, cystoid macular edema with resultant decreased phacomorphic glaucoma in our country, LMWH is a good option to prevent or decrease the rate of postoperative inflammation and related complications.

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