

The role of heparin sodium in the prevention of capsular opacification after phacoemulsification

Thesis submitted for partial fulfillment of MD Degree in ophthalmology

By

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2008

ABSTRACT

Purpose: To evaluate the effectiveness of heparin containing irrigating solution in preventing capsular opacification and improving postoperative visual outcome after phacoemulsification.

Patients and methods: a prospective study was conducted on 50 eyes of 50 patients who had undergone cataract extraction by phacoemulsification . Patients were divided into two groups. Group one received heparin sodium 10 IU/ml on the irrigating solution during phacoemulsification , as for group two (25 pateints) the irrigating solution used was lactated ringer solution without heparin sodium and this group was considered the control group. Hydrodynamic polishing was conducted in all cases. Analysis of the grade and severity of PCO was done using two methods: Sellman and Lindstrom grading system and POComan software system.

Results: This study proved that heparin sodium is effective in delaying rather than completely preventing PCO . This was evidenced by the fact that the average BCVA in the first month was 0.71 ± 0.056 in group 1 and 0.54 ± 0.037 with p value 0.006 which was statistically highly significant while later on(after sixth month) the average BCVA was 0.67 ± 0.042 in group 1 and 0.54 ± 0.022 in group 2 with a p value 0.01 which was statistically significant. This data may suggest that in a longer follow up duration, this difference may vanish. This study also showed the role of heparin sodium in lowering the postoperative IOP, or at least preventing postoperative acute elevation of IOP. The average postoperative IOP(1st day) in group 1 was $14.6 \text{ mmHg} \pm 6.1$ which was significantly lower than the average preoperative IOP which was $16.7 \text{ mmHg} \pm 15.25$.however this effect was very transient lasting for less than one week and thus is of no benefit in hindering IOP elevation during Nd:YAG capsulotomy. Also this study showed that POComan analysis system is user friendly, reproducible, cheap and easy to use.

Conclusion:This study had shown the role of heparin sodium in delaying rather than preventing posterior capsular opacification. This effect per se is beneficial as the latter the YAG capsulotomy the less the complications it may result in.

Key words: PCO, ACO, POComan analysis system, heparin sodium, pharmacological prevention of PCO.

ACKNOWLEDGEMENT

First of all thanks to **God** the most merciful and giving, for making me able to accomplish this work.

I would like to express my gratitude to Prof. Dr. **Magdah salah el Dein Abdelaziz**, for her step by step supervision and revision of this work.

I would also like to express my sincere feeling of thank to Prof. Dr. **Hala Saad el Dein Ahmed** for her continuous guidance , care and support.

No words can express my gratitude to dear **Prof Dr Ahmed Mostafa Abdelrahman**, for teaching me a lot both in and outside this work. I feel proud to be one of his students.

I would like to express my appreciation and gratitude to Prof. Dr. **Effat Ali Abdelnabi**, head of ophthalmology department and our department all through this work , who first made me interested in ophthalmology, who taught me everything I know in life, and who gave me a higher example to try to achieve.

I would also like to express my deepest sense of gratitude to my father General Major Prof. Dr. **Maher Sami**, for his relentless and continuous push to make the best of me.

I would like also to express my thanks to all my colleague , friends and members of my family for their continuous support and care.

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INTRODUCTION

Capsular opacification is the most common postoperative complication that faces cataract surgeons and affects the resultant visual acuity, it may also cause glare or give rise to monocular diplopia. It occurs in the form of anterior or posterior opacification. (*kanski, 2003*).

One of the factors that play a role in the pathogenesis of capsular opacification is the break of blood ocular barrier with release of inflammatory mediators and cells into aqueous humor. These cells may precipitate on the anterior and posterior capsule resulting into anterior and posterior capsular opacification.(*Saxby,1999*).

Prevention of posterior capsular opacification (PCO) is a highly challenging issue. Measures to prevent capsular opacification can be divided into two categories. One strategy is to minimize the number of retained lens epithelial cells [LECs] and cortex through cortical cleanup. The second strategy is to prevent the remaining LECs from migrating posteriorly. This can be achieved by surgical prevention, IOL design and material, pharmacological and physical prevention.(*Pandey et al , 2004(a)*).

Pharmacological methods of capsular opacification prevention such as 5 fluorouracil, octreotide, mitomycin, and EDTA may have a role in preventing capsular opacification but they are potentially toxic with a lot of expected complications (*Nishi, 1995; Cochener et el,2003*)

Heparin sodium showed to inhibit capsular opacification , specially the fibrous type through the following mechanism:

- Inhibiting proliferation of anterior epithelial cells.
- Preventing formation of cellular membranes , which is an essential for chemotactic attraction of inflammatory cells.
- Prevent adherence of inflammatory cells that prevent fibrinous film formation. (*Mastropasqua et al, 1997*)

Several factors in PCO prevention have been identified (*Vargas et al,2002*). among the surgical factors, hydrodissection enhanced cortical clean up is the most important (*Peng 2000*). It has been demonstrated that hydrodissection using balanced salt solution or lactated ringer is an effective , practical and inexpensive method for cortex removal, but alone it does not completely eliminate lens epithelial cells LECs. (*Vargas et al,2003*).

The use of heparin is recommended in pediatric cataract surgery. The use of heparin in the irrigating solution may decrease the incidence of acute inflammatory response and postoperative fibrous PCO. (*Zaturinsky et al, 1990*). Heparin added to the standard irrigating solution reduced disturbances of the blood aqueous barrier in the early postoperative period. Infusion of heparin during cataract surgery may minimize the postoperative inflammation and reduce the number of postoperative inflammatory related complications including PCO .(*Rumelt et al,2006*). Intracameral administration of heparin during surgery, has an inhibitory effect on secondary cataract formation in rabbit eyes(50% reduction in incidence of PCO).(*Zaturinsky et al,1990*).

Transforming growth factor (TGF-) plays an important role in the cell biology of PCO. It is a serine-threonine kinase and a member of a member of a superfamily of growth factors which has diverse effects on the growth and differentiation of many cell types.(**Massague,1990**). Basic fibroblast growth factor (b-FGF) is a polypeptide which influence the proliferation and differentiation of many cells, it binds heparin which is necessary for recruitment to its receptors on the cell surface and action. (**Burgess and Maciag,1989**).

In addition to the well known anticoagulant activity , heparin has anti inflammatory and antiproliferative properties (**Nelson et al,1993**).Experimental and clinical studies demonstrate the antiproliferative effect of heparin on lens epithelial cells and its additive effect to prevent PCO(**Nelson et al,1993; Bayramlar et al,2004**) .

AIM OF THE WORK

To evaluate the effectiveness of heparin containing irrigating solution in preventing capsular opacification and improving postoperative visual outcome after phacoemulsification.

ANATOMY

THE LENS CAPSULE

The lens capsule is the ensheathing elastic basement membrane that helps to maintain epithelial cells and lens fibers as one unit. It acts as a semi-permeable membrane that allows the passage of small molecules into and out of the lens. The lens capsule is the thickest basement membrane in the body as it is continuously produced throughout life. The capsule is produced anteriorly by the basal membrane of the epithelial cells while posteriorly it is produced by the basal membrane of elongating fiber cells. The thickest region of the capsule is located just anterior and posterior to the equator (up to 23 microns). The thinnest area is that of the posterior pole (4 microns).(*Forrestre et al, 1996*).

By light microscope the capsule is homogenous, transparent membrane that under polarized light appears birefringent indicating a lamellar structure. (*Seland, 1992*).

The capsule is basically formed of type IV collagen but also contain type I and III collagens in addition to other extracellular matrix components as laminine, fibronectin , heparin sulphate proteoglycan ,entactin and vitronectin (*Dische and Zelmenis , 1965;Lisa,1999*).

EPITHELIAL CELLS

The lens epithelium arises as a single layer of cells beneath the anterior capsule and extending to the equator of the lens (figure 1). There is no corresponding posterior layer since the posterior embryonic epithelium is involved in the formation of the primary lens fibers. (*Anthony et al., 1997*).

The central cells are located near the anterior pole. They are polygonal with rounded nuclei that show no mitotic figures except when stimulated mechanically. Peripheral to the central cells, the cells become smaller and more cylindrical. Mitosis is occasionally seen. The pre-equatorial and equatorial cells are the major site of cell division although mitotic figures are still rare. From these cells new cells migrate posteriorly to form lens fibers. **(Bron et al, 1997).**

By electron microscope the epithelial cells show few organelles as rough endoplasmic reticulum, Golgi apparatus, free ribosomes and small mitochondria lying in coarse granular cytoplasm. Elements of cytoskeleton are present in the equatorial cells. Cytoskeletal proteins are formed including actin, vimentin, microtubular protein, spectrin and myosin. **(Yeh et al, 1986; Rafferty and Scholz, 1989;).**

The basal surface of the epithelial cells adheres to the capsule. The rest of the cell membrane is relatively complex. The lateral margin shows undulations whereas the apical membrane shows interdigitations with the underlying lens fibers. The cells are attached to each others by desmosomes and to the underlying capsule by hemidesmosomes. Gap junctions lie between the cells allowing free movement of small molecules. **(Bron et al, 1997).** With age the height of the epithelial cells decreases and the width increases. No anatomical features of the epithelium exist that influence surgical technique, but all ophthalmic surgeons recognize that the epithelium is exquisitely sensitive to trauma as during cataract extraction. **(Chylack, 1995).**

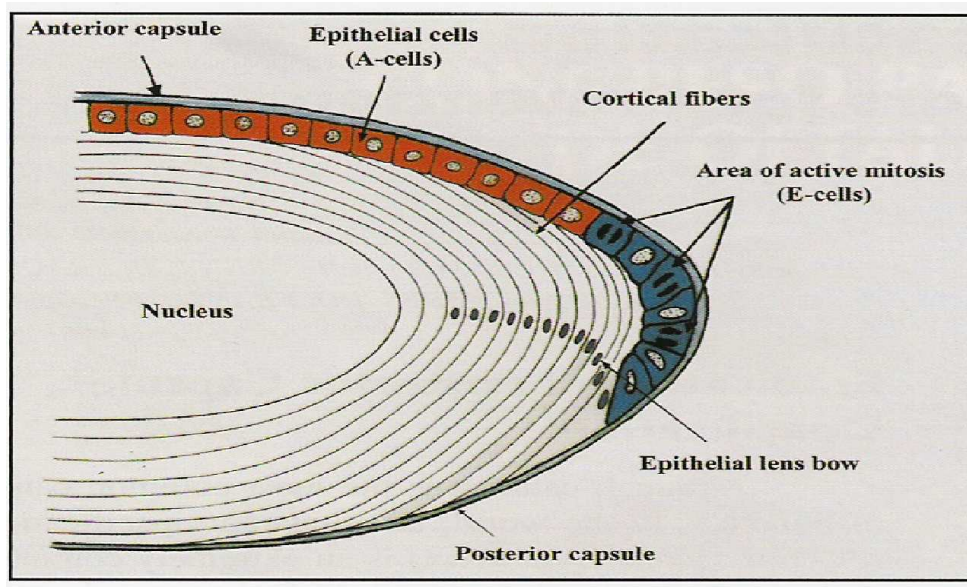


Figure (1): Anatomy of the anterior and posterior capsule. A cells: anterior subcapsular cells. E cells: equatorial cells. (Pandey et al, 2004 (a)).

PATHOGENESIS

Capsular opacification is a misnomer as it is not really an opacification of the lens capsule but an opaque material that lines the capsule rendering it non transparent. **(Pandey et al 2004 (b))**. This opaque material could be:

- 1 Capsular remnants.
- 2 Capsulolenticular remnants.
- 3 Inflammatory or haemorrhagic elements. **(Powe et al, 1994)**.

The pathogenesis of capsular opacification is multifactorial. . **(Ram et al, 2003)**. It has been found that anterior epithelial cells undergo fibrous metaplasia whereas equatorial cells proliferate and migrate. **(Apple et al, 1992)**.

Normally no cells line the posterior capsule. Pathological cells lining the capsule in posterior capsular opacification are either epithelial cells or fibrocytes. **(Nagamato et al, 1992)**.

The anterior lens epithelium proliferates onto the posterior capsule at the site of apposition of the anterior capsule flaps to the posterior capsule .The contraction caused by the myoblastic features, acquired through fibrous metaplasia produces wrinkling of the posterior capsule. **(McDonnell et al, 1983)**.

Postoperative lens epithelial cell proliferation is also involved in the pathogenesis of other entities. These include anterior capsular opacification (ACO) and interlenticular opacification (ILO), a more recently described complication related to piggyback IOLs. Thus there are three distinct anatomic locations within the capsular bag where

clinically significant opacification may occur postoperatively. (**Werner et al, 2002**).

Another factor in the pathogenesis of capsular opacification is the breakdown of blood ocular barrier with release of inflammatory mediators and cells into the aqueous humour. These cells may precipitate on the anterior and posterior capsule resulting into anterior and posterior capsular opacification. (**Saxby, 1999**). Pigmentations arising from the posterior surface of the iris and ciliary body may also play a role in posterior capsular opacification. (**Saxby et al, 1998**).

Delayed localized endophthalmitis is another condition that may lead to capsular opacification. (**Clayman and Jaffe, 1988**). Apoptosis, programmed cell death, was found in residual epithelial cells after cataract extraction. Apoptosis can be induced by many cell surface-specific factors as withdrawal of cytokines, growth factors and ultraviolet radiation. (**Nishi et al, 1996**).

Certain chemical substances play a role in the pathogenesis of capsule opacification namely: Cytokines: peptides secreted from cells. (**Duncan et al, 1997**). Transforming growth factor –beta [TGF-b]: promotes cellular adhesions and hyperplasia. (**Hynes, 1987**). Hepatocyte growth factor [HGF]: secreted by mesenchymal cells influencing migration of epithelial cells (**Grierson et al, 2000**). Osteopontin: extracellular matrix (**Saika et al, 2003**). Fibroblast growth factor [FGF]: increases epithelial mitosis. (**Nishi et al, 1996**).

PATHOLOGY

Pathological types of capsular opacification include:

1. Elschnig pearls.
2. Soemmering's ring.
3. The fibrous type.
4. Anterior capsule contraction syndrome. (Capsular phimosis).
5. Lentoid of Theil.
6. Capsular changes.

Each pearl (figure 2) develops as a result of epithelial cell failing to differentiate into a lens fiber thus pearl shows a mixture of the characteristics of cells and fibers. They arise from equatorial cells however anterior capsular epithelium may be involved. The mass of cells resembles the Wedle cells of cataract. (*Saxby, 1999*).



Figure (2): Elshnig pearls. (www. Redatlas.com)

Development of posterior capsular opacification (PCO) is a very dynamic process that includes not only growth of preexisting structures and occurrence of new Elschnig pearls , but also reorganization and even disappearance of pearls within a short time period (2-4 weeks). The latter in

particular is not well known but has been reported. (*Buehl et al, 2005(b)*).

Soemmerrings' ring is formed after cataract extraction when the remaining of the anterior capsule becomes attached to the posterior capsule by fibrous tissue. The trapped cortical fibers and epithelial cells keep on growing by the proliferation and differentiation of the equatorial cells into lens fibers . Some cells may escape the ring and migrate on the anterior surface of the anterior capsule. (*Saxby, 1999*).

The fibrous type (figure 3) occurs when the residual anterior capsular epithelium undergoes metaplasia and changes into fibroblasts that proliferate and migrate on the posterior capsule. On contracture they form wrinkles in the posterior capsule. (*Saxby, 1999*).

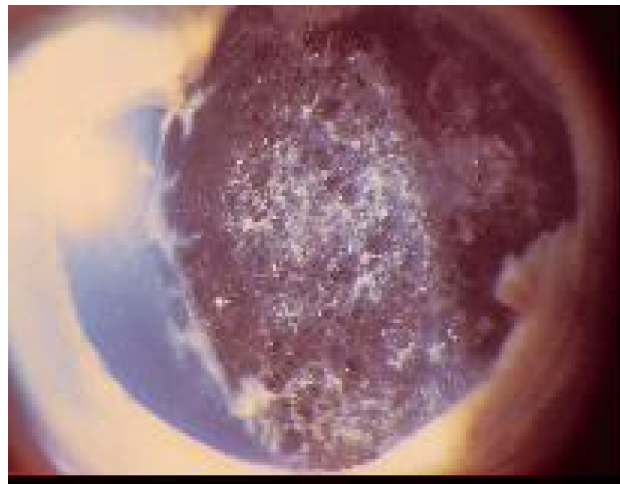


Figure (3): The fibrous type of PCO. (www.redatlas.com)

Anterior capsular contraction syndrome (figure 4) occurs when residual lens epithelial cells proliferate and undergo fibrous metaplasia resulting into reduction of the overall capsular bag size and anterior opening narrowing. (*Kimura et al, 1998*).