Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: The Moorfields Safer Surgery System: new techniques revolutionise glaucoma surgery.

1. Summary of the impact (indicative maximum 100 words)

Glaucoma is the commonest cause of irreversible blindness world-wide and, in many parts of the world, surgery to create a new drainage channel is the only practical treatment. The commonest cause of surgical failure is scarring, and the use of injections of cytotoxic agents prevents scarring but has many complications. Our research identified how convenient single 5-minute treatments with cytotoxic drugs work and led us to carry out pilot and randomised trials, which showed they reduced post-operative scarring. Combined with other refinements of surgical technique (named the Moorfields Safer Surgery System) this has improved outcomes of glaucoma surgery world-wide.

2. Underpinning research (indicative maximum 500 words)

Glaucoma affects approximately 70 million people world-wide, of whom 7 million are blind. A key risk factor for the development and progression of glaucoma is increased intraocular pressure. A surgical approach to this problem is to create a drainage pathway for fluid to escape which in turn lowers intraocular pressure. The most important cause of failure of these so-called filtration surgery procedures is scarring of the drainage pathway under the conjunctiva, the thin membrane that covers the white of the eye.

Research in the early 1990s at the UCL Institute of Ophthalmology developed in vivo cell culture models of the ocular wound healing process. This led to the discovery that very short (five minute) applications of anticancer agents including 5-fluorouracil (5-FU) and mitomycin-c (MMC) had long lasting effects on ocular fibroblasts that were responsible for scarring after surgery **[1]**. A series of intracellular protective events including the expression of p53 were associated with the cells going into long term cell growth arrest but not death. At that time 5-fluorouracil was given clinically, as a series of 14 painful injections around the eye in the first two weeks after surgery. Our experiments suggested that an equivalent effect could be achieved with a single inexpensive five-minute painless exposure at the time of surgery. We then developed a much more consistent and predictable model of glaucoma surgery in the rabbit and used this to establish that a single administration of 5-FU was equivalent to seven injections in terms of accumulation of scar tissue and cellularity and functioning of the drainage area. We also carried out a series of experiments which clarified the principles of focal, titratable long term inhibition of scarring in the subconjunctival area **[2]**.

We then carried out the world's first pilot human trials with five minute exposures to 5-FU which strongly suggested that this treatment (which costs just £1) is efficacious **[3]**. We undertook further randomised trials with colleagues in in Africa **[4]** and Asia **[5]** which showed that 5-FU was effective in reducing scarring after glaucoma filtration surgery.

The principles of how to use of anticancer agents including the associated surgical technique were further developed, based on our early studies and clinical observation, into the Moorfields Safer Surgery System. **These principles of which are now used around the world to make surgery much safe**r than in the past **[6].**

3. References to the research (indicative maximum of six references)

[1] Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz G, McGorray S. Prolonged localized tissue effects from 5-minute exposures to fluorouracil and mitomycin C. Arch Ophthalmol. 1993

Feb;111(2):263-7. http://dx.doi.org/10.1001/archopht.1993.01090020117035

[2] Khaw PT, Doyle JW, Sherwood MB, Smith MF, McGorray S. Effects of intraoperative 5-fluorouracil or mitomycin C on glaucoma filtration surgery in the rabbit. Ophthalmology. 1993 Mar;100(3):367-72. Copy available.

[3] Lanigan L, Stürmer J, Baez KA, Hitchings RA, Khaw PT. Single intraoperative applications of 5-fluorouracil during filtration surgery: early results. Br J Ophthalmol. 1994 Jan;78(1):33-7. http://dx.doi.org/10.1136/bjo.78.1.33

[4] Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. Br J Ophthalmol. 2001 Sep;85(9):1028-30. http://dx.doi.org/10.1136/bjo.85.9.1028

[5] Wong TT, Khaw PT, Aung T, Foster PJ, Htoon HM, Oen FT, Gazzard G, Husain R, Devereux JG, Minassian D, Tan SB, Chew PT, Seah SK. The singapore 5-Fluorouracil trabeculectomy study: effects on intraocular pressure control and disease progression at 3 years. Ophthalmology. 2009 Feb;116(2):175-84. http://dx.doi.org/10.1016/j.ophtha.2008.09.049.

[6] Jones E, Clarke J, Khaw PT. Recent advances in trabeculectomy technique. Curr Opin Ophthalmol. 2005 Apr;16(2):107-13. http://www.ncbi.nlm.nih.gov/pubmed/15744141

4. Details of the impact (indicative maximum 750 words)

Glaucoma affects 70 million people worldwide, of whom seven million are blind. It is the commonest cause of irreversible blindness in the world, and the commonest neuropathy in the world. There are no well-established figures for the number of glaucoma surgeries which are carried out globally. However, based on relatively conservative figures it is likely that more than 2% of glaucoma sufferers will require surgery during their lifetime – that is around 1.4m individuals. Our work has improved treatments – both pharmacological and surgical – for these patients, enabling the surgery to be used more widely and with greater success.

1) Intraoperative application of 5-FU

The use of 5-Fluorouracil (5-FU) to modify the wound healing in glaucoma surgery was first investigated in the early 1980s, with the treatment initially consisting of a series of post-operative injections. Our work established that a single intra-operative application of 5-FU can be used with the same effect. The benefits to patients are a reduction in the number of visits, and reduction in discomfort or pain from the injections. There is also a reduced cost, which has enabled the treatment to be extended widely, particularly in developing countries. A recent Cochrane review (2009 update) stated that "*Clinicians now appear to prefer the intra-operative application of agents for the modification of wound healing and routine postoperative injections of 5-FU are now rarely used*" **[a]**.

Our work is referenced extensively in the European Glaucoma Society's guidelines on use of 5-FU in glaucoma surgery, which recommend a five-minute sponge exposure for intra-operative use **[b]**. Intra-operative use of 5-FU is also recommended in Asia-Pacific glaucoma guidelines, which also specifically reference our work with regard to mode of application and surgical techniques **[c]**.

2) Improved surgical techniques

Glaucoma surgery has in the past had significant complications, including soft eye with bleeding and visual loss, and late infections from thin areas of fluid drainage associated with the surgery. Previously, virtually all of these complications would increase with the use of anticancer agents. The principles learnt from our earlier cell culture and in vivo experiments enabled us to establish how these agents worked as local applications and thus develop the Moorfields Safer Surgery System. This consists of several simple changes to surgical techniques, and the development of improved components which dramatically reduced the incidence of potentially blinding

complications. The incidence of infection of the drainage area due to thinning varies from 6% to 20% in three- to five-year follow up. This is reduced to approximately 0.5 -1% with the wide area anticancer treatment technique in the Moorfields system **[d]**.

A review of clinical practice in 2011 stated that: "*While complications are a risk, modern glaucoma surgery techniques as developed by Khaw and colleagues have greatly reduced the risk of both intra- and postoperative complications*" **[e]**.

One of the main benefits to the Moorfields Safer Surgery system is that the techniques described are relatively inexpensive and can be accessed by most surgeons around the world including those from the poorer countries. This has enabled the system to spread widely, and it is now the standard technique used around the globe **[f]**.

We have distributed information about this techniques free online **[g]**, and the system has reached all continents. Khaw has given many invited lectures in the USA, South America, Africa, India, South East Asia and Australia to highly receptive audiences, who have in turn spread the Moorfields Safe Surgery system. One surgeon from the All India Institute of Medical Sciences, who was trained in our techniques in 2005, now reports that "*Currently all residents and fellows that pass from our university are trained in the Moorfields Safe Surgery System… This system is now being adopted across all major ophthalmic centres in our country and also in south east Asia. The Moorfields Safe Surgery system has significantly impacted both general ophthalmologists and glaucoma specialists, improved the standard of care and also the quality of life of glaucoma patients across India*" **[h]**.

In addition, Khaw has worked with a UK commercial company, Duckworth & Kent, to develop a comprehensive set of instruments which can be used in line with the Safer Surgery System **[i]**.

The complications of trabeculectomy surgery have improved considerably since the UK national survey of trabeculectomy 15 years ago. Early complications occurred in 46.6% and late complications in 42.3%. With the Safer Surgery System and 5-FU there were no cases of endophthalmitis, hypotonous maculopathy, retinal detachment or blindness. Studies around the world have found similar improved outcomes using our protocols which is of direct relevance to many hundreds of thousands of individuals across the world **[j]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] Wormald R, Wilkins MR, Bunce C. Post-operative 5-Fluorouracil for glaucoma surgery. Cochrane Database Syst Rev. 2001 http://dx.doi.org/10.1002/14651858.CD001132

[b] European Glaucoma Society guidelines. http://www.eugs.org/eng/EGS_guidelines.asp. See section 3.6

[c] Asia-Pacific Glaucoma guidelines. http://www.apglaucomasociety.org/toc/APGGuidelinesNMview.pdf

[d] Wells AP, Cordeiro MF, Bunce C, Khaw PT. Cystic bleb formation and related complications in limbus- versus fornix-based conjunctival flaps in pediatric and young adult trabeculectomy with mitomycin C. Ophthalmology. 2003 Nov;110(11):2192-7. http://dx.doi.org/10.1016/S0161-6420(03)00800-5

[e] King AJ, Stead RE, Rotchford AP. Treating patients presenting with advanced glaucoma--should we reconsider current practice? Br J Ophthalmol. 2011 Sep;95(9):1185-92. http://dx.doi.org/10.1136/bjo.2010.188128

[f] Corroborating testimonies provided by:

- Professor of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of

Medicine. Copy of letter available on request.

- Head of Ophthalmology, University of Melbourne / Managing Director, Centre for Eye Research Australia. Available on request.

[g] http://www.ucl.ac.uk/ioo/research/khawlibrary and see also www.glaucomatoday.com/art/0305/0305sp.pdf

[h] Corroborating letter from Professor of Ophthalmology, Dr. Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences. Copy available on request.

[i] http://www.duckworth-and-kent.com/products/feature_Khaw.asp

[j] Examples of studies showing improved outcomes using our protocols:

- Gruber D. Trabeculectomy according to P. Khaw's protocol: medium-term results.J Fr Ophtalmol. 2008 Jan;31(1):17-22. http://www.ncbi.nlm.nih.gov/pubmed/18401294

- Shah P, Agrawal P, Khaw PT, Shafi F, Sii F. ReGAE 7: long-term outcomes of augmented trabeculectomy with mitomycin C in African Caribbean patients. Clin Experiment Ophthalmol. 2012 May-Jun;40(4):e176-82. http://doi.org/bvmkjd

- Solus JF, Jampel HD, Tracey PA, Gilbert DL, Loyd TL, Jefferys JL, Quigley HA. Comparison of limbus-based and fornix-based trabeculectomy: success, bleb-related complications, and bleb morphology. Ophthalmology. 2012 Apr;119(4):703-11. http://doi.org/fznpcm