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CLINICAL STUDY

Beta irradiation: new uses for an old treatment: a review

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Abstract

Beta radiation has a long history as a treatment modality in ophthalmology. It is a convenient and practical method of applying radiation and has the advantage of minimal tissue penetration. There has been a recent resurgence in the use of beta radiation in other areas in medicine, such as the prevention of restenosis after coronary artery stenting. Beta radiation has been shown *in vitro* and *in vivo* to inhibit proliferation of human Tenon's fibroblasts, which enter a period of growth arrest but do not die. Effects on the cell cycle controller p53 have been shown to be important in this process.

In ophthalmology, beta radiation has been used widely for the treatment of pterygium and is under evaluation for treatment of age-related macular degeneration and for controlling wound healing after glaucoma drainage surgery. In this latter role, beta radiation may be particularly appropriate for use in developing countries to improve the results of trabeculectomy while potentially avoiding some of the side effects of other antimetabolites.

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Introduction

Beta radiation is a convenient and practical method of applying ionising radiation focally and may be precisely applied to ocular structures. Scarring in ocular structures is a major pathogenic factor in many eye diseases: both in the context of a neovascular scarring process such as in exudative age-related maculopathy and in dysfunctional, inappropriate, or excessive wound healing. There is a resurgence of interest in the role of beta radiation in other medical disciplines. In vascular medicine and cardiology, the use of beta radiation in the prevention of restenosis following coronary balloon angioplasty or stenting is highly topical. Placement of ^{32}P wires markedly reduced subsequent restenosis rates in a recently reported randomised controlled trial, and extensive investigation continues in this field.[1,2] In ophthalmology, the role of both external beam radiation and brachytherapy in the management of age-related macular degeneration (ARMD) and the role of beta radiation in trabeculectomy are currently under evaluation. It is therefore appropriate to revisit the role of beta radiation in ophthalmology.

Beta radiation

Beta radiation is a particulate radiation consisting of high-speed electrons, which are rapidly attenuated by biological tissues (2 MeV beta particles have a range of only 1 cm in water). This makes it very useful for superficial radiation treatments where deep tissue penetration is undesirable. Strontium-90 (^{90}Sr), an unstable fission product of uranium-235 (^{235}U), has been found to be a clinically useful source of beta radiation as it has a long half-life (28.7 years) and emits only high-energy beta particles as it decays. Ruthenium-106 (^{106}Ru) primarily emits beta radiation but also emits a small but significant gamma component.[3] ^{106}Ru has been primarily used in the treatment of choroidal melanoma.[4,5] Penetration depends on the energy of particles released in the decay process of a particular source. Of emitters used in ophthalmology, the ^{90}Sr source has the most marked attenuation in biological tissues, making it particularly suitable for use in ocular surface treatment. The half thickness of ^{90}Sr is 1.5 mm, that is, the radiation dose rate is attenuated by 50% after 1.5 mm penetration through water—the corresponding distance for ^{106}Ru is 2.4 mm. One potential problem with beta radiation is in the generation of secondary X-rays, termed *Bremsstrahlung*, caused by braking of the high-energy electrons by the material the source is

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embedded in. This may also be relevant if the material is shielded by very proximally placed material with a high atomic number (eg lead). The production of Bremsstrahlung is usually minimal with the low atomic number atoms found in biological soft tissues.

Method of delivery

The ^{90}Sr source is commercially available for use in pterygium surgery (Nycomed Amersham, UK) (Figure 1). The sources remain clinically useful for at least 10 years. Recalculation of the dose rate is required periodically as the activity of the emitter slowly decays.

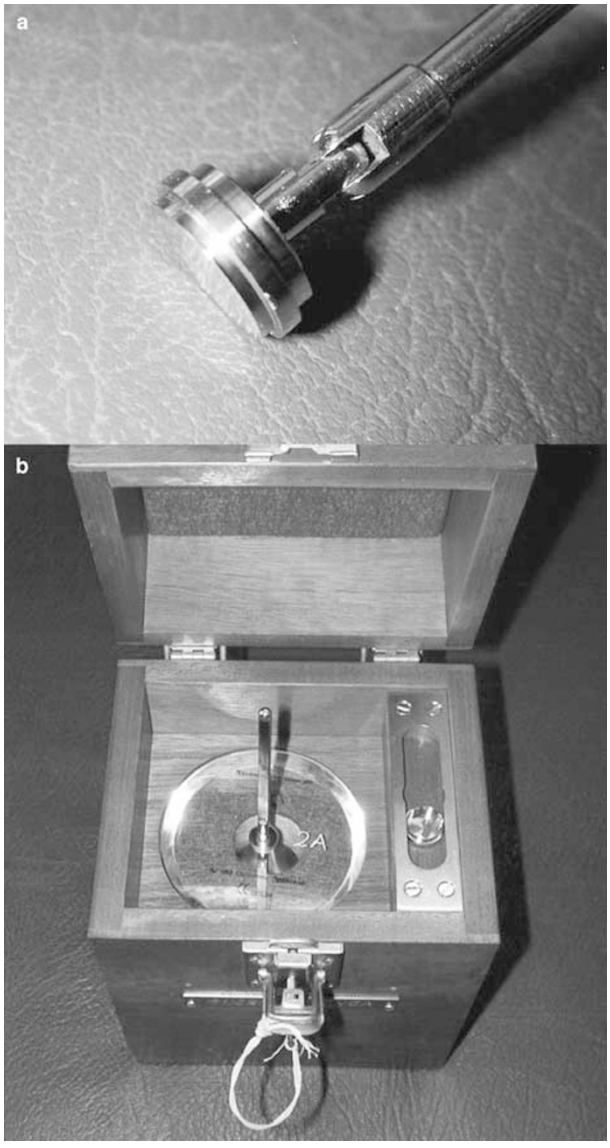

Figure 1 (a) Tip of ^{90}Sr emitter (Nycomed Amersham, UK). (b) Emitter in protective case with lid open to reveal emitter handle and perspex shield.

Typically, this is done every 6 or 12 months. These sources have also been used with trabeculectomy. The dimensions of this source, 11 mm diameter (round) and 3 mm thickness, are not ideal for trabeculectomy, as excellent exposure is required for application. However, smaller sources are also available (BEBIG, Berlin). In future, a custom-shaped device may be available. The source we are using is available with a mask to allow delivery to particular areas; however, to ensure reliable dosimetry, we use these without masking. The dose rate depends on the individual characteristics of a particular source and how much ^{90}Sr is in a particular emitter. With a new source, a dose of 1000 cGy (rad) may be administered over approximately 20 s. After some years, the exposure time may be in the order of several minutes.

Cellular effects of beta radiation

The fundamental biological effect of ionising radiation is the process of ionisation, where the absorption of energy by an atom or molecule results in the ejection of one or more of its orbiting electrons, resulting in unstable and highly reactive compounds. From its earliest clinical use, it has been clear that radiation influences tissue healing.[6] In 1932, Desjardins noted that a proportion of irradiated cells exhibited either a temporary inhibition of metabolic activity, or a complete and permanent disintegration, and in 1957, Puck *et al* demonstrated that the growth of normal fibroblasts *in vitro* could be inhibited by radiation.[7,8] In the eye, radiation has been shown to inhibit corneal wound healing, with prominent effects on fibroblast proliferation.[9] Radiation therapy has also been utilised as a means of preventing proliferative vitreoretinopathy (PVR).[10,11]

The conjunctival fibroblast is at the core of the healing response following trauma to the conjunctiva; their proliferation, contraction, collagen production, and eventual quiescence determine the extent of the overall wound healing response. In rabbit models, which show a considerably more aggressive healing response than man, focal beta radiation attenuates wound healing and prolongs bleb survival.[12,13] These studies demonstrated reduced fibroblast numbers, without excessive inflammation. Additionally, collagen deposition and bleb thickness tended to be reduced. Concerns that focal beta radiation treatment may actually induce rather than inhibit postoperative inflammation have not been borne out, however, either in animal models or in clinical practice.[12,14]

The first *in vitro* experimental data on beta radiation on ocular cells were published by Nevarez *et al*[15] in 1987, who studied proliferation of cultured monkey fibroblasts following single doses of irradiation. Proliferation was reduced to 14% with doses of 1000 cGy or more in this

Table 1 Susceptibility of ocular structures to radiation damage

Ocular tissue	*Radiation dose*	*Latency*	*Effects*
Conjunctiva	5000 cGy	4–6 weeks	Conjunctivitis
	3000–5000 cGy[23,72,73]	2–4 weeks	Late onset telangectatic vessels (27% of cases)[72,73]
	>5000 cGy		Epithelial keratinisation[23]
			Conjunctival cytological changes
	5000 cGy	12 years	Symblepharon
Cornea	2000 cGy[23,74]	4–6 weeks	Mild punctate keratitis[23,74]
	Higher doses[73]		Epithelial ulceration and stromal oedema[73]
Sclera	750 cGy	>10 years	One isolated case of scleral thinning after treatment
	2400 cGy[35,36,75]	3–20 years	Scleral necrosis, infective scleritis[35,36,75]
Uvea	1000–2000 cGy[76]	3–4 days	Mild transient uveitis[76]
	6000–8000 cGy	6–8 weeks	Persistent, delayed onset uveitis
Lens	250 cGy	6 months–20 years	Nonprogressive lens opacity
	750 cGy[21,22]		Cataract (50% progressive)[21,22]
Retina	1500 cGy[77]	8–24 days	Mild radiation retinopathy rarely reported (single report)[77]
	3000 cGy[49]	>6 months	Higher risk of radiation retinopathy[49]

aggressive model. Following this, in 1991 Khaw *et al*[16] described the effects of beta radiation on *in vitro* cultures of human Tenon's fibroblasts, and similarly found a significant inhibition of fibroblast proliferation compared to control cells over a 14-day period. Constable *et al*[17] examined the effect of beta radiation on human Tenons fibroblasts over a longer time period and examined the effect on cell cycling. They showed that dose-dependent inhibition of human Tenon's fibroblast proliferation up to a plateau at exposures of 1000 cGy is due to cellular growth arrest rather than to cell killing. Cellular p53 levels were also measured. p53 is a neuropeptide that prevents cell replication in the presence of DNA damage, that is, it acts as a 'guardian of the genome'. Levels of p53 were found to be significantly increased over the 30-day study period, presumably in response to DNA damage caused by the radiation.

One important issue is how these cellular effects compare to those of 5-fluorouracil (5FU) and mitomycin C (MMC). Khaw *et al* showed that 5FU (25 mg/ml) and MMC (0.1 mg/ml) both reduce fibroblast proliferation by at least 50% by inducing growth arrest in a manner similar to that following radiation. However, the effects of MMC do differ in an important way. Single applications of 0.4 mg/ml MMC rapidly lead to high levels of cell death by apoptosis, an effect not seen after clinically relevant doses of radiation.[18]

Suseptibility of ocular structures to radiation damage

The safety of any therapeutic approach is of paramount importance and there are considerable data on the radiosensitivity of the ocular structures to ionising radiation. Chalupecky[19] first studied the effects of radiation on the eye over 100 years ago. Current data on the susceptibility of ocular structures to radiation are summarised in Table 1.

Radiation and the lens

The lens has been recognised for many years to be the most radiosensitive structure in the eye. Many clinical and experimental studies have been published investigating the tolerance of the lens to radiation.[20–22] Cataracts have not been reported with lens doses of radiation below 200 cGy, but nonprogressive lens changes have been sporadically recorded with doses just above this level. Merriam *et al*[23] concluded that the minimum cataractogenic dose for a single treatment was 200 cGy to the lens epithelium, with the probability of cataract approaching unity for a dose of 750 cGy, although only 50% of these cases showed progressive change. The latent period for the onset of these lens opacities has been reported as varying between 6 months and 35 years, and appears to be inversely related to the total dose administered. Hilgers[20] concluded that a surface dose (ie to the bare sclera) of 3000 cGy could be considered a safe noncataractogenic dose of ^{90}Sr beta radiation. Given the dose considerations above, the degree of penetration of beta radiation is crucial. Although the events leading to lens opacity are not fully understood, the germinative zone in the lens epithelium is considered to be the most important area. This part of the lens is relatively close to the limbus and may receive a particularly high proportion of radiation compared to the whole lens when beta radiation as applied to the anterior segment. Dose to the lens has been calculated assuming exponential decay of the surface dose. Using

more sophisticated modelling, Gleckler *et al*[24] estimated that the dose to the germinative epithelium is approximately 14% of the surface dose applied after pterygium surgery onto the bare sclera. The additional attenuation by the conjunctiva with a thickness of approximately 1 mm means that the lens dose following application after trabeculectomy is likely to be less than 10%.[24]

Attenuation is difficult to model through a structure such as conjunctiva (particularly, immediately after conjunctival surgery) because the presence of tissue, fluid, and air space causes interfaces which may have significant effects on transmission of beta radiation, that is, attenuating it further than through a homogenous medium. Individual variations in ocular anatomy, including anterior chamber depth, may also have an effect on the lens dose for a given surface dose.

In the use of trabeculectomy as a primary treatment for glaucoma in the developing world, the problem of subsequent development of lens opacity is particularly important. In a recent study from Tanzania, where trabeculectomy with mitomycin C was evaluated, 33% of patients developed significant cataract. This is clearly a major problem in such a setting where re-presentation for cataract extraction may not be feasible. There is some suggestion that trabeculectomy with mitomycin C and 5-fluorouracil may accentuate development of lens opacity more than trabeculectomy alone. The role of beta radiation in cataract progression after trabeculectomy is of great clinical importance. It is reassuring that beta radiation (750 cGy) has been used at Moorfields Eye Hospital on children and young adults for nearly 20 years and no patients have required cataract surgery. There is evidence that mitomycin C does penetrate the sclera and has intraocular effects in man, but to what degree and how often this occurs is, in clinical practice, as yet unclear.

Beta radiation in ophthalmology

Pterygium

The most common use of beta radiation has been in the management of pterygium, with local application of a ^{90}Sr source to prevent recurrence. Iliff suggested that beta radiation may be particularly useful in ophthalmology in 1947, following from an earlier report by Burnam; however, its usefulness was limited by the need to use naturally occurring radon seeds.[25–27] Friedell was the first to describe the clinical use of a ^{90}Sr source in 1950. It was suggested for a variety of uses including treatment of superficial tumours, vernal conjunctivitis, tuberculosis, and corneal vascularisation.[28] In the treatment of pterygium, initially a high dose of beta radiation was applied without surgical excision, the aim being to induce regression of the lesion. Administration after surgery, particularly for recurrent pterygia, was widely adopted, with subsequent reports indicating a low recurrence rate. Many reports were from Australia with a high prevalence and recurrence rate, presumably due to high levels of ultraviolet radiation. Doses administered varied considerably. Mead[29] administered 2400 cGy in a single dose. Other reports used doses from 1000 to 4000 cGy, often in divided fractions.[30–33] Aswad and Baum[34] performed a trial that indicated that administration immediately after surgery was more effective than later administration. Typical doses have been of the order of 2000–6000 cGy, frequently given in fractions. A randomised controlled trial by de Kaiser demonstrated that beta radiation was effective in reducing the rate of recurrence. Beta radiation became widely used, particularly in Australia and the southern USA from the 1970 s.

Adverse effects with beta radiation for pterygium have been widely reported. Earlier reports concentrated on lens opacity, conjunctival telangectasia, and other side effects of doses much higher than those used clinically after pterygium surgery. Cameron reported five subjects with varying degrees of scleral necrosis: he attributed these to poor surgical technique in four cases (excessive cautery) and overdosage (7200 cGy) in another. Subsequently, Tarr and Constable reported a large series of eyes from western Australia. They reported 51 cases of scleral ulceration. The time lag between therapy and presentation was between 3 and 20 years, mean 12 years. They estimated a 2.6% rate of significant scleral necrosis in the long term after treatment. In all but one of the cases the patients had received at least 2400 cGy.[35] One patient received 750 cGy and developed a small (1.5 mm diameter), punched-out ulcer covered with 'slightly' abnormal conjunctiva 10 years later. The other ulcers were larger, frequently very deep, with avascular conjunctival covering. Subsequent reports from the same centre reported on infective scleritis, with devastating ocular consequences, all patients having received over 2000 cGy.[36] A subsequent report suggested that using lower doses was also associated with scleral infection. Mackenzie reported long-term follow-up (10 years) on 585 of an original 1102 patients in Queensland, Australia. Overall recurrence rate was 12%. It was reported that 13% of eyes had some degree of scleral thinning and 4.5% had a significant degree of scleral thinning—defined as at least 50% reduction in scleral thickness over an area at least 2 mm in diameter. The surgery was performed using a bare sclera technique and it is possible that this exacerbated the risk of late melting.

Use of beta radiation for pterygium has diminished, with conjunctival autografting and topical mitomycin C now being widely used. Currently, there is no conclusive

evidence as to the optimum therapy conjunctival autografting is reasonably effective and appears to be safe; however, it is considerably more time consuming than other methods.[37] Comparative data for beta radiation and mitomycin C are conflicting: a retrospective comparison from Japan suggested that mitomycin C was more effective; a study from Turkey suggested the converse, a Dutch study suggested equivalence; and a randomised controlled study from Australia suggested that beta radiation was more effective than either conjunctival autografting or mitomycin C.[38–41] While initial reports indicated good safety with mitomycin C, late complications of mitomycin C use, including scleral necrosis and corneal perforation, have been reported that are remarkably similar to those of beta radiation.[42–44]

Age-related macular degeneration

In recent years, there has been persisting interest in the role of ionising radiation in the management of exudative ARMD following the first report by Chakravarthy *et al*[45] using external beam therapy. Radiation has been shown to inhibit vascular endothelial cell proliferation and angiogenesis—both of which are key elements in the development of choroidal neovascularisation.[46–48] The use of external beam treatment necessitates fractionation as individual doses of more than 500 cGy or regimes with a total dose of more than 5000 cGy result in unwanted side effects.[23,49] However, the dose required to induce regression of vascular tissues in clinical practice is close to this level.[50,51] Given these considerations, an alternative approach has been the use of an episcleral plaque placed close to the area of treatment. Brachytherapy has utilised either palladium-103 (^{103}P), a low-energy gamma emitter, or ^{90}Sr. Studies have reported doses of between 500 and 2400 cGy to the target tissue.[52,53] Dosimetric studies have demonstrated that a local approach leads to a considerably smaller radiation dose to the lens and optic nerve than for external beam therapy. When these doses are administered by an external beam, the dose given to the lens may be sufficient to induce cataract, as up to 50% of the maximum dose may fall on the posterior lens. The disadvantages include the need for incisional surgery. Whether these theoretical differences provide any practical advantage remains to be seen, however, external beam radiation has not been shown to be effective in trials reported so far.[54–56]

Glaucoma drainage surgery

The earliest publication specifically addressing the use of beta radiation with drainage surgery was by Iliff in 1944. In a review of surgical management of glaucoma in African-Americans, he reported an overall success rate of 40% in a historical control group, with eight of 11 cases receiving beta radiation having a successful outcome with at least 1-year follow-up. He reported that 'post operative beta radiation gave encouraging results, and was worthy of further trial'.[25] A further report by Cohen *et al*[57] using a ^{90}Sr emitter showed success in eight of 10 patients. Cameron[58] reported success in a small series from Australia on patients that had previously failed surgery.[58] In 1991, Miller and Rice[14] published the follow-up data in a series of 66 eyes with congenital glaucoma, 31 of which had been treated with 750 cGy beta radiation at the end of surgery. Analysis at 3 years showed that beta radiation was significantly protective against failure as compared to controls. O'Donoghue *et al*[59] presented 1-year follow-up of a randomised controlled trial of beta radiation compared with postoperative 5-fluorouracil. They concluded that the antiscarring effect of these two treatments was similar, but importantly that fewer of the irradiated eyes developed cystic blebs or corneal toxicity.[59] In the same year, Lai and Ho presented their 1-year results in a prospective trial of the use of beta radiation combined with trabeculectomy compared to trabeculectomy alone in a cohort of uncomplicated cases of primary open-angle glaucoma in Hong Kong. Surgical failure was significantly reduced in the irradiated eyes (9.52%) compared to the control eyes (26.09%).[60] Barnes *et al*[61] recently reported on the use of beta radiation in white subjects with a low risk of failure. They did not see a significant difference in intraocular pressure or failure rate as there was a high success rate in both arms of the study and the study power was very limited.[61]

Why beta radiation in glaucoma surgery

The use of antiproliferatives has revolutionised glaucoma drainage surgery.[62] However, the use of liquid antimetabolites may be associated with problems. The variability of the delivery of the drug between the impregnated sponge and the subconjunctival tissues means that accurate dosimetry has proven extremely difficult.[63] They are used in liquid form, delivered by placing microsurgical sponges soaked in the drug directly onto the operative site. Furthermore, because they are liquids, they carry the risk of leakage away from the treatment site, leading to extraocular or, more seriously, intraocular toxicity.[64,65] Both treatments have been associated with the development of extremely thin, avascular filtration blebs, and these are associated with an increased risk of sight-threatening complications including profound hypotony and endophthalmitis.[66–68]

As previously illustrated, beta radiation has certain features that may make it suitable for use in glaucoma

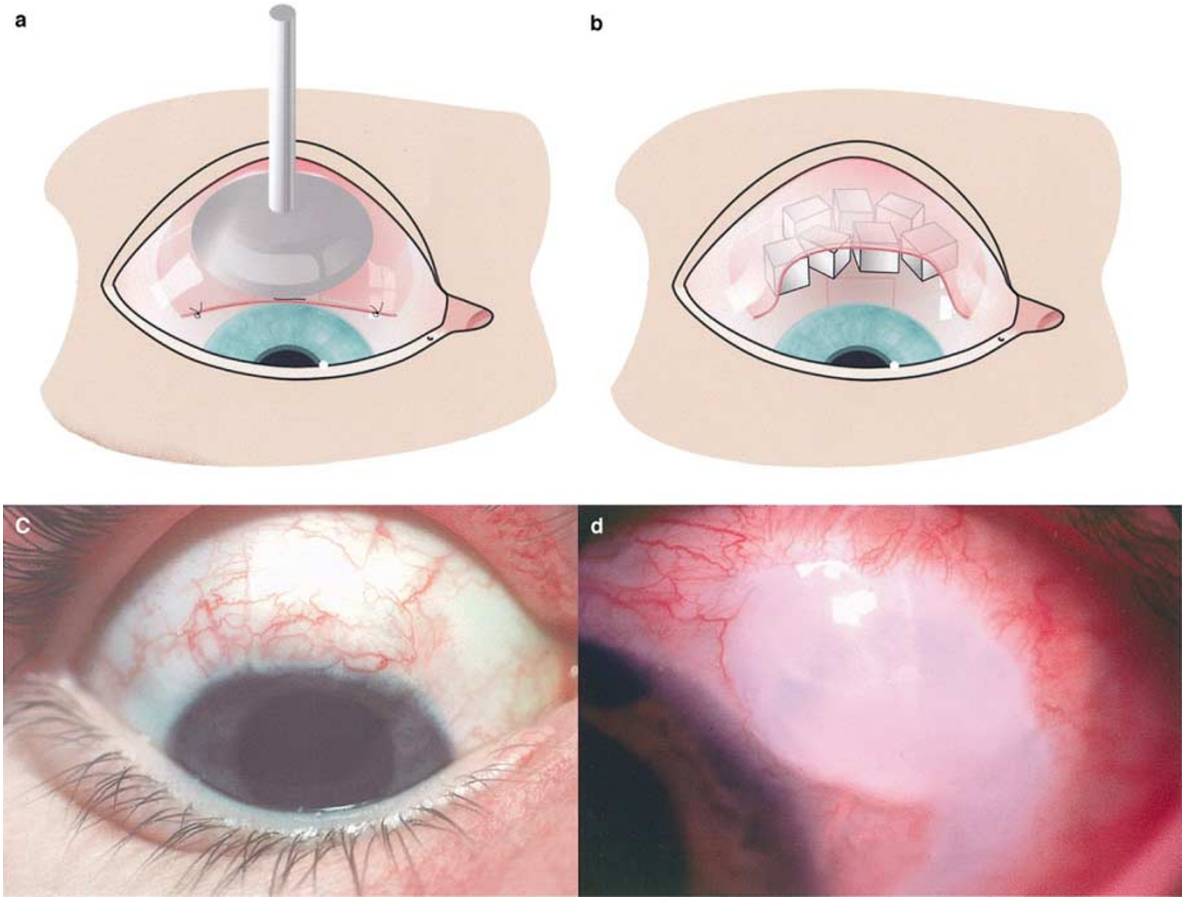

Figure 2 (a) Diagram illustrating placement of beta radiation at completion of surgery. (b) In contrast, extensive dissection required to apply antimetabolites to large area of sclera. (c) Bleb with diffuse morphology following application of beta radiation. (d) Focal, avascular bleb produced by focal application of MMC under a limbus based conjunctival flap.

surgery. Application of beta radiation is rapid and convenient, and the focal nature of application reduces the risk of accidental overdosage. Both dosimetry and the area treated can be controlled with accuracy. The size of the application area of antimetabolites has been shown to be important in the way that blebs develop, and large treatment areas seem to be more favourable.[69] This is easy to control without extensive dissection if a custom-sized applicator is applied to the desired area, whereas more extensive dissection is required if a large treatment area is required with a liquid antimetabolite. Additionally, there is no risk of leakage outside the treatment area, with which a liquid antimetabolite may lead to nonhealing of the wound edge. The actual nature of the bleb formed is different from that produced with MMC or 5FU, tending to be thicker and less avascular. This has been noted in clinical studies and also in animal models.[59,70] Whether this is a result of treatment size effects or intrinsic differences between these modalities is unknown, but may be important in minimising the incidence of bleb complications including endophthalmitis (Figure 2).

For the developing world, there are additional practical advantages with beta radiation. The stability and long half-life of ^{90}Sr means that once obtained, an emitter can have a long working life (20 years plus), with only occasional recalibration. Sources are stable and easily stored, with no refrigeration required, and sustainability issues such as maintaining a good supply of drugs, and ongoing costs are not a problem. In the UK, capital outlay is currently significant (approximately UK £5000), but emitters could be made more cost-effectively. Clearly, the unit cost drops with increased turnover. Strict licensing laws may discourage use in many countries, as clinicians are required to obtain a special licence.

In comparison to its use for pterygium, beta radiation in glaucoma surgery may be safer for the following reasons. The dose of 1000 cGy used is the optimum dose as determined in *in vitro* and *in vivo* studies.[17] This is between 20 and 50% of the dose used for pterygium.

Reports of scleral necrosis with this dose are extremely uncommon. The applicator is placed on the conjunctiva immediately following surgery rather than on bare sclera. This reduces the dose received by the sclera, as a significant proportion of the radiation is attenuated passing through the conjunctiva (approximately 30% assuming a thickness of 1 mm). Trabeculectomy is performed in the superior location, under the upper lid. The protection of the upper lid is important for providing protection to the bleb. It is known that interpalpebral blebs have a far greater incidence of bleb-related complications, particularly after antiscarring agents have been used. This is quite different from the situation following pterygium surgery where the bare sclera is interpalpebral and de-epithelialised. Both these factors may render the scleral tissue more susceptible to infection. Beta radiation has been used at Moorfields Eye Hospital for over 25 years in the management of paediatric glaucoma cases. During this time, the use of beta radiation has had an excellent safety profile, with no evidence of neoplastic effects or radiation-associated lens opacity.

Summary

Beta radiation is a practical method of applying radiation focally. In clinically used doses, it is effective in reducing the proliferative wound healing response, causing growth arrest without inhibiting other cellular functions. Its ocular safety profile is relatively well understood. Beta radiation has been in clinical use longer than most other methods of controlling scarring and was widely used for pterygium. Its use in that role has diminished with the uptake of other modalities, albeit without a strong supportive evidence base. Owing to its longevity, we are more aware of its long-term effects than is the case with other modalities. It may have clinical use in the management of ARMD and also for glaucoma surgery.

With the development of biotechnology-based approaches to the control of wound healing, it may be tempting to reject older and perhaps 'blunter' tools in our quest for better results.[71] However, the applicability of these approaches to the bulk of the world's glaucoma population in the near future is questionable and it is appropriate to fully exploit our current approaches to controlling ocular wound healing. As the use of beta radiation may be especially suitable for use in the developing world, particularly in Africa, we are currently performing a randomised controlled trial of beta radiation in South Africa. Patients with primary glaucoma are randomised to standard trabeculectomy or trabeculectomy augmented with 1000 cGy of beta radiation immediately after surgery. We hope that this trial will help to improve treatment options in the management of this blinding condition.

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