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General review

The role of radiotherapy in the treatment of pterygium: A review of the literature including more than 6000 treated lesions

Rôle de la radiothérapie dans le traitement du ptérygion : revue de la littérature incluant plus de 6 000 lésions traitées

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ABSTRACT

Pterygium is a benign conjunctival neoformation usually treated by surgical excision, but recurrences may affect 30% to 89% of cases, so that adjunctive therapies like conjunctival autografting, antimitotic drugs and beta-irradiation (β-irradiation) are often used to improve the rate of local control. Our essay has reviewed relevant studies addressing the role of postoperative irradiation in the treatment of pterygium in the last 30 years through an Internet-based search and hand search in libraries. Sixteen studies on β-irradiation and one on soft X-ray irradiation were accessible. They covered more than 6000 lesions treated by surgical excision and postoperative β-irradiation using strontium-90 (^{90}Sr) applicators at doses varying from 10 to 60 Gy/1–6 fractions/1–6 weeks starting within 3 days postoperatively. The rates of local recurrence were in general lower than 15% and major complications such as scleral thinning, ulceration, infections, or radiation-induced cataract were rarely encountered. Early postoperative β-irradiation at a dose of 30 Gy/three fractions/2–3 weeks starting within 24 h from surgical excision is an effective and safe procedure with local control rates comparable to chemotherapeutic agents and conjunctival autografting and superior to simple excision alone.

Mots clés :
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RÉSUMÉ

Le ptérygion est une tumeur bénigne d'origine conjonctivale. Son traitement est avant tout chirurgical, mais l'exérèse seule est grevée de près de 30 à 89 % de récidives, c'est pourquoi des traitements adjuvants comme l'autogreffe conjonctivale, les substances cytotoxiques, l'irradiation postopératoire au moyen de rayons bêta sont largement utilisées pour réduire ce risque de récidive. Nous avons cherché sur Internet et aussi dans les bibliothèques des études concernant le rôle de la radiothérapie postopératoire dans le traitement de ces lésions pendant les 30 dernières années. Seize études sur le traitement postopératoire à l'aide d'un émetteur bêta (strontium-90) et une seule étude sur les rayons X sont accessibles. Ces études ont inclus plus de 6000 lésions traitées au moyen de l'exérèse chirurgical suivie par une irradiation aux doses de 10 à 60 Gy en une à six séances sur une à six semaines débutées dans les trois jours postopératoires. Les taux de rechute ont globalement été inférieurs à 15 % et les effets secondaires majeurs comme l'atrophie de la sclère, l'ulcération, des infections et la cataracte ont rarement été reportées. Cette revue permet de conclure que l'irradiation postopératoire précoce (notamment l'irradiation bêta), à une dose de 30 Gy en trois fractions et deux à trois semaines, débutée dans les 24 heures suivant l'acte chirurgical, est un traitement efficace et sans effets secondaires majeurs, assurant un taux de contrôle local comparable à celui obtenu par les injections locales de substances cytotoxiques ou par l'autogreffe conjonctivale, et significativement supérieur à celui obtenu par l'exérèse chirurgicale seule.

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1. Introduction

Pterygium is a common conjunctival disorder of unknown etiology [37,43]. It typically develops between the ages of 20 to 50 especially in tropical and subtropical areas and characterized by fibrovascular reaction, chronic inflammatory cells infiltration, angiogenesis, fibroblastic proliferation and invasion [13,21,31,77]. Some studies have indicated that excessive production of extracellular matrix is implicated in its pathogenesis [9,37]. More recently, positive immunostaining for fibroangiogenic growth factors in pterygium has suggested their interactions in cellular proliferation, inflammatory reaction, remodeling of extracellular matrix and angiogenesis of pterygium [8,41]. Also, the demonstration of higher counts of circulating CD34+ and c-kit+ bone marrow derived progenitor cells in correlation with higher levels of systemic and local cytokines and stronger expression of progenitor cell markers such as CD34, c-kit, vascular endothelial growth factor (VEGF1 and VEGR2) in pterygial tissues, especially recurrent ones, than in normal conjunctiva suggested that these progenitor cells are involved in its pathogenesis and environmental factors such as UV, heat and wind might cause chronic inflammation and sublethal hypoxia that triggers the migration of these cells, which can differentiate into mature endothelial cells, to the limbus [43,63]. Anti-apoptotic mechanisms have also been suggested in its pathogenesis, and recent data demonstrated expression of cyclooxygenase-2 (COX-2) and anti-apoptotic protein, survivin, in primary pterygia [19,52]. Such information can provide a base towards the development of novel therapeutic strategies that involve the use of COX-2 and survivin inhibitors [52].

The main treatment of pterygium is surgery [45,49]. Although excision of pterygium with bare sclera technique is the quickest method with the least surgical intervention but it is by far the least satisfactory method with respect to recurrence rate, so that, adjuvant therapy such as conjunctival autografting (CAG), cytotoxic agents like mitomycin C (MMC) and β-irradiation is needed for prevention of recurrences [32,33,35,48].

Although CAG is considered safe and effective procedure with infrequent complications such as epithelial inclusion cysts, corneoscleral dellen, graft oedema, it needs surgical expertise, technical ability and more time to secure the graft with sutures [36,69,72]. However, using fibrin glue instead of sutures was found to shorten the operative time, minimize postoperative discomfort and improve local control [26,36]. Recurrence rates reported with CAG ranged from 5.4 to 39% for primary [2,4,18,45,46,72] and from 5.3 to 33.3% for advanced and recurrent pterygia [2,38,45,72].

Including limbal stem cells in the conjunctival autograft (LCAG) is suggested to act as a barrier to conjunctival cells migrating onto the corneal surface and help preventing recurrence [7]. Some authors reported that LCAG is more effective than CAG with recurrence rates ranged from 1.9 to 7% for primary and up to 14.6% for recurrent lesions [1,2,23,30,39,54,79]. However, it is technically more demanding and time-consuming to perform [7].

Using MMC in treatment of pterygium dates back to 1963 [18]. Some studies reported that low dose topical MMC (0.2 mg/ml twice daily for 5 days to three times daily for 1 week) after excision of pterygium has been as effective as CAG with comparable recurrence rates varied between 3.7 and 38% while others found it was associated with even lower recurrence rate to that achievable with CAG (9.4% versus 24.9%, respectively) [18,46,49]. In view of the various complications reported with postoperative topical MMC such as secondary glaucoma, iritis, cataract, scleral necrosis, scleritis and perforation, a single intraoperative instillation of MMC at concentrations from 0.02% for 3–5 min to 0.04% for 3 min has been considered safe and effective alternative to postoperative MMC as it had been found associated with recurrence rates from 4.08 to 15.9% compared to 29.27–75% for excision alone in primary pterygia and recurrent ones, along with very low rates of side effects such as superficial punctate keratitis, limbal avascularity, superficial scleral melting, scleral dellen and conjunctival cysts [1,6,7,16,22,24,42,50,51,60,65,79].

Utilization of β-irradiation in postoperative treatment of pterygium has a long history being convenient and practical method in inhibiting the repopulation of endothelial cells. It is characterized by minimal tissue penetration and absence of unwanted gamma rays [29,40,53,58,77]. Early studies reported success rates up to 90% with bare sclera excision and postoperative β-irradiation, but others reported it might lead to iatrogenic ocular diseases [20,71]. Few studies have compared between postoperative β-irradiation and MMC and even fewer those compared between β-irradiation and CAG. While some reported lower recurrence rates in favour of intraoperative and postoperative MMC for primary pterygium, others reported better results with β-irradiation compared with postoperative MMC in primary and recurrent pterygia and better, yet marginal, outcome of β-irradiation over CAG in primary pterygia [6,17,21,68]. Our review of literature aims at evaluating the role of postoperative irradiation in reducing the recurrence rate of pterygium and the complications associated with it.

2. Method of review

References enrolled in our review were collected through an Internet-based survey using the PubMed® data searching for English language publications on pterygium and irradiation as well as a hand research in libraries. We have focused on studies reporting on the results of treatment of pterygium whether primary or recurrent by both surgical excision and postoperative ionizing irradiation. Studies on other modalities of treatments and those having incomplete information from published data were not focused on. The study to be relevant to our review had to report on the impact of such a combined treatment on the local control and/or recurrence rates as well as the side effects. We were able to access to 17 studies that composed the bulk of our review. These studies included a total number of more than 6000 treated lesions.

3. Treatment

Treatment of pterygium with β-irradiation using 90Sr applicator is a mould brachytherapy. 90Sr is a nuclear reactor fission product of uranium-235. Its half-life is 29.12 years and decays to yttrium-90 [59]. The applicators consist of silver cups containing the radioisotopes incorporated onto them with thin metallic covering to remove low energy β-particles. Plane sources are typically about 10–12 mm while concave ones from 9 to 23 mm in diameter. The applicator is put manually in contact with the surgical bed and the dose is delivered to the surface. The maximum energy of β-particles emitted from 90Sr is estimated at 0.546 Mev while those from yettrium-90 at 2.27 Mev [53]. The depth dose was found to be 20% at 2 mm, and almost 0% at 5 mm under the surface [10,27,34].

4. Results

4.1. Randomized studies

Prospective randomized trials on treatment of pterygium with surgery and postoperative irradiation are scarce [33,35]. Jürgenliemk-Schulz et al. conducted a prospective, randomized, multicenter, double-blind study included 96 pterygia (Table 1). They analyzed the results of 86 pterygia excised by bare sclera technique followed either by β-irradiation using 90Sr applicator at a dose rate between 200 and 250 cGy/min (44 eyes) or sham radiotherapy using non 90Sr containing applicator (42 eyes). Recur-