·Review·

Current management of submacular hemorrhage in age-related macular degeneration

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Received:2009-01-09 Accepted:2009-02-05

Abstract

• Submacular Hemorrhage (SMH) in age-related macular degeneration (AMD) represents a challenging disorder for vision protection. Varied surgical interventions have been suggested in its management. The author herein reviewed some aspects related to SMH in AMD such as its risk factors, secondary damages, natural course and surgical management including different techniques, outcomes and complications.

• KEYWORDS: submacular; hemorrhage; macular degeneration; surgery

Liu W. Current management of submacular hemorrhage in age-related macular degeneration. *Int J Ophthalmol* 2009;2(1):77-81

INTRODUCTION

Submacular Hemorrhage (SMH) is a common ocular disorder which leads to significant vision loss. Causes of SMH are more related to Bruch's membrane damages that usually occurred in age-related macular degeneration (AMD), presumed ocular histoplasmosis, angioid streaks, polypoid choroidal vasculopathy and choroidal rupture. Other causes include ocular trauma, macroaneurysm and tumor.

Submacular Hemorrhage in AMD may come from the choroidal neovascularization (CNV), or tear in the area of pigment epithelium detachment (PED), or even with retinal pigment epithelial (RPE) atrophy[1].

RISK FACTORS OF SMH

It has been shown that anticoagulant warfarin sodium may increase the risk of massive intraocular hemorrhage in AMD [2]. Patients with occult CNV who are receiving warfarin therapy and undergoing repetitive PDT appear to be at risk of SMH, which occurs within 1-2 weeks after the treatment [3]. Iguchi *et al* [4] suggested that SMH may be also related to systemic hypertension.

DAMAGES OF SMH

Sequential damage of SMH is related to the extent and duration of the hemorrhage. It has been shown in experimental studies that damages to photoreceptors may occur within 24 hours in rabbits[5], and degeneration of the outer retina within 7 days in cats [6]. Large SMH may cause severe visual loss and obstructs expected treatment. In general, the SMH will resolve within 6-8 months in average, resulting in scar, atrophic change or RPE tears. The mechanism of damage caused by SMH includes iron toxicity from the blood, mechanical barrier of the clot, clot retraction and shearing of photoreceptors (PR), as well as the damage to RPE cells[6].

NATURAL COURSE OF SMH

The natural course of SMH varies in different reports. Data from retrospective studies are reviewed herein. One study showed that no visual acuity (VA) improved in 12 eyes with large size of SMH in 2-3 years of follow-up[7] Another study found that VA in 3 of 41 eyes decreased 3.5 lines in average within 3 years, and decreased more than 6 lines in 44% of the affected eyes[8].Scupola *et al*[1] reported that SMH was absorbed within 2-28 months, but VA decreased in 80% of, and SMH recurred in 38% of the 60 eyes after 2 years follow-up. Berrocal *et al*[9] observed that VA improved in 40%, unchanged in 30% and decreased in 30% of the 20 eyes. Most SMH was absorbed in 2 years, resulting in scars[9]. In China, it was reported that repetitive SMH occurred in 23 of 25 eyes with SMH[10].

Prognostic factors for the SMH are still controversial. Since RPE and PR are more severely damaged in AMD, SMH will result a worse visual outcome in majority of

these eyes [7]. It was suggested that size and thickness of the SMH might be related to the visual outcome[8], while others found that visual outcome was only related to the CNV membrane in these patients[9].

MANAGEMENT OF SMH

Patients with SMH in AMD could be managed with one or more of the following choices: observation, systemic medical treatment, treatment on CNV, and surgery. Surgeries of SMH may be divided into vitrectomy *vs* non-vitrectomy, and either of them may be adjuvant with or without the use of tissue plasminogen activator (tPA), which could be used intravitreally or subretinally.

Reported surgical techniques include: 1) vitrectomy and removal of subretinal CNV membrane and the clot[11], 2) subretinal injection of tPA and drainage of the liquefied hemorrhage [12,13], 3) subretinal injection of tPA with perfluorocarbon liquids (PFCL) steamrolling[14], 4) subretinal injection of tPA with gas tamponade [15, 16], 5) pneumatic displacement with tPA [17-20], and 6) pneumatic displacement without tPA[21,22].

Vitrectomy and Subretinal Clot Removal Surgical methods include a retinotomy at the site of SMH, subretinal lavage/drainage, clot/membrane removal with forceps, and fluid-gas exchange. Early reports on the surgical outcome were not encouraging. Many eyes had postoperative complications, especially retinal detachment[23]. Postoperative re-bleeding may occur, with no VA improvement[24,25]. In contrast to these poor visual outcomes, VA improvement was reported in China in 12 of the 14 eyes (85.7%) after surgery[26].

Vitrectomy with Subretinal tPA and Hemorrhage Removal Surgical methods include subretinal injection of tPA 6-50μg, waaiting for 40-45 minutes, enlarging the incision and drainage of liquefied hemorrhage. Lewis[13] reported a good result with this technique; VA improved in 83% of the eyes, and he suggested that better effect came with earlier (within 14 days) intervention. However, others reported unfavorable results later on. Postoperative VA declined continuously in majority of the patients with longer follow-up[27]. There was even no difference in final VA regardless of using or not using tPA[28]. Submacular Surgery Trials (SST) Research Group reported that no significant difference was found between groups of observation and complete removal of SMH with CNV after 2 years follow-up [29]. Complications include super-choroidal hemorrhage, retinal tear and retinal detachment[28].

Vitrectomy and Subretinal tPA with PFCL Steam–rolling Surgical methods include subretinal tPA injection and PFCL steamrolling instead of subretinal lavage, which may cause less damage to RPE and PR [27]. With this method, Kamei *et al*[14] reported VA improvement in 82% of the treated eyes.

Vitrectomy and Subretinal tPA with Gas Tamponade Surgical methods include subretinal injection of tPA with 39G or thinner needle followed by fluid-gas exchange. SMH may be displaced with less retinal damage in this way. Chaudhry *et al* [30] and Kimura *et al* [31] suggested that tPA might be used 24 hours prior to the surgery for eyes with larger and thicker SMH. Olivier *et al* [15] reported that 25 of the 29 eyes were successful in complete displacement of the SMH without use of long-acting gas, and 8 of these eyes received following treatment. Recurrence of SMH was reported in 27% of eyes[16].

Pneumatic Displacement Pneumatic displacement (PD) describes the technique of intraocular gas injection with/without tPA. Advantages of PD include simplicity, less invasive, fewer intraocular complications, and non-direct damage to PR and RPE. Indications for PD are SMH within 3 weeks, better preoperative VA, smaller SMH in size and thicker SMH. Mechanism of PD involves a combined effect of buoyancy of the gas bubble and gravity on the SMH. To achieve better efficiency, it was suggested that the displacement plane should be best kept parallel to gravity force direction, so that face down position may not be appreciated[32].

Intraocular Gas and tPA Injection This technique was first report by Heriot and was termed pneumatic displacement. The method includes intravitreal injection of 0.1mL tPA (25-50μg) and long-acting gas[33]. It was reported that SMH might be displaced within 1-5 days postoperatively [33], and complete displacement was achieved in 71% of the 14 eyes [18]. A report from Thailand showed that 63% of the Asian patients gained VA improvement after 6 months [34]. An uncontrolled study suggested the result would be better if eyes were treated within 14 days of bleeding, although recurrence of hem-

orrhage occurred in 21% of eyes [35]. The relation between duration of SMH and visual outcome has not been found[17]. Complications include vitreous hemorrhage (15.7%) and retinal detachment[34].

Intraocular Gas without tPA Injection Pure C_3F_8 injection has been recommended if tPA is not used simultaneously. It was reported that this technique was less effective for small SMH [22], and that it was suitable for non-AMD patients comparing to AMD ones [36]. Johnson suggested that tPA could be injected 24-48 hours after gas injection in non-responded cases[33,37].

ISSUES OF tPA USAGE

As a biological agent, tPA should be kept in deep low temperature storage with asepsis and be diluted 4 hours prior to injection. Safe dosage for intraocular injection is between 18-50g. Maximal effect of intraocular tPA occurs at 4-24 hours post-injection. A waiting time of 20-30 minutes before gas injection is suggested, as well as avoidance of using tPA for SMH within 3 days.

Safety of intraocular tPA is another concern about its use in SMH surgery. Vitreous hemorrhage was reported after tPA injection[38]. Disagreement still exists among doctors on the safety dosage of tPA, and dosage $\leqslant 25\mu g$ is considered safe by the majority. There were reports concerning retinal toxicity of tPA. Chen *et al*[39] reported posterior pigment and ERG changes after two successive injections of 50μg tPA. Hesse *et al*[20] reported exudative retinal detachment after 100μg tPA intravitreal injection. It was also concerned that injection of frozen prepared tPA may increase the risk of endophthalmitis. There was report of two cases of post-tPA injection endophthalmitis with S. mitis culture positive[40].

COMPARISON OF DIFFERENT MANAGEMENTS

In a retrospective study of 42 eyes with SMH $\geqslant$12 disc size, two techniques were compared. One was subretinal removal of clot and membrane, the other was subretinal tPA with gas tamponade. The results of one year follow-up showed that 48% of eyes in the first group and 13% of eyes in the second group gained VA improvement >3 lines, which suggests that the former technique is better[41]. SST (1998-2001) studied 336 eyes with SMH +/-CNV. The inclusion criteria were patients with SMH+/-CNV $\geqslant$3.5 disc size and SMH $\geqslant$50% of the lesion size. Patients were divided into surgical group and observation group. After 24 months follow-up, no VA stabilization or improvement was found in both groups. Surgery was only of benefit in decreasing severe visual loss comparing to observation (21% *vs* 36%), but with increasing risk of retinal detachment (16% *vs* 2%). The study also suggested that large SMH and poor preoperative VA predisposed a high risk of retinal detachment. Postoperative subretinal or sub-RPE hemorrhage existed in 93% of the operated eyes[29].

COMPLICATIONS OF SMH SURGERY

The reported incidence of surgical complications includes vitreous hemorrhage (8%-20%)[15, 20, 33, 35, 38], retinal detachment (3%-25%)[14, 20, 28, 38], endophthalmitis (7%)[33], and epiretinal membrane (9%)[14]. In SST report, 16% of the operated eyes developed rhegmatogenous retinal detachment during the 12-month follow-up, while only 2% in the observation group had rhegmatogenous retinal detachment within 36-month follow-up[29].

Many factors may contribute to the poor outcome of patients with SMH, which include irreversible photoreceptor damage, RPE atrophy, CNV and scar. Other related factors affecting the outcome of SMH include preoperative VA, duration and extent of SMH, severity of AMD, and follow-up period. Efficiency of intraocular tPA is still of considerable diversity. VA improvement ranges from 21% to 93% of the tPA-cases reported. There was study showing that tPA can not penetrate through retina[42].

The relation between SMH and CNV is uncertain. It has been reported that CNV presented in 18%-68% of the cases with SMH, and CNV was found in 1/3 of the eyes with recurrence of SMH[43].

In view of the risk-benefit ratio and the outcome of SMH, it seems that surgical management of SMH is not strongly emphasized. In current clinical practice, surgery for SMH is usually not the first choice. Doctors should not solely rely on surgical intervention in the management of SMH[44].

Evidence-based study is needed in future to validate the effect of intravitreal tPA and its theoretical basis. New therapeutic methods and their roles, such as anti-VEGF therapy and micro-invasive surgery also warrant further studies[45].

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