

8. Design and current status of the SPR study

8.1. Introduction

The discussion about the “right choice” of operating method to treat certain forms of RRD and the debate about the pros and cons of PPPV have been going on for more than a decade now. This is reflected by the still increasing number of editorial comments on this issue with most of them asking for a prospective randomised trial to solve this continuing problem [7, 11, 54, 55, 59, 61, 62, 67, 105]. Such a trial, the “Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment (SPR Study)”, was initiated by the Retinologic Society on its meeting in Travemünde, Germany, in 1994. The applicant was part of the team originating the trial and writing the study design, which was published by the applicant and coworkers in Graefe`s Archive of Experimental and Clinical Ophthalmology, and is a member of the endpoint committee [41].

8.2. Objectives

In the “Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment study” (SPR-study), a randomised prospective comparison of scleral buckling techniques and primary vitrectomy is to be carried out in patients with RRD. The goal of the clinical trial is the improvement of the surgical therapy of RRD with respect to functional as well as anatomical success.

8.3. Outcome measures

The outcome of retinal detachment surgery will be evaluated using five main endpoint criteria: 1. Change in visual acuity (logMAR-scale) from the initial examination to visit 4 using letter-by-letter-scoring on ETDRS-charts, irrespective of any intermediate cataract surgery. Should a cataract be present at visit 4, cataract surgery is recommended and the visual acuity six weeks after immediate cataract surgery is used. 2. Postoperative occurrence of PVR grade B or C, irrespective of any reoperation. 3. Retinal

reattachment after one year without any retina-affecting reoperation. A 'retina-affecting reoperation' is any manipulation that reattaches the retina or ensures its attachment (prophylaxis). 'Retinal reattachment' refers to attachment of the retina central to the equator. 4. Retinal reattachment after one year (any kind of reoperation permitted). 5. Development of cataract in phakic eyes using the lens opacity classification system LOCS-III [18]. 'Development of cataract' means an increase of at least 1.0 on any of the LOCS-III grading scales from initial examination to visit 4. 6. Number of retina-affecting reoperations (see definition of endpoint 3). Endpoints 2, 3 and 4 will be assessed by the endpoint committee using photo documentation.

Every patient has to be examined at four scheduled follow-up visits: within the first week after surgery; eight weeks after surgery; six months after surgery; and one year after surgery. Additional examinations will be performed in the case of reoperations or at any additional unscheduled visit (e.g. because of concomitant therapy or adverse event).

8.4. Inclusion and exclusion criteria

The inclusion and exclusion criteria are displayed in Table 16 and Figure 8.

Preoperatively, "unclear hole situations" are present in aphakic / pseudophakic patients in a higher percentage compared to phakic patients. Therefore, "unclear hole situations" have been included into the aphakia / pseudophakia group, whereas they will be excluded from the phakic group. In the aphakia / pseudophakia group, only cataract surgeries without any damage to the posterior capsule or zonular dialysis are permitted; secondary YAG-laser capsulotomy, however, can be performed. Patients with a history of cryotherapy or photocoagulation for retinal breaks can be included into both subtrials. The validity of inclusion criteria will be checked by the acknowledged study surgeons is reviewed by the Endpoint committee.

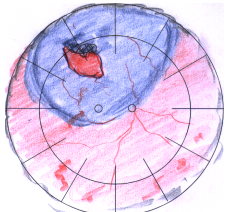
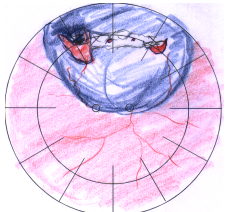
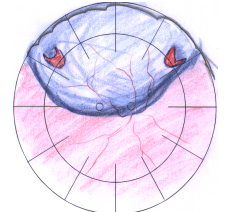
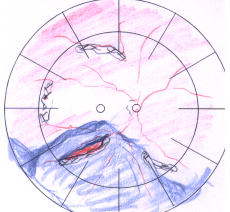
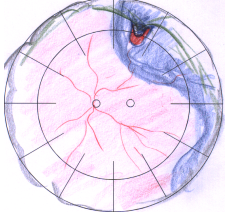
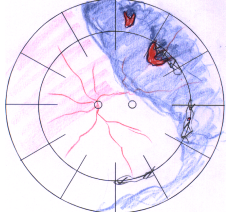
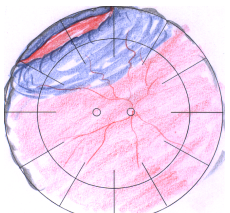
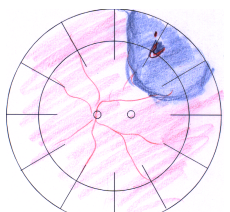
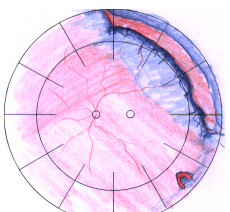
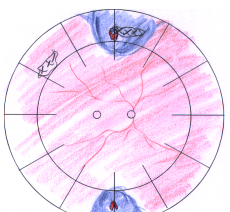
To be included		
 Large breaks	 Multiple breaks	 Superior bullous detachment
 Central extension of break	 Marked vitreous traction	 Different a./p. localisation
	 Retinal tear < 2 clock-hours	
To be excluded		
 Small single break or neighb. small breaks	 Retinal tear > 2 clock-hours	 Multiple breaks with localised detachment(s)

Figure 8: Fundus drawings of typical inclusion and exclusion criteria for the SPR Study (drawings by Prof. Dr. N. Bornfeld)

Aphakic / Pseudophakic Subtrial	Phakic Subtrial
1. Aphakia / pseudophakia	1. Phakia
2. Unclear hole situation	2. Clear hole situation
3. One or more retinal holes, which cannot be treated sufficiently with a single 7.5 x 2.75 mm silastic™ sponge (e.g. large holes, multiple holes, multiple holes of varying anterior-posterior localisation, massive traction)	
4. Absence of breaks at or posterior to the vessel arcades	
5. Absence of PVR stage B or C	
6. Absence of other eye diseases that may significantly influence VA	
7. Absence of other intraocular operations apart from cataract surgery without implantation of an intraocular lens or with implantation of an intracapsular intraocular lens	7. Absence of intraocular operations
8. Absence of myopia of more than –7.0 diopters	
9. Absence of severe systemic disease that may alter the postoperative course of the healing process	
10. Absence of pregnancy	
11. Age > 18 years	
12. Written consent	
13. Willingness and ability of the patient to participate in all follow-up examinations	
14. No participation of the patient in other studies	

Table 16: Inclusion criteria for the SPR Study

8.5. Surgical procedures

Two operating methods are compared in this study. As study surgeons differ in their opinion about the necessity of additional scleral buckling in primary vitrectomy, scleral buckling should either always or never be used when performing primary vitrectomy. The operating procedures fixed in the study protocol are described in Table 17. The surgeon is allowed to use any additional tool or method if anatomical success cannot be achieved with the assigned procedure alone (e.g. performing an additional vitrectomy, if anatomical success cannot be achieved with scleral buckling alone during the first intervention).

Scleral Buckling Procedure	Primary Vitrectomy Procedure
<ol style="list-style-type: none"> 1. Usage of silicone sponges and / or silicone encircling bands or a combination of both according to the surgeon's choice, 2. Treatment of retinal breaks using cryopexy, 3. Intraocular tamponade with injection of BSS, air or SF6 (optional, no other gases permitted), if necessary, 4. Drainage of subretinal fluid with a needle or using electrolysis (optional), and 5. Puncture of the anterior chamber (optional). 	<ol style="list-style-type: none"> 1. Standard three port pars plana vitrectomy, 2. Usage of an encircling band based on the surgeon's decision (surgeons should apply their routine technique throughout the study, e.g. always use an additional encircling band or never), 3. Removal of the flap of the retinal tear to reduce persistent traction on the break (optional), 4. Usage of PFCL (optional), 5. Treatment of the retinal break with cryotherapy or endolasercoagulation, 6. Intraocular tamponade with a 20-40 % SF6 / air mixture (air, C3F8 or silicone oil not permitted as an initial tamponade), and 7. Draining retinotomies if needed.

Table 17: Surgical procedures in the SPR Study

8.6. Statistical aspects

8.6.1. Sample size

Recent retrospective data regarding the primary endpoint criterion “change of VA” has only been published in the population of aphakic / pseudophakic patients. Based on this data, a mean change of VA (measured as the difference to the preoperative value on logMAR-scale) of 0.50 (SD: 0.75) is to be expected in the vitrectomy group and of 0.20 (SD: 0.85) for the scleral buckling group [8]. This approximately resembles a low ($\Delta = 0.2$) to medium ($\Delta = 0.4$) effect. Assuming a 10-20 % drop-out rate, 200 patients per treatment group are reasonable to compare the mean difference in VA between the two groups of patients ($\Delta = 0.35$, power = 90 %). Due to the lack of reliable data regarding the primary endpoint criterion „change of VA“ in phakic patients, the same number of patients per treatment group (n = 200) will be recruited in the phakic subtrial. Only one eye per patient is included in the study. If both eyes of one patient fulfil the inclusion criteria, the surgeon determines which eye will be examined in the study.

8.6.2. Randomisation and blinding

Randomisation is carried out in permuted blocks of varying size, stratified by the surgeon and takes place in the operating theatre following the preoperative fundoscopy, which must be performed for a final check of the validity of the inclusion criteria. „Blinding“ of the measurement of the main endpoint criterion „change in VA“ was not performed because of practical reasons, e.g. lack of manpower.

8.6.3. Statistical analysis

In both subtrials, the two operating methods will be compared based on the differences in visual acuities using separate two-factor analysis of variance models (factor „operation method“; block factor „surgeon“; no interaction). Any missing postoperative VA value will be substituted by the last postoperative value recorded. In case no postoperative value is available or the pre-operative value is missing, the corresponding worst case scenario is adopted. The test of the main effect „operating method“ will be performed at the two-sided 5 % significance level. While the phakic subtrial will be analysed according to fixed sample reasoning, an adaptive interim analysis will be performed in the aphakic / pseudophakic subtrial. Complete details on statistical analysis of outcome variables will be specified in the statistical analysis plan, a study document to be finalized well before any inspection of study patient data.

8.7. Current status (December 2004)

In total, 45 surgeons in 25 centres of 5 European countries participated in the SPR Study. Patient recruitment was initialized in August 1998 and ended in July 2003. Overall, 664 patients (407 phakic and 257 pseudophakic/aphakic) were recruited and 326 PPPV versus 338 SBS were performed. Monitoring of patients is completed on 65% (436/664) of patients. The results of the study are expected to be published in June 2005.

8.8. Summary

The SPR Study is the first prospective multicenter and randomised trial comparing PPPV against SBS in more complex situations of RRD in phakic and aphakic/pseudophakic patients. Inclusion criteria were patients with RRD that could not be treated with a single 7.5mm scleral buckle and had multiple breaks, large breaks, central breaks, marked vitreous traction, bullous detachments or unclear hole situations (pseudophakic patients). Exclusion criteria were proliferative retinopathy, PVR grade B or C, giant retinal tears and clouding of the optic media. The main endpoint criterion is visual acuity one year postoperatively. Secondary endpoints are redetachment rates, postoperative PVR, cataract development and rates of secondary surgeries.

In total, 45 surgeons in 25 centres of 5 European countries enrolled 664 patients (407 phakic and 257 aphakic/pseudophakic) between 1998 and 2003. The results of the study are to be expected in June 2005.