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Friday, 16th May 2008

14.00 **Opening ceremony** **11th Vitreoretinal Symposium** **Marburg-Frankfurt 2008**

14.00 **1st scientific session:** ↘ **Imaging the vitreoretinal** 16.15 **interface**

Chairmen and moderation:
Paul B. Griggs (Seattle)
Eduardo B. Rodrigues (Florianopolis)

- 1 **Stephan Schulze** (Marburg)
Visualization and Documentation of the Vitreoretinal Interface (Funduscopy, Biomicroscopy, Fotodocumentation)
- 2 **Stefan Clemens** (Greifswald)
Vitreoretinal Correlation in Ultrasound
- 3 **Robert Rejda**^{1,2,4}, A. Petzold³, T. Zarnowski², S. Thaler⁴, F. Kruse⁵, E. Zrenner⁴, A.G.M. Jünemann⁵ (¹Warsaw, ²Lublin, ³London, ⁴Tübingen, ⁵Erlangen)
A New Biomarker for Retinal Degeneration: Vitreous Neurofilaments
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- 6 **Jörg C. Schmidt** (Marburg)
Sandwich Colouring of the Vitreoretinal Interface
- 7 **Vincenzo Ferrara** (Arona)
Blue Dying: Clinical Experience
- 8 **Eduardo B. Rodrigues**¹, M. E. Farah², C. H. Meyer³, S. Mennel⁴, M. Maia² (¹Florianopolis, ²Sao Paulo, ³Bonn, ⁴Marburg)
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Italian Style to Color the Eye

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18.15

Chairmen and moderation:
Hermann D. Schubert (New York)
Einar Stefánsson (Reykjavík)

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Triamcinolone or anti-VEGF in DME – Debate

13 **Nicole Eter** (Bonn)
Anti-VEGF Therapy for Diabetic Macular Edema

14 **Hans Hoerauf** (Göttingen)
Pro Triamcinolone, contra Anti-VEGF

15 **Einar Stefánsson** (Reykjavík)
The Role of the Vitreous in Diabetic Macular Edema

16 **Horst Helbig** (Regensburg)
Vitrectomy with or without ILM-Peeling in Diabetic Macular Edema

17 **Pohl-lecture**
Borja Corcóstegui (Barcelona)
Anti-VEGF Assisted Vitrectomy in Diabetic Retinopathy

Saturday, 17th May 2008

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➔ The vitreoretinal interface

10.30

Chairmen and moderation:
Jerry Sebag (Huntington Beach)
Peter Wiedemann (Leipzig)

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Jerry Sebag (Huntington Beach)
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Peter Wiedemann (Leipzig)
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Steve Pakola (New York)
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➔ AMD – New hypothesis in the pathogenesis

11.30

Chairmen and moderation:
Susanne Binder (Vienna)
Stefan Clemens (Greifswald)

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Susanne Binder¹, W. Brannath², C. Glittenberg¹, F. Zeiler¹, J. Sebag³, I. Krebs¹
 (¹Department of Ophthalmology, Rudolf Foundation Clinic, The Ludwig Boltzmann Institute for Retinology and Biomicroscopic Lasersurgery, Vienna, ²Core Unit, Medical Statistics and Informatics, Medical University Vienna, ³VMR Institute Huntington Beach, USA / Department of Ophthalmology, University of Southern California, USA)
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Salvatore Grisanti (Lübeck)
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12.00

5th scientific session:

➔

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13.00

Chairmen and moderation:
Borja Corcóstegui (Barcelona)
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38 **Michael J. Koss** (Frankfurt/Main)
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18.00 **At the end! What's new?**

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Final remarks and closing ceremony
Peter Kroll (Marburg)

1st scientific session: Imaging the vitreoretinal interface

1. **Visualization and Documentation of the Vitreoretinal Interface (Funduscopy, Biomicroscopy, Fotodocumentation)**
Stephan Schulze (Marburg)



The posterior vitreous cortex is normally invisible when being attached to the retinal surface and presenting no opacities or densifications. Parts of it will become visible during the physiological or pathological process of posterior vitreous detachment (PVD), especially in the papillary area. Nevertheless, the foveal situation often remains unclear, even though just an abnormal PVD and a persisting macular attachment are considered to be responsible for many diseases of the vitreoretinal interface. Usual ophthalmological diagnostic tools like slit lamp biomicroscopy or contact lenses don't obtain high enough specificity and sensitivity concerning the question whether the vitreous is adherent to the macula or detached. So further investigations with the aid of ultrasound or OCT are often needed.

2. **Vitreoretinal Correlation in Ultrasound**
Stefan Clemens (Greifswald)



Introduction: Currently commercially available equipments for ultrasonography with B-scan contain a 10 MHz transducer faintly focussed in the posterior vitreous cavity. Are the informations of further relevance for indications at the vitreoretinal border?

Subject: Vitreoretinal adhesion syndroms and epiretinal membranes where examined with high resolution laser imagination procedures and ultrasonography for sensitivity in different physiologic and pathologic structures.

Results: With ultrasound B-scan one quadrant can be depicted simultaneously including vitreoretinal adherences and membranes. Motility phenomena can be seen during movement of patient eyes. The gel compartment of the vitreous can be delineated. Disadvantages of ultrasound are the much lesser axial resolution 10 fold and transverse 40 fold less than laser imaging. By ultrasound examination through hazy media is possible. Membranes in laser imaging can be visualized independent of the rectangular impact of energy. Ultrasound is inferior in delineating cystic processes of the central retina.

Discussion: Laser imaging gives sufficient information for surgical indications at the vitreoretinal interface. Additionally by ultrasound topographic relations around the whole rear part of the vitreoretinal correlation can be imagined simultaneously. Connections of gel compartments via membranes to the retina can be differentiated for maybe better summarising the mechanical adhesion effect at the retinal border.

Summary: Ultrasound gives additional information about the vitreoretinal interface comparing to laser imaging and may be useful in questions of topography, compartmentalisation of the vitreous and appropriate adhesion effects.

Comments:

3. **A New Biomarker for Retinal Degeneration: Vitreous Neurofilaments**

Robert Rejdak^{1,2,4}, A. Petzold³, T. Zarnowski², S. Thaler⁴, F. Kruse⁵, E. Zrenner⁴, A.G.M. Jünemann⁵ (¹Warsaw, ²Lublin, ³London, ⁴Tübingen, ⁵Erlangen)



Purpose: An important cause for loss of visual function is thinning of the retinal nerve fibre layer due to loss of axons. Degenerating axons release cell-type specific proteins such as neurofilaments into the adjacent compartment.

Here we tested whether the phosphorylated neurofilament heavy chain (NfH-SMI35) could be measured from human vitreous body homogenate or anterior chamber fluid using a standard ELISA technique.

Methods and Results: We found NfH-SMI35 to be quantifiable from the vitreous body homogenate, but not from the anterior chamber fluid. Patients suffering from retinal detachment had significantly higher vitreous NfH-SMI35 levels compared to those suffering from epiretinal gliosis or macular holes, but not compared to organ donors. This suggests that some of the patients with retinal detachment may already have suffered from considerable axonal loss prior to surgery. High vitreous body fluid NfH-SMI35 levels in retinal detachment may therefore represent a poor prognostic sign.

Conclusions: The presented method may be useful for testing new neuroprotective strategies in a range of models developed to study the loss of retinal axons and their ganglion cells experimentally, as well as serving as a biomarker for future human studies.

4. **Spectralis High Resolution Angiography/OCT with Heidelberg Angiography**

Carsten H. Meyer (Bonn)



To evaluate simultaneous confocal scanning laser ophthalmoscopy (cSLO) and high-speed, high-resolution, spectral-domain optical coherence tomography (OCT) to visualize macular pathologies.

Methods: OCT-images and simultaneous recording of fluorescein angiography, indocyanine green (ICG) angiography, infrared, redfree, or fundus autofluorescence (FAF) images were obtained with a novel imaging device (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). An optically pumped solid state laser generates the excitation wavelength (488 nm) required for redfree, FAF and fluorescein angiography images. For ICG angiography and infrared imaging diode laser sources at 790 and 815 nm are used. For OCT 40.000 A-scans are acquired per second with 7 μm depth and 14 μm lateral optical resolution. The B-scans with an angle of 30 degrees have a scan width up to 1.536 A-scans with a digital lateral resolution of 6 $\mu\text{m}/\text{pixel}$, a scan depth of 500 pixel with 4 $\mu\text{m}/\text{pixel}$ resolution and a scan rate up to 50 B-scans/sec. In addition volume scans can be obtained at 15, 20 and 30 degrees. An integrated eye tracking allows for live averaging of cSLO-images as well as OCT B-scans.

Results: Dry and vascular age-related macular degeneration, macular telangiectasia, retinal arterial and branch vein occlusion were evaluated and cSLO and OCT frames correlated. Fluorescein and ICG-angiographic phenomena recorded in cSLO images could be accurately analysed in corresponding OCT-cross sections. Abnormal FAF-signals were correlated to alterations at the outer retinal/retinal pigment epithelial cell layer in high resolution OCT-scans. Three-dimensional OCT enabled comprehensive retinal coverage. The imaging software accurately tracked eye movements. Averaging of live B-scans considerably enhanced image quality.

Conclusion: The combined cSLO/OCT system allows for simultaneous recordings of topographic and tomographic images. Particularly the pixel-to-pixel correlation between the confocal angiograms, FAF images and other imaging modes with the OCT scans may provide a better understanding of the pathogenesis of retinal pathologies, and improve diagnosis and management of patients with macular diseases.

5. **3D Ultrahigh Resolution OCT in Detecting the Vitreoretinal Interface**

Wolfgang Drexler (Cardiff)

The presentation has been called off.

6. Sandwich Colouring of the Vitreoretinal Interface

Jörg C. Schmidt (Marburg)



Background: Initial historic considerations to perform a pars plana vitrectomy were made for opaque vitreous cortex due to dense asteroid hyalosis or vitreous hemorrhages. However current indications for a vitreo-retinal surgery include mainly vitrectomies in eyes with a clear vitreous e. g. retinal detachment, epiretinal membranes or macular holes, thus a proper visualization of the transparent vitreous gel during surgery is helpful.

Material and methods: The transparent structure of the vitreous cortex as well as thin epiretinal membrane may become visible during surgery by mild vitreal hemorrhages or intravitreal application of 0.05 ml crystalline triamcinolone acetonide. The inner limiting membrane (ILM) can be stained by indocyanine green (ICG) in the fluid filled eye.

Results: Mild accidental intraoperative bleedings or intended injection of 0.05 mg autologous blood may help to stain transparent vitreous structures and visualize remaining vitreous. Intravitreal triamcinolone crystals attach to the surface of vitreous cortex, bursa premacularis or retina itself allowing better visualization of a controlled vitreous removal. Whereas the vitreous gel can be visualized by triamcinolone, ICG is necessary to selectively stain the ILM.

Discussion: A safe and complete removal of clear vitreous or transparent membranes may be achieved by the intraoperative application of autologous blood or triamcinolone. The application of different dyes is helpful to colour different structures of the vitreoretinal interface.

7. Blue Dying: Clinical Experience

Vincenzo Ferrara (Arona)



Purpose: The complete peeling of all the different layers of the vitreoretinal interface has become routine for the majority of vitreoretinal surgeons in macular surgery. Different dyes have been introduced to facilitate a complete, safer and faster peeling. In our Institution the use of Indocyanine Green (ICG) was abandoned after the clinical experience of two cases of retinal pigment epithelium (RPE) toxicity related to its intraoperative use.

Methods: Since the year 2002, 1240 eyes have been treated for macular pucker, macular hole, edema following venous occlusions or diabetic macular edema. Two surgeons (V.F. V.B.) performed standard three-port pars plana vitrectomy (20\23\25 gauges) with an Accurus® 800 CS Surgical System. Light source were the Halogen lamp included into the machine or a Xenon lamp (Alcon High Brightness Illuminator). A Sapphire 90 mm or a Bullet Shielded were used as illumination probe (15 % energy setting for the Xenon lamp and 30 % for the Halogen). A single 0,2 ml Triamcinolone (IVT® Intra Vitreal Triamcinolone, Sooft Italia SpA) injection was applied in most of cases for a better visualization of the posterior hyaloid which was always removed by active suction. Therefore a 0,15 % solution of Trypan Blue (TB) (Membrane Blue® D.O.R.C. International) was injected into a Bss filled eye with a complete washout after 20 seconds. In the last 6 months a 0,18 % solution of Brilliant Blue (BB) (Brilliant Peel® Fluoron, GMBH 0,25 mg) was used as alternative, following the same procedure. There were no differences in the demographic and macular surface characteristics of the BB and TB groups. After a complete washout of the dye the epiretinal membranes (ERM) and the internal limiting membrane (ILM) were peeled with ILM forceps.

Results: Staining of ERM was clearly evident after a single injection of TB whereas the BB didn't coloured them efficiently even after several injections. On the contrary removal of ILM was easier after a single injection of BB comparing to repeated injections of TB. No significant difference was noted in postoperative visual acuity recovery between the two groups considered. Two accidental subretinal migration of TB happened due to a briskly injection. There were no cases of retinal or RPE toxicity in both groups.

Conclusions: Blue-assisted vitrectomy represents a safe way to achieve a complete and safe removal of both cellular and acellular membranes overlying the macula. In our experience the use of TB or BB lead to good anatomical and functional results comparable with ICG without evidence of dye-related adverse effects. TB seems especially indicated for staining epiretinal cellular membranes whereas the BB appears to be more effective for the staining and peeling of the acellular ILM. Their specific indication for the intraocular surgery use seems an additional reason to prefer them to other 'off-label' solutions.

8. Progresses in Chromovitrectomy

Eduardo B. Rodrigues¹, M. E. Farah², C. H. Meyer³, S. Mennel⁴, M. Maia²
(¹Florianopolis, ²Sao Paulo, ³Bonn, ⁴Marburg)



Background: Chromovitrectomy facilitated intra-operative identification of fine pre-retinal membranes and tissues. Progresses in chromovitrectomy may enable discovery of new dyes with better safety profile and with new tissue-affinity properties. In addition, improved techniques may enable minimization of concentration of dye in contact with the retina.

Methods: **1.** To evaluate the retina toxicity of two doses 0.05 % and 0.5 % of six novel dyes for chromovitrectomy in rabbits eyes: light green (LG), fast green (FG), evans blue (EB), brilliant blue (BriB), bromophenol blue (BroB) or indigo carmine (IC); **2.** To evaluate the staining affinity of LG, FG, EB, BriB, and BroB to the ILM, ERM, and vitreous in animals and human donor eyes; **3.** To investigate the overlap of light irradiance of vitrectomy light sources in comparison to light absorbance of vital dyes; **4.** To analyze the osmolarity and pH of nine vital dyes; **5.** To describe a technique to paint epiretinal membranes with vital dyes.

Results: **1.** Histology examination disclosed slight focal retinal changes in eyes exposed to 0.05% LG, IC, FG, BriB, and BroB, similar to the control. At the higher dose of 0.5 %, BroB, LG and EB promoted cellular edema and vacuolization within the ganglion and bipolar cells, whereas 0.5 % FG and IC caused slight retinal alterations similar to BSS injection. Intravitreal injection of 0.5 % EB caused significant loss of neuroretinal cell counts in comparison to control eyes ($p < 0.05$). **2.** BriB possesses best staining affinity to ILM, while BroB, EB and LG may also stain the ILM. Most vital dyes bind to vitreous and cellular ERM. **3.** Spectrophotometry analysis revealed that most vital dyes except ICG have remarkable overlap with every available vitrectomy light source at absorbance from 550nm to 680nm. Overlap of irradiance of endoillumination fiberoptics and absorbance of vital dyes was greater in Grieshaber GLS and Alcon Accurus H3. Photon 2 had the lower overlap area among all light sources; **4.** Osmolarity of all nine dyes diluted in water decreased to very low value ranging from 0 to 54 mOsm, while dilution in BSS and glucose promoted small but clinically relevant changes in osmolarity and pH in ranges from 260 to 340mOsm. **5.** The use of the VINCE may allow fine epiretinal painting.

Conclusions: Novel vital dyes possess much variable properties in toxicity, staining affinity, osmolarity and pH, which may influence their retinal biocompatibility. Intra-operative light exposure during chromovitrectomy should be minimized. The progressive order of retinal biocompatibility of novel dyes, from safest to most toxic, was IC, FG, BriB, BroB, LG, EB.

9. Subhyaloidal vs Sub-ILM Hemorrhage – Localization and Classification

Stefan Mennel (Marburg)



Hemorrhage at the macula may cause visual deterioration within seconds or minutes. Biomicroscopy reveals a dome-shaped bleeding in the macular area, but the precise localisation of the blood, i.e. subhyaloidal or macular, is by funduscopy mostly indistinguishable unknown. Histologic analysis following vitrectomy show in many cases a sub-ILM location of the hemorrhage. It seems questionable whether available diagnostic tools allow a reliable pre-operative location of the cleavage plane.

Patients with presumed subhyaloidal hemorrhage were examined by funduscopy, ultrasound and optical coherence tomography (OCT). Additionally, literature research was performed to find diagnostic tools to differentiate subhyaloidal and sub-ILM hemorrhage.

Our preliminary results show that only in selected cases funduscopy, ultrasound and OCT allow to elucidate the location of the hemorrhage. These examinations seem to be more reliable if the posterior hyaloid is already detached. After performing laser puncture, OCT presents as an optimal method to differentiate subhyaloidal and sub-ILM hemorrhage.

The absence of a definitive biomicroscopic characteristic to clinically distinguish between subhyaloidal and macular hemorrhage, which may be important for therapeutical decisions in the future, emphasizes the need to develop additional diagnostic techniques.

10. Italian Style to Color the Eye

Cesare Forlini, M. Forlini, A. Aversano, P. Rossini (Ravenna)



Aim of this presentation is to show a new pharmacological product introduced for the vitreo-retinal surgery and two surgical techniques routinely used for the macular surgery.

The introduction of Triamcinolone acetonide in the vitreo-retinal surgery allows to perform a more complete and radical vitrectomy, thank to its capability to link and show the vitreous fibrils. Moreover, it links the posterior hyaloid and the epiretinal membranes, facilitating their removal.

IVT[®] (BIOOS, Italy) is a new micronized Triamcinolone Acetonide in sterile syringe approved for intraocular surgical use. It is a carbopolimer suspension containing crystals with an average diameter of 30 microns. We show the use of this suspension during the common manoeuvres performed during the common vitreo-retinal surgery.

The advantages of this new molecule are:

- Uniform and complete opacification
- Lower dosage
- Lack of adverse effects
- Lack of systemic effects
- Safety of use
- Guaranteed sterility
- Not toxic for retinal or other tissues.

Perfluorocarbon liquids (PFCL) are heavier-than-water liquids introduced in the middle '80 years by Dr. Stanley Chang to flatten intraoperatively the retina during the vitreo-retinal surgery for retinal detachment. The Indocyanine Green (ICG) is a dye used in vitreo-retinal surgery to stain the internal limiting membrane (ILM). We show the combined use of PFCL and ICG to peel the ILM in case of vitrectomy for retinal detachment.

After put the PFCL on the posterior pole to flatten the retina, the long-cannula is positioned into the PFCL bubble, very near to the retinal surface and the ICG is injected. This allows the dye goes directly under the PFCL bubble (pushed by the weight of the liquid) and to stain the ILM. Then it is possible easily to perform the ILM peeling. The described technique avoids also the ICG passes into the subretinal space, because the dye is injected between the PFCL and the retinal surface, without dispersion in the vitreous chamber.

Finally, a combined use of IVT[®] and ICG is showed. Because of well known toxic effects produced by ICG in the retinal pigment epithelium (RPE), we inject the IVT[®] on the hole, before the staining, to protect the inner layers of the retina. After closing the infusion, a little amount of IVT[®] is put on the macular hole and then, the ICG is injected. Opened the infusion line the ICG in excess is removed and it is possible to observe that the hole is not stained.

In conclusion, the combined use of IVT[®], PFCL, ICG, allows the vitreo-retinal surgeon more radical and certain surgical manoeuvres.

Disclosure: ALL THE AUTHORS HAVE NOT FINANCIAL INTERESTS.

2nd scientific session: Diabetic retinopathy

11. DME – The Pathogenesis and which Treatment May be Effective?

Hermann D. Schubert (New York)



The macula, the central and thickest portion of the retina, features a high concentration of glia and up to four layers of blood vessels. Based on the mere volume of tissue and dual blood supply from inner retina and choroid, the macula is particularly sensitive to ischemia and breakdown of the blood ocular barrier. Whereas capillary closure is mediated by leukostasis and changes in basement membrane by hyperglycemia, multiple upstream cellular mediators, cytokines and growth factors (the cascades) have been found to be elevated in the diabetic vitreous. Among them are VEGF, interleukin 6, hepatocyte growth factor, and early and advanced glycation end products. Decrease in visual acuity correlates highly with size of foveal avascular zone, perifoveal intercapillary area and vitreous fluorophotometry penetration ratios as well as patient age. The average age of patients in western studies of diabetic macular edema is 61 plus-minus ten years superimposing the ischemia which is related to age. Swelling in macular edema thus depends on what and which cell has survived the chronic ischemia related to overall retinopathy grade, disease duration and age of patient. There is always the possibility of an edematous atrophy of increased thickness. Poor visual correlation attests to this.

Treatment of diabetic edema consists of control of diabetes, hypertension, and hyperlipidemia to delay ischemia. Spontaneous improvement of vision and macular thickness has occurred among the placebo treated eyes in recent random-

ized studies and in eyes assigned to delayed photocoagulation in the ETDRS. Focal laser is the only approved treatment for DME in the US and is being restudied and compared to newer modalities recruiting large numbers of patients in several trials (www.DRCR.net). First results of these will be available in late 2008. Vitreous traction can be addressed surgically; cytokines and growth factors can be downregulated or blocked either with a shot gun approach or by targeting isolated cellular mediators. There will always be more mediators. Apart from side effects and possibly limited duration of visual benefit, treatment is cumbersome and often anxiety producing to patients, longterm with uncertain endpoint, and costly to society. Delaying the symptomatic visual threshold by earlier combined interventions may be the most effective and least invasive strategy.

12. Triamcinolone or anti-VEGF in DME – Debate

Stefan Mennel (Marburg)

Intravitreal triamcinolone has been extensively proven as an effective treatment for diabetic macular edema. In most cases the effect is limited to a period of three to six months and complications such as secondary cataract formation and increase of intraocular pressure have been observed in up to 50 % of cases.

Anti-VEGF effectively decreases retinal thickness in case of exudative age-related macular degeneration. Case series as well as preliminary results of two prospective randomized clinical trials using MacugenTM and LucentisTM have shown positive effects in the treatment of diabetic macular edema. Nevertheless the reduction of retinal thickness is limited in many cases. Despite a higher frequency of application (four to six week interval) anti-VEGF present a lower incidence of complications.

In the following debate two experts, Prof. Dr. Nicole Eter and Prof. Dr. Hans Hoerauf, will discuss about the treatment of diabetic macular edema. Eter will defend the use of new anti-VEGF drugs while Hoerauf will present the benefits of triamcinolone.



13. Anti-VEGF Therapy for Diabetic Macular Edema

Nicole Eter (Bonn)

Inhibition of vascular endothelial growth factor (VEGF) has become the standard of care in neovascular age-related macular degeneration. The effect of VEGF in other proliferative diseases such as diabetes also suggests a role for this approach in the management of diabetic macular edema (DME). Chronic hyperglycemia leads to oxidative damage to retinal endothelial cells, which in turn leads to ischemia and subsequent overexpression of a number of growth factors including VEGF.

Pegaptanib sodium (MacugenTM) has recently been studied in a phase II trial for DME. In that study, 172 subjects with DME were randomized to receive a series of 3 intravitreal injections of pegaptanib (at entry and every 6 weeks) in 1 of 3 doses, or sham injections, and were followed for 36 weeks. Mean visual acuity had improved to 20/50 in the pegaptanib 0.3-mg group versus only 20/63 in the sham group. Mean central retinal thickness decreased by 68 μ m in the 0.3-mg group, whereas it increased by 4 μ m in the sham group.

Ranibizumab (LucentisTM) is currently investigated in a Phase II trial (RESOLVE study). 150 patients with DME have been randomized to receive either 1 of 2 doses of ranibizumab, or sham treatment. Three uploading injections are given in monthly intervals, followed by on-demand-treatment until month 12. First interim analysis after 6 months showed a reduction in macular edema and an increase in visual acuity in both treatment groups as opposed to the control group.

Bevacizumab (AvastinTM) has been investigated in smaller case series so far, where it also demonstrated potentials for edema reduction. Thus, anti-VEGF therapy for DME shows promising results in preliminary studies. Larger studies are ongoing. VEGF inhibition may represent an important component of DME therapy in the future.



14. Pro Triamcinolone, contra Anti-VEGF

Hans Hoerauf (Göttingen)

Intravitreal steroids and anti-VEGF-substances are injected regularly, can reduce the edema and may - if photoreceptor recovery occurs – enhance visual acuity, however, cannot cure diabetic edema so far. In this talk the advantages of intravitreal triamcinolone acetonide (IVTA) and the disadvantages of anti-VEGF-treatment, both currently used “off label”, will be presented.

There are several observations in favour of IVTA:

- 1) its longer lasting effect and reduced reinjection rate
- 2) an inhibitory effect of TA on osmotic glial swelling
- 3) a stronger effect of TA on edema resorption in contrast to bevacizumab
- 4) the pathogenesis of DME may not only be attributable to VEGF-dependency but also to other mechanisms suppressed by corticosteroids

Con-arguments against Anti-VEGF therapy:

- 1) VEGF acts as a key regulator of angiogenesis
- 2) VEGF blocking may increase macular ischemia
- 3) systemic side effects of repeated anti-VEGF reinjections in diabetic individuals are unclear.



15. The Role of the Vitreous in Diabetic Macular Edema

Einar Stefánsson (Reykjavík)

Vitreotomy replaces the vitreous gel with another medium, usually an aqueous saline solution followed by aqueous humour, or with silicone oil, air etc. In all cases the viscosity of the medium is changed and this influences the diffusion of all molecules and fluid currents in the vitreous cavity.

The Stokes Einstein equation shows that the diffusion coefficient depends inversely on the viscosity of the medium in which diffusion takes place. The more viscous a solution, the slower is diffusion through it. Similarly, the Hagen Poiseuille equation shows that fluid currents are slower in a more viscous solution. Since diffusion and fluid currents are the only transport mechanisms available to any molecule in the vitreous cavity, this means that the transport of any molecule will be slower if the medium is highly viscous and faster if the medium becomes less viscous.

Vitreous humour is many times more viscous than water or saline solutions. Reported viscosity measurements of vitreous gel vary somewhat. Our measurements in the pig indicate that the viscosity of the vitreous humour is biphasic, with a lower viscosity component that is about 6 centipoise, six times more viscous than water, and a higher viscosity component well above 100 centipoise.

When we replace vitreous gel with six times less viscous saline, the transport of any molecule in the vitreous cavity becomes six times faster. Initially our eyes were on the transport of oxygen. Stefansson et al (TAOS, 1981) reported that following vitrectomy and lensectomy in cats the oxygen tension fell in the anterior chamber and rose in the vitreous cavity and at the retinal surface, indicating a rapid transport of oxygen between the front and back of the one chamber eye filled with saline. Retinal ischemia increased the oxygen transport from front to back even more.

In a vitrectomized eye, oxygen transport through the vitreous cavity can supply oxygen to an ischemic area with BRVO and improve the retinal oxygen tension (Stefansson et al, IOVS 1990). Holekamp and Beebe (AJO 2005) have shown in the human eye that oxygen fluxes increase following vitrectomy and oxygen tension gradients are flatter, which agrees well with the previous reports and the classic rules of physics above. The improved transport by diffusion and fluid currents applies to all molecules, not only oxygen. Nutrients and growth factors for example will also diffuse faster in the vitrectomized eye. This may have significant clinical effects.

In an ischemic area of the retina, for example in BRVO or diabetic retinopathy, oxygen will diffuse to that area through the vitrectomized vitreous cavity and at the same time VEGF will diffuse away from the area into the cavity. This reduces the concentration of VEGF through 2 mechanisms, reduced production due to improved oxygenation and clearance away from the tissue. This may explain the beneficial effect of vitrectomy on ischemic retinopathies and at the same time why neovascularization may take place on the iris after vitrectomy as oxygen now diffuses away from the anterior segment while retinal VEGF diffuses forward.

Vitreotomy influences the pathophysiology of diabetic macular edema in several ways. Firstly, by improving retinal oxygenation, the production of VEGF decreases. Secondly, VEGF is cleared away from the retina into the vitreous cavity more rapidly than before. The decreased VEGF concentration will decrease the permeability of the retinal microcirculation to osmotically active molecules and counter edema formation according to Starling's law. Thirdly, the improved oxygenation will also constrict the arterioles (Gottfredsdottir et al, AJO 1993), decrease the hydrostatic pressure in the microcirculation and decrease edema formation according to the hydrostatic arm of Starling's law (Stefansson, Survey Ophthalm. 2006).

Finally, we may speculate that following a posterior vitreous detachment the diffusion characteristics of the vitreous cavity will be somewhat similar to the vitrectomized eye. This may have beneficial and harmful consequences. On one hand ischemia might be helped, as was outlined above. On the other hand the retina might be releasing important nutrients, neurotransmitters and growth factors into the vitreous cavity at a faster rate than would be normal, when the vitreous gel is attached. Whether some of the degenerative age related retinal diseases, such as age related macular degeneration and glaucoma, relate to this remains to be investigated, but it is interesting that many of them seem to start at about the same time in life many of us experience a posterior vitreous detachment.



16. Vitrectomy with or without ILM-Peeling in Diabetic Macular Edema

Horst Helbig (Regensburg)



The gold standard for the treatment of diabetic macular edema (DME), based on the results of large randomized controlled clinical trials, still is laser coagulation. Clinical experience however has shown disappointing results in diffuse forms of DME. Vitrectomy is the standard of care for complications of proliferative diabetic retinopathy. It has been observed however, that diffuse DME improved after vitreous surgery, especially when a taut attached hyaloid membrane was removed from the macula. Many case series have been described so far, showing more or less reduction of DME after vitrectomy. Functional results however were disappointing in most series. Another unsolved question is, whether the ILM should be removed. Small comparative case series do not give clear answers.

Introduction of OCT in the preoperative diagnostics has shown that in some cases vitreofoveal traction is present, not visible on biomicroscopy alone. In other cases however no tractive component is present and DME nevertheless improved after vitrectomy. Possibly, removal of a cytokine depot in the vitreous on the retinal surface and improvement of oxygen supply to the inner retina may contribute to the observed therapeutical effects.

In contrast to intravitreal drug injections, vitrectomy offers a long term positive effect without the necessity for repeated treatments. On the other hand, the potential for complications is high with vitreous surgery. Recent developments have introduced new therapeutic options for the treatment of diffuse DME but the optimum strategy has not been defined yet. Clinical trials are urgently needed to compare the effects of laser, vitrectomy and intravitreal injections of anti-VEGF drugs and triamcinolone.

Pohl-lecture

17. Anti-VEGF Assited Vitrectomy in Diabetic Retinopathy

Borja Corcóstegui (Barcelona)



Intravitreal Anti-VEGF and other anti-angiogenic drugs shows promise in the treatment of complications of diabetic retinopathy (PDR). Not only can be used for macular edema and iris neovascularization, anti-VEGF can be used for retinal neovascularization, post-vitrectomy recurrent vitreous hemorrhage, and at the end of vitrectomy to avoid repletions and recurrent bleeding.

To treat retinal neovascularization, 0.05 ml (1.25mg) of Intravitreal Avastin was injected preoperatively one week prior to vitrectomy in 28 patients with severe PDR. The follow-up period was at least six months. Pre- and post-injection FA and OCT was performed in 20 eyes. Vitreous hemorrhage precluded a good visualization in the other 8 eyes. By ophthalmoscopy following IVA, Avastin appeared to decrease neovascular vessels, shrinkage of the collagen tissue and decrease the caliber of the retinal vessels. A few cases were shown demonstrating such retinal NV regression. Post-vitrectomy recurrent vitreous hemorrhage is relatively frequent (3-7 %) and typically is a consequence of fibrovascular proliferation at the sclerotomy site(s). We injected 2.5 mg of Avastin in 12 eyes affected with mild vitreous hemorrhage three times in three months. In four of these cases, he combined cryotherapy at the three sclerotomy sites with IVA. After 6 months of follow-up, only 1/12 eyes rebled. To avoid repletions and rebleeding at the sclerotomy sites after vitrectomy surgery in severe PDR, the author injected 2.5mg of Avastin prior to removing the last cannula.

The high dose was chosen to presumably have a longer half life in the vitreous cavity. The author also assumed that the first week after surgery is the most critical period to have the anti-angiogenic effect of Avastin. Other potential factors that may influence repletions and rebleeding is the use of 23 and 25 gauge instruments which may decrease scleral irritation more than conventional entries.

In conclusion, Avastin is very useful as a pre-surgical treatment for PDR and will be used for most of his severe PDR cases in the future. Avastin appears to be effective in controlling recurrent vitreous hemorrhage in his small cohort and can potentially help repletions at the sclerotomy sites.

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3rd scientific session: The vitreoretinal interface

18. Anomalous PVD and Vitreoschisis

Jerry Sebag (Huntington Beach)



Invisible *by design*¹, vitreous is a viscoelastic extracellular matrix that is normally a gel because of the intricate organization of its macromolecular components². During aging, there is liquefaction of the gel and weakening of vitreo-retinal adhesion, resulting in posterior vitreous detachment (PVD). Liquefaction without concurrent vitreo-retinal dehiscence results in *Anomalous PVD*³. The clinical manifestations of Anomalous PVD vary, depending upon where traction is exerted. In the periphery, retinal tears and detachments result while at the optic disc, anomalous PVD contributes to diabetic vitreoretinopathy⁴. At the macula, there can be vitreo-macular traction syndrome, a phenomenon which may play a role in exudative age-related macular degeneration⁵. A split in the posterior vitreous cortex, known as vitreoschisis, may play a role in the development of macular holes and pucker.⁶ Studies have shown that about half of patients with macular hole and macular pucker have evidence of vitreoschisis on combined OCT-SLO imaging⁷. Thus, the unifying concept of anomalous PVD provides insight into disease pathogenesis and guides new avenues of research and development, such as Pharmacologic Vitreolysis.⁸

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19. Pathogenesis of Epiretinal Membranes

Peter Wiedemann (Leipzig)



Macular surface disorders comprise cellophane maculopathy, surface wrinkling maculopathy and macular pucker; these entities are also described as idiopathic premacular gliosis. This disorder is related to premacular secondary fibrosis and vitreomacular traction syndrome. Primary epiretinal membranes (ERM) are globally adherent to the retina, secondary focally. Premacular gliosis is seen in up to 8 % of patients and is bilateral in 30 %. Significant bilateral loss is not common.

ERM are composed of a wide variety of different cell types: glial cells (including microglia, Müller cells and fibrous astrocytes), epithelial cells originating from the RPE and ciliary body, blood-derived immune cells (such as macrophages, lymphocytes, and neutrophils), and myofibrocytes. Within the membranes, glial and RPE cells transdifferentiate into contractile myofibrocytes. Epiretinal membranes develop at sites where Müller cells proliferate and migrate onto the inner surface of the retina (probably in response to growth factors present in the vitreous), and where hypertrophied Müller cell processes extend into the vitreous cavity. The membranes are focally connected with the retinal tissue via fibers of Müller cells. Enhanced amounts of growth factors in the vitreous direct the progression of epiretinal membranes. Among these factors, especially the hepatocyte and platelet-derived growth factors stimulate the scattering, migration, and proliferation of retinal cells such as glial and RPE cells. The contraction of epiretinal membranes is stimulated by vitreal factors, especially insulin-like and and platelet-derived growth factors, which are also present in blood serum extravasated into the vitreous. Blood-derived immune cells within the vitreous are attracted to sites of glial reactivity in the retina after glial expression of inflammatory factors like monocyte chemoattractant protein-1. The phase of separation in posterior vitreous detachment may be of fundamental importance in the formation of ERM.

Spontaneous separation of ERM from the retina is seen. Peeling of epiretinal membranes may improve the delivery of oxygen and glucose from the vitreal fluid to the underlying ischemic retina, and the exchange of ions across the inner retinal surface which is important, for example, for retinal potassium buffering.

20. ILM Removal: 20 Years Experience

Didier Ducournau, Y. Ducournau (Nantes)

After having discovered in 1987 for MEM, in 1991 for MH and in 2000 for CME that ILM Removal gives a higher improvement than vitrectomy with posterior hyaloid removal alone, the authors, upon pathological studies, try to give their explanation on "How does ILM Removal work". The improvement does not seem to be linked to the removal of a pathologic process but rather to the induction of a cellular retinal response at the level of the Muller cells.



21. Plasmin-Assisted Vitrectomy in PDVR

Mike T. Trese (Royal Oak)

Purpose: This is a pilot study to assess the use of autologous plasmin enzyme (APE as an adjunct to vitreous surgery in eyes with advanced diabetic retinopathy.

Design: Prospective noncomparative interventional case series.

Participants: Seven patients with advanced diabetic retinopathy selected at random from our practice population.

Methods: Seven eyes were treated with APE as an adjunct to standard vitreous surgery. Six eyes had macular tractional retinal detachments, and one eye had refractory macular edema. Three fellow eyes had standard vitreous surgery performed for macular tractional retinal detachments without APE. All 10 eyes had macular edema and background diabetic retinopathy.

Main outcome measures: The main outcome measures included induction of a posterior vitreous detachment, retinal reattachment, improvement in visual acuity, and resolution of macular edema.

Results: All seven APE-treated eyes achieved spontaneous or easy removal of the posterior hyaloid including one eye that had vitreoschisis over areas of detached retina. All eyes treated with APE had resolution of intraretinal edema. Retinas of all eyes treated with APE were reattached. The three fellow eyes were treated by vitreous surgery without APE. Two of the three fellow eyes had reattached retinas, but none had resolution of intraretinal edema without further focal photocoagulation treatment. Mean visual acuity improvement was 0.7 logarithm of the minimum angle of resolution (LogMAR) units in APE-treated eyes and 0.1 LogMAR units in eyes without APE. The average follow-up period was 14 months.

Conclusions: This pilot study suggests that APE may be beneficial in the surgical management of diabetic retinopathy.



22. Microplasmin: Update on Clinical Development for Treatment of Vitreoretinal Disorders

Steve Pakola (New York)

Microplasmin is a recombinant, truncated form of plasmin with retained protease activity. Given that microplasmin cleaves both laminin and fibronectin, it is considered an ideal candidate for pharmacologic vitreolysis. After completion of pharmacology experiments demonstrating the expected ability to induce posterior vitreous detachment (PVD), an initial clinical trial evaluating microplasmin intravitreal injection in 60 patients undergoing vitrectomy was completed (the MIVI I trial). Final results demonstrated that the drug was generally well tolerated, with numerous cases of spontaneous PVD reported.

Based on these results, three additional trials were initiated and are currently ongoing:

MIVI II DME trial – 60 pt trial in patients with DME (Europe)

MIVI II Traction trial – 60 pt trial in patients with vitreomacular traction (Europe)

MIVI III trial – 120 pt trial in patients scheduled for vitrectomy (U.S.)

To date approximately 200 patients have received microplasmin via intravitreal injection. Study drug has been generally well tolerated. Additionally, as presented at the American Society of Retina Specialists (ASRS) annual meeting on December 4, 2007, microplasmin has shown evidence of benefit in numerous patients. Specifically, in the MIVI II Traction trial, 9 of 24 microplasmin treated patients (75 to 125 µg) achieved resolution of their vitreomacular traction (including macular hole closure in 2 of the 4 macular hole cases) without the need for vitrectomy. In contrast, none of the 6 sham injected patients had resolution of their vitreomacular traction (including two patients with macular hole). Current status of the ongoing trials and future directions for microplasmin clinical development will be discussed.



23. **Effect of Microplasmin on the Vitreoretinal Interface**
Anselm Kampik (Munich)

4th scientific session: AMD – New hypothesis in the pathogenesis

24. **Posterior Vitreous Adhesion: a Potential Risk Factor for Exudative AMD**

Susanne Binder¹, W. Brannath², C. Glittenberg¹, F. Zeiler¹, J. Sebag³, I. Krebs¹
(¹Department of Ophthalmology, Rudolf Foundation Clinic, The Ludwig Boltzmann Institute for Retinology and Biomicroscopic Lasersurgery, Vienna, ²Core Unit, Medical Statistics and Informatics, Medical University Vienna, ³VMR Institute Huntington Beach, USA / Department of Ophthalmology, University of Southern California, USA)



Background: To evaluate posterior hyaloid behaviour in eyes with exudative, non exudative AMD and age-matched controls in a prospective observational case series.

Methods: B-scan ultrasonography and OCT were performed in 163 eyes from 82 subjects over 55 years of age. 50 eyes with exudative AMD, 57 with non-exudative AMD and 56 control eyes. Main outcome measures: The number of eyes with complete posterior vitreous detachment (PVD) by ultrasound and the number of eyes with central vitreo-macular adhesion by OCT.

Results: By ultrasonography, 17/50 (34 %) of eyes with exudative AMD had PVD as compared to 41 (71.9 %) eyes with non-exudative AMD ($p = 0.00002$) and 34/56 (60.7 %) of controls ($p = 0.017$). OCT demonstrated persistent central vitreo-retinal adhesion surrounded by a detached posterior vitreous cortex in 19/50 (38 %) eyes with exudative AMD, significantly higher than in non-exudative AMD (4/57 = 7% $p < 0.0001$) and controls (6/56; $p = 0.002$). High risk eyes with dry AMD showed a trend toward higher vitreous adhesions as well.

Conclusion: Persistent attachment of the posterior vitreous cortex to the macula might be an additional risk factor inducing exudative AMD

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25. **The Role of the Vitreous in the Pathogenesis of Retinal Diseases**

Jörg C. Schmidt, S. Mennel (Marburg)

Background: Due to the immediate neighborhood of vitreous and retina, retinal diseases are frequently associated with changes of the vitreous.

Material and methods: During the last years, the condition of the vitreous and a posterior vitreous adherence were diagnosed biomicroscopically, by ultrasound and by OCT. The findings were then compared with findings during vitrectomy.

Results: In almost all vitrectomies for macular and retinal diseases we found an attached posterior vitreous intraoperatively, which seemed especially adherent at the posterior pole. This correlated only partly with preoperative findings, where a posterior vitreous detachment was described frequently.

Discussion: The literature describes a high percentage of complete posterior vitreous detachment in patients, increasing with age. In patients that undergo vitreoretinal surgery for macular or retinal diseases, an attached posterior vitreous is found frequently. We postulate, that this finding, which is untypical for that age group, may be a causative agent for retinal or vascular disease and prevents a successful treatment of AMD and other diseases because of macular traction. An early removal of the posterior vitreous may support treatment of these diseases.



5th scientific session: Pathological adhesions to the vitreoretinal interface

28. Vitreoretinal Interface and Retinal Vein Occlusion – a New Aspect of a Well-known Disease?

Lars-Olof Hattenbach, K. Köhler, F. Höhn, A. Mirshahi (Ludwigshafen)



Current data suggest that the intravitreal administration of antiangiogenic agents or steroids has the potential to improve major clinical outcomes in branch or central retinal vein occlusion. However, the task of determining the appropriate therapeutic approach in retinal vein occlusion is complicated, because severity of the disease and intervals between the patients' first symptoms and presentation differ widely. Vision loss is related to the extent of macular damage from intraretinal edema, hemorrhage or capillary non-perfusion. Moreover, there is increasing evidence that the status of the posterior vitreous may have an impact on the visual prognosis in retinal vein occlusion. Several clinical studies on the management of retinal vein occlusion are reviewed to determine prognostic factors. Moreover, we report on the evaluation of the posterior vitreoretinal interface with OCT scan and contact B-scan ultrasound in retinal vein occlusion patients who underwent treatment with intravitreal drugs.

29. Vitrectomy vs. New Treatment Strategies in BRVO

Ulrich Mester, H. Kaymak (Sulzbach)



Over a long time period no significantly efficacious treatment for BRVO was available. The standard therapy was isovolemic hemodilution with limited success. A new area of surgical intervention was initiated by Osterloh and Charles in 1988, and gained worldwide interest after the favourable results with arteriovenous sheathing published by Opremcak and Bruce in 1999.

Meanwhile numerous publications showed significantly functional and anatomical improvement in BRVO after vitrectomy, vitrectomy combined with sheathotomy and/or ILM-peeling. Therefore, the key factor of this surgery remains uncertain:

Decompression of the vein, improvement of oxygen supply, release of vitreous traction, or the removal of a diffusion barrier in front of the macular?

A different and much easier approach to perform was the intravitreal injection of triamcinolone. Several studies showed a reduction of the macular edema with improved visual outcome after this procedure. A significant drawback of intravitreal triamcinolone is the high incidence of secondary glaucoma.

Based on the pathogenetic impact of VEGF in macular edema the intravitreal application of anti-VEGF drugs appears to be more efficacious with less side effects. Several studies demonstrated a significant beneficial effect of Bevacizumab and Ranibizumab in eyes with BRVO. On the other hand, this effect was not sustained in most cases, necessitating repeated injections.

These new treatment modalities enlarged our therapeutic armamentarium for BRVO. The therapy should be selected according to the individual findings.

Comments:

30. Vitrectomy vs. New Treatment Strategies in CRVO

Josep Callizo (Marburg)



Purpose: To evaluate different therapeutical options available for the treatment of central retinal vein occlusion (CRVO) and its secondary macular edema.

Methods: In this retrospective study 89 patients with CRVO were included. The treatments performed were repeated intravitreal injection of bevacizumab (30 patients), repeated intravitreal injection of triamcinolone (19 patients), grid pattern laser photocoagulation (9 patients) and vitrectomy with radial optic neurotomy (RON) (31 patients). Main outcome parameters were optical coherence tomography measurements, visual acuity and retinal perfusion.

Results: The mean baseline visual acuity and central retinal thickness were $0,28 \pm 0,16$ and $575 \pm 184 \mu\text{m}$ (bevacizumab), $0,18 \pm 0,08$ and $578 \pm 136 \mu\text{m}$ (triamcinolone), $0,26 \pm 0,17$ and $531 \pm 329 \mu\text{m}$ (grid photocoagulation), $0,13 \pm 0,04$ and $614 \pm 277 \mu\text{m}$ (vitrectomy). The mean number of bevacizumab injections was $3,2 \pm 1,8$ and of triamcinolone was $2,1 \pm 1,7$. Mean follow-up was 26,3 weeks.

A significant improvement ($p < 0.05$) in visual acuity and central retinal thickness after bevacizumab and triamcinolone persisted until 3 months after the last injection but the visual improvement lost significance one month later. A trend for vision improvement without statistical significance was observed in eyes treated with grid pattern laser photocoagulation ($p = 0.754$). A significant visual improvement by the last control was observed only after vitrectomy with RON ($p = 0.042$). Only vitrectomy with RON was able to improve the retinal perfusion.

Conclusion: None of the modalities achieved a clear functional improvement in the long-term. Vitrectomy with RON reached an improvement of the retinal perfusion. The early functional benefit of intravitreal bevacizumab and triamcinolone were not sustained without repeated injections. Regarding triamcinolone, transient benefits need to be balanced with a range of potential adverse effects, such as development of cataract or glaucoma, which may increase after repeated injections. On the other hand, the promising short-term efficacy and safety of intravitreal bevacizumab allow the presumption of its value. Larger randomized controlled trials are needed to elucidate its best regimen of application.

31. Vitrectomy vs. New Treatment Strategies for ROP

Mike T. Trese (Royal Oak)



I. Visual Outcomes after Lens-Sparing Vitrectomy for Stage 4A Retinopathy of Prematurity

Purpose: To assess the visual outcomes of patients with stage 4A retinal detachments (RDs) from retinopathy of prematurity (ROP).

Design: Retrospective review of a consecutive case series of children referred to the pediatric retina service of Associated Retinal Consultants, Royal Oak, Michigan.

Participants: Forty-five eyes of 39 children.

Methods: The stage of RD for each patient was determined during an examination under anesthesia. All patients underwent a lens-sparing pars plana vitrectomy (PPV) with membrane peeling. Postoperative anatomic status was determined by ophthalmoscopy either during an office examination or during an examination under anesthesia. Visual outcomes were ascertained by consulting pediatric ophthalmologists using either Teller or Allen acuities. **Main outcome measures:** Anatomic and visual outcomes.

Results: Formalized visual acuity (VA) measurement was performed in 23 eyes of 20 children, and was not performed in 22 eyes of 19 children. All 23 eyes that were formally tested had successful retinal reattachment. The macula appeared to be normal and without distortion in 19 of 23 eyes (83%) during the follow-up period. Average logarithm of the minimum angle of resolution VA was 20/58. Three eyes had acuities of 20/200, and 4 had acuities of 20/100. All other eyes were 20/80 or better. Average age at time of VA was 3.51 years.

Conclusions: Patients with ROP and stage 4A RDs can be treated successfully with respect to anatomic and visual outcomes utilizing lens-sparing PPV.

II. The Block-ROP Study (Avastin for ROP)

Retinopathy of prematurity (ROP) continues to be a leading cause of blindness in children in developed countries around the world, and an increasing cause of blindness in developing countries. The current standard of treatment is ablation of the peripheral avascular retina. The treatment for ROP has evolved from cryotherapy, as established by the CRYO-ROP study, to laser treatment as indirect laser delivery systems have become available. Screening and intervention is now directed by the criteria established by the ETROP study. The ETROP Study demonstrated superior results compared to the Cryo-ROP study but also recommends earlier treatment with laser ablation. In the children requiring laser treatment the peripheral retina is ablated and destroyed for future use. The ablated retina is not functional and is not amenable to regeneration. In addition, morbidity from laser can include cataract as well as anterior segment ischemia, which can lead to phthisis (death of the eye).

The mechanism of development of retinopathy of prematurity is in large part dependent on vascular endothelial growth factor (VEGF). The normal biochemistry of the developing eye is altered due to the change in environment when a baby is premature. Specifically, the relatively hyperoxic environment that the premature baby is introduced to shuts down the produc-

tion of VEGF (Phase 1) and leads to delayed retinal maturation. The second phase, when the developing fetus will normally be reducing VEGF levels, becomes dysregulated due large areas of avascular retina creating tissue hypoxia. This results in abnormally high levels of VEGF and heralds the pathological changes seen in ROP. With the advent of FDA approved drugs for anti-VEGF treatment, the possibility of treating eyes with anti-VEGF drug has become possible. Drugs that are available include the drug pegaptinib (Macugen) for partial blockage of VEGF-A, or complete blockage of VEGF-A with drugs such as ranibizumab (Lucentis) and bevacizumab (Avastin). For purposes of this study, we have chosen to study the drug Avastin as we feel that it has less retinal penetration and is more likely to restore VEGF homeostasis within the developing retina. Avastin is limited in its ability to penetrate tissues as it is a full antibody, whereas Lucentis is an antibody fragment and was designed to have better tissue penetration. VEGF is required in the developing retina for normal angiogenesis and our goal is to block the excessive levels of VEGF trapped within the overlying vitreous which is responsible for the abnormal vasculature in ROP. Additionally, Avastin has widely been used for other VEGF dependent diseases such as age-related macular degeneration and diabetic macular edema in adult eyes and found to be both safe and effective.

In this study, in a controlled and careful fashion, we will examine the use of a reduced dose of the drug Avastin in premature infants' eyes for the problem of retinopathy of prematurity. The current adult dose used in the United States is 1.25 milligrams in .05 ml volume. This dose has been shown to be efficacious in the treatment of choroidal neovascularization and diabetic macular edema. The drug itself is FDA approved for use in colon cancer, and has been used in ophthalmology for several years now for its anti-VEGF effect in VEGF-dependent diseases such as choroidal neovascularization and diabetic macular edema.

Although retinopathy of prematurity may actually involve higher levels of vascular endothelial growth factor than seen in other retinal diseases, the vascular endothelial growth factor activity is endogenously down-regulated at the time of the due date. There is evidence that endogenous TGF beta, which elevates at the due date may be a factor down-regulating the vascular endothelial growth factor. Because of this, it is likely that children will only require one or perhaps two injections of anti-VEGF drug. This differs from patients undergoing treatment for chronic diseases, such as the treatment of choroidal neovascular membranes and diabetic macular edema, where it may be required to do injections for two years or more into the vitreous cavity. In this study the infant will be exposed to a single dose of Avastin at a reduced concentration. The drug itself hopefully will induce reduction in vascular activity and perhaps control the disease, not requiring destruction of the entire peripheral retina. In addition, this drug therapy may be much less expensive than laser therapy, which would make it amenable for treatment in developing countries where lasers are less accessible.

6th scientific session: Alternative treatments to vitrectomy

32. Vitrectomy Development Anti-VEGF Antibody: Preclinical, Clinical and Postclinical Studies

Ulrich Schraermeyer and the Tübingen Bevacizumab Study Group (Tübingen)

Purpose: Penetration of intravitreally injected bevacizumab (Avastin®) through the retina was studied, due to speculation that a full-length antibody might not be able to penetrate the retina as easily as an antibody fragment.

Methods: Six cynomolgus monkeys (*Macaca fascicularis*) were used. Two runs of intravitreal injection into the right eyes, one with Avastin (group 1, four animals) and the other with Avastin labelled with ¹²⁵I (group 2, one animal). Group 1 animals were sacrificed 1, 4, 7 or 14 days afterwards for subsequent histological analysis of the eyes by immuno-histochemistry, and the group 2 animal was sacrificed 7 days afterwards for autoradiography and electron microscopy. Funduscopy was performed before the injection and at several points afterwards. Blood samples were collected at a different point from the group 2 animal. The sixth (control) animal remained untreated.

Results: No pathological changes were obvious in the funduscopic images. Bevacizumab immunoreactivity was found in the choroid and inner layers of the retina one day after injection and spread to the outer layers and the choroid within the following days, particularly to photoreceptors and blood vessels. Using Avastin® labelled with ¹²⁵I, radioactivity could be detected in blood serum one day after the intravitreal injection, and remained relatively stable until day 7.

Conclusions: The results show that the bevacizumab molecule can penetrate the retina and is also transported into the retinal pigment epithelium, the choroid and particularly the photoreceptor outer segments after intravitreal injection of Avastin®. Active transport mechanisms are involved.



33. Intravitreal TPA: a Precursor of Anti-VEGF Therapy?

Lutz Hesse (Heilbronn)



Today intravitreal application of recombinant tissue plasminogen activator (rTPA) followed by gas injection is a sufficient, convenient and worldwide used technique for effective removal of freshly formed submacular hemorrhage caused by various diseases.

This technique was first introduced in 1996 by Wilson Herriot. Tissue-type plasminogen activator and its substrate plasminogen are key components in the fibrinolytic system. rTPA is a proteolytic enzyme that mediates the cleavage of plasminogen into plasmin. The serine protease plasmin subsequently dissolves fibrin clots. When this technique was introduced most ophthalmologists believed that rTPA is not really necessary to dislodge the blood from the macula and/or the large enzyme can not cross the retina. However, a few years later the therapeutic principle of this procedure was accepted: enzym induced lysis of the clot and subsequent mechanical displacement through the gas bubble. Crossing of intravitreal rTPA through the retina is possible and may be facilitated by mechanically induced microlesions of the retina. After enzymatic treatment of subretinal hemorrhage further growth of the underlying choroidal membran was rare indicating an unknown effect of the therapy.

Recent laboratory angiogenesis research demonstrated further biological effects of plasmin activation. Fibrin is a temporary matrix which not only covers a wound, but also provides a structure for invading endothelial cells in angiogenesis like a subretinal choroidal neovascular membran. Destroying the fibrin matrix inhibits the tubular formation of endothelial cells. A second anti-angiogenic effect is a plasmin-catalyzed cleavage of the vascular endothelial growth factor (VEGF). A loss of its carboxyl-terminal heparin-binding domain causes a significant loss in its bioactivity (100 fold).

Conclusion: Intravitreally injected rTPA + gas is not only a mechanical therapy but reduces the risk of further growth of the underlying neovascular membran. Consequently intravitreal injected rTPA in submacular hemorrhage was the first anti-angiogenic agent used in ophthalmology.

34. Pharmacologic Vitreolysis – the First Decade

Jerry Sebag (Huntington Beach)



Concurrent weakening of vitreo-retinal adhesion and liquefaction of the gel results in posterior vitreous detachment (PVD)¹. Liquefaction without concurrent vitreo-retinal dehiscence results in **anomalous PVD**², where traction is exerted upon the retina and/or disrupts the posterior vitreous cortex resulting in **vitreoschisis**². In the periphery, retinal tears and detachments result while at the macula there can be vitreo-macular traction syndrome, macular holes, or macular pucker. Anomalous PVD also plays a role in diabetic vitreo-retinopathy³. Thus, it would be desirable to develop new approaches to improve and facilitate vitreo-retinal surgery, as well as to prevent anomalous PVD. To this end, several agents have been tested in an attempt to alter the gel state of vitreous and separate the posterior vitreous cortex from the retina. This approach is known as **Pharmacologic Vitreolysis**⁴, a term that was first introduced in 1998.

During the past 10 years, the various agents being developed for Pharmacologic Vitreolysis can be grouped into two classes. Those inducing liquefaction of the gel vitreous can be referred to as "**liquefactants**", while those that cause dehiscence at the vitreo-retinal interface and vitreo-retinal separation can be called "**interfactants**". Some agents are only liquefactants, such as hyaluronidase, and some are only interfactants, such as dispase. Other agents are both, such as chondroitinase, plasmin or microplasmin, and nattokinase.

No single agent available today may be able to achieve both of the desired components of pharmacologic vitreolysis; i.e., liquefaction of the gel and vitreoretinal dehiscence. Indeed, vitreous molecular morphology is so complex and there are so many different changes that occur with aging and various diseases, that the future will probably see the use of a combination^{6,7} of two or more agents whose relative concentrations will need to be adjusted depending upon the patient's age, disease, and the desired effect. It is important to note, however, that pharmacologic vitreolysis should begin by inducing vitreo-retinal dehiscence, followed by liquefaction of the gel vitreous. Reversing this sequence might induce iatrogenic anomalous PVD and untoward sequelae.

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35. Microplasmin-induced Vitreous Detachment and the Role of Oxygenation

Mike T. Trese (Royal Oak)



Purpose: To determine if enzymatic induction of a posterior vitreous detachment (PVD) and/or vitreous liquefaction affects O₂ concentration in the vitreous cavity in animals with vascularized and avascular retinal circulations.

Methods: Either microplasmin or hyaluronidase was injected intravitreally into guinea pigs (avascular retinal circulation), brown Norway rats (vascularized retinal circulation without fovea), or cats (vascularized retinal circulation with fovea) with the contralateral eye used as a control. One to 2 weeks post injection, vitreal oxygen concentration was measured using a highly sensitive, platinum-based fluorophore O₂ sensor. In addition, control and microplasmin-injected rats, guinea pigs, and cats were exposed to 100 % oxygen and vitreal O₂ levels were measured over time. Scanning electron microscopy (SEM) was used to evaluate the vitreoretinal interface for the presence of a PVD.

Results: In animals with a vascularized retinal circulation (brown Norway rats and cats), intravitreal injection of microplasmin with induction of a PVD significantly increased baseline O₂ concentration in the vitreous cavity compared to hyaluronidase injected eyes and controls in rats (35, 25, and 23 mm Hg, P <0.001 and P <0.001, respectively and cats (26, 18, and 16 mm Hg, P <0.01 and P <0.001, respectively). Interestingly, intravitreal injection of hyaluronidase (vitreous liquefaction without induction of a PVD) did not significantly increase vitreal O₂ levels in any of the animal species (P >0.1). Upon exposure to 100% oxygen by facemask, microplasmin injected animals showed a rapid increase in vitreal oxygen levels compared to hyaluronidase injected animals and controls, indicating that the presence of a PVD allows rapid O₂ exchange within the vitreous cavity. Similarly once O₂ was discontinued, the O₂ concentration decreased in a similarly rapid rate. SEM showed smooth retinal surfaces in microplasmin-injected cat eyes, indicating the presence of a PVD which was not present in hyaluronidase injected or control eyes.

Conclusion: The results suggest that enzymatic-assisted PVD with microplasmin increases vitreal O₂ levels and increases the rate of O₂ exchange within the vitreous cavity.

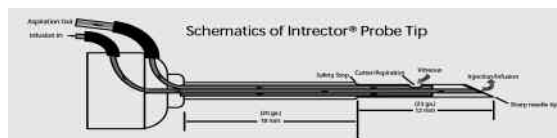
36. Combination Treatment Including a Limited Vitrectomy

Frank H. J. Koch (Frankfurt / Main)



Purpose: To introduce a combination treatment strategy including a portable single entry step 23 gauge vitrectomy instrument for simultaneous drug delivery / infusion and aspiration / vitreous cutting all with the same probe tip.

Methods: This instrument has separate drug delivery or infusion of any substance and simultaneous aspiration/vitreous cutting channel which end in the same single 23 gauge probe needle tip. Pars plana vitrectomy can thus be performed displacing the conjunctiva through an oblique self-sealing sclerotomy. This vitrectomy requires peribulbar or tropical anaesthesia. Aspiration and injection are performed by an assistant therefore allowing for anterior, core and central vitrectomy with any desired volume being removed. Illumination of the probe needle tip can be achieved by the microscope (in an O.R. or A.S.C. setting), slit lamp (with or without a flat contact viewing lens) or with an indirect ophthalmoscope (with a viewing lens). The cutting rate is up to 360 C.P.M. delivered by compact battery operated power controlling unit.



The Intrector® allows synchronic aspiration / injection through two different channels in a single tip.

Results: By incorporating a core pars plana vitrectomy into the drug injection regimen the need for retreatment has been drastically reduced (see references).

Conclusions: Various vitreo-retinal procedures like combined pharmacological procedures for ARMD, DM or Retinal Venous occlusion can be conducted in an effective and controlled manner. Other indication for uveitis, endophthalmitis, or a modified gas injection during pneumatic retinopexy are also possible, making a vitrectomy (intrectomy) with the Intrector® a simple, less costly, office based, A.S.C., or operating room procedure.

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37. **Is there an Evidence for an Adjunctive Intravitreal Pharmacotherapy in Vitreoretinal Surgery?**

Andreas Wedrich, M Velikay-Parel, A. Haas, G. Langmann, B, Vidic (Graz)



Since Machemer's first vitrectomy in 1971 the development of instruments, surgical tools, tamponades including the recent developments of sutureless vitrectomy has allowed therapy in a still increasing number of vitreo-retino-choroidal pathologies with decreasing surgical trauma. Looking at the success/complication rates of various indications adjuncts to vitreoretinal surgery seem to be warranted to overcome the limitations of pure mechanical vitrectomy.

These include proliferative vitreoretinopathy (PVR), within this field the induction of posterior vitreous detachment, submacular hemorrhage and vasoproliferative disease ranging from retinopathy of prematurity (ROP) to proliferative diabetic retinopathy (PDR)

We performed a pubmed research in the above mentioned fields with a time cut-off December 2007 and selected all clinical studies with adjunctive intravitreal pharmacotherapy for further analysis. The studies found were then classified according to the evidenc level classification provided by the German "Ärztlichen Zentrum für Qualität in der Medizin" which has four levels ranging from level 1 for systematic reviews (meta analysis) over a number of randomized controlled studies to level 4 meaning opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

In the field of PVR we found four evidenc level 2 reports studying daunorubicin, 5-fluorouracil with high molecular weight heparin, aspirin-silicone oil and dexamethasone.

In the area of pharmacological induction of PVD so far there is no published evidence level 2 study. This is the same in the field of the use of recombinant tissue plasminogen activator for submacular hemorrhage and the use of anti-VEGF drugs in vasoproliferative disease although level 3 studies in these fields show promising results.

Summarizing there is good evidence for the role of adjunctive pharmacotherapy in PVR, but less in other complex fields of vitreoretinal surgery. Potent drugs are coming up and wait for testing in future high evidence level studies.

38. **Limited Vitrectomy: Liquifaction and Posterior Vitreous Detachment? Experimental Results and Clinical Observations**

Michael J. Koss (Frankfurt/Main)



Purpose: To evaluate the efficacy of a quadruple therapy regimen (low flouresence photodynamic therapy (PDT), intravitreal steroid injection, intravitreal Avastin injection, and a limited core pars plana vitrectomy) and a triple therapy regimen (intravitreal steroid injection, intravitreal Avastin injection, and a limited core pars plana vitrectomy) in the treatment of classic versus occult choroidal neovascularization patterns, respectively, in the treatment of exudative age-related macular degeneration (AMD).

Methods: Patients with exudative AMD were grouped on the basis of choroidal neovascularization pattern on intravenous flourescein angiogram. Eyes in group I had predominantly classis lesions and eyes in Group II had predominantly occult lesions. Patients in both groups were treated with a limited core pars plana vitrectomy, intravitreal steroids, and intravitreal Avastin. Patients in Group I were pretreated with PDT. Visual acuity (VA) and macular thickness were measured at initial and subsequent evaluations.

Results: One hundred fifty eight eyes were included in the study with 52 in Group I and 106 in Group II. At mean time points of 3.2, 8.7, and 13.6 months post intervention, group I showed an increase in VA of 1.1, 1.9, and 1.6 lines ($p < 0.01$) respectively, while VA in group II improved 0.9, 1.3, and 1.2 lines ($p < 0.01$) respectively. At the final measurement macular thickness had decreased from baseline by 211 microns ($p < 0.01$) in group I, and 195 microns ($p < 0.01$) in group II. Adverse events included a rise in intraocular pressure in 11/106 (10%) eyes, a pseudohypopyon in 2/106 (1.9%) eyes, and a rhegmatogenous retinal detachment in 1/106 (0.9%) eye. The retreatment rate was 25 % (13/52) for group I, and 55% (58/106) for group II.

Conclusions: Combination therapy for the treatment of exudative AMD, including the use of a limited core pars plana vitrectomy, yields a sustained improvement in visual acuity and macular thickness in eyes with predominantly classic and predominantly occult CNV. We believe the induction of a posterior vitreous detachment alters the physiology of the eye in a way that complements concurrent pharmacologic therapy for neovascular AMD.

39. **The Use of Anti-VEGF Inhibitors in Wet AMD: Balancing the Risks**

Ralf Blank (Rüsselsheim)



Two drugs that inhibit vascular endothelial growth factor have been improved for use in the treatment of choroidal neovascularization (CNV) in age-related macular degeneration (AMD). Pegaptanib sodium (Macugen, OSI /Eyetech and Pfizer New York) selectively inhibits the most biologically active isoform of VEGF, VEGF 165. Ranibizumab (Lucentis, Genentech, San Francisco) nonselectively targets all known isoforms of VEGF-A. Another VEGF-blocking drug, Bevacizumab (Avastin, Genentech) has also recently been used for treatment of CNV in AMD, although it was not developed for ocular use and has not been approved for that indication.

Although VEGF inhibition is the goal of all these drugs as well as several other compounds in development for the treatment and prevention of CNV, it should not be forgotten that VEGF is an important compound for the normal function of the human body.

Several epidemiologic studies have shown an increased risk of cardiovascular disease, hypertension, and cardiovascular events including stroke and myocardial infarction, in people with AMD. Given that systemic nonselective VEGF inhibition may be associated with an increased risk of thromboembolic events, and that repeated intravitreal delivery of VEGF inhibitors inevitably involves systemic exposure of these VEGF-blocking agents, it is important to consider the systemic safety of these ocular treatments in AMD patient population, especially over the long term.

40. **OCT Guided Anti-VEGF Therapy for Neovascular AMD**

Stephan Michels (Zürich)



In the past retreatment decisions for laser treatments in neovascular AMD were commonly based on fluorescein angiography (FA). Within the last years anti-VEGF therapy has become the first line therapy for neovascular AMD. Phase III clinical trials using ranibizumab and pegaptanib have used retreatment regimens independent from CNV activity.

The PrONTO study was the first prospective study on ranibizumab in neovascular AMD to use an OCT guided retreatment regimen. This regimen allowed reducing the mean number of treatments over 2 years to 9.9. Despite an increased risk for CNV recurrence at any point in follow-up functional and anatomic outcomes were quite promising and comparable to outcomes of studies using continuous VEGF suppression. At 2 years follow-up mean visual acuity improved by 10.7 letters and central retinal thickness decreased (CRT) by 215µm.

A prospective study comparing intravitreal bevacizumab to PDT plus intravitreal triamcinolone for neovascular AMD used an OCT based retreatment regimen for the bevacizumab treatment arm. The mean number of bevacizumab treatments was 6.8 within one year follow-up. Visual outcomes were significantly better in the bevacizumab treated group showing an improvement of 8 letters at month 12. Reduction of CRT as measured by OCT was comparable for both groups.

OCT is the first imaging technology to be used for anti-VEGF retreatment decisions in prospective clinical trials. The recent development of spectral domain OCTs will further increase the value of this technology for anti-VEGF retreatment decisions.

41. **Anti-VEGF: Developments, Comparison, New Drugs**

Salvatore Grisanti (Lübeck)



In the field of age-related macular degeneration (AMD) the treatment philosophy is shifting from a destructive to a more disease modulating strategy. Current approaches and developing treatments for choroidal neovascularization are based on a growing understanding of the molecular mechanisms of angiogenesis. After the exciting introduction of drugs sequestering vascular endothelial cell growth factor (VEGF), one of the major players of angiogenesis, the next decade promises to be as exciting as the previous one. Numerous new treatments with differing mechanisms of action are currently under development. These include beside the inhibition of free VEGF, such as with the *VEGF trap*, also the blockade of the intracellular signalling pathway with *inhibitors of tyrosine kinases* or the silencing of contributing genes using *small interfering RNA*.

Whether inhibition of the VEGF signalling alone is sufficient to target the different stages of the disease is under debate. Combined targeting of other factors, e. g. platelet-derived growth factor B (PDGF-B) that is essential for pericyte recruitment may have a synergistic effect by sensitizing the vasculature to the effects of anti-VEGF therapy. Future interventions may also include gene therapy with adenoviral vectors to up-regulate natural inhibitors of endothelial angiogenesis such as pigment epithelium-derived factor (PEDF).

The effective approach in the future treatment of exudative AMD will combine and titrate different strategies targeting endothelial cell proliferation, extracellular matrix proteins, vessel wall modelling and endothelial cell survival as well.

7th scientific session: At the end! What's new?

42. Macular Hole Surgery without Vitrectomy

Paul Tornambe (Poway)

Some macular holes may be repaired without vitrectomy surgery, without ILM peeling and even without a gas bubble. This may be accomplished with watchful waiting, pneumatic retinopexy, and injection of drugs. Case selection and surgical technique will be discussed using specific cases to demonstrate these concepts.



43. The Mischievous Macular Hole: a Case Series

Paul B. Griggs (Seattle)

Purpose: To review the clinical results of macular vitreoretinal interface surgery with atypical clinical outcomes.

Methods: Patients were identified in which surgery was performed for macular hole, pucker, and/or vitreomacular traction. Records were analyzed for Snellen visual acuity, central foveal thickness on OCT, and fluorescein angiographic characteristics in selected cases. The number of procedures and period of time over which they were administered was evaluated. The analysis included the clinical status of each patient at the initiation of therapy and at the time of data analysis.

Results: The initial evaluation revealed the presence of macular hole, epiretinal membrane, and/or vitreomacular traction in one or both eyes. Pars plana vitrectomy was performed in all patients. Posterior vitreous hyaloid separation was confirmed and/or performed in all patients. Epiretinal membrane dissection was performed when indicated. Internal limiting membrane dissection was performed in all cases of macular hole. Secondary procedures were performed as clinically indicated.

Conclusion: Vitreoretinal interface abnormalities affecting the macula are one of the most common clinical entities encountered in the vitreoretinal practice. Surgery for macular hole, pucker, and vitreomacular traction is typically uncomplicated and results in clinical improvement. Presented herein is a group of patients who underwent uncomplicated surgery and responded with atypical clinical outcomes.



44. Sutureless Vitreo Retinal Surgery

Sundaram Natarajan (Mumbai)

25G and later 23G vitrectomy has ushered an era of sutureless vitrectomy. However, in cases requiring scleral buckling in addition, the buckling elements required suturing. Also, the conjunctival peritomy wound needed to be sutured for closure.

In the presentation, a suture less technique of combined scleral buckling and 23G vitrectomy is described where both the tier and the band were inserted into partial thickness scleral tunnels followed by 23 G Vitrectomy. Furthermore, the conjunctival peritomy was repaired by fibrin tissue glue thereby doing away with sutures altogether.

In a consecutive series of twenty three eyes of 23 patients who underwent the above procedure (over a period of 9 months), good coverage of retinal breaks and adequate buckle height was seen in all cases, retina was attached in all but 2 cases. There was no buckle related complication. Incomplete closure of conjunctival peritomy wound was seen in 1 case. In selected cases this procedure of sutureless vitreoretinal surgery can replace conventional sutured procedures and can do away with suture-related complications and concerns.



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