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Research Article

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Vitreous hemorrhage of unknown origin in adult non-diabetic non-traumatic eyes: a retrospective analysis and the lessons we learn from it

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Abstract

Objective: *To analyse the causes of vitreous hemorrhage (VH) of unknown origin in non-diabetic non-traumatic eyes and evaluate the results regarding the underlying cause and time of surgery.*

Methods and Analysis: *Retrospective analysis of 125 eyes with a dense VH of unknown origin, who underwent vitrectomy at a varied time point. Preoperative and postoperative data were compared between the groups with the three major causes of VH as well as between the eyes with an early (≤5 days after presentation) and a late (>5 days after presentation) vitrectomy.*

Results: *Most common causes of VH were retinal vessel occlusion (RVO; 39/125; 31.1%), retinal tears (36/125; 28.8%) and submacular hemorrhage (34/125; 27.2%). Postoperative visual acuity improved significantly in all eyes (2.14 vs. 1.04 logMAR, p<0.01) with better outcome in eyes with retinal tears. Early vitrectomy group had better functional outcome regardless of underlying cause (p=0.02). Final visual outcome correlated significantly with the underlying cause of VH (p<.001) and time to treatment in the retinal tear group (p<.001).*

Conclusion: *We encourage performing early minimal invasive vitreoretinal surgery in cases of non-diabetic, non-traumatic VH. More than three of four of the cases are caused by retinal tear/retinal detachment, submacular hemorrhage and RVO. Early surgical treatment had better functional outcome on the longer run.*

Keywords: Vitreous Hemorrhage, Non-Diabetic, Pars Plana Vitrectomy

Introduction

Treatment approach in acute vitreous hemorrhage (VH) depends strongly on the underlying disease, which caused the hemorrhage. While in diabetic eyes the conservative approach is the favorable one with good outcomes and clearing of the hemorrhage in most cases, the right procedure for treating non-diabetic dense vitreous hemorrhages of unknown origin represents an ophthalmological dilemma. On the one hand, we have the conservative treatment with upright head positioning, immobilizing and regular visits to the ophthalmologist with ultrasonography to ensure there is no retinal detachment going on. In this case, the disadvantage lies in the unknown cause of the disease. Regarding already published studies, the most common reasons for a vitreous hemorrhage in an adult without diabetes or trauma are retinal vein occlusion, retinal tear with/without retinal detachment, age-related macular degeneration with submacular hemorrhage, vasculitis, retinal macroaneurysm [1-6]. While some of these conditions can be treated conservatively with good results, others represent an ophthalmological emergency and should be treated as soon as possible. Waiting several weeks for VH to clear might result in severe complications with irreversible visual loss. Tan et al. have already demonstrated the potential danger of a conservative treatment approach in case of retinal tears as underlying cause of the vitreous hemorrhage [3].

On the other hand, in the era of safe microinvasive vitrectomy surgery (MIVS) with a very low complication rate, surgical treatment option should also be considered for cases of vitreous

hemorrhages of unknown origin in order to prevent further visual loss and in favor of quick rehabilitation of the patient.

Zhang et al. could show in a large study of patients with non-diabetic non-traumatic vitreous hemorrhage, that surgical treatment with early vitrectomy is associated with good anatomical and visual outcomes and a low complication rate [2].

In another work of Hayashida et al., patients with VH of unknown origin and surgical treatment within 2 weeks after symptom onset showed better functional outcomes than patients with vitrectomy done after 2 weeks with regard to any underlying disease cause [1].

Our retrospective study was conducted to investigate the functional outcomes of patients suffering from VH without a history of diabetes or trauma. We especially focused on the effects of time between VH and surgery (early vs. late) with regards to the different underlying retinal pathology (retinal vein occlusion, retinal tear/detachment, submacular hemorrhage).

The following results should help physicians to develop a better strategy for treating patients with dense vitreous hemorrhages of unknown origin.

Materials and Methods

The present study was approved by the Institutional Review Board of Saxony (Dresden, Germany) and adhered to the tenets of the Declaration of Helsinki. Informed patients' consent was waived because of the retrospective anonymous design and because no study-related investigations were necessary.

The patient database in the Chemnitz Hospital was reviewed for billing codes of VH according to the International Classification of Diseases, 10th Revision between January 2015 and September 2020.

Patients included in this study met the following criteria: 1) diagnosed with dense VH (grade 3 and 4 of Lieberman et al. [7]); 2) unknown origin of the VH; 3) B-scan ultrasonography done and interpreted by an experienced ophthalmologist according to general standards established by Ossoinig et al. [8].

The exclusion criteria were: 1) history of diabetes with more than mild diabetic retinopathy in the contralateral eye; 2) history ofr trauma; 3) clearly seen retinal detachment on ultrasonography.

All patients underwent a complete ophthalmic examination of both eyes including BCVA, applanation tonometry, slit-lamp biomicroscopy, indirect binocular ophthalmoscopy, B-scan ultrasonography. Furthermore, risk factors in patients' history like previous retinal tears or retinal detachment in both eyes, flashes preceding the onset of vitreous hemorrhage, history of retinal vessel occlusion (RVO), therapy with systemic anticoagulation drugs and myopia were evaluated. Preoperative ultrasonography was documented with suspicion of retinal detachment, vitreous traction or subretinal hemorrhage. Cases with clearly seen retinal detachment on ultrasonography were excluded from the analysis.

Surgical treatment details and postoperative complications were also documented. The data were compared across the three largest groups of VH causes as well as between the early (surgery within 5 days after first presentation) and the late (>5 days after initial presentation) vitrectomy groups.

All subjects underwent a standard three-port sutureless vitrectomy (23 gauge or 25 gauge) under general anesthesia (standard surgery procedure in this clinic). In case of significant cataract, combined surgery with phacoemulsification and intraocular lens implantation prior to vitrectomy was performed.

IBM SPSS Statistics, version 27.0.0.0 for Windows (IBM, Armonk, NY, USA) was used to perform the analysis. Visual acuity measurements were converted from decimal numbers to logMAR for all analyses. Severe visual impairment was converted to logMAR as following: counting fingers=2.3 logMAR; hand movements=2.5 logMAR; light perception=2.8 logMAR; no light perception=3.0 logMAR.

Data for continuous variables are expressed as mean ± standard deviation. Differences between the baseline and the final data were calculated using paired two-sided t-test for dependent samples. Differences across the different groups were calculated using one-way multivariate ANOVA with post hoc Sidak's test. For representing statistical significance, $p<0.05$ was chosen. Linear regression analysis was performed to identify the risk factors for final visual outcome.

Results

In total, 125 eyes from 125 patients were included in this study. The demographic characteristics of the study participants and the causes of VH are summarized in Table 1. The three most common underlying causes of VH were retinal tear, breakthrough of advanced AMD with submacular hemorrhage and previous RVO.

Table 1: General characteristics of included patients.

Characteristic	Overall, N=125
Age, year (mean ± SD)	74 ± 10
Male (%)	68 (54%)
Right eyes (%)	72 (58%)
Cause of VH	
Retinal tear (%)	36 (29%)
AMD (%)	34 (27%)
RVO (%)	39 (31%)
Retinal macroaneurysm (%)	7 (6%)
Other (%)	3 (2%)
Unknown (%)	6 (5%)
Mean follow up time, months	6 ± 6

SD: Standard deviation; VH: Vitreous hemorrhage; VH: Vitreous hemorrhage; AMD: Age-related macular degeneration; RVO: Retinal vessel occlusion.

In Table 2 summarizes the clinical data of the whole study population as well as of these 3 separate groups regarding the underlying cause of VH. Overall, a statistical significant visual improvement could be seen after surgery in all the groups, with retinal tear group having significantly better visual outcomes, but a better preoperative BCVA as well.

Table 2: Clinical data across the different groups according to the cause of vitreous hemorrhage.

Group/ Characteristic	All eyes, N=125	Retinal tear, N=36	AMD, N=34	RVO, N=39	P Value
Preoperative BCVA, logMAR					
mean ± SD	2.14 ± 0.77	1.77 ± 0.91	2.34 ± 0.67	2.30 ± 0.63	<0.01*
95% CI	1.99-2.29	1.46-2.08	2.11-2.58	2.10-2.51	
Postoperative BCVA, logMAR,					
mean ± SD	1.04 ± 1.07	0.23 ± 0.55	1.87 ± 0.88	1.22 ± 1.14	<0.01*
95% CI	0.93-1.35	0.11-0.47	1.60-2.21	0.86-1.62	
P-Value pre- vs. postoperative	<0.01*	<0.01*	<0.01*	<0.01*	
logMAR of BCVA					
Age, year (mean ± SD)	74 ± 10	69 ± 9	80 ± 8	73 ± 8	<0.01*
95% CI	72-76	66-73	77-83	71-76	
Risk factors					
lashes	11 (9%)	9 (25%)	2 (6%)	0 0 (0%)	<0.01*
History of retinal tear	10 (8%)	10 (28%)	0 (0%)	0 0 (0%)	<0.01*
Retinal tear in fellow eye	5 (4%)	4 (11%)	0 (0%)	1 (3%)	0.06
Retinal detachment in fellow eye	6 (5%)	4 (11%)	0 (0%)	2 (5%)	0.13
History of retinal vessel occlusion	21 (17%)	0 (0%)	1 (3%)	20 (51%)	<0.01*
Myopia	11 (9%)	5 (14%)	4 (12%)	2 (5%)	0.42
Preoperative ultrasonography assessment					
Retinal detachment suspicion	12 (10%)	4 (11%)	5 (15%)	2 (5%)	0.39
Vitreous traction	18 (14%)	8 (22%)	1 (3%)	8 (21%)	0.48
Subretinal hemorrhage	29 (23%)	2 (6%)	22 (65%)	3 (8%)	<0.01*
Lens status					
phacic	78 (62%)	28 (78%)	17 (50%)	25 (64%)	0.05
pseudophacic	47 (38%)	8 (22%)	17 (50%)	14 (36%)	0.05
Surgery type					
vitrectomy	55 (44%)	11 (31%)	17 (50%)	17 (44%)	0.24
vitrectomy with phaco	70 (56%)	25 (69%)	17 (50%)	22 (56%)	0.24

Notes: P value across the groups was calculated using ANOVA and post-hoc Sidak's test. P value between the pre- and postoperative data was calculated using paired two-sided t-test. *Statistically significant.
Abbreviations: BCVA: Best corrected visual acuity; SD: Standard deviation; logMAR: Logarithm of minimum angle of resolution; CI: Confidence interval; AMD: Age-related macular degeneration; RVO: Retinal vessel occlusion; IOP: intraocular pressure; n/a: Not applicable because of too small numbers in each group; TTT: Time to treatment-time from initial presentation to surgery.

The group with retinal tears differed from other groups with statistically significant higher rates of flashes preceding VH as well as history of retinal tears. Furthermore, retinal tears or retinal detachment in the fellow eye were observed more often in the retinal tear group, but without reaching statistical significance. In 6 of 36 eyes (17%) in the retinal tear group, an intraoperative retinal detachment was detected with 4 of 6 eyes with macula-off detachment.

The AMD group, however, had significantly older patients with mean age of 80 and more often suspected subretinal hemorrhage on ultrasonography. RVO group differed significantly from two other groups with 51% of eyes having had a history of previous retinal vessel occlusion.

In most of the groups, there were more phakic than pseudophakic eyes. Therefore, combined phakovitrectomy was performed more often in these groups, respectively.

The most common postoperative complication was a mild VH in AMD and RVO groups, which cleared up spontaneously in all 17 cases in the following weeks. The lowest complication rate was observed in retinal tear group with only 1 case (3%) of retinal detachment following surgery.

The time between the first presentation in our clinic and surgery (TTT=time to treatment) varied very strongly in all the groups. Table 3 illustrates the differences between the eyes regardless of the underlying cause divided into the early vitrectomy group (=surgery within 5 days after first presentation) and late vitrectomy group (=surgery >5 days after initial presentation). With similar preoperative BCVA, postoperative BCVA differed statistically significant between the groups in favor of the early vitrectomy group. Figure 1 and 2 illustrate the different clinical course and functional outcome of 2 patients from our study with VH due to AMD and submacular hemorrhage.

Table 3: Pre- and postoperative clinical data on eyes with vitreous hemorrhage regarding the time frame between the first presentation and the surgery.

Characteristic	Surgery within 5 days after presentation n=39	Surgery after ≥ 5 days after presentation n=86	P Value
Preoperative BCVA, logMAR			
mean ± SD	2.00 ± 0.89	2.20 ± 0.71	0.17
95% CI	1.71-2.29	2.05-2.36	
Postoperative BCVA, logMAR,	0.71 ± 1.04	1.18 ± 1.06	0.02*
mean ± SD	0.38-1.05	0.96-1.42	
P-Value pre- vs. postoperative logMAR of BCVA	<0.01	<0.01	
Age, year (mean ± SD)	71 ± 11	75 ± 9	0.07
95% CI	68-75	73-77	
Cause of vitreous hemorrhage			
Retinal tear	20 (51.3 %)	16 (18.6 %)	0.12
AMD	10 (25.6 %)	24 (27.9 %)	
RVO	7 (17.9 %)	32 (37.2%)	
Other	2 (0.5 %)	8 (9.3%)	
Unknown	0 (0.0 %)	6 (6.9 %)	
Lens status			
phacic	26 (66.7 %)	52 (60.5 %)	0.51
pseudophacic	13 (33.3 %)	34 (39.5 %)	0.51
Surgery type			
vitrectomy	15 (38.5 %)	40 (46.5 %)	0.40
vitrectomy with phaco	24 (61.5 %)	46 (53.5 %)	0.40
Vitrectomy type			
23 gauge	24 (61.5 %)	83 (96.5 %)	<0.01*
25 gauge	15 (38.5 %)	3 (3.5 %)	<0.01*
TTT, days (range)	2 (0-5)	41 (6-218)	<0.01*
95% CI	1.65-2.55	33.21-49.62	

Notes: P value: was calculated using paired two-sided t-test. *Statistically significant.
Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; SD, standard deviation; logMAR, logarithm of minimum angle of resolution; AMD, age-related macular degeneration; RVO, retinal vessel occlusion; TTT, time to treatment-time from initial presentation to surgery.

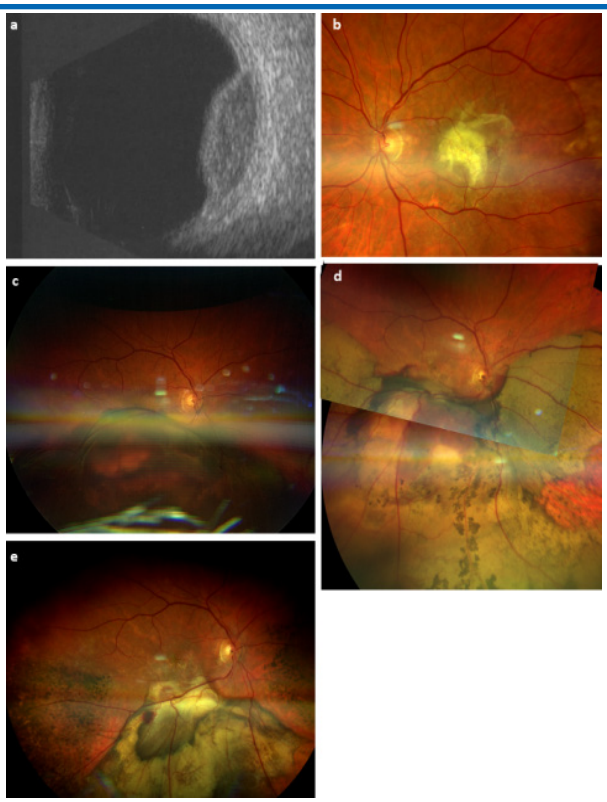

Figure 1: Clinical course of an eye presenting with dense vitreous hemorrhage of initially unknown origin, which underwent vitrectomy 2 days after symptom onset. a) as no fundus view was possible at initial presentation, b-scan-ultrasonography of the right eye was performed raised suspicion of a prominent subretinal hemorrhage in the macular area; visual acuity was hand motion (2.5 logMAR); b) color fundus photograph of the left fellow eye shows extensive macular scarring with very poor visual acuity of 0.05 (1.30 logMAR); c) color fundus photography 1 week after early vitrectomy shows a huge prominent subretinal hemorrhage with macular involvement in the inferior part; the shadow effect superior is caused due to the small gas bubble; d) color fundus photograph of the same eye 2 months after surgery; e) the same eye 4 months after surgery with visual recovery to 0.3 (0.52 logMAR). logMAR: Logarithm of minimal angle of resolution.

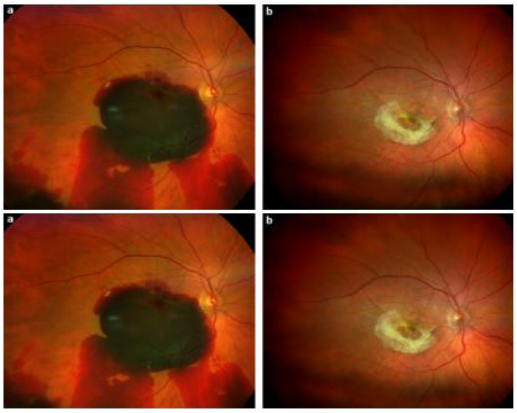

Figure 2: Clinical course of an eye presenting with dense vitreous hemorrhage of initially unknown origin, which underwent vitrectomy 4 weeks after symptom onset. a) color fundus photograph of the right eye after vitrectomy shows a large subretinal hemorrhage involving almost the whole macular area; visual acuity is 0.03 (1.52 logMAR); b) color fundus photography of the same eye 2 months after late vitrectomy with extensive macular scarring involving the fovea; visual acuity remained at 0.03 (0.52 logMAR).logMAR: logarithm of minimal angle of resolution.

All the other parameters did not differ between the early and late group: causes, lens status and, hence, combined vitrectomy with/without phakoemulsification were equally distributed. Interestingly, in cases of older VH the 23g approach was chosen significantly more often.

The multivariate linear regression analysis demonstrated in the whole study cohort, that the final BCVA was significantly associated with the underlying disease cause ($p<0.001$) and strongly-although not statistically significantly-associated with TTT ($p=0.077$). Furthermore, in the subgroup analysis of retinal tears, TTT was again significantly associated with the final visual outcome ($p<0.001$), while in the groups with RVO and wet AMD, no significant correlation between the TTT and final visual acuity could be found ($p=0.037$ and 0.326 in the regression analysis, respectively).

Discussion

The present study identifies the three most common causes for a non-diabetic non-traumatic vitreous hemorrhage and underlines favorable functional results in the group with early surgical treatment. Significant correlation between the time to treatment and final visual acuity could be demonstrated for the whole study group with earlier surgery showing better results.

Vitreous hemorrhage of unknown cause in adults without previous history of trauma or diabetes represents a treatment dilemma for ophthalmologists all over the world. As long as the VH is dense and obscures the fundus, the determination of the underlying cause is nearly impossible.Ultrasonography might help to evaluate the posterior eye segment status, but its sensitivity and specificity is limited and differs a lot regarding to the experience of the ophthalmologist using it and interpretation of what is to be seen on B-scan images or A-scan-reflectivities [9].

Establishing the underlying cause of VH is essential for choosing the best treatment strategy in every case. The findings of our study support the previously published results with retinal tears, RVO and AMD being the most common reasons of VH in non-diabetic patients [1-6]. However, in our study, the rate of AMD as the cause of VH was higher than in other works: Hayashida et al. found it in only 15.9% of the cases [1], while Zhang et al. could identify polypoidal choroidal vasculopathy as the cause for VH in only 5.7% of the cases [2].These differences might be due to older study population in our work. As we know, the risk of advanced AMD and consecutive VH is higher in elderly people.

In our study, 70 of 125 eyes (52%) presented with VH caused by either a retinal tear or AMD. Retinal tears occur in the course of posterior vitreous detachment. Hemorrhagic posterior vitreous detachment was shown to cause one or more retinal tears in 75% of

cases and retinal detachment in 44% of cases, with 28.6% of eyes with macula-off retinal detachment [10]. Tan et al. also describe 46.4% of new retinal tears identified during vitrectomy, which were missed during the preoperative assessment in eyes with dense VH [3]. These findings illustrate the risk a conservative approach might bear in these VH cases. In our study subgroup of patients with retinal tears, linear regression analysis showed significant correlation between the time to treatment and final BCVA. Furthermore, in 6 out of 36 eyes in the retinal tear group, retinal detachment could be detected intraoperatively, 4 of them with macula-off situation.

Regarding the second cause of VH-AMD we should consider that these cases are usually associated with subretinal hemorrhage in the macular area. The VH is caused due to the breakthrough of the hemorrhage into the vitreous cavity. In our study, all the 34 cases (100%) in the AMD group showed large prominent submacular hemorrhages. This might explain why there was no significant correlation between the time to surgery and final BCVA in this group of patients-large submacular hemorrhages lead to strong and sadly irreversible visual impairment, which might not have been influenced by early intervention in our study. Some other published works could show significantly better functional outcomes in these patients in case of early surgical treatment [11-13]. The differences in these results might be due to different sizes of submacular hemorrhage, as it influences the visual acuity significantly. There are also experimental studies showing irreversible damage of neuroretinal structures after as early as 24 hours in submacular hemorrhage [14]. Therefore, time in these patients might play a role depending on the size of the hemorrhage and the amount of damage to the central retina. Still, these patients showed also a significant visual improvement postoperatively irrespective of the time point of surgery.

Conservative approach with waiting for the VH to clear in these eyes might result in large subretinal scarring, while surgery with tissue plasminogen activator injection, early anti-VEGF-injections and pneumatic displacement of the hemorrhage might have much better functional results. Furthermore, surgery in these cases makes the submacular hemorrhage clearly visible and might-in addition to the first dose given during surgery- enable early, continuous and frequent anti-VEGF-treatment possible and plausible.

The third most common cause of VH of unknown origin in our study was neovascularization secondary to retinal vessel occlusion. Here, also a significant postoperative visual improvement could be observed, while there was no significant association between the time to surgery and final visual acuity. Here, visual improvement depends strongly on the underlying type of retinal vessel occlusion and possible involvement of the central retina. Therefore, the time factor seems to play not the major role for final BCVA in these cases.

Unfortunately, there are no reliable investigative methods, which help us to definitely determine the underlying cause of a dense vitreous hemorrhage in an adult without diabetes or trauma. Using the medical history of the patient and evaluating the known risk factors might help us to predict the underlying cause (Table 2, risk factors). Still, surgery presents the only way to clearly identify the underlying cause. Waiting for the VH to disappear might result in irreversible vision loss, when we consider that retinal tear might cause a longstanding macula-off retinal detachment situation, AMD often accompanied with submacular hemorrhage will destroy retinal photoreceptors close to the blood clot and long standing macular edema due to vein occlusion will go undetected and untreated. As those three groups represent more than five out of six of the included patients, this is of high clinical importance.

Before performing vitrectomy, we certainly have to analyze the possible risks of this surgical procedure. In the era of MIVS, the cumulative rate of endophthalmitis was reported to be 0.18% in a large metaanalysis of more than 12,000 cases [15]. Furthermore, a recently conducted metaanalysis of Chen et al. proved a significant lower risk of intraoperative retinal breaks (12.78% vs. 6.29%; $p<0.0001$) and postoperative retinal detachment (2.52% vs. 1.57%; $p=0.003$) in MIVS compared to 20 gauge vitrectomy [16]. In our study population, we observed similar results with no cases of endophthalmitis and 1 case (0.8%) of rhegmatogenous retinal detachment following vitrectomy. These data on very low severe complication rate of MIVS compared to the rate of possible complications of conservative treatment approach for VH of unknown origin underline the higher chance of good visual recovery with early surgery. Moreover, we should also consider the faster patient's visual rehabilitation in case of early vitrectomy and no need of long-lasting follow-up visits every week waiting for VH to clear up. The last fact is of high importance especially in the time of covid pandemic.

Because of the retrospective design and the clinical setting without a proper study protocol, there are of course certain possible biases and downsides to this investigation. As we wanted to have a sample of VH patients without any suspicion of what the underlying cause of VH was we decided to accept the downsides of this approach.

First is the absence of a control group, although we believe that the comparison of doing the surgery early vs. late should serve an appropriate approach to overcome this problem. Second, the a priori exclusion of diabetic patients might bias the statistics. Of course, there might be the same problems like retinal rip, detachment or submacular hemorrhage and especially retinal vein occlusion of which diabetes is a major risk factor. Nevertheless we decided to exclude those patients as in those cases the watch-and-wait-approach has been proven to be useful. Third, the exclusion of sonographically identified retinal tears or detachments might influence the statistical results. We decided to exclude them because in a case of suspected retinal tear or detachment there is no reason for postponing surgery and therefore the treatment approach is clear. Fourth, a problem which cannot be overcome easily, not even in a prospective study, is that interval between first symptoms and first examination/presentation in a hospital might not be clearly and easily found out due to different alertness of the patients.

Conclusion

Based on this data, we encourage performing early minimal invasive vitreoretinal surgery in cases of non-diabetic, non-traumatic VH. The three most common, but not in every case identifiable causes of retinal tear, submacular hemorrhage because

of AMD and retinal vein occlusion represent nearly 90% of the causes. Significant association of final visual outcome and time to surgery could be seen in eyes with VH of unknown origin.

In every aspect, early diagnosis of underlying disease leads to early treatment and better functional outcome on the longer run. We consider the more stressful situation for the patient in the days before and after the surgery to be acceptable compared to weekly visits and the unpredictability whether surgery will have to be performed later on anyway.

Acknowledgement
None

Ethics
The present study was approved by the Institutional Review Board of Saxony (Dresden, Germany) under the number EK-BR-108/19-1 and adhered to the tenets of the Declaration of Helsinki. Informed patients' consent was waived because of the retrospective anonymous design and because no study-related investigations were necessary.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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None.

Author Contributions
OF: Data acquisition; data interpretation and analysis; manuscript draft and revision; approval of the submitted version.
EM: Data interpretation and analysis; manuscript revision; approval of the submitted version.

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