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The Benefit of Oral Bromelain on the Spontaneous Disappearance of Vitreous Hemorrhage: An Animal Study

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Abstract: Introduction: Vitreous hemorrhage (VH) is caused by several etilogies, and it always makes the patients decreased vision and even blindness. In the past, the majority of eye doctors should adopt the method of waiting for spontaneous absorbance within 3 - 6 months. If VH persisted without disappearance for a peroid of time, pars plana vitretomy (PPVT) should be peformed. Nevertheless, only simpe waitng associated with some complications would be found such as retinal scar or prolifertative vitreoretinopathy. Besides, PPVT combined with Argon laser may induce intrageneic cataract, galucoma, retinal detachment and re-bleeding. In our research, we tried to analyze the effectiveness of oral bromelain for dissolving VH by the animal study. **Methods:** Total 35 SD rats aged 7 and 8 weeks were enrolled. First, one mouse was sacrificed and the eyeball was removed for understanding the anatomy for futher study. First, VH mode of rats was created by 26 gauge needle puncture at the size just posterior to the pars plana of all left eyes from 24 SD rats, All mice were randomly and averagely seperated into four groups (6 rats in one group). It included the placebo (20 mg/day vitamin C), low dose group (LDG) (bromelain 20 mg/day), middle dose group (MDG) (bromelain 30 mg /day), and high dose group (HDG) (bromelain 40mg/day). All rats were fed by gastric tubes. The whole experiment took 6 weeks and we observed the changes of Vhin each week by indirect ophthalmoscope. Moreover, the definition of success of VH is " redution of the amounts at least 3/4 volumn or the optic disc may be seen that can not seen before bromelain supplementation. **Results:** We discovered that the percent of disapperance of VH was 0%, 33.3% (2/6) (P<0.05), 50% (3/6) (P<0.05) and 66.6% (4/6) (P<0.05) in placebo, LDG, MDG, and HDG, respectively. It meant bromelain would singnificantly decrease the amount of blood. Besides, the abilities of redeced VH showed a dependent-dose manner. Further, no body weight loss and unsteady gait were noted during the study. In addition, no any damaged cells of livers and kidneys were detected from histopathological examinations under light microscope after toal SD rats by CO sacrifice. **Conclusion:** We made a forward-looking suggestion oral bromelain should be an alternative method for treating VH, especially the blood from proliferative diabetic retinopathy, posterior vitteous detachment with or withour retinal tear and blunt trauma. Moreover, the human study should be prospected and scheduled for deeper investigation in the future. [Mei Fang, Jen-Lin Hung, and Chi-Ting Horng. **The Benefit of Oral Bromelain on the Spontaneous Disappearance of Vitreous Hemorrhage: An Animal Study.** Life Sci J 2023;20(11):] (ISSN:1097-8135). http://www.lifesciencesite.com.
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1. Introduction

The vitreous is an optically clear "jelly" that occupies almost the entirety of the back of the eye and is anchored to the lens, optic nerve, and retina. It constitutes about 80% of the total eye volume and is promarily composed of collagen, hyaluronic acid, and water [1]. Normally, vitreous is closely approximated to the adjacent structures of eyes, but as we age the vitreous should begin to liquefy and shrink such as vitreous syneresis) and eventually detaches (i.e., posterior vitreous detachemnt (PVD)). Vitreous hemorrhage (VH) is defined as the presence of extravasated blood in vitreous cavity between the posterior lens capsule and zonules of the lens anteriorly, the non-pigmented epithelium of ciliary body and internal limiting Membrane (ILM) laterally, and ILM

posteriorly [2]. In other word, VH is the extravasation of blood into one of the several potential spaces formed within and around the vitreous body. Thses condition should be due to retinal tears, and neovascularization of the retina that may lead to bleeding from preexisting blood vessels in the structures. To date, VH is thought to be one of the more sereve ocular diseases which should result in vision loss. If not well controlled the bleeidng condtions, various symptoms including decreased viusal acuity, color deficiency, poor contrast sensitivity, images distortion, reduce night vision could happen [3].

intermediate uveitis, proliferative sickle cell retinopathy, retinopathy of prematurity, rhegmatogenous retinal detachemnt, haemolytic glaucoma, intra-ocular tumors, retinoschisis, Tersons' syndrome, Valsalva retinopathy, blood dyscrasias Eales' disease, a few haematological disorders (i.e.: anemia, leukemia) , retinal vascular occlusions, PVD with tear and neovascular age-related macular degeneration were also mentioned in numerous documents [4]. Moreover, severe ocular trauma, and retinal tear should also change into serious VH and even retinal detachemnt [5]. In fact, the natural history and the prognossi of VH depends on the underlying causes, and we found that spontaneous VH without underlying disorders are more favorable becasuse of the good outcome [6]. It was found VH may depend on population characteristic, geographic feature, and clinical symptoms [7]. For example, poorly controlled blood sugar for years in these patients with proliferative diabetic retinopathy are at high risk for VH. Besides, VH is one of the most common causes of sudden, painless loss of vision in adults, and rarely in pediatric group. The persons younger than 40 with VH often have a history of recent ocular trauma [8]. However the cause of VH in older, non-diabetic people is ofen due to acute PVD and/or retinal tear [9]. The most common cause of VH in children is blunt or penetrating trauma. According to the statistics, the incidence of VH was up to 7 cases per 100 000 person-years globally. Besides, Lindgren and his teams demonstrated the incidence of VH was between 31.5 % and 54% in the United States [10]. Wang and his collegues stated that the incidence to be much higher at 4.8 cases per 10,000 person-years that was more with old age (mainly 40 to 59 years), male gender, and taking anti-coagulation drugs in Taiwan [11]. Furthermore, Kim et al. suggested the people taking antiplatelet or anticoagulant medications including aspirin, clopidogrel, P2Y2 inhibitor, and warfarin should lead to VH that the incidence was around 3.72 events /1000 patient-years, especially at older adults older than 65 years, in Korean society [12]. In addition, Xu and his co-workers reported the prevalence of VH and retinal hemorrhage in adult Chinese (mean age: 64.6 ± 6.8 years) was 56.3% that the etilogies were attributed to retinal vessel occlusion and diabetic retinopathy [13]. In European, the incidence of VH was 6 %, 11.5% and 19.1% found in London (UK), France and swedish, respcetively [14,15,16]. Notably, from the above data of VH in various regioins, it revealed that the different incidences of VH may be due to the distinct climate, diffferent habits, leaving various prone to disease trends in different race and medical capabilities for treating and handling VH [17].

Now we submit the pathophysiology in detail for careful discussion. Generally speaking, multiple pathological mechanisms are associated with development of VH including disruption of abnormal vessels, and extension of blood from the adjacent source. At first, the hemorrhage into the vitreous body would results in rapid clot formation and clears at a rate of approximately 1% per day. At first, the erythrocytes may exit through trabecular meshwork, hemolysis occur, phagocytosis, or persist within the vitreous cavity for several months [18]. Nextly, if the blood did not absorbe spontaneously after a period of time, it should bring positive and aggressive therapy for enhancing intraocular hemorrhage assimilate perfectly. We must keep in mind that non-clearing and long-term persistence of VH is dangerous for the whole retina and even optic nerve by toxic reactions from blood clots [19]. Most patients with VH is caused by dilation of obstructed blood vessels, and rupture of retinal neovascularization that should speed up the bleeding in the vitreous cavity. Under the patines with severe massive and dense VH for a few monts. The victims may showed acute and subacute decreased vision. If hemorrhage combied with the damaged erythrocytes including hemoglobins, hemes, and ferrous iron (Fe^{2+}) existed for a long time, a lots of ferric iron (Fe^{3+}) may be released exhaustly and slowly becoms toxic substance to the whole eyeball structures and many cells may de destroyed with poor initial physiological function [20]. Various compliations including extensive unabsorbed intraocular blood could lead to profiferative reactions in the vitreous, form abnormal neovascular fibrous membnranes and cause massive and dense hemorrhage [21]. Furthermore, hemosiderosis bulbi, ghost cell glaucoma, hemolytic glaucoma and even hemosiderotic glaucoma from the non-clearing VH should happen that may hurt the patients' eyes and possibly result in total blindness [22,23].

As for the condtion of VH progressed, the timely and proper methods for controlling VH were necessary for the eye doctors without any treatments maybe alleviates or disappears completely. Hence, the opthalmologists may try to process various types of therapies and take the suitable time into consideration. In fact, further managements depend on the underlying diseases of VH,

the visual acuity of patients' another eyes rather than the VH eye and the
appropriate methods for the exact diagnosis and disease courses [24]. For example, Sharma et al. proposed early vitrectomy for VH patients was the dominant strategy and highly cost- effective for the victims [25]. On the other hand, immediate surgical removal of VH for older people is very important. The causes in older subjects with VH are more complicated and serious. Besides, the types of VH easily makes the victims poor vision if delayed treatments. Moreover, early surgery for the old people with VH and subsequently improving the vision may give the added benefit of allowing a full examination of the underlying retina [26]. Hence, the excellent physician would make a good decision and perform the selected method to treat VH absolutely [27].

There are many developing and developed methods in the therapies of VH that belongs to more complicated protocols and strategies. Besides, most of the methods bleong to invasive approaches and combied with different complications. Thus, the ophthalmologists must make efforts to requires wise choice for the optimal treatment without few side effects while used. In this study, we got a new idea about the medical effects of oral bromelianm maybe decreased or dissolved VH. Therefore, our research team wanted to detemine the possibility and efficacy
by a desinged anmial study.

2. Methods and Materials

This properspective study included 25 consecutive eyes of 25 SD rats were enrollled. Our funding of this research was supported by Koahsiung Arrmed Forces General Hospital and the animal study was approved by the Animal Ethics Committee of the hospital. This experiment
started at the animal laboratory of Kaohsiung Armed Forces General Hospital (Kaohsiung, Taiwan). Total of the experiment took total 6 weeks and was performed between September and November in 2023. At the beginning, 25 SD mice aged 7 and 8 weeks (mean age: 7.5 weeks) were recruited. They were all maintained at standard laboratory condition (a 12 hour light/dark cycle and the temperature of 22.2 ± 3°C). Standard chow (contained > of 25% crude protein, > 4.5% crude fat, < 12% water and < 9% ash) and sterile water were also availabel and libitum. First, one mouse was sacrificed and the left eyeball was eviscerated for inspecting the detailed structure of eyeball. Moreover, we understood the associated tisssues of anatomy of eyeball for next plan. Afterwards, VH mode was created by the 26 gauge needle puncturing directed toward the pars plana region (just 1mm posterior to pars plana) and into the vitreous cavity of the other 24 SD rats. From the help of indirect ophthalmoscope, we examined the intraocular bleeding within the eyeballs of 24 SD rats (all left eyes) and recorded the degree of hemorrhage in viteous cavity [28]. All 24 mice were randomly and averagely seperated into 4 groups (6 rats were gathered in each group). It included placebo (vitamin C 20 mg/day), low dose group (LDG) (bromelain 20 mg/day), middle dose group (MDG) (bromelain 30 mg /day), and high dose group (HDG) (bromelain 40mg/day). Further, all SD rats were fed according to the desiged protocols of differnt medications by gastic tubes.

During the 6-week observational time, we followed the changes of amount of intraocular hemorrhage in each rats (4 groups) weekly by indirect ophthalmoscope. Further, the definition of "success" of treatment of VH is " redution of the amount of VH about 3/4 volume or the optic disc may be seen eventually that could not be seen before treatment [29]. We also recorded the outcome carefullly. After 6 weeks, all rats were sacrificed by inhalation of carbon monoxide (CO) and excised livers and kidneys of all rats for biopsy and H& E staining was done. Besides, the histopathologic assessment was performed and we observe the specimens under optical microscope.

After the ending of our experiment, the body weight body, fur color, daily activity of all SD rats were followed particularly. In addition, the morphologic changes of livers and kidneys of total mice were recorded carefully. Furthermore, the percent of "success" after therapy was also calculated. All the data were presented as mean ± standard devation (SD) and analyzed by using SAS 9.0 (SAS Inst., Cary, NC, USA). We tried to comapre the success rate of each group after 6 weeks with placebo by paired t test. Besides, the p value < 0.05 was considered statistically significant.

3. Results

After 6-week follow-ups, we found the percent of "success" of treating VH by means of various treatments was 0% (0/6), 33.3% (2/6), 50%(3/6) and 66.6% (4/6) in placebo, LDG, MDG, and HDG, respectively. Besides, it is instersting to find that the effectiveness of redeced VH should show a dependent-dose manner. Further, no apprent body weight loss, weakness, general malaise, unsteady gait and even death were noted. We concluded that oral bromelain is relatively safe for the animals.

4. Discussion

Vitreous body is bounded posterolaterally by the ILM of the retina, anterolaterally by the nonpigmented epithelium of ciliary body, and anteriorly by lens zonular fibers and posterior lens capsule. The retrolental space of Erggelet and the canal of Petit are potential spaces. These two spaces are located between anterior hyaloid membrane, posterior lens capsule, and the orbiculoposterocapsular portion of zonular fibers.

The hyaloideocapsular ligament separates them from each other. VH is defined as the presence of extravasated blood within the sapce outlined by the ILM posterior and laterally the non-pigmented epithelium of ciliary body antero-laterally and the lens zonular fibers and posterior lens capsule anteriorly. Briefly speaking, the blood leaks into vitreous cavity was called “VH”. Furthermore, bleeding into the retrohyaloid or subhyaloid spaces and for the sub–internal limiting membrane hemorrhage was also considered as VH [30]. From another view, the vitreous is transparent and highly hydrated (98.5% water) extra-cellular matrix (ECM) attached to retina. Vitreous is primarily maintained by collagen fibrils including collagen type II, V/VX, IX, I and III. The structure is preserved by a network of long, thin, collagen fibrils [31]. When people aging, collagen fibrils to aggregate and liquefy acoomapined by vitreous shrinkage and clumping, which formed various shapes of shadows on retina which were perceived as ocular floaters or symptomatic vitreous opacities (SVOs) [32]. Further, another elements such as hyaluronic acid should loss and abnormal ECM could aggregate. Blood could enter the vitreous cavity and furtherly mix the damaged and misloading collgen fibrils, and ECM that was condiered as the compositions of VH. As for the intraocular hemorrhage, VH is seen as blood floating in the vitreous, occluding the view of retina variably. Besides, the typical boat shape of subhyaloid hemorrhage may be noted [33].

Early detection of VH by the persons themselves is vitally important because the proper, and suitable treatments should be arranged and implemented for the good outcome. Hence, how to realize the phenomenon is significant [34]. When VH appeared in front of the human eyes, various clinical presentation may be observed. The patients with VH always complained about haze, floaters, cloudy, smoking signals, photophobia, perception of shadows and the shape of cobwebs. Besdies, patients with VH alos suffered from reduced contrast sensitivity, stereo-acuity and metamorphopsia [35]. Moreover, VH induced SVOs may be associated with various psychological distress such as unhappy mood, mental stress, and anxiety [36]. Besies, VH induced floaters may also affect the life quality and vision dependent tasks, for example, night driving [37]. Patients with small VH often is perceived as multiple floaters, moderate VH is felt like as dark streaks, and dense VH tends to obscure the whole retinal morphology and optic disc that could possibly block the visual axis and result in decreased visual acuity and total blindness without ocular painful sensation [38,39]. If severe loss of vision happened, VH even bring great ecomic burden to patients’ families and society [40]. Visual acuity should be affected variably depending upon the amount of blood in the visual axis. Thompson and his reserch team reported a 12.5 microliters of diffuse blood in 5 ml aphakic eye and 10 microliters in 4ml phakic eye should result in vision decreased to hand motions [41]. Some of patients with VH could present with flasshes of ligh, especially at night. The sympotoms of lightflash maybe becomes worse in the morning, because lying down could cause blood to pool in the back of eye. If there were light-flashes, retinal detachment or retinal tear should present [42]. More significant hemorrhage could limit vision and visual fields or cause scotomas. Patients often percept the worse vision in the morning as blood has settled to the back of eye, covering the macula. Besides, the terrible retinal detachemnt maybe happened if the İightflash were noted by patients themselves. When massive and dense VH happened and visual acuity decreased
simultaneously, surgical intervention were necesssary urgently [43].

VH is a relatively common cause of acute vision loss, and it is frequently encountered by ophthalmologists and Emergency Room professionals alike due to its often rapid onset which causes painless, but substantial vision loss. Because the desne VH may obscure the etinal fudus, the diagnosis of VH only depended on ultrasonography(B-scan) which was also used to evaluate the outcome and prognosis from different therapies. It is esential for eye doctors to realize the underlying etiologies associated VH because the ophthalmologists could measily make a decision to design the treating plans [44]. Firstly, we summarized the etiologies of VH owing to the characteristics of the study population because the frequency of the etiologies of VH is diverse. The causes of VH could be classified into ischemia caused by abnormalities in vascular, abnormalities of retinal vascular which did not relate to retinal ischemia, the normal rupture of retinal blood vessels and the subretinal hemorrhage which penetrates vitreous. The three most common causes of VH are (1). proliferative diabetic retinopathy (32%), (2). PVD with or without retinal tear (30% and 8%), and (3) ocular trauma, which account for 59 - 88.5% of all VH cases [44]. In addition, less common etioligies were retinal vein occlusion, retinal vasculitis, proliferative sickle cell retinopathy, retinal arterial macroanuerysm, Terson’s syndrome, Valsalva retiniopathy, X-linked retinochisis, retinopathy of prematurity, familial exudative vitreoretinopathy, intermediate uveitis, blood dyscrasias/coagulation disorders, and neovascular age-related macular degeneration. It is important to seek for the risk factors of various VH for prevention and subsequent treatment [45, 46]. Today, it is well known VH is always the results that underlying diseases provoke retinal sichemia and futherly result in hypoxia that finally lead to the production of hypoxia induced factor (HIF). This factor should enhace the expression

of various angiogenic factors including insulin-like growth factor -1, basic fibroblast growth factor, erythropoietin, and vascular endothelial growth factor (VEGF) which are present in the vitreous cavity. Some blood could easlty leak from the newly formed vessels whcih are induced by the functions of VEGF and have the fragile characteristic and produce the neovascular tissue. If the tissues proliferate, it may invades the potential space between the retina and the posterior hyaloid face and later the posterior lamellae of the cortical vitreous, producing a firm adhesion [47].

The blood vessels begin to proliferate and subsequently develop into fibrous components. Localized traction from posterior hyaloid face or contraction of fibrous element of fibrovascular complex leads to traction on the friable neovascular tissue and retina, leading to the existence of VH. Firstly, VH was predominat symptoms rather than other disorders in 32% patients with VH. Bleeding should occur from neovascularization due to retinal ischemia causing elevated various angiogenic factors. The hemorrhage into vitreous cause decreased vision and follow by fibrosis, leading to retinal detachment. Panretinal laser photocoagulation of new vessels has been the standard of care for proliferative diabetic retinopathy. Diabetic VH secondary to proliferative diabetic retinopathy is a cause of severe vision loss and even total blindness in patients with DM [48]. Secondarily, the common complications from PVD are retinal breaks, retinal henmorrhage, optic disc hemorrhage, retinal detachment as well as SVOs from the massive VH. Moreover, severe PVD should dramatically induced retinal tear, VH, and retinal detachment. In Taiwan, the patients with VH showed 8-19% of cases were PVD without retinal tear and 8% of cases with retinal tear that led to VH formation after preliminary assessment. For most people, a PVD is a benign (harmless) event with no symptoms and no vision loss. Others may notice a lot of vitreous floaters [49]. Floaters can be bothersome but usually become less noticeable over time. For a small amount of people having the PVD, problems occur when the vitreous detaches from retina, espcially involving whether the action of tear break or not and the possibility of draggin out the blood vessels, thereby VH formation. Thirdly, ocular trauma is a major etilogy of monocular blindness in the world [50]. Besides, it also becomes the common causes of VH in patients less than 40 years of age. The patients with VH reveals nearly 24.5% of subjects who suffered from VH. Ocuar trauma induced VH is associated with serous or hemorrhagic choroidal detachments. Further, several complications such as retinal dialysis, choroidal rupture, Berlin's edema, optic nerve avuylsion and vitreous base avulsion. Because prognosis is relatively poor in this type of VH, early vitrectomy at correct timing may significantly improve the efficacy, and outcomes.

In Taiwan, taking anticoagulants and antiplatelet agents, health supplements or Chinese herbs (i.e.: aspirin, warfarin, clopidogrel, astaxanthin, deep sea oil, and Ginkgo Biloba) may enhance the intraocular bleeding [51]. What's more, the subjects with systemic coagulation disorders and blood dyscrasias such as leukemia and thrombocytopenia may increase the higher prevalence of VH. Therefore, we must pay attention to the associated risk factors for the purpose of reducing the occurence of VH. However, long-term VH without therapy should induce various complications such as synchysis scintillans (Cholesterol deposit in vitrous appearing as small white floaters freely moving in the posterior part of eyes), hemoglobin spherulosis (the red blood cells break down and release free haemoglobin which aggregates and form spherules Hemoglobin) and vitreous cylinders (condensated collagen fibers which resuited in vitreous opacity). The other complications included ghost cell glaucoma, hemolytic glaucoma and hemosiderotic glaucoma that may obstruct the pathway of trabecular meshwork, levate IOP and even impact the retina and optic nerve function [52]. Therefore, the timing for further approach is very important.

The prognosis of VH depends on the underlying etilogies and various treatment options [53]. Patients with VH would be classified to different degrees in clinics. For example, severe bleedings may cause a sudden and complete loss of vision, while mild ones cause blurred vision or floaters. The treatment for VH should include simple observation, photo-coagulation with Argon laser, intravitreal injections (IVI) of anti-VEGF, and surgery (pars plana vitrectomy). The timing of aggressive treatment deserves deep thought. Dhing and his colluges proposed early operation for the fundus – obscuring spontaneous dense VH from PVD seens worth [54]. Hayashida et al. elaborated early surgical intervention within 2 weeks for dense VH after the onset of symptoms benefits to prevent the disease progression and lower visual outcome [55] Fassbender et al. postulated early vitrectomy for VH due to proliferative diabetic retnopathy apparently should decrease time spent with vision loss and the need for further Argon laser therapy [56]. Newman et al. stated that early vitrectomy contributes to a lower likelihood of rebleeding, better quality of life , higher patients' satifaction, quicker visual recovery and a more rapid return to daily activities [57]. Melamud found some literature on the management of patients had fundus-obscuring VH, prompt and early surgery is necessary when VH is owing to the results of retinal tear or retinal detachment [58]. However, early operation may carry some risks such as intraoperative bleeding, retinal detachment and endophthalmitis. Besides, VH would clear and absorb spontaneously or persist with time.

Spontaneous clearance of blood from the vitreous is a slow and constant process, and much more common in diseases which have no tendency of recurrent bleeding. syneresis of vitreous gel, in elderly and aphakic patients. Sometimes, early surgery is not absolutely indicated and most eye doctors may suggest the VH subjects wait until the blood absorbing. However, the blood in the vitreous does not clear spontaneously in patients with proliferative diabetic retinopathy [59]. Besdies, longstanding VH without handling should accumulate red cells and red cell debris and mix with vitreous collagen fibers which could clinically present as an ochre membrane at times. Hence, how to choose the applicable treatments becomes the advanced strategy and skill. Thus, it is important to differential and decide for the patients with VH who receive operation early or lately which is based on a thorough evaluation of each patients' clinical presentation, potential benefits and underlying pathologies. It seems that late surgery may be a good choice. Even Kim et al. recommended late vitrectomy for a peroid of time may wait for breaking through VH and lightly clear intraocular hemorrhage and show better visual outcome [60]. Therefore, when to arrrange operation becoms controversial that depends on the individual ophthalmologist's decision and wisdom.

There are many methods for managing various etilogies of VH simultaneously. Besides, the prognosis of VH depends on the underlying causes and various treatment options. Firstly, simple observation for the spontaneous ansorbance in VH is the easy and non-invasive choice. Fresh VH often clear in days to weeks and hence the wait-and-see method is usually adopted. In addition, retinal detachment induced VH can't wait and needs early vitrectomy for trying to save the victims's vision. Therefore, we must perform by ocular ultrasound to confirm the case with macula-off retinal detachment. Obsearvation is the easiest method for mild and moderate blood disppearance. The patients should take a rest with the head in an elevated position and reevaluate after 3-7 days to ascertain the possible source of hemorrhage. Nevertheless, the success rates cannot be predicted, Most ophthalmologists founded that most of the waiting time for absorbance was approximate to 3–6 months.and even one year. However, the people with dense VH do not dispappear at times. Unfortunately if VH did not disminish spontaneously within half a year, it should develop into glial and fibrovascular proliferation, tractional retinal detachemnt, retinal breaks, neovascular glaucoma, ghost cell glaucoma, retinal damage, haemolytic glaucoma, haemosiderotic glaucoma, haemosiderosis bulb. and permanent loss of vision. Hence , the proper time of surgery is quite debatable by physicians [57,61]. Secondrialy, argon laser photocoagulation is also anthor technique for decreased the amounts or incidence of VH. However, only the fundus can not obscure by the VH that argon beam may enter vitreous cavity and ophthalmologists would focus the retina. When the laser beam would smoothly penetrate into the eyeball, the engery would be absorbed by retinal pigment layers and coagulates the newly formed and fragile blood vessels whch is due to the effects of VEGF. Hence, we could stop the blood leakage after sealing blood leaking from retinal vessels by the mechanism of coagulation. Besides, argon laser could prevent recurrent bleeding that made VH become more serious. In addition, laser should derease the oxygen demand of the retina whcih would help to redirect enough oxygen and nutrients for retina, thereby changing the hemodynamics. Nevetheless, the complications would limit the medical effetcs of argon laser including cataract, decreased night vision, retinal damage and scar, glaucoma, retinal vessels rupture, choroidal detachment, and corneal burns since all of those would compromise visual acuity [62,63].

Thirdly, intravitreal injection (IVI) with bevacizumab (Avastin®) is well known to decreae VH by diminishing the amounts VEGF. Avastin® is is a recombinant, full-length, humanized antibody that binds all VEGF isoforms. It is effective in treating neovascularization which is the primary cause of VH. Besides, it may be able to degrade cleaved collagens, fibronectin, laminin, overgrowth tissue, ECM, vitreous fibrils and intraocular hemorrhage. For the subjects with VH, a single IVI of 0.125 mg Avastin® could be used to cut VH, vitreous opacity and the amount of blood clots showed disappearance rate of 26.5% at Day 28. However, several complications have been reported after IVI of Avastin® that makes the ophthalmologists hesitatation. Ocular side effects like the subconjunctival hemorrhage, rise of intraocular pressure, uveitis, cataract, conjunctival chemosis, iatrogenic vitreous hemorrhage, rhegmatogenous retinal detachment, progression of diabetic tractional retinal detachment, endophthalmitis, vision loss and even blindness. Furthermore, systemic complications are the acute rise of blood pressure, mild irritation and allergic dermal reaction, myocardial infarction, stroke, and death. Because the sight-threatening conditions and even death, and eye doctors may condiser other alternative method for VH now [64,65]. Fourthly, undergoing the opeation (pars plana vitrtectomy) is the better option for directly and completely for clearing the persistent, larger, diffuse and severe VH, especially within the visal axis. The poster-operative Snellen visaul acuity would increase during 8-44 months follow-up. Some patients expressed satisfaction with the surgical outcome. However, various principal complications such as recurrent VH (about 30%), cystoid macular edema, retinal tear, cataract, elevation of intraocular pressure, rubeosis iridis, troublesome endophthalmitis,

loss of vision, phthisis bulbi and intragenic eyeball rupture Hence, surgery is still popular for eye doctors that may completely eliminate intraocular hemorrhage [66,67].

Now the concept of pharmacological vitreolysis of eliminiating the pathogenetic role of human ocular flaoters is proposed by our reserch team is these years [68].We suggested that bromelain extracted from pineapple would play a vital role in the mechanism. There are many medical functions for pineapple and its derived ingredients. For instance, bromelain is one of the most popular enzymes which is primarily from the stem and fruit of pineapple. Acccording to classification, bromelain was introduced and applied to any protease from the plant family Bromeliaceae. Several documents revealed that the medical advantages of bromelain may be due to its proteolytic and hydrolytic activities. Furthermore, bromelain also has the hydtolytic, antifibrinolytic, anti-inflammatory and antithrombotic properties. In this article, we singificantly found that bromelain should reduce the forrmation of VH which is the mixtures of intraocular blood clots, damaged collagenous fibrils and ECM [69,70].

5.Conclusion:

In this study, we demonstrated that oral enough bromelain should significantly dissolve and absorbe VH in a dose-dependent manner. Further, good applicabilityin and no side effects were noted. Moreover, oral bromelain is better than the tranditional methods of therapy of VH suh as simple observation, argon laser, IVI of Avastin® and pars plana vitrtectomy because it is relatively safe for the subjects. Hence, we make a forward-looking suggestion oral bromelain may be an alternative method for VH. Furthermore, the human study should be arranged and scheduled for deeper investigation in the future.

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