

Issue 102

Monday October 15 , 2012

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

Ophthalmology. 2012 Oct 6. pii: S0161-6420(12)00677-X. doi: 10.1016/j.ophtha.2012.07.042. [Epub ahead of print]

Baseline Predictors for One-Year Visual Outcomes with Ranibizumab or Bevacizumab for Neovascular Age-related Macular Degeneration.

Ying GS, Huang J, Maguire MG, Jaffe GJ, Grunwald JE, Toth C, Daniel E, Klein M, Pieramici D, Wells J, Martin DF; Comparison of Age-Related Macular Degeneration Treatments Trials Research Group*.

Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Electronic address: gsying@mail.med.upenn.edu.

OBJECTIVE: To determine the baseline predictors of visual acuity (VA) outcomes 1 year after treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

DESIGN: Cohort study within the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

PARTICIPANTS: A total of 1105 participants with neovascular AMD, baseline VA 20/25 to 20/320, and VA measured at 1 year.

METHODS: Participants were randomly assigned to ranibizumab or bevacizumab on a monthly or as-needed schedule. Masked readers evaluated fundus morphology and features on optical coherence tomography (OCT). Visual acuity was measured using electronic VA testing. Independent predictors were identified using regression techniques.

MAIN OUTCOME MEASURES: The VA score, VA score change from baseline, and ≥ 3 -line gain at 1 year.

RESULTS: At 1 year, the mean VA score was 68 letters, mean improvement from baseline was 7 letters, and 28% of participants gained ≥ 3 lines. Older age, larger area of choroidal neovascularization (CNV), and elevation of retinal pigment epithelium (RPE) were associated with worse VA (all $P < 0.005$), less gain in VA (all $P < 0.02$), and a lower proportion gaining ≥ 3 lines (all $P < 0.04$). Better baseline VA was associated with better VA at 1 year, less gain in VA, and a lower proportion gaining ≥ 3 lines (all $P < 0.0001$). Predominantly or minimally classic lesions were associated with worse VA than occult lesions (66 vs. 69 letters; $P=0.0003$). Retinal angiomatous proliferans (RAP) lesions were associated with more gain in VA (10 vs. 7 letters; $P=0.03$) and a higher proportion gaining ≥ 3 lines (odds ratio, 1.9; 95% confidence interval, 1.2-3.1).

Geographic atrophy (GA) was associated with worse VA (64 vs. 68 letters; $P=0.02$). Eyes with total foveal thickness in the second quartile (325-425 μm) had the best VA ($P=0.01$) and were most likely to gain ≥ 3 lines ($P=0.004$). Predictors did not vary by treatment group.

CONCLUSIONS: For all treatment groups, older age, better baseline VA, larger CNV area, predominantly or minimally classic lesion, absence of RAP lesion, presence of GA, greater total fovea thickness, and RPE elevation on optical coherence tomography were independently associated with less improvement in VA at 1 year.

PMID: 23047002 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Oct 8;1-7. doi: 10.1001/2013.jamaophthalmol.91. [Epub ahead of print]

Ranibizumab for Edema of the Macula in Diabetes Study: 3-Year Outcomes and the Need for Prolonged Frequent Treatment.

Do DV, Nguyen QD, Khwaja AA, Channa R, Sepah YJ, Sophie R, Hafiz G, Campochiaro PA; for the READ-2 Study Group.

OBJECTIVE: To assess the benefit of increased follow-up and treatment with ranibizumab between months 24 and 36 in the Ranibizumab for Edema of the Macula in Diabetes (READ-2) Study.

DESIGN: Prospective, interventional, multicenter follow-up of a randomized clinical trial.

METHODS: Patients who agreed to participate between months 24 and 36 (ranibizumab, 28 patients; laser, 22; and ranibizumab + laser, 24) returned monthly and received ranibizumab, 0.5 mg, if foveal thickness (FTH, center subfield thickness) was 250 μm or greater. Main outcome measures were improvement in best-corrected visual acuity (BCVA) and reduction in FTH between months 24 and 36.

RESULTS: Mean improvement from the baseline BCVA in the ranibizumab group was 10.3 letters at month 36 vs 7.2 letters at month 24 (ΔBCVA letters = 3.1, $P = .009$), and FTH at month 36 was 282 μm vs 352 μm at month 24 ($\Delta\text{FTH} = 70 \mu\text{m}$, $P = .006$). Changes in BCVA and FTH in the laser group (-1.6 letters and -36 μm , respectively) and the ranibizumab + laser group (+2.0 letters and -24 μm) were not statistically significant. The mean number of ranibizumab injections was significantly greater in the ranibizumab group compared with the laser group (5.4 vs 2.3 injections, $P = .008$) but not compared with the ranibizumab + laser group (3.3, $P = .11$).

CONCLUSIONS: More aggressive treatment with ranibizumab during year 3 resulted in a reduction in mean FTH and improvement in BCVA in the ranibizumab group. More extensive focal/grid laser therapy in the other 2 groups may have reduced the need for more frequent ranibizumab injections to control edema.

APPLICATION TO CLINICAL PRACTICE: Long-term visual outcomes for treatment of diabetic macular edema with ranibizumab are excellent, but many patients require frequent injections to optimally control edema and maximize vision.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00407381.

PMID: 23044909 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Oct 12. doi: 10.1038/eye.2012.199. [Epub ahead of print]

Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: incidence, features, risk factors, and outcomes.

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Purpose: To describe the incidence, features, management, and risk factors of post-intravitreal anti-VEGF endophthalmitis (PIAE) in patients undergoing treatment for exudative age-related macular degeneration in the United Kingdom.

Methods: Prospective observational case control study. Forty-seven cases of PIAE were identified through the British Ophthalmological Surveillance Unit from January 2009 to March 2010. Data collected at diagnosis and at 6 months follow-up included patient demographics, intravitreal injection details, pre- and post-injection management, visual acuity, clinical features and management of PIAE, causative organisms, and clinical outcomes. Details were compared with 200 control cases from 10 control centres to identify potential risk factors.

Results: Estimated PIAE was 0.025%. Culture-positive PIAE incidence was 0.015%. Mean age of presentation was 78 years. Mean number of intravitreal injections before PIAE was 5. Mean days to presentation was 5 (range 1-39). Positive microbiology culture was found in 59.6%. The majority of causative organisms were Gram positive (92.8%). Significant risk factors were failure to administer topical antibiotics immediately after the injection ($P=0.001$), blepharitis ($P=0.006$), subconjunctival anaesthesia ($P=0.021$), patient squeezing during the injection ($P=0.021$), and failure to administer topical antibiotics before anti-VEGF injection ($P=0.05$).

Discussion: The incidence of PIAE in the United Kingdom is comparable to other studies at a rate of 0.025%. The most common causative organisms were Gram positive. Measures to minimise the risk of PIAE include treatment of blepharitis before injection, avoidance of subconjunctival anaesthesia, topical antibiotic administration immediately after injection with consideration to administering topical antibiotics before injection. Eye advance online publication, 12 October 2012; doi:10.1038/eye.2012.199.

PMID: 23060022 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Oct 4. pii: S0181-5512(12)00240-9. doi: 10.1016/j.jfo.2012.01.015. [Epub ahead of print]

Bevacizumab versus ranibizumab in the treatment of exudative age-related macular degeneration: A retrospective study of 58 patients.

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AIM: To compare the efficacy and safety of bevacizumab versus ranibizumab in the treatment of patients with neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS: Retrospective case-controlled series of 30 patients treated with intravitreal bevacizumab and 28 patients treated with intravitreal ranibizumab for exudative AMD. Main outcomes measured included best-corrected visual acuity (BCVA), central macular thickness (CMT) and foveal thickness, quantity of subretinal fluid, neovessel size and total number of injections over the first year treatment period. A secondary outcome was the report of any adverse events in both groups.

RESULTS: BCVA stabilized and increased from LogMAR 0.70 to 0.47 in the bevacizumab group and from 0.55 to 0.54 in the ranibizumab group ($P>0.05$). CMT decreased in the bevacizumab group from 369 to 284 μ m and in the ranibizumab group from 340 to 271 μ m ($P>0.05$). The number of injection was significantly lower (4.8) in the bevacizumab group than in the ranibizumab group (5.8) ($P<0.05$). No serious ocular adverse events were noted in both groups.

CONCLUSION: This retrospective study failed to show a difference in visual and anatomic outcomes

between bevacizumab and ranibizumab. The number of re-treatment was lower in the bevacizumab group (P=0.03).

PMID: 23040443 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2012;6:1519-25. doi: 10.2147/OPTH.S31010. Epub 2012 Sep 17.

A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration.

Williams PD, Callanan D, Solley W, Avery RL, Pieramici DJ, Aaberg T.

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PURPOSE: This prospective multi-center pilot study compares the use of half-fluence photodynamic therapy combined with ranibizumab with ranibizumab monotherapy for the treatment of neovascular age-related macular degeneration.

METHODS: All patients presenting with untreated subfoveal neovascular age-related macular degeneration were considered for inclusion. Patients were randomized to receive either ranibizumab with half-fluence photodynamic therapy or ranibizumab alone. Patients in the ranibizumab alone group were given three consecutive monthly ranibizumab injections and were followed monthly. They were treated with ranibizumab as needed, based on clinical discretion, using vision and optical coherence tomography. Patients in the combined group were given one same-day combined ranibizumab and half-fluence (25 j/cm (2)) photodynamic therapy treatment and were treated monthly as needed. Outcomes included changes in standardized visual acuity, optical coherence tomography foveal thickness, and percentage of as-needed injections to maintenance examinations.

RESULTS: Fifty-six out of 60 enrolled patients completed the twelve month primary outcome visit; this consisted of 27 patients receiving ranibizumab alone and 29 receiving combined treatment. The average age was 79.1 for the ranibizumab alone group and 79.3 for the combined group. The mean visual acuity in the ranibizumab alone group improved from 52.9 Early Treatment of Diabetic Retinopathy letters initially to 62.8 letters at twelve months. The mean visual acuity in the combined group improved from 49.2 letters to 51.8 letters at twelve months. The differences in visual acuity improvements were not statistically significant based on a two-tailed t-test (P = 0.2). Due to the presence of outliers in each group, a Mann-Whitney U test was performed to confirm the results (U = 325; P = 0.28). The mean optical coherence tomography foveal thickness improved 92.5 microns and 106.7 microns in the ranibizumab alone and the combined group, respectively. The difference was not significant based on a two-tailed t-test (P = 0.6). The ranibizumab alone group received an average of 6.8 injections, while the combined group received an average of three injections. This difference was not significant based on a chi-square test (P = 0.11).

CONCLUSION: The groups appeared similar based on statistical analysis, but larger studies are needed to determine possible small differences between combination therapy and monotherapy.

PMID: 23055673 [PubMed]

J Clin Ultrasound. 2012 Oct 11. doi: 10.1002/jcu.21989. [Epub ahead of print]

Evaluation of retrobulbar blood flow by color doppler ultrasonography after intravitreal ranibizumab injection in patients with neovascular age-related macular degeneration.

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PURPOSE: This study aimed to evaluate the changes in retrobulbar blood flow by using color Doppler sonography in patients who had undergone intravitreal ranibizumab injection for neovascular age-related macular degeneration (AMD).

METHODS: The study comprised 37 AMD patients who had undergone intravitreal 0.5 mg ranibizumab injection. The ophthalmic artery, central retinal artery, and short lateral posterior ciliary artery of both eyes of patients were evaluated by color Doppler sonography. Peak systolic velocity, end-diastolic velocity, and resistance index were calculated before injection, and after injection on day 7 and day 30. The pre- and postinjection values were compared using Wilcoxon signed rank test.

RESULTS: In a comparison with the preinjection values of peak systolic velocity, end-diastolic velocity, and resistance index, the postinjection values at both day 7 and day 30 showed no statistically significant difference in ophthalmic artery, lateral posterior ciliary artery, and central retinal artery ($p > 0.05$). Similarly, for the same parameters, pre- and postinjection values in the uninjected fellow eye showed no statistically significant difference ($P > 0.05$).

CONCLUSIONS: Intravitreal ranibizumab injection for neovascular AMD does not cause a significant change in the retrobulbar blood flow in either the injected eye or the fellow eye.

PMID: 23055187 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Jpn J Ophthalmol. 2012 Oct 4. [Epub ahead of print]

Visual prognosis of eyes with submacular hemorrhage associated with exudative age-related macular degeneration.

Ueda-Arakawa N, Tsujikawa A, Yamashiro K, Ooto S, Tamura H, Yoshimura N.

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PURPOSE: To study the retinal structural changes associated with submacular hemorrhage due to exudative age-related macular degeneration (AMD) and their relationships with visual prognosis.

METHODS: We retrospectively reviewed the medical records of 31 consecutive patients (31 eyes) with visual impairment due to an acute submacular hemorrhage associated with typical AMD (10 eyes) or polypoidal choroidal vasculopathy (21 eyes).

RESULTS: Optical coherence tomography (OCT) revealed that submacular hemorrhage exhibited intense hyperreflectivity beneath the neurosensory retina and often seemed to infiltrate it. In the OCT sections, mild to moderate amorphous hyperreflectivity and/or hyperreflective dots were observed within the neurosensory retina, resulting in the loss of the junctions between the inner (IS) and outer (OS) segments of the photoreceptors. Of the 31 eyes, the foveal IS/OS line could be seen incompletely in 12 eyes and was totally absent in 16 eyes. The initial integrity of the foveal photoreceptor layer was correlated with the final visual acuity; the initial detection of the IS/OS just beneath the fovea was correlated with good final visual acuity ($r = 0.375$, $p = 0.038$).

CONCLUSION: As a hallmark of integrity of the foveal photoreceptor layer, the initial detection of the IS/OS just beneath the fovea may predict good visual outcomes.

PMID: 23053632 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Oct 9. [Epub ahead of print]

Construction of an inexpensive, hand-held fundus camera through modification of a consumer "point & shoot" camera.

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Purpose: To construct a low cost, easy-to-use, high image quality mydriatic fundus camera with "point & shoot" operation, and to evaluate the efficacy of this camera to accurately document retinal disease.

Methods: A prototype portable fundus camera was designed by interfacing a novel optical module with a Panasonic Lumix G2 consumer camera. Low cost commercially available optics were used to create even illumination of the fundus, providing a 50° retinal field of view. A comparative study assessing the image quality of the prototype camera against a traditional tabletop fundus camera was conducted under an IRB-approved study.

Results: A stand-alone, mydriatic camera prototype was successfully developed at a parts cost of less than \$1000. The prototype camera was capable of operating in a point-and-shoot manner with automated image focusing and exposure, and the image quality of fundus photos was comparable to existing commercial cameras. Pathology related to both non-proliferative and proliferative diabetic retinopathy and age-related macular degeneration was easily identified from fundus images obtained from the low cost camera.

Conclusions: Early prototype development and clinical testing has shown that a consumer digital camera can be inexpensively modified to image the fundus with professional diagnostic quality. The combination of low cost, portability, "point & shoot" operation, and high image quality provides a foundational platform on which one can design an accessible fundus camera to screen for eye disease.

PMID: 23049089 [PubMed - as supplied by publisher]

Pathogenesis

Front Immunol. 2012;3:296. doi: 10.3389/fimmu.2012.00296. Epub 2012 Sep 21.

The privileged immunity of immune privileged organs: the case of the eye.

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Abstract

Understanding of ocular diseases and the search for their cure have been based on the common assumption that the eye is an immune privileged site, and the consequent conclusion that entry of immune cells to this organ is forbidden. Accordingly, it was assumed that when immune cell entry does occur, this reflects an undesired outcome of breached barriers. However, studies spanning more than a decade have demonstrated that acute insults to the retina, or chronic conditions resulting in retinal ganglion cell loss, such as in glaucoma, result in an inferior outcome in immunocompromised mice; likewise, steroidal treatment was found to be detrimental under these conditions. Moreover, even conditions that are associated with inflammation, such as age-related macular degeneration, are not currently believed to require immune suppression for treatment, but rather, are thought to benefit from immune modulation. Here, we propose that the immune privilege of the eye is its ability to enable, upon need, the entry of selected immune cells for its repair and healing, rather than to altogether prevent immune cell entry. The implications for acute and chronic degenerative diseases, as well as for infection and inflammatory diseases, are discussed.

PMID: 23049533 [PubMed] PMCID: PMC3448293

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Angiogenesis. 2012 Sep 29. [Epub ahead of print]

Synergy between a collagen IV mimetic peptide and a somatotropin-domain derived peptide as angiogenesis and lymphangiogenesis inhibitors.

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Abstract

Angiogenesis is central to many physiological and pathological processes. Here we show two potent bioinformatically-identified peptides, one derived from collagen IV and translationally optimized, and one from a somatotropin domain-containing protein, synergize in angiogenesis and lymphangiogenesis assays including cell adhesion, migration and in vivo Matrigel plugs. Peptide-peptide combination therapies have recently been applied to diseases such as human immunodeficiency virus (HIV), but remain uncommon thus far in cancer, age-related macular degeneration and other angiogenesis-dependent diseases. Previous work from our group has shown that the collagen IV-derived peptide primarily binds $\beta 1$ integrins, while the receptor for the somatotropin-derived peptide remains unknown. We investigate these peptides' mechanisms of action and find both peptides affect the vascular endothelial growth factor (VEGF) pathway as well as focal adhesion kinase (FAK) by changes in phosphorylation level and total protein content. Blocking of FAK both through binding of $\beta 1$ integrins and through inhibition of VEGFR2 accounts for the synergy we observe. Since resistance through activation of multiple signaling pathways is a central problem of anti-angiogenic therapies in diseases such as cancer, we suggest that peptide combinations such as these are an approach that should be considered as a means to sustain anti-angiogenic and anti-lymphangiogenic therapy and improve efficacy of treatment.

PMID: 23053781 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2012 Oct 11. [Epub ahead of print]

Polymorphisms in ARMS2/HTRA1 and complement genes and age-related macular degeneration in India: findings from the INDEYE study.

Sundaresan P, Vashist P, Ravindran RD, Shanker A, Nitsch D, Nonyane BA, Smeeth L, Chakravarthy U, Fletcher AE.

Department of Genetics, Aravind Medical Research Foundation, Dr. G. Venkataswamy Eye Research Institute, Aravind Eye Hospital, Madurai, Tamil Nadu, India.

Purpose: Association between genetic variants in complement factor H (CFH), factor B (CFB), component 2 (C2) and in the ARMS2/HTRA1 region with age-related macular degeneration (AMD) comes mainly from studies of European ancestry and case control studies of late stage disease. We investigated associations of both early and late AMD with these variants in a population-based study of people aged 60 years and over in India.

Methods: Fundus images were graded using the Wisconsin Age-Related Maculopathy Grading System and participants assigned to one of 4 mutually exclusive stages based on the worse affected eye (0=no AMD, 1-3=early AMD, 4=late AMD). Multinomial logistic regression was used to derive risk ratios (RR) accounting for sampling method and adjusting for age, sex and study centre.

Results: Of 3569 participants, 53.2% had no signs of AMD, 45.6% had features of early AMD, and 1.2% had late AMD. CFH (rs1061170), C2 (rs547154) or CFB (rs438999) were not associated with early or late

AMD. In the ARMS2 locus, rs10490924 was associated with both early (adjusted RR 1.22, 95%CI: 1.13-1.33, $p < 0.0001$) and late AMD (adjusted RR 1.81, 95%CI: 1.15-2.86; $p = 0.01$), whilst rs2672598 was associated only with early AMD (adjusted RR 1.12, 95%CI: 1.02-1.23; $p = 0.02$); . rs10490923 was not associated with early or late AMD.

Conclusions: Two variants in ARMS2/HTRA1 were associated with increased risk of early AMD, and for one of these, the increased risk was also evident for late AMD. The study provides new insights into the role of these variants in early stages of AMD in India.

PMID: 23060141 [PubMed - as supplied by publisher]

Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2012 Oct;29(5):570-2. doi: 10.3760/cma.j.issn.1003-9406.2012.05.015.

[Association study between age-related macular degeneration and R1210C mutation of CFH gene in Chinese population].

[Article in Chinese]

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OBJECTIVE: A R1210C mutation of complement factor H (CFH) gene has been associated with age-related macular degeneration (AMD) in Caucasian population. This study was to verify above association in Han Chinese population.

METHODS: The mutation was detected by direct sequencing in 258 patients with wet AMD and 426 matched controls.

RESULTS: The R1210C mutation has not been identified in either sample.

CONCLUSION: The R1210C mutation in CFH gene is not associated with AMD in Han Chinese population.

PMID: 23042396 [PubMed - in process]

Diet

Am J Clin Nutr. 2012 Oct 10. [Epub ahead of print]

The putative role of lutein and zeaxanthin as protective agents against age-related macular degeneration: promise of molecular genetics for guiding mechanistic and translational research in the field.

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Age-related macular degeneration (AMD) is the primary cause of vision loss in elderly people of western European ancestry. Genetic, dietary, and environmental factors affect tissue concentrations of macular xanthophylls (MXs) within retinal cell types manifesting AMD pathology. In this article we review the history and state of science on the putative role of the MXs (lutein, zeaxanthin, and meso-zeaxanthin) in AMD and report findings on AMD-associated genes encoding enzymes, transporters, ligands, and receptors affecting or affected by MXs. We then use this context to discuss emerging research opportunities that offer promise

for meaningful investigation and inference in the field.

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Clin Ophthalmol. 2012;6:1471-6. doi: 10.2147/OPTH.S35139. Epub 2012 Sep 7.

Efficacy of various antioxidants in the protection of the retinal pigment epithelium from oxidative stress.

Kagan DB, Liu H, Hutnik CM.

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BACKGROUND: Oxidative stress induced retinal pigment epithelium (RPE) dysfunction is hypothesized to be fundamental in the pathogenesis of age-related macular degeneration (AMD). This study investigated whether vitamin C, vitamin C phosphate, vitamin E, propofol, betaxolol, and N-acetyl cysteine (NAC) protect human RPE cells from oxidative stress.

METHODS: ARPE-19 cells were pretreated with the compounds under investigation. The chemical oxidant tert-butyl hydroperoxide (t-BOOH) was used to induce oxidative stress. Cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

RESULTS: Exposure to t-BOOH resulted in a dose- and time-dependent reduction in ARPE-19 cell viability. Compared with cells given t-BOOH alone, vitamin E and NAC pretreated cells had significantly improved viability, propofol and betaxolol pretreated cells had no significant difference in viability, and vitamin C and vitamin C phosphate pretreated cells had significantly reduced viability.

CONCLUSION: Of the compounds studied, only vitamin E and NAC significantly mitigated the effects of oxidative stress on RPE cells. Because of their potential therapeutic value for AMD patients, these and other RPE protective compounds continue to merit further investigation.

PMID: 23055666 [PubMed]

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