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Abstract

Topic: To compare the accuracy of Optical Coherence Tomography (OCT) with alternative tests for monitoring neovascular age-related macular degeneration (nAMD) and detecting disease activity among eyes previously treated for this condition

Clinical Relevance: Traditionally FFA has been considered the reference standard to detect nAMD activity but FFA is costly and invasive. Replacement of FFA by OCT can be justified if there is a substantial agreement between tests.

Methods: Systematic review and meta-analysis. Index test: OCT. Comparator tests: visual acuity, clinical evaluation (slit lamp), Amsler chart, colour fundus photographs, infra-red reflectance, red-free images/blue reflectance, fundus autofluorescence imaging (FAF), indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. We searched the following databases: MEDLINE, MEDLINE In Process, EMBASE, Biosis, SCI, the Cochrane Library, DARE, MEDION and HTA database, last literature search: March 2013. We used QUADAS-2 to assess risk of bias.

Results: We included eight studies involving over 400 participants. Seven reported the performance of OCT (three TD-OCT, three SD-OCT, one both types) and one the performance of ICGA in the detection of nAMD activity. We did not find studies directly comparing tests in the same population. The pooled sensitivity and specificity (95% CI) of TD-OCT and SD-OCT for detecting active nAMD was 85% (72% to 93%) and 48% (30% to 67%), respectively. One study reported ICGA, with sensitivity of 75.9% and specificity of 88.0% for the detection of active nAMD. Half of the studies were considered to have high risk of bias.

Conclusions: There is a substantial disagreement between OCT and FFA findings in detecting active disease in patients with nAMD who are being monitored. Both modalities may be needed to comprehensively monitor patients with nAMD.

Introduction

Anti-vascular endothelial growth factor (VEGF) therapies have revolutionized the treatment of neovascular age-related macular degeneration (nAMD). Visual outcomes following anti-VEGF therapy[1-4] have been unparalleled by previous therapies which included laser photocoagulation[5-6] and photodynamic therapy.[7] The effectiveness of anti-VEGF drugs depends, however, on frequent monitoring and early diagnosis of reactivation of the condition. "Fundus fluorescein angiography (FFA) interpreted by an ophthalmologist was in the recent past the reference standard for the detection of active nAMD among those eyes already treated[8,9] as it directly detects the presence of the active neovascularisation. However, FFA is an invasive and a time-consuming test with, although rare, potentially serious side effects. Other alternative monitoring technologies are available of which the most widely used is optical coherence tomography (OCT)."

OCT, including time-domain (TD-OCT) and the most recently developed spectral-domain (SD-OCT), is a light-wave based technology that allows the imaging of the retina and choroid, obtaining "sections" through areas with neovascularisation and surrounding tissues. Scan rates and resolution parameters have greatly improved over the last decade and continue to develop. OCT is a non-invasive, non-contact test typically undertaken by trained medical photographers or technicians and interpreted by ophthalmologists. If OCT were to be able to accurately detect the re-activation of nAMD then FFA would not be needed.

The aim of this study was to evaluate the accuracy, interpretability and acceptability of OCT alone or in combination with other tests compared with clinical evaluation of FFA for the detection of active disease in patients with nAMD under treatment and surveillance.

Methods

The target condition was nAMD of any phenotype. Eligible participants were individuals who had been previously treated for nAMD with any type of treatment, and who were monitored to detect active disease. Thus, patients could have active or stable neovascular disease

"The index test was OCT, alone or in combination with other tests, i.e., we included studies that used OCT alone or associated with other test or tests to detect nAMD disease activity, including any of the following: clinical evaluation with slit lamp biomicroscopy, visual acuity, Amsler grid, colour fundus photography, infra-red reflectance, red-free images, fundus autofluorescence imaging (FAF), indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FFA. Participants were individuals with known, treated nAMD, with any type of treatment, and who were monitored for the condition to detect active disease. We considered direct (head-to-head) comparisons in which all participants received the index test, comparator test(s) and the reference standard; indirect comparisons (e.g. case control studies) in which estimates of the accuracy of the respective tests were obtained in different study groups, and randomised controlled trials evaluating effectiveness outcomes where e.g. treatment was based on OCT compared with FFA findings. We also included studies evaluating the acceptability and/or interpretability of the tests.

We identified published, unpublished and ongoing studies from searches of electronic databases (from 1995 to March 2013) and appropriate websites. There were no language restrictions. We searched MEDLINE, MEDLINE In-Process, EMBASE, Biosis and Science Citation Index (SCI) for all reviews. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) for additional reports of RCTs reporting effectiveness outcomes and PsycINFO and ASSIA for studies reporting acceptability data. The Cochrane database of Systematic Reviews (CDSR), Database of Abstracts of reviews of Effects (DARE), MEDION and HTA database were searched for relevant systematic reviews and

HTA reports. We searched abstracts and presentations from recent conferences (from January 2009 to September 2012) of the Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), and the European Association for Vision and Eye Research (EVER) and also the WHO International Clinical Trials Registry Platform (ICTRP), Clinical Trials.gov and EU Clinical Trials Register for ongoing studies. Websites of key journals, professional organisations and manufacturers of equipment were also consulted. We also evaluated reference lists of all included studies for possible inclusion and we contacted authors for details of additional potentially relevant reports.

Two reviewers independently screened the titles and abstracts (if available) of all reports identified by electronic searches. We obtained full-text copies of all potentially relevant papers and two reviewers independently assessed them for inclusion. Two reviewers independently assessed the risk of bias and applicability concerns of included full-text studies, using an adapted version of the updated quality assessment of diagnostic accuracy studies (QUADAS-2) checklist.[10] The QUADAS-2 checklist is designed to be adapted to the specific review topic. The investigators resolved disagreements by consensus or arbitration by a third reviewer. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias. The first three domains are also assessed for concerns regarding their applicability in terms of whether (i) the participants and setting, (ii) index test, its conduct or interpretation and (iii) target condition as defined by the reference standard match the question being addressed by the review. Within each domain signaling questions are included to assist in making a judgment about the risk of bias, with the standard tool containing 11 such questions across the four domains.

QUADAS-2 was designed to be adaptable to a specific review topic. For this review, QUADAS-2 was modified by adding an additional signaling question to domain 1 (patient selection) to assess whether participant pre-selection had been avoided. Domains 2 (index test), 3 (reference standard) and 4 (flow and timing) were retained in their entirety. Therefore the modified tool contained 12 signaling questions, with each worded so that a rating of 'Yes' was always optimal in terms of methodological quality. If any signaling questions within a domain were rated 'No' then that domain was judged to be at high risk of bias. With regard to question 9 in the modified tool (appropriateness of the time interval between the index test and the reference standard), it was agreed that to be considered appropriate, the time interval between the index test and reference standard should be no longer than one week."

Regarding the statistical analysis we calculated sensitivity and specificity of individual studies when possible. Where two or more studies reported sufficient data we planned to create summary receiver operating characteristic (SROC) curves. We intended to fit meta-analysis models using the hierarchical summary receiver operating characteristic (HSROC) model[11] with the SAS software (version 9.1) when possible. We used a symmetric SROC model, as it allows estimation of random effects for the threshold and accuracy effects accounting for the active and non-active sample sizes in each study. We arranged to produce the SROC curves from the HSROC models on the corresponding SROC plots. We planned to report a point estimate and 95% confidence interval (CI) for each model for the summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs).

Results

We identified 4682 titles and abstracts, of which 179 reports were evaluated in full-text (Figure 1). Eight[12,13,14,15,16,17,18,19] were monitoring studies involving people previously diagnosed with nAMD and under follow-up surveillance; one study, by Salinas-Alaman et al.,[17] reported results for both diagnosis and monitoring (Table 1). No studies evaluated the performance of OCT associated with other test(s).

Of the eight included studies, four were prospective,[15,16,17,19] three were retrospective[12,13,14] while in the study by van de Moere et al.[18] this information was not reported. In five studies the participants were a consecutive sample.[13,14,16,17,19] The eight studies enrolled 463 participants.

Four studies were judged to be high risk of bias for reasons such as inappropriate exclusions and pre-selection of participants, length of time between the index test and the reference standard, and not all participants being included in the analysis (Figure 2). All of the monitoring studies were judged to be applicable to our study question.

Some studies reported the "eye "as the unit of analysis, i.e., only data of a single examination/comparison of an eye at one point in time was included in the study. Other studies reported an "examination" as the unit of analysis, i.e., a patient or eye was examined several times over a period of time, and the authors included data of several examinations of the same patient and eye. Of the seven studies reporting OCT, five used the eye as the unit of analysis (number of eyes analysed = 363);[12,13,14,18,19] in four of these one eye per patient was analysed (n = 304 eyes).[13,14,18,19] Two studies reported examination as the unit of analysis (both TD-OCT).[15,17] Two studies reported detection of classic and occult CNV;[14] pigment epithelial detachment (PED) and cystoid macular oedema.[18] The studies by Henschel et al.[15] and van de Moere et al.[18] also reported the performance of OCT in detecting intraretinal and subretinal fluid.

In two studies[12,14] the participants had received anti-vascular endothelial growth factor (anti-VEGF) therapy while in five[13,15,17,18,19] the treatment was photodynamic therapy (PDT). In the study reporting ICGA[16] the participants had received laser photocoagulation.

The median (range) prevalence of active nAMD across five studies where this information was available at participant level was 57.9% (49.2% to 83.3%).[12,13,14,18,19]

Three TD-OCT studies[12,13,19] and two SD-OCT reports,[12,14] with the eye as the unit of analysis, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. Figure 3 shows forest plots of the sensitivity and specificity of the individual studies and SROC curves for (a) all OCT studies, (b) the three TD-OCT studies and (c) the two SD-OCT studies, respectively. Table 2 shows the pooled estimates for these studies. For all OCT studies, the pooled sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, the pooled sensitivity and specificity (95% CI) was 70% (56% to 80%) and 65% (48% to 79%). For TD-OCT and the group of all four OCT studies the likelihood ratio and DOR values reported were below the level suggestive of strong evidence. It was not possible to calculate pooled estimates for the two SD-OCT studies due to insufficient data. These studies reported sensitivities of 94%[14] and 90%[12] and specificities of 27%[14] and 47%,[12] which suggests that SD-OCT has higher sensitivity than TD-OCT but lower specificity.

Two studies used examination as the unit of analysis. Henschel et al.,[15] in an analysis of 61 pairs of TD-OCT and FFA examinations from 14 patients, reported sensitivity of 96.8% and specificity of 36.7% for CNV based on detection of intraretinal and/or subretinal fluid. Salinas-Alaman et al.,[17] in an analysis of 176 pairs of TD-OCT and FFA examinations (number of patients not stated), reported sensitivity of 95.7% and specificity of 59.0% based on detection of intraretinal or subretinal fluid.

Four studies[12,14,15,18] reported the sensitivity of OCT in detecting active nAMD phenotypes or active nAMD based on detection of intraretinal/subretinal fluid (see Table 3). The study by Giani et al.[14] reported high sensitivity for the detection by SD-OCT of both classic and occult CNV activity (90.9% and 100% respectively). In the studies by Henschel et al.[15] (unit of analysis: examination) and van de Moere et al.[18] (unit of analysis: eye) sensitivity was higher for nAMD activity based on detection of intraretinal fluid (90.3% and 82.9% respectively) compared with subretinal fluid (71.0% and 47.1% respectively). Van de Moere et al.[18] also reported sensitivity of TD-OCT for detection of cystoid macular oedema and pigment epithelial detachment, both low at 22.9% and 5.7% respectively. In the study by Khurana et al[12] the sensitivity of SD-OCT was higher than that of TD-OCT for nAMD activity based on the detection of intraretinal fluid, retinal cystoid abnormalities or subretinal fluid.

One study, by Khurana et al.,[12] compared TD-OCT with SD-OCT in an analysis of 59 eyes of 56 participants. Although sensitivity was considerably higher for SD-OCT than for TD-OCT (89.7% versus 58.6%), specificity was lower (46.7% versus 63.3%).

One study, by Regillo et al.,[16] in an analysis of 54 pairs of indocyanine green angiograms compared with fluorescein angiograms, obtained from 24 eyes of 21 patients, reported sensitivity of 75.9% and specificity of 88.0% in detecting nAMD activity.

No studies were identified that met our inclusion criteria providing information on clinical effectiveness outcomes (e.g. visual acuity) when treatment was based on OCT compared with FFA findings. Only one monitoring study, by van de Moere et al.,[18] reported information relating to the interpretability of the tests. This TD-OCT study reported that, of 136 participants enrolled, 17 (12.5%) were excluded from the analysis due to the poor quality of the OCT or FFA images. The study did not specify how many of these poor quality images were OCT images and how many were FFA. No studies were identified that met our inclusion criteria reporting the acceptability of the tests, either to those providing the tests or to those receiving them.

Discussion

Due to the burden of nAMD to patients and health care providers, an effective and efficient monitoring strategy to detect active disease is needed. The use of frequent (monthly or two-monthly) FFA is not recommended. FFA is hampered by its cost, the fact that it is a relatively time-consuming invasive imaging technology and, although rare, possible risks. Current Preferred Practice Patters by the AAO advise the use of FFA”depending on the clinical findings and judgement of the treating ophthalmologist”.[9] OCT is now routinely used for monitoring eyes with nAMD previously treated.

We identified a relatively small body of evidence comparing OCT against a reference standard of FFA for the diagnosis of active nAMD in patients under surveillance and treated for this condition. We included eight monitoring studies (all full-text) involving over 400 participants. Seven reported the performance of OCT (five TD-OCT, one SD-OCT, one both types) and one the performance of ICGA in the detection of nAMD activity.

To compare the performance of diagnostic tests ideally direct comparisons of the accuracy of different tests applied to the same population would be most informative. Alternatively it is possible to evaluate studies of different tests applied to different populations against a common reference standard, using models to indirectly compare tests. In this review four of the OCT studies provided sufficient data for inclusion in a meta-analysis. The pooled sensitivity (95% CI) for all OCT was moderately high at 85% (72% to 93%) but with low specificity at 48% (30% to 67%). For TD-OCT, the pooled sensitivity and specificity was moderate at 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates for the two SD-OCT studies using hierarchical summary receiver operating characteristic (HSROC) methodology due to insufficient data. These studies reported sensitivities of 94%[14] and 90%[12] and specificities of 27% [14] and 47%.[12] Other than OCT, one study reported ICGA, with sensitivity of 75.9% and specificity of 88.0% for the detection of active nAMD. We did not find other studies reporting the performance of alternative technologies.

This study suggests that SD-OCT may be more sensitive but less specific in detecting active nAMD than TD-OCT. It is likely that SD-OCT can detect small amounts of fluid in the retina (due to its high resolution) better than TD-OCT. However, fluid does not always indicate active CNV but may indicate RPE malfunctioning, for instance related to RPE atrophy, which has now been recognised to occur frequently in eyes with nAMD undergoing anti-VEGF therapies.[2, 3, 20, 21] Some of the observed heterogeneity among studies results can be explained by the different populations, phenotypes, proportion of active cases, type of treatment, and methodological quality.

In terms of strengths of this study, a comprehensive literature search was undertaken and both English and non-English language studies were included. We assessed risk of bias using a modified version of the QUADAS-2 questionnaire, tailored to the needs of this review. We used a robust method, HSROC model, for the analysis, which takes account of the trade-off between true/false positives and models between-study heterogeneity.[22]

The reference standard test used for this review was FFA interpreted by an ophthalmologist, and therefore was assumed to have perfect sensitivity and specificity. Consequently it was not possible to address the question of whether OCT might actually be a better test than FFA and have higher sensitivity or specificity than the current reference standard. One approach that has been suggested for determining when a new test should replace the reference standard is that proposed by Glasziou et al.[23] Glasziou et al. suggested the use of a third, 'fair umpire' test, which although potentially less accurate than either the new test or the reference standard, could be considered nonetheless a fair umpire test if its errors were independent of the other tests.[23] However, the authors acknowledged that this would usually be difficult to demonstrate. Unfortunately, none of the included OCT studies involving a third test provided a sufficient level of detail to allow us to explore this approach.

The false positive rate of OCT was high. A few studies suggested possible explanations for their false positive results. Subretinal or intraretinal fluid, readily detected by OCT, especially by SD-OCT, may not necessarily indicate active neovascular AMD and may be seen over disciform scars and even atrophic areas.[24] If the diagnosis of active nAMD is established by the presence of fluid on OCT false positives could, thus, be made, leading to unnecessary treatments. Similar lack of agreement between OCT and FFA to diagnose nAMD in high risk eyes have been observed by Do et al.[25]

The clinical implications of this review are potentially important as we found evidence of substantial lack of agreement between OCT and FFA to determine activity of nAMD lesions. There are also potential implications regarding the interpretation of results of landmark studies that have used only OCT to guide decisions to treat nAMD, such as the prn arms of the CATT study[2] and the HARBOR study.[26] It is possible the differences in efficacy between monthly and prn arms might be explained in part by a sub-optimal of diagnostic accuracy of OCT to detect active nAMD.

In conclusion, our review identified a relatively small number of studies, of variable quality, on the performance of OCT in the monitoring of people with treated nAMD under surveillance to detect disease activity. The available evidence suggests that although OCT is a sensitive test for detecting reactivation of nAMD, it has poor specificity. Consequently, it is not recommended that OCT is used alone to detect reactivation of nAMD in patients under surveillance. According to current evidence OCT should not replace the reference standard of FFA for monitoring patients with nAMD.

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Figure legend

Figure 1. Flow diagram outlining the screening and selection process of articles