What effects has the cataract surgery on the development and progression of age-related macular degeneration (AMD)?
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Health political background

The cataract (Cataracta senilis) is the most frequent eye disease of elderly people worldwide. The recovery of sight through an operative treatment has been proven to be an efficient and save procedure. In Germany, the cataract-operation - with currently 450000 interventions each year the most frequent operation in ophthalmology – can be seen as routine surgery.

The age related macular degeneration (AMD) is another very common, age related eye disease and the most frequent cause of blindness of elderly people in industrial nations. In Germany, approximately 300000 new cases of AMD are diagnosed each year. Between one and 4.5 million people altogether are affected by this disease. The therapeutic options are limited and little promising for the majority of the affected people. Despite the much higher incidence of cataract and the high numbers of cataract operations at the same time, AMD is the most frequent cause of severe visual impairment in Germany, being responsible for 50 % of the cases.

As a result of the demographic changes, the number of persons suffering from cataract as well as AMD will rise. The special health political relevance of this HTA report is determined by the fact, that people who fall ill by AMD after cataract operations or experience a progression of the already existing disease, do not achieve a lasting recovery of sight. This is associated with a loss in quality of life and additional costs in health care. This coincidence explains the growing interest in the question of a reciprocal interference of both diseases respectively their therapies.

Scientific background

The age related cataract is a degenerative disease of the lens, which mostly emerges in elderly people from the age of 60. It is caused by the growing opacity of the naturally transparent lens. The increasing age is associated with a loss of elasticity as well as a decline of the water content and a worse nutrient-supply, leading to an opacity of the lens. This causes the “blurred vision” and leads to a reduced vision. This phenomenon is physiological and can be found in most elderly people. In case of extremely limited vision, an operation is the only promising treatment option. Within the operative intervention, the methods of phacoemulsification and extracapsular extraction are used. In extracapsular extraction the core of the lens is removed as a whole via incision, while in phacoemulsification ultrasonic waves are used to reduce the core to small pieces, which are extracted by suction afterwards. Nowadays 80 % of cataract extractions in Germany are done by phacoemulsification.

The AMD involves a damage of the central retina (Fovea centralis) which leads to a loss of central visual acuity and can conduct in a complete deterioration of the central visual field. The AMD is caused by deposits of sediments of metabolites in the retinal pigment epithelium, underneath the photoreceptor cells of the macula, in the centre of the retina. In the early stages of AMD these deposits appear as so called drusen, which are yellowish-
white, close-packed small spots and pigment changes. The later stages can be subdivided into dry or atrophic and wet or neovascular AMD. The atrophy of the retinal pigment epithelium and the sensory retina are in the centre of attention in case of the dry form of AMD. This form is more frequent and becomes noticeable through a slow, staged and insular impairment of sight. In case of the wet form, fluid trespasses into the space under the retinal pigment epithelium and retina and is followed by the formation of choroidal vessels (subretinal neovascularisation). Increasing age is seen as the main risk factor for AMD. Up to now, the progression of the disease can only be inhibited for a minority of the affected with neovascular forms of AMD.

Research questions

The aim of this report is the evaluation of the effects of cataract operations on the development or progression of AMD. Out of medical perspective, the following research questions are asked:

- Does cataract operation contribute to a first manifestation of AMD?
- Does cataract operation lead to a progression of early stages of AMD?
- Does cataract operation lead to further impairment in late stages of AMD?

Out of health economics perspective, the following questions are of particular importance for the efficiency examination:

- Does the development or progression of AMD influence the cost-effectiveness of cataract operations?
- Do cataract operations influence the cost-effectiveness of AMD treatment?
- Which economic or health political consequences arise from the potential effects of cataract operations on the development or progression of AMD for the German health care system?

Methods

The relevant publications for this report were identified by DIMDI via structured data base enquiry as well as common, self-made enquiry. The following electronic literature data bases were included: DAHTA; INAHTA (NHS-CRD-HTA); NHSEED (NHS-EED); CDAR94 (NHS-CRD-DARE); CDSR93 (Cochrane Library); ME83 (MEDLINE); EM83 (EMBASE); CB85 (AMED); BA90 (BIOSIS Previews); MK77 (MEDIKAT); CCTR93 (Cochrane Library – Central); GA03 (gms); SM 78 (SOMED); CV72 (CAB Abstracts); I78 (IISTPB + ISSHP); ED93 (ETHMED); AZ72 (GLOBAL Health); AR 96 (Deutsches Ärzteblatt); ME04 (MEDLINE Alert); EA08 (EMBASE Alert); IS90 (SciSearch); CC00 (CiCMed); IN73 (Social SciSearch); KR03 (Karger Publisher Database); KL97 (Kluwer Publisher Database); SP97 (Springer Publisher Database; SPPP (Springer Publisher Database PrePrint); TV01 (Thieme Publisher Database).

The search items were attained from combination of terms describing the research questions. The literature inquiry referred to German and English publications as from 1983. The selection of literature was accomplished to the criteria of evidence-based medicine.

To rate the methodical quality of the medical studies, checklists of the Ger-
man Scientific Work Group Technology Assessment for Health Care were used. To evaluate the influence of cataract operations on the development or progression of AMD, basically all types of clinical as well as epidemiological studies (cross-sectional studies, longitudinal studies, case-control studies) were included. For clinical studies neither randomisation nor blinding were required, however a controlled study design was inalienable. A clear chronological sequence of cataract operations and subsequent AMD development or progression had to be recognisable.

The documentation of methodical quality of the economic studies took place in consideration of the checklists to evaluate the methodical quality of health economic procedures and the German Scientific Working Group Technology Assessment for Health Care.

Results
Quantitative results
The database enquiry generated a record of 2769 issue-related publications. Of these, 183 publications were selected for further analysis as full texts. Of the selected articles, 143 concerned medical, 33 health economical, and 7 ethical issues. No publications on legal aspects could be identified. Eight medical publications that presented results of three epidemiological cohort studies and two non-randomised clinical trials, were considered to be relevant and of sufficient methodological quality and were therefore included in the analysis. One supplementary abstract, including results on another epidemiological study, was viewed. No relevant studies on health economics or ethics could be included, not even after the softening of the exclusion criteria.

Qualitative results
Epidemiological studies
All identified epidemiological studies were longitudinal cohort studies. Publications were available on the Beaver Dam Eye, Blue Mountains Eye and Copenhagen City Eye studies. Beaver Dam and Blue Mountains Eye studies used very similar methods and were therefore soundly comparable. Results of the Beaver Dam Eye Study were presented in two publications, one after five and the other after ten years of follow up. Both displayed a higher risk for first manifestations of early stages of AMD and for progression to a late stage of AMD from a prevalent early stage, following cataract extraction before baseline. These developments were statistically significant for the progression to a late stage of AMD only. The pooled analysis of the data from Beaver Dam and Blue Mountains revealed a higher risk for the development of late stages of AMD after cataract extractions. However, disease status at baseline was not taken into account. The increase in risk was significant for the pooled dataset, and for only one eye each in the single studies. The Copenhagen City Eye Study could clearly be distinguished from the others by its different methodology, especially the retrospective assessment of cataract operations. This study found an increased rate of cataract extractions in the group of participants with incident AMD within the 14 years of follow up. Also an increased rate of cataract extractions was seen in the group with development of a late stage of AMD, irrespective of disease status at baseline. These results did each not reach statistical significance. On the other hand, results of the Age Related Eye Disease Study (AREDS), which were solely presented in an abstract, demonstrated a very similar risk of progression of a prevalent AMD in participants with or without cataract
extraction. The possible effect of a cataract extraction on prevalent late stages of AMD was not investigated in one of the epidemiological studies.

**Clinical trials**

One clinical trial from Great Britain and one from Israel, with two publications each, could be included. The British trial compared patients who had undergone cataract extraction to patients without surgery. Whereas the Israeli study compared both eyes of the same patients, after cataract operation had been carried out on one eye. Both trials examined progression of prevalent early AMD after cataract extraction as outcome variable. Neither study performed statistical tests, but on a numeric level they came up with contrary results. In Israel an increased rate of progressions was observed within the first year after cataract extraction, compared to the second eye that had had no operation. All observed progressions led to wet AMD. A year later, part of these patients also underwent cataract extraction in the second eye, whereupon the first eyes served as comparison group. The rate of progressions of early AMD within the first postoperative year was equally increased. In Great Britain no differences between the operated and the non-operated patients with regard to progressions of early AMD could be seen within either presented follow up period of four respectively twelve months. This study also looked at the progression of prevalent late stage AMD and likewise could not see any differences between the groups. The risk of first manifestations of an AMD was not investigated in either clinical trial.

**Discussion**

**Discussion of medical aspects**

Aim of the medical part of the present HTA report was to determine the effect of cataract operations on the development and progression of an age related macula degeneration on the basis of the included articles. The presentation of the evaluated literature made clear that only a small number of publications dealt with the development of age related macula degeneration in consequence of a cataract extraction. The overall scientific level of evidence of these articles was not very high. It was not possible to identify any trials of top level evidence, which are randomised controlled trials (RCT) or systematic reviews of RCT. Solely non-randomised clinical trials and observational studies, here longitudinal cohort studies, could be analysed. Both of which are rated as a level two on the five ary hierarchy of levels of evidence for medical studies. Furthermore both included clinical trials especially showed distinct deficiencies, leading to a reduced explanatory power. Comparability in regard to methodology also was limited. One major problem of these trials was the small number of participants. In addition they were affected by the problem of potential confounding, due to the absence of randomisation. The included epidemiologic studies did control for different familiar confounders. They however did not adequately consider the potential bias that might be exerted by the former cataract status on their results, as the cataract status is believed to independently influence the risk of AMD. Moreover the effect of unknown confounders could not be acquired. Therefore it was not possible to obtain a well-defined conclusion on the effect of a cataract extraction on the development or progression of an age related macula degeneration from the available studies.
Discussion of economic aspects

No relevant publications with economic background could be identified. It was also not possible to make a tendentious statement due to the missing valid medical results.

Discussion of ethical, social and legal aspects

No relevant publications dealing with ethical, social or legal aspect of the topic could be identified in the course of this HTA report.

Conclusions / Recommendations

The analysis of the recent literature on the development and progression of an AMD as consequence of a cataract extraction, reveals that the degree of information is not sufficient to draw a well-defined conclusion about the medical findings. Additional well conducted clinical trials, that offer a sufficient number of patients, length of study period and adequate control for confounding variables like age and severity of cataract, are urgently needed. Health economic, ethical, social and legal aspect of the problem could and should be investigated after clarification of the mentioned medical issues. On the basis of the aforesaid arguments, the authors suggest to perform a repeated HTA report on the subject of the effect of a cataract extraction on the development and progression of an AMD at a later date, when enough scientific literature on this topic is available.

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