Selected Summaries

Treatment of primary angle-closure glaucoma: Does early lens extraction help?

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SUMMARY

The EAGLE study was designed to compare the safety and efficacy of trabeculectomy to standard care, a laser iridotomy, with or without medications in primary angle-closure (PAC) or primary angle-closure glaucoma (PACG) eyes. Of 419 participants enrolled, 155 had PAC and 263 PACG; 208 were assigned to clear-lens extraction and 211 to standard care.

PACG was defined as reproducible glaucomatous visual field (VF) defects (i.e. reproducible defect, in at least two consecutive visual fields, of two or more contiguous points with $p<0.01$ loss or greater, or three or more contiguous points with $p<0.05$ loss or greater in the pattern deviation plot, or abnormal glaucoma hemifield test), or glaucomatous optic neuropathy with localized absence of the neural rim or, cup disc ratio of 0.7 or more, or asymmetry of cup disc ratio of 0.2 or more in similar-sized eyes/optic discs, and an intraocular pressure (IOP) >21 mmHg on one or more occasions). PAC was diagnosed by IOP $\geq$30 mmHg on at least one occasion. Visual field loss and glaucomatous optic neuropathy, as defined above, were not present.

Three hundred and fifty-one patients (84%) had complete data on health status and 366 (87%) on IOP. The mean (SD) health status score (0.87 [0.12]), assessed with the European Quality of Life-5 Dimensions (EQ-5D) questionnaire, was 0.052-times higher (95% CI 0.015–0.088, p=0.005) and mean IOP (16.6 [3.5] mmHg) 1.18 mmHg lower (95% CI –1.99 to –0.38, p=0.004) after clear-lens extraction than after standard care. The incremental cost-effectiveness ratio (ICER) was £14 284 for initial lens extraction versus standard care. Irreversible loss of vision occurred in 1 patient who underwent clear-lens extraction and in 3 who received standard care. No patient had serious adverse events.

COMMENT

Laser peripheral iridotomy is generally used as the initial treatment for PAC disease to alleviate the element of relative pupillary block. While ultrasound biomicroscopy and anterior segment optical coherence tomography-based studies show a thickened and anterior-positioned lens playing a role in the pathogenesis of PACG, cataract extraction as a first line of treatment for lowering the IOP in post-iridotomy PACG eyes, remains debatable.[1–4] A 2006 Cochrane systematic review by Friedman and Vedula,[5] of lens extraction for PACG, found no randomized controlled trials of lens extraction versus alternative treatment options for PACG. As this is a controversial topic, the results of the EAGLE study were eagerly awaited.

The EAGLE study was a multicentre, pragmatic, randomized trial. A well-designed explanatory trial that controls for confounders and biases is essential to understand whether an intervention works, and if so, how. Pragmatic studies only complement such trials, as they imply an inclusion of variable practitioner expertise and variable standards of care, only to see if an intervention known to be efficacious, works in real life. Pragmatic trials cannot replace explanatory ones, but rather complement them.[6,7] Therefore, the EAGLE study methodology and results need to be carefully examined.

The definitions of PAC and PACG are not standard,[8] iridotrabecular contact without mention of a primarily narrow angle/occludable angle could be due to causes other than PAC. In PAC, a single recording of IOP >30 mmHg could imply a subacute attack of angle closure, in which the IOP returns to normal within minutes, without therapy, or an error of tonometry in an apprehensive patient. PACG was defined to have an IOP >21 mmHg at least once. This IOP was just 2 mmHg higher than the suggested 'target' IOP.

All therapy such as a choice of synechiolysis, iridoplasty, choice and number of medications, target IOP, etc. was adjustable by 'local protocols'. There was also no prescribed medical algorithm, so that the first medication could have been either a prostaglandin analogue or dorzolamide drops, which have a widely differing efficacy.

The baseline IOP measurement was an average of two readings, but there is no mention of subsequent measurements being done at the same time of day. A PACG eye diagnosed at 21 mmHg needed a drop of 2 mmHg to reach 'target' IOP. There is an inherent variability of Goldmann applanation tonometry with an accepted variation of 1.5–2.0 mmHg.[9,10] The achieved IOP difference of 1.18 mmHg between eyes treated with an iridotomy and those undergoing phacoemulsification, is within the range of applanation tonometry error, as well as diurnal variations of IOP, and could also be attributed to differences in 'local protocols' of medications prescribed. This marginal difference in IOP at 3 years was achieved at a significant cost differential.

Quality of life (QoL) appears to be the most significant outcome measure, with the participant being the unit measured, the eye being treated was not evaluated separately. A previous study by the same group[11] reported: 'The majority of patients (after cataract surgery) appear to have improvement in patient-reported VR-QoL, including those with good preoperative visual acuity…' The EQ-5D and the Glaucoma Utility Index are based largely on visual status. The ICER was also based on bilateral visual status. The differences recorded were probably related to improved contrast sensitivity, and not angle-closure status.

Since PAC and PACG eyes had different inclusion criteria, presumably different 'target' IOP, etc., they should have been analysed and reported separately

A study by Ko *et al*. revealed that corneal endothelial cell density decreased by 14.5%$\pm$25.8% after phacoemulsification in eyes with occludable angles.[12] Kubota and associates found that

corneal endothelial cell count decreased by 18.3%±17.2% during phacoemulsification and intraocular lens implantation for PACG after the relief of pupillary block.[13] PACG and operated trabeculectomy eyes appear to have lower endothelial counts, and a further decline in post-phacoemulsification becomes an area of concern in such patients. Many reviews of cataract surgery outcomes around the world have shown significant complications and poor visual outcomes in a large percentage of people.[14–19] The safety of cataract surgery as generally performed, cannot therefore be equated with that of a laser iridotomy.

The hypotheses in the initially published study protocol for the EAGLE study[20] were that those randomized to early lens extraction will have a higher EQ-5D QoL score (mean difference of 0.05), lower IOP (mean difference of 1.75 mmHg) and a 15% lower glaucoma surgery rate than those randomized to standard care at 3 years.

In this publication, the authors have concluded that clear-lens extraction showed greater efficacy and was more cost-effective than laser peripheral iridotomy, and should be considered as an option for first-line treatment. However, if their three primary outcomes are reviewed, the patient-centred QoL was probably related to changes in contrast sensitivity, the change in IOP was clinically within the range of tonometric and diurnal fluctuations, not 1.75 mmHg, and the glaucoma surgery rate was not significantly different between iridotomy and clear-lens extraction groups, and economically, the clear-lens extraction cost significantly more than standard care.

The EAGLE study was an attempt to compare the efficacy of a relatively safe, non-invasive laser iridotomy with surgical clear-lens extraction, with or without medications. However, the only difference in outcome was probably related to patients' perceived improvement in clarity of vision after cataract surgery, and therefore QoL.

The comparison of cataract surgery and laser iridotomy in PACG for long-term control of IOP needs to be evaluated by a more rigorously planned study before advocating a surgical intervention which is more costly, did not significantly lower IOP and has potentially more complications in less trained surgical hands around the world.

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