The expectation effect and cardiac pacing for refractory vasovagal syncope
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CRD summary
This review evaluated the efficacy of permanent pacemaker therapy for the prevention of recurrent vasovagal syncope. The authors concluded that the available evidence does not support the use of permanent cardiac pacing as first-line therapy. Whilst this was a well-conducted systematic review, the authors’ conclusions are not fully supported by the evidence presented. Their recommendation for larger double-blinded trials appears appropriate.

Authors’ objectives
To assess the efficacy of permanent pacemaker therapy in preventing recurrent vasovagal syncope.

Searching
MEDLINE, EMBASE, the Cochrane Library, SIGLE, National Research Register and HSRProj were searched from 1966 to January 2005; the search terms were reported. No language restrictions were applied. In addition, the bibliographies of retrieved articles were checked, internet links (www.clinicaltrials.gov and www.controlled-trials.com) were searched, and experts in the field were contacted for further articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing the use of permanent pacemakers with medical therapy or no therapy, or comparing different pacing algorithms to prevent vasovagal syncope, were eligible. The included studies compared: pacemakers with medical therapy or no therapy; pacemakers with active pacing of different algorithms; or active pacing with inactive pacing in patients who received a pacemaker.

Participants included in the review
Studies of patients aged 18 years or older with refractory vasovagal syncope were eligible. The mean age of the included participants was 55 (+/- 16) years.

Outcomes assessed in the review
The primary outcomes were recurrent vasovagal syncope and adverse events related to pacemaker therapy. The diagnosis of vasovagal syncope was made by history and positive tilt-table test in all but one study; one study used the adenosine triphosphate test. The duration of follow-up ranged from 6 to 62 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies, with any disagreements resolved by consensus. The reviewers were not blinded to author, journal or type of publication.

Assessment of study quality
Study quality was evaluated on the basis of generation of treatment allocation sequence, concealment of allocation sequence, patients lost to follow-up and blinding. The authors did not report how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved by consensus. Data were extracted to calculate odds ratios (ORs) and their 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The pooled OR and CI were calculated using Peto and Mantel-Haenszel methods when there was no statistical heterogeneity; the random-effects method of DerSimonian and Laird was used otherwise. Publication bias was visually assessed by funnel plots and tested using Begg’s rank correlation test and Egger’s method.

How were differences between studies investigated?
The presence of statistical heterogeneity was assessed by the chi-squared test and the I-squared (I²) statistic. An I² above 75% was considered indicative of high statistical heterogeneity. Sensitivity analyses were conducted by excluding individual studies one at a time, and by grouping studies by control therapy and based on the presence of double-blinding. A subgroup analysis was conducted for patients with a baseline cardioinhibitory response on tilt-table testing.

Results of the review
Nine RCTs (430 patients) were included in the review. Two studies were double-blinded and six reported allocation concealment.

Compared with control treatment, pacemaker therapy was associated with a significant reduction of recurrent vasovagal syncope (OR 0.15, 95% CI: 0.05, 0.42, p=0.0004); there was evidence of statistical heterogeneity (p=0.0009; I²=69.6%). The benefit was found in studies comparing active pacemaker with medical therapy or no therapy (OR 0.09, 95% CI: 0.04, 0.22, p=0.00001), as well as in trials comparing pacemaker algorithms (OR 0.04, 95% CI: 0.01, 0.23, p=0.0004), whereas no advantage was shown in double-blinded trials in which patients received a pacemaker but the control group had inactive pacing. Awareness of permanent pacemaker implantation was associated with a significant lower incidence of recurrent syncope (OR 0.16, 95% CI: 0.06, 0.40, p=0.0001). Therefore, the authors suggested that the primary mechanism of benefit from permanent pacemaker therapy was an expectation response.

In the subgroup of patients with baseline cardioinhibitory response on tilt-table testing, pacemaker therapy reduced the risk of recurrent syncope (OR 0.21, 95% CI: 0.05, 0.88, p=0.03); there was evidence of statistical heterogeneity (p=0.02; I²=61.6%).

Overall, the rate of complications following pacemaker procedures was 7.0% (95% CI: 4.6, 10.6). There was no evidence of statistically significant publication bias using Begg’s rank correlation test or Egger’s test. The authors suggested that the asymmetry on the funnel plot was due to methodological differences between the studies.

Authors’ conclusions
Small unblinded trials overestimated the treatment effect of pacemakers. Double-blinded trials suggested that the apparent treatment response is due to expectation response. Therefore, the available evidence does not support the use of permanent cardiac pacing as a first-line therapy for recurrent vasovagal syncope. Larger double-blinded trials are required to examine whether a sustained benefit exists.

CRD commentary
This review had clearly stated inclusion criteria for study participants, intervention, study outcomes and study design. Three databases and several trial registers were searched in an effort to find published and unpublished articles. The potential influence of publication bias was considered and not found. No language restrictions were applied, which limited the potential for language bias. The authors attempted to minimise bias and errors during the review process by carrying out the study selection and data extraction in duplicate.

Study quality was assessed using appropriate criteria but, since it was unclear whether the assessment was performed by independent reviewers, reviewer error and bias at this stage cannot be excluded. The authors assessed the presence and possible sources of statistical heterogeneity. The pooling methods used were appropriate.

The small number of trials, with small sample sizes and lack of blinding, reduced the reliability of the results of the included trials and limited any conclusions that could be drawn.

Implications of the review for practice and research
Practice: The authors stated that a pragmatic approach might be to advocate pacing in select patients with problematic symptoms, accepting that the primary benefit would be due to the expectation response.
Research: The authors stated that large double-blinded RCTs with long-term follow-up were needed. They specifically recommended such an RCT in patients with spontaneous bradycardia during tilt testing.

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