Clinical research

Use of implantable loop recorders in the diagnosis and management of syncope

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Background Syncope is a common, disabling symptom. The most useful data for diagnosing and managing syncope is the recording of physical parameters such as the ECG and blood pressure during a spontaneous event. Implantable loop recorders (ILR) provide an opportunity to record ECG data from a spontaneous event. The purpose of the Eastbourne Syncope Assessment Study (EaSyAS) was to investigate the impact of ILRs on an unselected population of syncopal patients presenting acutely to our institution.

Methods All patients presenting acutely with recurrent, unexplained syncope over a 16-month period, were randomised after a basic clinical workup to receive the Reveal Plus ILR or conventional investigation. All patients were followed up for at least 6 months (mean 276 ± 134 days) following randomisation. The primary outcome measure was time to ECG diagnosis.

Results Four hundred twenty-one patients presented, 201 were eligible, median age 74 years (interquartile range 61–81 years), 54% female, with a median of three previous syncopes (IQ range 2–6). Thirty-three percent of ILR patients and 4% of conventional patients had an ECG diagnosis (hazard ratio 8.93, 95% CI 3.17–25.2, p < 0.0001). Introduction of ECG-directed therapy was quicker for ILR patients (hazard ratio 7.9, 95% CI 2.8–22.3, p < 0.0001). ILR patients had fewer post-randomisation investigations and fewer hospital days, resulting in a saving of costs, £406 versus £1210 (mean difference £809, 95% CI £123–£2730). There was no difference in the number of subsequent syncopal episodes, mortality, or quality of life.

Conclusions ILR significantly increased the rate of diagnosis in an unselected Western population with recurrent syncope. There was a significant decrease in the rates of hospitalisation and investigation in patients receiving an ILR.

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KEYWORDS
Syncope; ILR;
Cost effectiveness;
Arrhythmia

Introduction

Syncope is a common disorder with an annual incidence of 1.3–2.7 episodes/1000 inhabitants/annum.1,2 Retrospective studies suggest that up to 40% of the general population have experienced an episode of syncope in their lifetime.3,4 It is the cause of 6% of all acute medical admissions and 3% of emergency room consultations.5–7

Determination of the cause of syncope is often made on the basis of history and examination alone. However, the gold standard of diagnosis remains the recording of physical observations during a spontaneous event.8 Syncope occurs at random and can be infrequent, although disabling.9 Due to the transitory nature of these symptoms, the opportunity to record such data seldom arises.

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Investigations such as head-up tilt testing, carotid sinus massage and electrophysiologic studies attempt to provoke syncopal symptoms. As with any provocation test, the specificity and clinical relevance of such investigations are hard to evaluate.

Continuous ambulatory monitors, recording the ECG, have been available for some time. However, technical restrictions require that such devices be applied for relatively short periods (7–10 days), making the recording of spontaneous syncopal events unlikely, unless they are very frequent.

The Reveal Plus (Medtronic, USA) implantable loop recorder (ILR) is small, equivalent in size to a pack of chewing gum, requires no intracardiac electrodes, and can be implanted, quickly and easily, subcutaneously under local anaesthetic. It records a single-channel ECG and can be manually or automatically triggered following a syncopal episode. Improved diagnostic rates in selected populations of undiagnosed, highly symptomatic, syncopal patients have been reported.10–13 The usefulness of the ILR in an unselected population with syncyne remains to be determined. The purpose of our trial was to compare the use of the ILR with conventional studies in the diagnosis and management of patients with recurrent syncpe presenting acutely to the Eastbourne District General Hospital, which is a busy, secondary referral centre on the southeast coast of England serving a population of 250,000, 24% of whom are 65 years or older. Ethical approval was granted by our local ethics committee.

Methods

Objectives

The purpose of the study was to determine the effectiveness of an ILR in the diagnosis of recurrent syncope in an unselected patient population.

Patients

From 1 September 2000 to 31 December 2001 (16 months), every patient presenting to our institution with syncope was assessed by the investigators. Consecutive patients with recurrent syncope and no definite diagnosis following initial clinical workup (comprising history and a physical examination, 12-lead ECG, full blood count, urea and electrolytes, plasma glucose and Holter monitoring in the patients with suspected cardiac syncope) were recruited into the Eastbourne Syncope Assessment Study (EsSyAS). All patients with syncope caused by structural heart disease were excluded at this point.

Interventions

All patients were investigated by upright carotid sinus massage (CSM) and tilt testing.14 Appropriate empirical therapies were commenced as dictated by the results of these investigations.15 16 Patients without a Class I indication for cardiac pacing based upon the result of CSM and tilt testing were randomised using independently-held, sealed envelopes, to either conventional investigation or implantation of a cariac loop recorder, ILR (Reveal Plus, Medtronic, USA). The ILR was positioned in the left pectoral region and gain- and sensitivity-programmed, as per the manufacturer’s instructions. It was set to record three patient activations and five automatic activations, allowing a trial activation prior to discharge. Automatic activation was programmed for a ventricular pause of more than 3 s, a ventricular rate of less than 40 beats/min, or a ventricular rate above 165 beats/min for more than 16 beats. The ILR was set to record the five most recent events. Patients were taught to use the device and were required to activate it once, unassisted, prior to discharge post-implantation.

Spontaneous ECG recordings were classified by heart rate as:

1. Bradycardia (heart rate of less than 40 beats/min or a 3-s pause).
2. Normal sinus rhythm.
3. Tachycardia (heart rate greater than 100 beats/min).

Primary and secondary outcomes are described below:

Outcomes: Primary: Time to ECG diagnosis.

Secondary: (1) Time to first recurrence of syncope following study induction.
(2) Time to second recurrence of syncope following study induction.
(3) Time to ECG-guided therapy.

Tertiary: (1) Quality of life. Measured by the 12-item short form of the Medical Outcomes Questionnaire (SF-12) and a visual analogue scale (VAS) at induction and at 3, 6 and 12 months.
(2) Cost effectiveness. Costs incurred by further hospital admissions and investigations for syncope, calculated from after-device-implantation to censorship, were based on local National Health Service (NHS) costs.18

Sample size

A sample size of 200 was considered appropriate to detect an 18% improvement in ECG diagnosis, assuming constant proportional hazards, with a power of 90% (1-ß = 0.05 (twin-tailed, equivalent to 0.025 single-tailed).17

Statistical methods

Randomisation was by random number tables. Patients were allocated by sealed envelopes held in the study centre. Analysis was by intention to treat. Time-to-event outcomes were described using Kaplan–Meier curves. The log rank test was used to describe differences between groups and hazard ratios were determined using Cox proportional hazards models, in which treatment group was the only factor included.19 The difference in mean cost was described, and the 95% confidence intervals for costs were derived using non-parametric bootstrap methods.20 In addition to examining survival curves, departure from the assumption of constant proportional hazards was assessed using a time-dependent explanatory variable. All analyses were undertaken using SAS 8.1 (SAS Institute, Cary, NC.).
Results

Four hundred twenty-one patients with syncope presented from 1 September 2000 to 31 December 2001 (16 months) (Fig. 1). Of these, 205 failed to meet inclusion criteria (Fig. 2). Twenty-two patients were diagnosed in the initial evaluation by history and examination alone, and 67 were diagnosed as having a neurologic cause of syncope. Of the remaining 332, 19 were diagnosed by 24-h Holter, two refused study enrolment and 13 required cardiac pacing after tilt test and CSM according to European Society of Cardiology and American College of Cardiology/American Heart Association guidelines. Two hundred and one patients were randomised; 103 received ILR and 98 underwent conventional investigation and management. Two patients who received ILR and one with conventional investigation were lost to follow-up.

The baseline clinical characteristics were similar for both groups (Table 1). The event rate prior to enrolment was 1.50 syncopal episodes/year.

By study census (30/6/02), all patients had been followed up for at least 6 months (mean follow-up was 276 ± 134 days). Seventy-five patients had a further syncopal event, 43 (43%) with ILR and 32 (33%) without. The mean syncopal event rate was approximately halved during follow-up (0.810 syncopes/year).

At censorship, 34 (33%) patients in the ILR group had an ECG diagnosis compared to four (4%) in the non-ILR group. The hazard ratio for ECG diagnosis was (8.93 [95%CI 3.17–25.19; p < 0.0001], Fig. 3). Eighteen of the 34 (53%) ILR diagnoses were made at the first syncope post-induction, 14 diagnoses were made at the second syncope and the remaining four diagnoses required more than two syncopes to be achieved. Failure to diagnose an episode occurred when the patient or spouse failed to activate the device and the data in the auto-Holter recorders at device interrogation failed to cover the time period of the syncope. Seven (21%) ILR diagnoses were made with data from the auto-activation feature of the device. Of the 38 patients who received an ECG diagnosis, 10 had bradycardia, one had supraventricular tachycardia and three had ventricular tachycardia (Table 2).

ECG recording of an event demonstrated sinus rhythm in 24 syncopal patients. These data and concurrent clinical information enabled this group to be further subdivided into 17 patients with vaso-vagal syncope, four with epilepsy and three with hyperventilation. Ten patients with ILR went on to receive pacemakers (nine with bradycardic and one with vaso-vagal syncope), whereas two non-ILR patients received device therapy: one pacemaker and one implantable cardioverter defibrillator (ICD). Thirty-three patients with ILR were commenced on ECG-guided therapies by time of census compared to four in the conventional group (Table 3). The frequency of ECG-directed therapy was higher for the ILR group (hazard ratio 7.9, 95% CI 2.8–22.3).

The time to first syncope recurrence was similar for patients in both study groups (Fig. 4). Thirty patients had a second syncope during follow-up, 14 (14%) with ILR and 16 (16%) without ILR. The time to second syncope recurrence was similar for both groups (Fig. 5).

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reveal, 103 patients</th>
<th>Control, 98 patients</th>
<th>Not enrolled, 220</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>57 (55.3%)</td>
<td>52 (53.1%)</td>
<td>119 (54%)</td>
</tr>
<tr>
<td>ECG abnormality</td>
<td>18 (17.5%)</td>
<td>28 (28.6%)</td>
<td>133 (60.5%)</td>
</tr>
<tr>
<td>Prior IHD</td>
<td>49 (47.6%)</td>
<td>51 (52.0%)</td>
<td>108 (49%)</td>
</tr>
<tr>
<td>Age (median, interquartile range)</td>
<td>73.9 (61.6–80.7)</td>
<td>74.1 (59.1–81.0)</td>
<td>76 (63–84)</td>
</tr>
<tr>
<td>Duration of symptoms (median, interquartile range)</td>
<td>12 (6–36)</td>
<td>18 (5–48)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Previous episodes (median, interquartile range)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>1 (1–2)</td>
</tr>
</tbody>
</table>
Quality of life measured by VAS and the SF-12 questionnaire was similar in both groups throughout the study period (Fig. 6).

Costs incurred post-randomisation (Table 4) were significantly lower in the ILR group, £406 versus £1210 (mean difference £809, 95% CI £123–£2770). This was the product of lower hospitalisation costs, £343 versus £1090 (mean difference £747, 95% CI £72.8–£2730) and a highly significant reduction in subsequent investigational costs £34.0 versus £95.4 (mean difference £61.4, 95% CI £35.2–£92.9).

### Adverse events

There were no device-related adverse events. There were nine deaths (4% mortality) at censorship, four in the ILR and five in the conventional group. Two of the deaths...
A large number of patients (47%) failed to capture their first syncopal event with the ILR. This was due to failure to activate the ILR or to a delay between the syncopal event and subsequent device interrogation, which allowed the automatic Holter recordings covering the time of the event to be overwritten by subsequently captured data. However, with careful follow-up only 10% of syncope patients failed to eventually achieve a diagnosis with the ILR. This is similar to other studies, which report a failure rate of 9–20%. The diagnostic rate of the ILR was notably enhanced by the use of automatic Holter recording. We recommend regular follow-up of patients with an ILR to interrogate the device, “fine-tune” the auto-Holter recorders and to reinforce patient training in the manual activation technique and encourage patients to consult promptly after any syncopal event to prevent overwriting of auto-Holter recordings and loss of diagnostic data.

Discussion

Syncope in the general population has a relatively benign prognosis. However, syncope secondary to a cardiac cause carries a one-year mortality of 18–33%. Patients suffering from recurrent syncope have a greatly reduced quality of life (similar to those with severe rheumatoid arthritis or chronic low back pain). This study investigated a typical, unselected, Western population suffering from recurrent syncope and shows that the use of the ILR substantially improved diagnostic rates. The study population underwent only a basic clinical workup before randomisation. All patients with any cardiac abnormality (history of heart disease, abnormal cardiac examination, or 12-lead ECG) were initially investigated by 24-h Holter recording (and echocardiogram when indicated). Only those without a diagnosis were subsequently enrolled into the randomised trial. This reflects European practise and furthermore is encouraged by UK guidelines for the use of implantable cardioverter defibrillators.

Only one study patient underwent diagnostic electrophysiologic (EP) testing (in the non-ILR group). EP studies only for syncope diagnosis are used much less frequently in European practise than in the United States. Our investigation differs from all other studies using the Reveal device, which have used diagnostic EP testing prior to Reveal implantation in patients with impaired left ventricular function or ECG evidence of abnormal intracardiac conduction.

Does the ILR record a diagnosis every time syncope occurs?

A large number of patients (47%) failed to capture their first syncopal event with the ILR. This was due to failure to activate the ILR or to a delay between the syncopal event and subsequent device interrogation, which allowed the automatic Holter recordings covering the time of the event to be overwritten by subsequently captured data. However, with careful follow-up only 10% of syncope patients failed to eventually achieve a diagnosis with the ILR. This is similar to other studies, which report a failure rate of 9–20%. The diagnostic rate of the ILR was notably enhanced by the use of automatic Holter recording. We recommend regular follow-up of patients with an ILR to interrogate the device, “fine-tune” the auto-Holter recorders and to reinforce patient training in the manual activation technique and encourage patients to consult promptly after any syncopal event to prevent overwriting of auto-Holter recordings and loss of diagnostic data.

Table 4 Costs incurred post-randomisation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Reveal</th>
<th>Control</th>
<th>Difference in cost (£) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography head</td>
<td>4</td>
<td>8</td>
<td>−5.30 (−13.86 to 1.92)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>1</td>
<td>1</td>
<td>−0.05 (−3.06 to 9.12)</td>
</tr>
<tr>
<td>Electroencephalogram</td>
<td>0</td>
<td>2</td>
<td>−2.04 (−4.80 to 0.72)</td>
</tr>
<tr>
<td>Carotid doppler</td>
<td>3</td>
<td>5</td>
<td>−2.19 (−8.14 to 2.89)</td>
</tr>
<tr>
<td>Echo</td>
<td>12</td>
<td>15</td>
<td>−8.54 (−25.31 to 6.54)</td>
</tr>
<tr>
<td>24-h Holter</td>
<td>4</td>
<td>11</td>
<td>−7.34 (−15.08 to −0.37)</td>
</tr>
<tr>
<td>ELR: ‘R Test’</td>
<td>5</td>
<td>28</td>
<td>−29.84 (−43.49 to −18.04)</td>
</tr>
<tr>
<td>Electrophysiologic study</td>
<td>0</td>
<td>1</td>
<td>−6.12 (−17.90 to 5.65)</td>
</tr>
<tr>
<td>Investigations</td>
<td>£34.0</td>
<td>£95.4</td>
<td>−61.43 (−92.92 to −35.16)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>£379</td>
<td>£1090</td>
<td>−747.30 (−1272.82 to −271.80)</td>
</tr>
<tr>
<td>Total costs</td>
<td>£406</td>
<td>£1210</td>
<td>−£808.72 (−£1234.22 to −£251.65)</td>
</tr>
</tbody>
</table>

Previous data would suggest an actuarial risk of further syncope occurring in the study group of 29%. Forty-three percent of ILR patients went on to have at least one more episode of syncope, a higher rate than expected. The ILR diagnostic rate was 33% and would have been higher if all syncopal events had been captured by the ILR. Achieving a diagnosis at the first event may have been hampered by the fact that our population was older and less symptomatic than previous groups studied. Therefore, they may have been less motivated to ensure that the ILR achieved a diagnosis. Older people had more difficulties in activating the ILR after syncope and in consulting promptly after a syncopal event, thus losing valuable auto-Holter recording data.

Improved diagnostic rate

The types and frequency of diagnoses achieved were similar to those observed by other investigators. Thirty-seven percent of study patients were syncopal due to an arrhythmia, according to accepted diagnostic criteria. Other studies have demonstrated greater frequencies of arrhythmia, but they specifically selected a patient population with confirmed heart disease. Sixty-four percent of patients demonstrated sinus rhythm during syncope episodes. Based on concurrent clinical findings, a more precise diagnosis was possible. This
enabled us to distinguish between neurologic seizures, vaso-vagal episodes and episodes of hyperventilation, and to use a greater variety of treatments in the patients investigated by ILR.

ECG-directed treatment

As a result of more rapid diagnosis, ECG-directed therapy was begun much earlier in the ILR group and a greater variety of therapies were commenced. All therapies were based on American Heart Association and European Society of Cardiology Class I guidelines.16,31

Of the treatments prescribed to treat syncope, only cardiac pacing has consistently been shown to improve symptoms.32,33 Only 11 patients went on to receive pacemakers. This may explain, in part, why the increased diagnostic rate observed in the ILR group failed to further reduce the frequency of syncope or increase the time to second syncope.

The incidence of syncope decreased dramatically during follow-up. This is a common finding in syncope studies.30 Due to this, only 30 patients went on to have a second episode of syncope during follow-up (16 controls and 14 ILR patients).

Adverse events

Other studies have reported few complications from ILR implantation.26 We report no major complications.

There was no difference in mortality between groups. The mortality rate of 4% is lower than reported by other studies.16,36

Costs

The initial cost of the ILR is high (UK list price £1350). However, this is offset by a subsequent reduction in investigational and hospitalisation costs that is equivalent to 60% of the purchase price of the device (overall cost offset £809, 95% CI £124–£2730).

Absence of device placebo effect

Syncope may be precipitated by abrupt physical or psycho-social stress. An open-label trial could be confounded by a placebo effect.37 The presence of an ILR made no difference in the time to the first recurrence of syncope. This observation would suggest that ILR does not have an important placebo effect in the prevention of syncope.

Quality of life

Patients with recurrent syncope have a greatly reduced quality of life,9 due mainly to fear of having another syncopal episode.38 Having failed to record any significant reduction in syncope recurrence, it is not surprising that we did not record any difference in quality-of-life measures in our two populations.

Study limitations

Time to second syncope

The usefulness of this endpoint was limited because 47% of patients failed to reach a diagnosis following their first syncopal episode post-enrolment. In these patients, the chance to introduce ECG-guided therapy to prevent a second syncope was missed. As previously discussed, few treatments for syncope have consistently proven to reduce syncopal recurrence. Therefore, the therapies introduced may have been ineffective in preventing further syncopes. Few patients reached this endpoint, reducing the power of the study to resolve any difference between groups. Ongoing follow-up may resolve this issue.

Quality of life

Assessment of quality of life in a syncopal population is complicated by the generally rare and random nature of the symptom. This decreases the sensitivity of the SF-12 questionnaire and VAS.

Conclusion

The use of ILR has led to substantially more diagnoses, more rapid introduction of therapy and a greater variety of therapies being used. Mortality was unaffected. The Reveal Plus has a high initial cost. However, 60% of this cost is recovered during follow-up due to the reduction in hospitalisation and subsequent investigations. The ILR failed to further reduce syncope. It therefore failed to improve quality of life, despite improving diagnostic rates. This may partly be due to the deficiency of currently accepted therapies for preventing syncope.

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Use of implantable loop recorders in the diagnosis


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