CLINICAL EFFICACY AND SAFETY OF AN IMPLANTABLE LOOP RECORDER IN INVESTIGATION OF THE CAUSES OF UNEXPLAINED AND/OR RECURRENT SYNCOPES

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Objective

The aim of this analysis was to assess diagnostic efficacy and safety of an implantable loop recorder (ILR) in patients with unexplained and/or recurrent syncope.

Introduction

Syncope is defined as sudden and transient, self limiting loss of consciousness and muscle tone, not requiring pharmacological intervention or electrical cardioversion. Although a great progress has been made in the field of cardiologic diagnostics, including stress testing, echocardiography, 24-hours Holter electrocardiography (ECG) monitoring and electrophysiological studies, still up to 40-49% of patients with syncope remain undiagnosed. It is partly a result of focusing on detection of abnormalities, that could plausibly cause the episode, while the probability of detection of a spontaneous syncope event during conventional workup remains rare, as a vast majority of patients with syncope is asymptomatic at the time of evaluation. A “gold standard” or reference test in establishment of syncope diagnosis should be detection of correlation between a syncope episode and variations of biological parameters at that time.

An ILR is a new diagnostic tool which enables the monitoring of bipolar electrocardiogram during syncope, other episodes of loss of consciousness, presyncope or palpitations for a long period of time, up to 36 months. It is triggered for loop storing either by the patient, bystander (mainly spouse) or automatically, if the heart rate decreases or increases beyond a programmed range of values.

According to the European Society of Cardiology (ESC) guidelines for management of syncope, ILR is recommended in patients with persistent but rare syncope episodes and in patients, in whom, despite completed conventional diagnostic process, the diagnosis of syncope etiology remains unknown, and electrocardiogram suggests the arrhythmic background of syncope or previously high risk syncope appeared, such as during driving or followed by fall and injury.

Methods

The comparison was based on a systematic review, carried out according to guidelines published by the Medical Services Advisory Committee (MSAC) and the Agency for Health Technology Assessment in Poland. The most important medical databases (MEDLINE, EMBASE, CENTRAL) were searched. Two reviewers independently selected trials, extracted data and assessed their quality (using the Jadad and QUADAS scales). The date of the last search was August 2008.

Quantitative analysis was impossible due to heterogeneity between the trials with respect to baseline characteristic of participants and significant differences in duration of observation periods between the ILR and CDT (Conventional Diagnostic Testing) groups. Assessment of specificity and sensitivity of ILR was not possible due to lack of reference tests in the included studies. Therefore, only qualitative analysis was performed.

Table 1. Inclusion and exclusion criteria

Population	• Unexplained and/or recurrent syncope
Intervention	• ILR (Implantable Loop Recorder)
Comparator	• Conventional Diagnostic Testing • Pacemaker implantation • Any other comparator
Endpoints	• Sensitivity/specificity/prognostic value of an ILR as a diagnostic tool • Number of patients with diagnosed syncope etiology • Quality of life • Mortality • Morbidity • Adverse events
Design of clinical trials	• Randomized controlled trials • Experimental non-randomized controlled trials • Observational studies • Case series
Other inclusion criteria	• Studies published in Polish, English, French or German • Studies published as full texts or conference abstracts • Studies with ≥10 patients
Exclusion criteria	• Use of ILR in patients without syncope or presyncope/palpitations, • ECG monitoring with ILR in patients with other clinical conditions than syncope (such as atrial fibrillation or epilepsy)

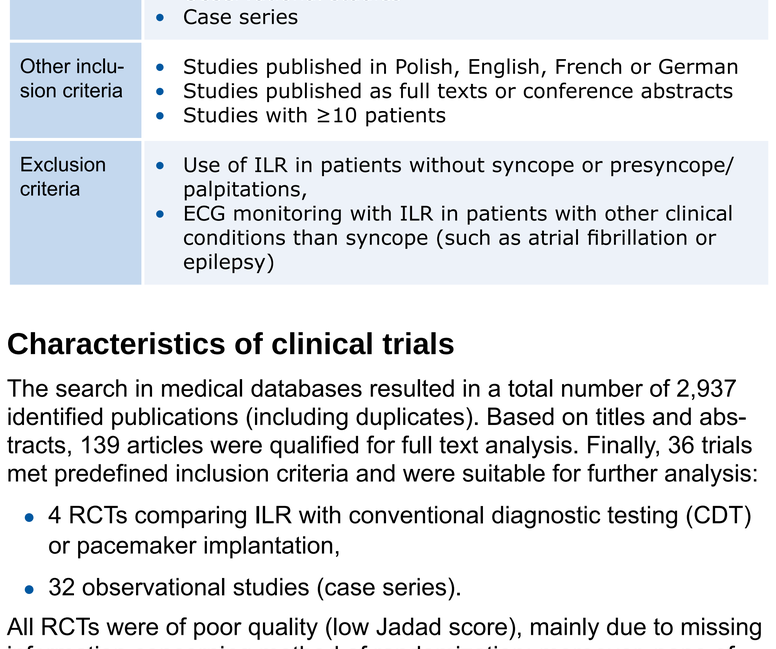
Characteristics of clinical trials

The search in medical databases resulted in a total number of 2,937 identified publications (including duplicates). Based on titles and abstracts, 139 articles were qualified for full text analysis. Finally, 36 trials met predefined inclusion criteria and were suitable for further analysis:

- 4 RCTs comparing ILR with conventional diagnostic testing (CDT) or pacemaker implantation,
- 32 observational studies (case series).

All RCTs were of poor quality (low Jadad score), mainly due to missing information concerning method of randomization; moreover, none of them was double-blinded. All the studies were characterized by a relatively low methodological value – 5 to 6 points out of 14 in the QUADAS scale, mainly due to missing reference test.

Selection process according to QUOROM



Results

The results of 4 randomized controlled trials (RCTs) and 32 case series (CSs) were included in the analysis. Overall, 2,286 subjects were studied, 343 in RCTs and 1943 in observational studies.

Efficacy analysis

In 3 RCTs, in which ILR was compared with conventional diagnostic testing, syncope/palpitations recurred in 42-77% patients assigned to the ILR group and in 33-38% patients in the control group. ILR led to more frequent establishment of syncope etiology diagnosis in comparison to diagnostic management used in controls (33-73% versus 4-21%). The results from 1 RCT indicate that ILR can reduce the rate of unnecessary pacemaker implantation in 88% patients with a bundle branch block or syncope of unknown etiology (either syncope or palpitations reoccurred in 35% of subjects in the ILR group versus 7% of the pacemaker group) during a mean observation period of 9 ± 6 months (range 2 to 38 months).

In CSs, recurrent syncope or presyncope was reported in 12%-100% patients, depending on the study. ILR enabled to establish a diagnosis in 62.5-100% patients with recurrent symptoms. High heterogeneity with respect to prevalence of ILR-based diagnosis of syncope etiology between the analyzed case series can be partly attributed to a different observation period or study population selection.

Table 2. RCTs included in the analysis

Study	Jadad score	ITT analysis	Population	Intervention	Control	Observation period
Krahn 2001	2/5	YES	recurrent, undiagnosed syncope (60)	ILR	conventional diagnostic testing	ILR: 1 year ELR: 2-4 weeks TTT & EPS: time required for test performance
Farwell 2004	3/5	YES	recurrent, undiagnosed syncope (201)	ILR	conventional diagnostic testing	no data
Gaida 2007	1/5	not clear	recurrent, undiagnosed palpitations (50)	ILR	conventional diagnostic testing	ILR: at least 1 year Holter: 24 hours ELR: 4 weeks
Hernandez 2004	1/5	not clear	recurrent, undiagnosed syncope (32)	ILR	pacemaker implantation	Till the end-point, ILR battery discharge, loss of the patient to follow-up or study cessation : max. 38 months

Table 3. Mortality regardless of the cause in RCTs

Study	ILR group			Control group		
	N	Deaths (n)	%	N	Deaths (n)	%
Krahn 2001	30	1	3.3%	30	0	0.0%
Farwell 2004*	103	4	3.9%	98	5	5.1%
Farwell 2004**	103	8	7.8%	98	9	9.2%
Hernandez 2004	17	0	0.0%	15	0	0.0%
Giada 2007	26	no data	no data	25	no data	no data

** – observational period of at least 6 months, ** – observational period up to 18 months.*

Table 4. Establishment of the final syncope etiology diagnosis in RCTs

Study	ILR group			Control group		
	N	Diagnosis (n)	%	N	Diagnosis (n)	%
Krahn 2001	27	14	51.9%	30	6	20.0%
Krahn 2001[1]	13	8	61.5%	6	1	16.7%
Krahn 2001[2]	40	22	55.0%	36	7	19.4%
Farwell 2004*	103	34	33.0%	98	4	4.1%
Farwell 2004**	103	43	41.8%	98	7	7.1%
Giada 2007	26	19	73.1%	24	5	20.8%

*1 – analysis before crossover, 2 – analysis before and after crossover, * – observational period of at least 6 months, ** – observational period up to 18 months*

Table 5. Prevalence of recurrent syncope and/or palpitations and establishment of the final syncope etiology diagnosis in CSs

Study	N	Prevalence of recurrent symptoms (%)	Final diagnosis in patients with recurrent symptoms (n, %)
Krahn 1998	24	87.50%	21 (100%)
Seidl 2000a	133	62.41%	72 (86.75%)
Seidl 2000b	20	55.00%	11 (100%)
Nierop 2000	35	68.57%	20 (83.33%)
Mieszczanska 2001	12	66.67%	5 (62.50%)
Krahn 2001	85	72.94%	53 (85.48%)
Ashby 2002	48	52.08%	25 (100%)
Krahn 2002	206	68.93%	132 (92.96%)
Vater 2002	149	39.60%	56 (94.92%)
Armstrong 2003	15	46.67%	7 (100%)
Sanfins 2003	10	80.00%	8 (100%)
Benditt 2003	38	57.89%	17 (77.27%)
Mason 2003	43	74.42%	26 (81.25%)
Donateo 2003	36	50.00%	16 (88.89%)
Ermis 2003	50	12.00%	6 (100%)
Garcia-Civera 2003	15	no data	8 (no data)
Boersma 2004	43	34.88%	9 (60.00%)[1]
Ng 2004	50	no data available	181 (100%)[2.3] 682 (17%)[2.4]
Krahn 2004	60	50%	30 (100%)
Solano 2004	103	54.37%	52 (92.86%)
Paisey 2005	41	65.85%	21 (77.78%)
Lombardi 2005	34	32.35%	9 (81.81%)
Garcia-Civera 2005	81	39.51%	32 (100%)
Schernthaner 2005	38	63.16%	24 (100%)
Deharo 2006	25	48.00%	31 (100%)[2]
Inamdar 2006	100	no data	45 (48.39%)[1]
Maggi 2007	18	100%	18 (100%)
Schernthaner 2008	55	72.72%	40 (100%)
Graf 2008	13	no data	6 (no data)
Pierre 2008	95	45.26%	43 (100%)
Pezawas 2008	70	85.71%	60 (100%)
Moya 2001	111	34.23%	32 (84.21%)
Brignole 2001	52	42.31%	19 (86.36%)
Menozzi 2002	35	17.14%	6 (100%)
Brignole 2002	198	33.33%	57 (86.36%)

1 – confirmation of arrhythmic origin of the symptoms, 2 – reffering to the number of syncope/presyncope episodes, 3 – manual activation of the ILR, 4 – automatic preprogrammed activation of the ILR

Safety analysis

In RCTs 2 medical events were reported, one (pocket infection) in the pacemaker group and the other (malfunction of the device due to battery discharge, another device was implanted) in the ILR group. Safety data were also reported in 20 out of 32 observational studies including 1,407 subjects.

The average risk of adverse events calculated based on those 20 studies was about 2%. The most common events reported were: infection of the ILR implantation pocket and injuries due to recurrent syncope. In 51 cases additional malfunction of the ILR took place. Reported deaths were mainly due to co-morbidities. None of the deaths observed in the analyzed studies was connected with implantation of the device or monitoring process. In most of the studies included in the review no deaths occurred or mortality was not reported.

Table 6. Adverse events and malfunctions of the ILR – the results of case series

Study	N	AE (n, %)	ILR malfunction (n, %)
Krahn 1998	24	0 (0.0%)	0 (0.0%)
Seidl 2000a	133	3 (2.26%)	9 (6.77%)
Seidl 2000b	20	0 (0.0%)	3 (15.0%)
Nierop 2000	35	no data	no data
Mieszczanska 2001	12	0 (0.0%)	0 (0.0%)
Krahn 2001	85	3 (3.53%)	0 (0.0%)
Ashby 2002	48	no data	no data
Krahn 2002	206	0 (0.0%)	no data
Vater 2002	149	4 (2.68%)	1 (0.67%)
Armstrong 2003	15	0 (0.0%)	0 (0.0%)
Sanfins 2003	10	0 (0.0%)	0 (0.0%)
Benditt 2003	38	no data	no data
Mason 2003	43	6 (13.95%)	no data
Donateo 2003	36	0 (0.0%)	no data
Ermis 2003	50	0 (0.0%)	no data
Garcia-Civera 2003	15	no data	no data
Boersma 2004	43	no data	no data
Ng 2004	50	no data	no data
Krahn 2004	60	0 (0.0%)	38 (63.33%)
Solano 2004	103	3 (2.91%)	no data
Paisey 2005	41	2 (4.88%)	no data
Lombardi 2005	34	0 (0.0%)	no data
Garcia-Civera 2005	81	no data	no data
Schernthaner 2005	38	no data	no data
Deharo 2006	25	no data	no data
Inamdar 2006	100	1 (1.0%)	no data
Maggi 2007	18	2 (11.01%)	no data
Schernthaner 2008	55	no data	no data
Graf 2008	13	no data	no data
Pierre 2008	95	no data	no data
Pezawas 2008	70	2 (2.86%)	no data
Moya 2001	111	2 (1.80%)	no data
Brignole 2001	52	0 (0.0%)	no data
Menozzi 2002	35	0 (0.0%)	no data
Brignole 2002	198	no data	no data

Limitations

- This analysis was based on studies not designed for specificity or sensitivity evaluation of ILR. There was no study in which ILR would be compared with a reference diagnostic tool (“gold standard”).
- All studies that met the inclusion criteria had low QUADAS and Jadad scores; however, due to absence of better quality studies, all available data were taken into consideration.
- Studies assessing ILR diagnostic value in settings other then syncope, presyncope or palpitations were not included into the analysis.

Table 7. Abbreviations

AE	Adverse Event
CDT	Conventional Diagnostic Testing
CS	Case Series
ECG	Echocardiography
ELR	External Loop Recorder
ESC	European Society of Cardiology
EPS	Electrophysiological Studies
ILR	Implantable Loop Recorder
ITT	Intention To Treat Analysis
MSAC	Medical Services Advisory Committee
N, n	Total number of subjects in the group
n/a	not applicable
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
TTT	Table Tilt Test

Conclusion

Based on a systematic review of available studies, ILR seems to be an effective technology in diagnostic evaluation of patients suffering from previously undiagnosed and/or recurrent syncope. It aids diagnostics of syncope etiology in patients who remain undiagnosed despite undergoing standard evaluation process. ILR is characterised by a favourable risk profile, with low rate of adverse events subsequent to the device implantation, mainly such as rare infections of the ILR pocket.