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The use of a single chamber leadless pacemaker for the treatment of cardioinhibitory vasovagal syncope

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ABSTRACT

Background: The use of pacemakers in the treatment of cardioinhibitory vasovagal syncope is controversial with a mixed message from the limited evidence base. Single chamber leadless pacemakers have been shown to be an effective alternative option to conventional pacemakers.
Objective: This study examines the use of leadless pacemakers in a cardioinhibitory vasovagal population in the United Kingdom.
Methods: Observational data on 32 patients implanted with the Micra Transcatheter Pacemaker System for vasovagal syncope are presented. Data was collected on implant indications, implant procedure and follow up data from 12 centres across the United Kingdom that had elected to use a Micra leadless pacemaker in this patient population.
Results: 32 patients aged 37 ± 14 years (range 18 to 64 years) with 62% of the patients being female were recruited to the study. Vasovagal syncope was diagnosed clinically and with the support of Holter monitoring, tilt table testing and implantable loop recorders. The duration of symptoms was 8 ± 8 yrs. with an average frequency of syncope being 4 ± 6 times/year. The Micra pacemaker was successfully implanted in all patients with a major complication rate of 3.1%. Patients were followed up for 404 ± 237 days (range 63–928 days). At follow up 28 (87%) patients were free from symptoms.
Conclusions: This observational study suggests that the use of a single chamber leadless pacemaker in the treatment of cardioinhibitory vasovagal syncope might be a reasonable clinical option.

1. Background

The use of pacemakers in patients with cardioinhibitory vasovagal syncope is controversial. Over the last decade it has fallen from a class 2A to 2B indication in international guidelines [1,2]. The reason for this is that the evidence base in support of its efficacy is limited with very few well-conducted studies in this area. Most fail to control the studies by not having an appropriate placebo-controlled group. Many patients with vasovagal syncope are young and so the consequences of pacemaker therapy are more far reaching than in a conventional older pacemaker population. It is well recognised that conventional lead-based pacing is an effective therapy but not without complication, both acute and long term.

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Leadless pacemakers have been developed over the last 5 years and initial studies have suggested that this is a procedure that can be performed safely and effectively and with favourable complication rates [3]. The Micra Transcatheter Pacing System (TPS) (Medtronic, Minneapolis, USA) is a catheter-delivered device that is placed via the femoral veins using a deflectable catheter. This allows the deployment of a fully functional rate responsive device (0.8 cc, 2 g) to enable pacing in the right ventricle [4].

In this retrospective observational study, we present the short-term United Kingdom experience of the use of a single chamber leadless pacemaker in patients with cardioinhibitory vasovagal syncope.

2. Methods

All 12 United Kingdom centres using the Micra Transcatheter Leadless Pacing System (Medtronic, Minneapolis, USA) were contacted by the first author. A dedicated data collection tool was developed to capture the UK experience of using the Micra TPS in patients with vasovagal cardioinhibitory syncope. Baseline characteristics and patient demographics at time of implantation, clinical indications and outcomes were requested. Data are presented as means ± standard deviations where appropriate.

The procedure of leadless pacing has been described previously [4]. Implanting centres were asked whether they had used the Micra device in patients with cardioinhibitory vasovagal syncope. If they responded positively an anonymised questionnaire was sent to them requesting data on the patient characteristics, the implant procedure and clinical outcomes. This was a retrospective study that was not conducted as part of a registry. Patient selection was made on clinical grounds based on clinicians' views on whether the patient might be considered suitable for a leadless pacemaker. All patients were given the option of conventional or leadless pacemakers and selected the latter.

The diagnosis of cardioinhibitory vasovagal syncope was a clinical diagnosis based upon history and use of Tilt Testing in some as supported in European Guidelines for the diagnosis of this condition [5]. The cardioinhibitory aspect was confirmed with monitoring and sinus node disease was excluded by the observation of infrequent pauses and associated symptoms.

Approval was received from the UK National Health Service (NHS) Health Research Authority confirming that this study did not require ethics submission and approval.

Consistent with published literature, major complications were defined as a complication that lead to death, hospitalisation, prolonged hospitalisation or loss of device function. Follow up was defined by the local hospitals' routine follow up procedure for patients with vasovagal syncope and patients with leadless pacemakers.

3. Results

3.1. Patient characteristics

32 patients were implanted with the Micra TPS between 2015 and 2018 for cardioinhibitory vasovagal syncope (Table 1). The mean age of the population was 37 ± 14 years (range 18 to 64 years) with 62% of the patients being female. The diagnosis of cardioinhibitory vasovagal syncope was made on the basis of the clinical presentation and supporting investigations. These included tilt table testing (32%), ambulatory Holter monitoring (16%) and implantable loop recorders (56%). Some patients had more than one diagnostic supporting investigation. The duration of symptoms was 8 ± 8 years with an average frequency of syncopal events being 4 ± 6 events/year. The longest recorded RR′ intervals in the population was 13 ± 7 s. Data on 3/32 patients (9.4%) was not available as they had been previously investigated at other hospitals prior to conventional leaded pacemaker implantation and had been referred for extraction of infected leaded pacemakers with re-

Table 1
Clinical characteristics of patients implanted with Micra Leadless Pacemaker.

Patient number	Age at implant	Sex (m/f)	Duration of symptoms (years)	Frequency of syncope (per year)	Diagnostic modality (tilt, Holter, ILR)	Longest RR′ interval (secs)	Implant duration (days)
1	50	m	5	6	Tilt	20	512
2	24	m	10	3	Tilt/ILR	21	186
3	23	f	1.5	12	Holter	24	312
4	18	f	1	4	ILR	9	171
5	58	f	3	2	Holter	8	131
6	37	m	2	6	ILR	8	373
7	25	m	16	2	ILR	7	424
8	21	m	7	1	Holter	6	842
9	35	f	5	2	ILR	11	928
10	57	f	8	3	ILR	12	119
11	46	m	38	26	Holter	4.9	484
12	40	f	2	3	ILR	4.2	616
13	31	f	6	1	ILR	8	484
14	22	f	8	0.5	ILR	19	932
15	29	m	20	1	ILR	10	787
16	34	f	3	4	Holter	5	131
17	55	f	2	2	ILR	15	309
18	27	m	5	1	ILR	11.2	337
19	27	f	20	6	ILR	29.8	361
20	18	f	4	1	Tilt	8	385
21	37	f	7	0.5	ILR	19	463
22	31	f	5	0.25	ILR	8	484
23	20	f	12	2	ILR	16	63
24	35	m	8	2	ILR	15	56
25	64	m	n/a	6	Tilt	n/a	309
26	37	m	n/a	0.5	Tilt	27	227
27	44	f	n/a	2	Tilt	5	697
28	64	f	n/a	2	Tilt	n/a	247
29	37	f	n/a	1	Tilt	6	278
30	45	f	n/a	20	Tilt	n/a	449
31	63	m	n/a	10	Tilt	22	401
32	31	f	2	1	ILR	10	434

m – male, f – female, n/a – not available, ILR – implantable loop recorder.

implantation of Micra TPS. The number of patients recruited per center was 2.7 ± 4.0 (mean ± S.D.).

3.2. Implant procedure

All patients were successfully implanted with the Micra TPS (Table 2). One patient experienced a major complication (3.1%) with a significantly elevated pacing threshold post procedure secondary to microdisplacement. This was successfully retrieved and redeployed one-week post implantation. Implant procedure time was defined as the time from placement of the introducer sheath to removal of the sheath. The mean duration of the procedure was 41 ± 16 min with 427 ± 237 s of fluoroscopy time. Two minor complications were reported. One patient had ventricular ectopy noted after device deployment that settled and one patient had a minor groin haematoma that was managed conservatively.

All patients were successfully deployed in ≦3 or less deployments with the majority requiring only 1 (62%). The mean acute pacing threshold at implantation was 0.66 ± 0.62 mV (pulse width 0.24 ms), with an R wave amplitude of 10.2 ± 4.7 V and impedance of 805 ± 234 Ohms.

A variety of different programming modes were used to treat this patient population with 17 (53%) having just a VVI back up rate 35–60 bpm. The remainder was programmed using hysteresis with lower rates varying from 30 to 50 bpm and upper rates between 50 and 80 bpm (Table 2).

3.3. Follow up

Patients were followed up according to National Guidelines with a first follow up 4 to 6 weeks post implantation and then annually. Patients have been followed up for 404 ± 237 days (range 63–928 days). Two patients were investigated for chest pain that was not attributed to the Micra TPS device or implantation procedure following appropriate investigations. At follow up 28/32 (87%) patients were free from symptoms, 2 patients (6.3%) had not had formal follow up and 2 further patients (6.3%) had ongoing symptoms. One of these had experienced less event frequency and severity and one had persistent pre syncopal events but no recurrence of syncope that had occurred prior to pacemaker implantation.

Table 2
Electrical characteristics and patient follow up (FU).

Patient number	Implant time (mins)	Fluoroscopy (sec)	Number of deployments	R wave (mV)	Threshold (V at 0.24 ms)	Impedance (Ω)	Pacing mode	Symptoms at follow up
1	25	460	2	15.4	0.38	680	Hyst 40/70	No
2	70	300	2	7.4	3.5	800	VVI 50	No
3	60	243	1	4.4	0.5	680	VVI 40	No
4	46	475	1	6.1	0.38	820	Hyst 40/50	No
5	n/a	n/a	2	10.1	0.5	760	VVI 50	No FU
6	34	234	1	5.7	0.25	670	Back up	No
7	40	420	1	7	0.63	620	Hyst 30/60	No
8	50	511	1	18.7	0.5	1500	VVI 40	No
9	48	619	2	7.5	0.5	550	VVI 60	No
10	40	269	1	9.2	0.25	810	Hyst 40/70	No FU
11	40	608	2	15.4	0.38	750	VVI 40	Yes
12	20	195	1	7.7	0.63	1430	Hyst 40/70	No
13	49	608	1	9.9	0.38	780	Hyst 40/80	No
14	42	752	2	12.9	0.63	620	Hyst 50/70	No
15	30	534	1	10.9	0.88	730	Hyst 30/80	No
16	26	512	1	6.2	0.5	670	Hyst 40/80	No
17	20	190	1	10.7	0.25	1150	Hyst 40/70	No
18	41	230	2	16.3	1.88	750	VVI 35	No
19	24	319	1	6.1	0.88	890	Hyst 40/70	No
20	40	278	2	5.3	0.375	790	Hyst 40/70	No
21	44	344	2	22.7	0.5	710	VVI 40	No
22	49	500	1	9.9	0.375	780	Hyst 40/80	Yes
23	93	1467	1	9.5	0.5	520	Hyst 40/80	No
24	40	218	1	8.9	1.63	610	Hyst 40/80	No
25	n/a	470	3	4.3	0.5	1100	VVI 40	No
26	n/a	108	1	7.7	0.38	700	VVI 40	No
27	n/a	282	1	20	0.63	760	VVI 40	No
28	n/a	282	2	13.6	0.38	1270	VVI 40	No
29	n/a	n/a	1	4.8	0.5	660	VVI 40	No
30	n/a	948	3	7.8	0.75	750	VVI 40	No
31	n/a	384	1	13.4	0.5	710	VVI 40	No
32	35	39	1	9.8	9.8	740	VVI 40	No

4. Discussion

This observational, retrospective cohort study of the use of the Micra TPS has indicated that in a population with cardioinhibitory vasovagal syncope there is a high incidence of complete symptom resolution (87%) following pacemaker implantation. The incidence of major complications is very low and consistent with currently published data on the use of the Micra TPS [3,4].

Conventionally, patients requiring pacing who are not in persistent or permanent atrial fibrillation are considered for a dual chamber device. This concept applies to a population being considered for vasovagal syncope so as to maintain as normal physiology as possible when there may be both a cardioinhibitory and vasodepressor component to symptoms. However, there are potential advantages to the use of Micra TPS in this specific patient population, particularly related to the avoidance of long-term complications of transvenous leads in a young patient population. Based on the results of this study UK device implanting physicians are using Micra TPS in patients with cardioinhibitory vasovagal syncope. We did not explore the motivation of physicians, but it may be that they consider that the theoretical benefits of leadless pacemaker implantation may outweigh the benefits of maintained atrioventricular synchrony with conventional dual chamber leaded pacemakers.

Pacemaker implantation in patients with vasovagal syncope remains controversial. This condition is considered to have a favourable prognosis without the use of pacemaker implantation. The use of pacemaker therapy in a younger population is not without risk. Risks includes issues related to compromised venous access, cardiac implantable electronic device (CIED) infection and extraction and the ongoing requirement for long term follow up and device revisions. Many patients requiring pacemakers at a young age will require multiple subsequent interventions. This may include the placement of additional leads due to lead failure, lead extraction and the inherent risk of device-based infection with each subsequent surgical intervention. The evidence base for pacemaker implantation in this population is weak and dominated by small studies lacking control groups or cross over design and with significant risk bias.

The Vasovagal Pacemaker Study (VPS Study) was one of the first randomised studies of the use of dual chamber pacemaker implantation in vasovagal syncope [6]. This study of only 27 patients randomised patients with cardioinhibitory VVS to dual chamber pacing versus standard therapy. The study was stopped early by the Data Monitoring Committee as there was a significant difference between the rate of recurrent syncope (22% versus 70% in the standard care group). This study was not blinded and as it was stopped early long term follow up data are not available.

Three subsequent studies examined the use of dual chamber pacemaker implantation compared to placebo using OVO pacing mode for the placebo-controlled arm. The second vasovagal pacemaker study (VPS II) showed a 42% recurrence rate of syncopal episodes in the placebo group compared to 33% in the active treatment group ($p = 0.14$) [7]. The Vasovagal Syncope and Pacing Trial (SYNPACE) examined 29 patients with VVS and showed recurrent syncope in 38% of the placebo group and 50% of the treatment group (p – ns) [8]. ISSUE 3 used implantable loop recorders to identify patients with cardioinhibitory or mixed vasovagal syncope. 77 patients underwent dual chamber pacemaker implantation and were randomised to DDD or ODO pacing modes. Syncope recurred in 57% of the placebo group and 25% of those paced ($p = 0.039$) [9]. The data supporting pacing in this population are, therefore, mixed but arguably in small studies. As a consequence, the indication for pacing in VVS has gone from a 2A to 2B indication in the guidelines [1,2]. It is important to note that there are significant differences in the ages of the populations in these studies compared to our study. In ISSUE 3 patients under the age of 40 years were excluded and the mean age of the overall study population was 65 years compared to 37 years in our study [9].

In our study population the degree of bradycardia was at the more extreme end of the spectrum with a mean RR' interval of 13 s (range 4.2–29.8 s). It might be argued that in a population with such profound symptomatic pauses associated with VVS that VVI pacing is likely to be better than asystole in haemodynamic terms. The relative high therapy success rate in this study is unlikely to represent superiority of single chamber leadless pacing but more likely to reflect the highly selective nature of the patients in this study with profound pauses associated with VVS. Furthermore, as events are short lived the frequency of events (0.25 to 26/year) is unlikely to have an impact on the perceived benefit of single chamber leadless pacing compared to dual chamber pacing. In some patients the symptom burden of vasovagal syncope may resolve with time. The Micra TPS has the unique ability to be programmed off. It could be a reasonable strategy to program the device off towards the end of the device's life to evaluate whether further pacing therapy is justified. Early studies of the Micra device have indicated that battery longevity may be as high as 14.9 years [10]. Based upon the mean pacing threshold of 0.66 mV seen in this study and a low pacing requirement projected longevity is 14.6 years. Patients with vasovagal syncope are likely to have low pacing percentages due to the infrequent nature of the condition. If patients have ongoing symptoms with a pacing indication, then management options may include implantation of a second Micra TPS device (with or without extraction of the old device) or a switch to conventional leaded pacemaker implantation having conserved the vasculature for a number of years with the use of an initial leadless pacing strategy. There are limited data on extraction of leadless pacemakers. Although the long-term sequelae of retained expired leadless pacemakers in humans are unknown, it is likely that avoidance of retained transvenous pacing leads or extraction of transvenous pacing leads in young patients without an ongoing indication for pacing will be beneficial. Even if future device re-implantation is indicated, it is difficult to predict the nature of CIED that will be viable therapeutic options in 10 years' time.

4.1. Study limitations

This is a multi-centre, observational study and can only describe a practice in a highly selected population within a single country. Wider generalisability is challenging but the observations of this study justify a well conducted prospective randomised study of the of leadless pacemaker implantation in patients with cardioinhibitory vasovagal syncope. The follow up of patients in this study is relatively short at 404 $\pm$ 237 days (range 63–928 days). However, Table 1 demonstrates that the selected population had a high rate of syncopal episodes that would justify clinical interpretation during the follow up period.

5. Conclusions

This observational study suggests that the single chamber leadless pacemaker implantation may be a reasonable clinical option in a highly selected group of patients with profound bradycardia associated with cardioinhibitory vasovagal syncope. This study has shown that the Micra TPS can be implanted effectively and safely with a high level of symptom improvement at early follow up.

Conflicts of interest

PRR has received honoraria from Medtronic for advisory board and speaking (not related to this manuscript).

CP has received honoraria from Medtronic for advisory board and speaking (not related to this manuscript).

CAR receives research funding from Medtronic.

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