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CLINICAL TRIAL PROTOCOL

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Placement Of Cardiac PacemaKEr Trial (POCKET) – rationale and design: a randomized controlled trial

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ABSTRACT

Background: A pacemaker system consists of one or two leads connected to a device that is implanted into a pocket formed just below the collarbone. This pocket is typically subcutaneous, that is, located just above the pectoral fascia. Even though the size of pacemakers has decreased markedly, complications due to superficial implants do occur. An alternative technique would be intramuscular placement of the pacemaker device, but there are no randomized controlled trials (RCTs) to support this approach, which is the rationale for the Placement Of Cardiac PacemaKEr Trial (POCKET). The aim is to study if intramuscular is superior to subcutaneous placement of a pacemaker pocket.

Methods: In October 2016, we started to enroll 200 consecutive patients with an indication for bradycardia pacemaker implantation. Patients are randomized to random block sizes, stratified by age group (cut-off: 65 years) and sex, and then randomized to either subcutaneous or intramuscular implant. A concealed allocation procedure is employed, using sequentially numbered, sealed envelopes. Pocket site is blinded to the patient and in all subsequent care. The primary endpoint is patient overall satisfaction with the pocket location at 24 months as measured using a visual analog scale (VAS) 0-10. Secondary endpoints are: complications, patient-reported satisfaction at 1, 12, and 24 months (overall satisfaction, pain, discomfort, degree of unsightly appearance, movement problems, and sleep problems due to device).

Conclusions: POCKET is a prospective interventional RCT designed to evaluate if intramuscular is superior to subcutaneous placement of a bradycardia pacemaker during a two-year follow-up.

Keywords: Arrhythmia, Complication, Pacemaker, Pocket, Randomized controlled trial

Introduction

Implantation of a cardiac pacemaker may be indicated in patients with a second- or third-degree atrioventricular block, significant sinus node dysfunction, tachycardia-bradycardia syndrome, bundle branch block with syncope, and in certain disease states, according to current guidelines (1). Annually, around 691 pacemakers per million inhabitants are implanted in Sweden (2). In the 16 Western European countries, there was a steady increase in implants from 2005, which plateaued in 2009 with 928 units implanted per million inhabitants. The rate of implanted units range from 607 per million in Ireland to 1291 per million in Germany, with an average of 938 throughout Western Europe in 2011 (1).

A bradycardia pacemaker system consists of one or two leads connected to a device that is implanted below the collarbone (3, 4). Vessel access is typically gained on the left side through the cephalic, axillary, or subclavian vein. The pacemaker device is typically inserted into a pocket just above the pectoral fascia (subcutaneously). In very thin patients with little subcutaneous fat, an intramuscular pocket between the pectoral muscular layers may be used. Even though technological advances have decreased the size of pacemakers markedly over time, complications due to superficial implants do still occur (5, 6). Occasionally, the device erodes through the skin, necessitating complete extraction of the system (7). More frequently, patients may complain about the device being too prominent, which sometimes requires surgical repositioning (5, 6). The device may create discomfort, pain, and an unsightly appearance (5, 6). The lateral corner of the device may impede shoulder movement or impair sleep; leads can become tangled or wound up within the pocket (Twiddler's syndrome). Minor branches of the supraclavicular nerves may become damaged, resulting in pain or discomfort. When vessels from the subcutaneous adipose tissue are displaced or distorted, extensive and painful hematomas may result.

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The development of a large hematoma is a known risk for infection (8, 9). In some cases, perfusion in the area of the operation may decrease and the amount of fat covering the device may be reduced to an unanticipated extent. The change-out of a device due to battery depletion can remove even more surrounding tissue. An alternative approach is an intramuscular placement of the device (10, 11). This has been advocated by Kistler et al based on personal experience, but there are neither systematic observational studies nor randomized controlled studies to support this approach (6). To our knowledge, no randomized controlled trial has ever addressed the question about the optimal placement of a bradycardia pacemaker.

Therefore, this paper presents the rationale and design of POCKET (Placement Of Cardiac PacemaKEr Trial), which aims to compare patient satisfaction with intramuscular versus subcutaneous placement of a pacemaker pocket.

Methods

Setting

Consecutive patients with an indication for a bradycardia pacemaker have been included starting in October 2016 in Region Gävleborg, Sweden. All implants are performed at Kardiologiskt Interventionscentrum in Gävle with an annual volume of 460 device procedures. Four experienced operators, all cardiologists, enroll patients into the study and perform the implants.

Inclusion and exclusion

Patients, aged ≥18 years, with an indication for a bradycardia pacemaker (DDDR or VVIR) are eligible for the study. Inclusion is restricted to *de novo* bradycardia pacemaker implants and excludes other devices (cardiac resynchronization therapy devices and implantable cardioverter-defibrillators) or device revisions (pacemaker or other devices). Exclusion criteria are severe cognitive impairment, drug addiction, a postal address other than Region Gävleborg at time of implant or other reasons that would prevent patients from being able to participate in follow-up at the clinic. Patients with a malignancy in the last five years (except basal-cell carcinoma) may have impaired healing and shorter life expectancy and are thus excluded from the study. Finally, patients who are extremely thin and deemed to need an intramuscular implant can be excluded from the study by the operator before enrollment.

Ethics and registration

The Regional Ethical Committee in Uppsala approved the study (protocol number 2016/371), which is conducted in compliance with the Declaration of Helsinki (12).

In order to declare the study protocol, including variables and pre-specified research questions, the study was registered at Clinical Trial Registration NCT02931760 and approved 11th of October 2016. Members of the research team all follow Guideline for Good Clinical Practice (13). Each patient is informed about the study in both oral and written form by the study physician and included after written consent.

Surgical procedure

The implantation procedure and vascular access are performed based on the preference of each operator. The pocket is created by blunt dissection and requires adequate local anesthesia. Typically, the patient is administered diazepam 5 mg preoperatively and then given local infiltrative anesthetics. Following surgery, paracetamol (acetaminophen) is recommended to control pain. The choice of pacemaker and lead(s) is made preoperatively before the patient's group allocation is revealed. The pacemaker systems available are either the Assurity™ pacemaker and Tenril™/Tendril MRI™ leads (St. Jude Medical, St. Paul, MN) or Proponent EL MRI™ and Ingevity MRI™ leads (Boston Scientific, Marlborough, MA).

Randomization

Randomization of the group allocation sequence was performed in permutated blocks with random block sizes, using stratification based on age (≤65 years and >65 years) and sex (female, male), creating four strata. Consecutive group allocations are stored in sealed opaque envelopes. The randomization was performed by a statistician with no involvement in the clinical work; patients' group allocations are revealed to the implanting physician by the assistant nurse at the start of the surgical procedure.

Power analysis

A power analysis based on expectations and clinical experience of the research group was performed. Figure 1 shows two hypothetical truncated lognormal distributions of patient overall satisfaction with the pacemaker, where median overall satisfaction of the intramuscular and the subcutaneous group are assumed to be 2.4 and 4, respectively. Monte Carlo simulations from these distributions showed that a total of 200 patients, 100 in each arm, would yield a statistical power of 90% for Mann-Whitney *U*-test at a significance level of 0.05.

In total, 200 consecutive patients with a bradycardia pacemaker indication are expected to be randomized in the study (100 patients in each arm, intramuscular vs. subcutaneous). In Region Gävleborg, the annual primary implant volume of bradycardia pacemakers is approximately 200.

Statistics

Frequencies, percentages, means, and percentiles describe numeric data. Continuous variables are summarized as means, standard deviations (SDs), and percentiles, and compared using *t*-tests; the chi-squared test is used for categorical variables. The Mann-Whitney *U*-test will be used for group comparisons of the VAS-scale results. For the test of changes in VAS estimations between 1, 12, and 24 months, pair-wise Wilcoxon signed-rank test is used.

A two-sided p value of <0.05 is considered statistically significant. The database in Excel 2010 (Microsoft Corporation, Redmond, WA) will import into SPSS version 22 (IBM, Armonk, NY).

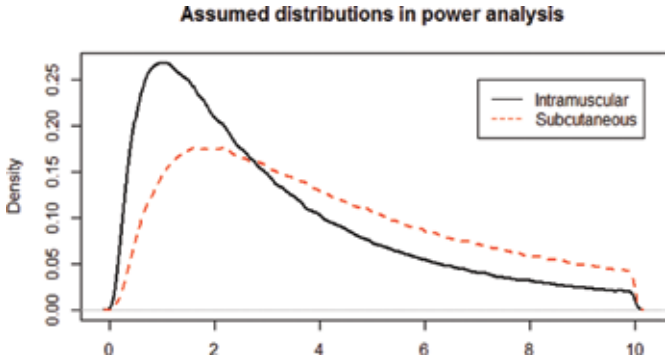

Fig. 1 - Assumed distributions of patient overall satisfaction in the power analysis, as measured by a visual analogue scale (VAS) where 0 means very satisfied and 10 means very dissatisfied. The intramuscular group is assumed to follow a lognormal distribution with mean 1.5 and standard deviation of 1 on the logarithmic scale. The subcutaneous patients are assumed to follow a lognormal distribution with mean 1.5 and standard deviation of 1 on the logarithmic scale.

Variables

Patient characteristics at enrollment, periprocedural variables and outcome variables at follow-up are presented in Table I.

Outcome and follow-up

Patients will be evaluated by a pacemaker nurse specialist at 1, 12, and 24 months. During these three clinical visits, a questionnaire will be distributed (see supplementary material available online at www.heart-int.com). The questionnaire asks patients to estimate their satisfaction with the device on a VAS scale (0-10) considering the following aspects: overall satisfaction, chronic pain, discomfort, degree of unsightly appearance, limited movement due to device, and sleep problems due to device. At 24 months, patients are asked to guess if the device was implanted in an intramuscular or subcutaneous pocket in order to validate the overall degree of patient blinding. The pacemaker nurse's evaluation of the unsightly appearance of the pocket (0-10, 10 worst) is blinded to the patient.

Certain complications might necessitate another surgery: pocket revision, lead dislodgment, hematoma requiring surgery, infection (local, systemic), pneumothorax, pericardial effusion requiring drainage, and other.

The questionnaire

We developed a questionnaire to assess the patients' pacemaker experience with a special emphasis on the pocket. The pacemaker-related questions were based on input from expert discussions with cardiologists and pacemaker-nurses experienced in the follow-up of pacemaker patients. The questionnaire was tested on lay people for language clarity and layout. It was decided to use a paper-version for the convenience of the patients evaluated. The questionnaire can be downloaded as supplementary material from www.heart-int.com.

TABLE I - Variables with regard to clinical characteristics, medication before and during implant, and surgical procedure

Patient characteristics
Age, mean (SD)
Male sex (yes/no)
Height (cm)
Weight (kg)
Coronary artery disease (yes/no)
Previous open heart surgery (no/yes)
Diabetes (0 = no, 1 = yes, insulin, 2 = yes, oral medication)
Kidney disease (yes/no)
Smoking history (current/ex-smoker/never smoker)
Medication before implant
Acetylsalicylic acid (yes/no)
Clopidogrel (yes/no)
Ticagrelor (yes/no)
Novel oral anticoagulant (yes/no)
Warfarin (yes/no)
Low-molecular weight heparin (yes/no)
Paracetamol (acetaminophen) (yes/no)
Nonsteroidal anti-inflammatory drugs (yes/no)
Opioid (yes/no)
Selective serotonin reuptake inhibitors (yes/no)
Sleeping pills (yes/no)
Other psychoactive drugs (yes/no)
Corticosteroids (yes/no)
Immunomodulation drugs (other than steroids) (yes/no)
Medication perioperatively
Paracetamol (acetaminophen) (0 = no, 1 = yes, dosage)
Opioid (0 = no, 1 = yes, dosage)
Diazepam (0 = no, 1 = yes, dosage)
Alfentanil (0 = no, 1 = yes, dosage)
Other analgesic (specify) (0 = no, 1 = yes, dosage)
Procedure variables
Vascular access (subclavian/axillaris/cephalic)
VVIR/DDDR
Fluoroscopy time (min)
Fluoroscopy (dosage)
Device brand/name
Device lead (atrium) brand/name
Device lead (ventricle) brand/name
Indication (sick sinus syndrome/atrioventricular-block/atrial fibrillation with tachycardia/bradycardia or solely bradycardia/other)

SD = standard deviation.

Discussion

Implantation of a permanent pacemaker is a common procedure and represents lifelong therapy. This implies that potentially chronic problems need to be considered in addition to procedural complications. The pacemaker device has undergone remarkable technological advancements and its weight and footprint have decreased drastically. Those relatively rare device recalls notwithstanding, most pacemakers provide reliable pacing support for a decade or more before the device needs to be replaced (14). Since many pacemaker patients are geriatric with comorbid conditions at implant, they may die before the device requires replacement (15). In those instances when long-term pacemaker failure occurs, it is often related to lead problems (typically involving either the wire or the insulation), and there can be tissue damage at the lead interface (16). Although national pacemaker registries report technical data about device system and complications, actual complication rates may be under-reported (5). Complications necessitating surgical intervention can be perceived as problematic by the patient, although they can usually be handled without long-term effects. Clearly, device-pocket-related problems may be troublesome for longer periods of time, which may affect patients both physically and emotionally. While pacemakers are usually inserted subcutaneously, intramuscular placement may offer advantages. To handle confounding factors, the RCT is an ideal design to address the question as to whether one approach is superior to the other with respect to different outcome measurements, including possible predictors thereof (17, 18).

Taking into account the potential global burden of pacemaker-related problems, the surgical approach to the pacemaker pocket needs to be evaluated. A better understanding of the optimal approach (subcutaneous vs. intramuscular) and its relationship to outcomes may result in improved long-term satisfaction with pacemaker therapy and might reduce the need for pocket revisions.

Strengths and weaknesses

This prospective RCT will elucidate whether an intramuscular or subcutaneous pacemaker pocket is preferred by patients and how its appearance is visually judged by a healthcare provider. The sample size has the power to answer the research question about overall satisfaction over the course of a two-year follow-up period. The two-year study duration does preclude explant due to elective replacement and very long follow-up periods.

Conclusion

POCKET is a prospective interventional RCT designed to evaluate if intramuscular pocket placement of a bradycardia pacemaker is superior to subcutaneous placement over a two-year follow-up.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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