Centre for Reviews and Dissemination

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To randomise or not to randomise: a matter of perspective?

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Introduction

Evidence from case series is rarely considered to be of value in assessing efficacy since any observed improvement in patient outcomes could be attributed to factors other than the effects of the intervention. However, in certain circumstances, could early evidence of efficacy from case series be so convincing as to jeopardise the equipoise required to undertake an ethical randomised study?

We present the case of a systematic review of radiofrequency catheter ablation (RFCA) for the treatment of atrial flutter.

Background

Atrial flutter (AFL) is an arrhythmia of the atria, which usually occurs in paroxysms lasting from a few seconds to several hours.[1] AFL is caused by a single electrical wave that circulates very rapidly in the atrium, about 300 times a minute, leading to a very fast, steady heartbeat. The most common symptoms are palpitations, dyspnoea, chest discomfort, dizziness and weakness.[1]

Curative percutaneous catheter ablation is a relatively new, invasive technique for the treatment of cardiac arrhythmias. The most well-established approach involves the percutaneous insertion of catheters which are guided by fluoroscopy to the heart. Ablation for atrial flutter is now well understood with defined targets for ablation of the arrhythmia substrate.[2]

Methods

A systematic review of radiofrequency catheter ablation for typical atrial flutter was conducted.[3] The review included RCTs (n>20), non-randomised controlled studies (n>100) and uncontrolled case series.

Why include case series?

- Literature dominated by uncontrolled case series
- Reviewers primarily considered only larger series to be of value for rarer complications/adverse events
- Clinical advisors convinced of near 100% effectiveness of RFCA on basis of small number of 'influential' case series
- Findings of any review excluding these case series "would not be taken seriously" by clinicians

Results

See Table 1.

Discussion

Why case series data might militate against a future RCT of RFCA

It could be argued that this intervention is a special case: RFCA is 'curative', the alternatives are not. The associations seen in case series between the direct effect of ablation on the cardiac muscle substrate and the alleviation of flutter imply causation. The results achieved with catheter ablation in these case series mean that the point of equipoise required for ethical randomisation has already passed.

Role of case series evidence in health technology assessments

If case series predominate and are influential, then they need to be acknowledged, if only to make explicit their limitations. These limitations must not be ignored: publication bias, pioneer bias; and poor reporting – relevant clinical and methodological details are frequently absent.

If the inclusion of case series is considered, the practicalities must be considered:

- The time required to screen, extract a potentially large number of small series.
- The difficulties of validity assessment
- Decisions about inclusion thresholds
- When to stop – adding weight or diminishing returns?

Table 1. Details of the two RCTs and 23 case series included in the review

	RCTs		Case series
	Da Costa[4]	Natale[5]	Feld,[6] Calkins,[7] Gilligan[8]
Number of patients	n=103	n=61	n=4,238
Comparator	Electrical cardioversion followed by amiodarone therapy	Antiarrhythmic drug therapy	None
Freedom from flutter at follow-up	RR 1.36 (95% CI: 1.13, 1.64)	RR 14.03 (95% CI: 3.67, 53.7)	68%-98%
Freedom from flutter at 12 months	Not reported	Not reported	Data from 3 cases series (n=354)[5-7] 72% to 95%; weighted mean 88% (95% CI: 85%, 92%)
Limitations	• Both favoured RFCA, but very different estimates • Neither provided data on important outcome of freedom from flutter at 12 months • Different populations, • Different comparators groups • Unusually strict monitoring of arrhythmia in Natale trial[4] • Inconsistent findings on occurrence of AF • Existing randomised evidence extremely limited; several important outstanding uncertainties.		• Complications and adverse events uncommon • Inconsistency in post-procedural drug treatment, where reported • Potential 'double counting' of patients could not be excluded • Case series evidence is partial and biased • Publication bias • 'Pioneer bias' • Represents the best that can be achieved, rather than what is likely.

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This poster is based on research commissioned and funded by the NIHR Health Technology Assessment Programme (Project number: 06/13/01). The views expressed in this poster are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.