Microwave **E**ndometrial **A**blation versus **T**hermal **Ball**oon Endometrial Ablation (MEATBall); five year follow-up of a randomised controlled trial

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Abstract

Objective: to compare long-term outcomes following microwave endometrial ablation (MEA™) and thermal balloon ablation (TBall).

Design: follow up of a prospective, double blind randomised controlled trial at five years

Setting: teaching hospital in UK

Population: 320 women eligible for and requesting endometrial ablation

Methods:.[1]. Eligible women were randomised in a 1:1 ratio to undergo microwave or thermal balloon ablation. Postal questionnaires were sent to participants at a minimum of five years post operatively to determine satisfaction with outcome, menstrual status, bleeding scores and quality of life measurement. Subsequent surgery was ascertained from the women and the hospital operative database.

Main Outcome Measures: the primary outcome measure was overall satisfaction with treatment. Secondary outcomes included evaluation of menstrual loss, change in quality of life scores and subsequent surgery

Results: of the women originally randomised 217/314 (69.1%) returned questionnaires. Non-responders were assumed to be treatment failures for data analysis. The primary outcome of satisfaction was similar in both groups (58% for MEA^{TM} versus 53% for TBall, difference 5% (95% CI -6% to 16%)). Amenorrhoea rates were high following both techniques (51% versus 45%, difference 6% (95% CI -5% to 17%)). There was no significant difference in the hysterectomy rates between the two arms (9% versus 7%, difference 2% (95% CI -5% to 9%)).

Conclusions: at five years post treatment there are no significant clinical differences in patient satisfaction, menstrual status, quality of life scores or hysterectomy rates between MEA^{TM} and Thermachoice 3, thermal balloon ablation.

Keywords: Heavy menstrual bleeding, endometrial ablation, randomised controlled trial, long term follow up.

Trial registration:- http://controlled-trials.com/ ISRCTN 28184453

Introduction

Few randomised trials comparing surgical interventions measure follow up of outcomes in the long term. This can lead to difficulty in establishing the true impact and worth of an intervention. Endometrial ablation is a well-researched treatment for heavy menstrual loss and a number of second generation ablative techniques are recommended by NICE for the treatment of this complaint.[1] Few of the commercially available second generation techniques available have been evaluated in independent, adequately powered randomised trials with meaningful clinical and economic outcomes. Fewer still have undergone scrutiny in the long term.

Both Microwave endometrial ablation (MEA™)[2] and Thermal Balloon (TBall)[3] endometrial ablation are NICE recommended ablative techniques[1]. Microwave ablation, although recently removed from the UK market, has been independently evaluated in randomised trials with published follow up data at five[4] and ten[5] years. This made it the ideal comparator for Thermachoice 3™, thermal balloon which required re-evaluation as data in the literature pertained to an earlier, perhaps less effective versions of the balloon.[3,6] The original results from this cohort demonstrated that the microwave technique was quicker to perform and required less post-operative analgesia, but clinical outcomes at one year were comparable between the two techniques[7]. Microwave ablation was likely to be more cost effective at one year.[8]

In this paper we will present and discuss the outcomes at five years post treatment.

Methods

Full methodological and operative details can be found in the original paper.[7] The trial protocol is held by the funding body:- Chief Scientist Office, Scottish Government Health Directorates, ref CZH/4/117 and also by Health Services Research Unit, Aberdeen University. Local ethics committee approval was obtained for long-term follow-up at five years. Women complaining of heavy menstrual loss that desired and were eligible for endometrial ablation were recruited from the gynaecology department of Aberdeen Royal Infirmary between January 2003 and January 2005. Eligible patients were pre-menopausal, had completed their families, and gave their informed consent to participate within the trial. They had a uterine cavity length of < 12 cms, no histopathological abnormalities of the endometrium and fibroids if present were < 3cms and not obstructing the uterine cavity. The patients did not routinely undergo hysteroscopy prior to recruitment unless an abnormality was identified on transvaginal ultrasound scan. Women with previous caesarean section were included if scar thickness was <10mm.

Sample size

The original power study determined that 290 recruits were required to give an 80% power of demonstrating a 12% difference in those totally or generally satisfied with treatment. Additionally this number gives 80% power to detect a 15% difference in amenorrhoea rates (2P<0.05) and 90% power to detect a difference in menstrual scores (pictorial assessment blood loss chart, PBLAC) of 10, again with significance at the 5% level.

Three hundred and twenty recruits were randomised in a ratio of 1:1 to the MEA^{TM} and TBall arms of the study after obtaining informed consent. Six post randomisation exclusions occurred hence 314 women were treated in the trial. The mode of treatment was not revealed to the women, or the statistician.

Objective/outcomes

Postal questionnaires were sent at a minimum of five years after the original procedure. The primary objective of this study was to detect any difference in patient satisfaction between the two treatments. Secondary outcomes were menstrual status, changes in health-related quality of life [Short Form-12 (SF12) and EQ-5D] and any further surgery received. The questionnaire was sent to the participant. Those who did not respond were sent a postal reminder and, finally, a telephone call to ascertain whether they wished to participate. Data were entered into an SPSS (version 16, SPSS Inc., Chicago, IL, USA) database. Subsequent operations were established from the questionnaires and from the hospital database for all recruited women.

Statistical Analysis

All statistical analyses were carried out using SPSS v20 (IBM Inc, Armonk, NY, USA) unless otherwise stated. Intention-to-treat analysis was used. Differences in proportions and 95% confidence intervals were calculated in Excel using Newcombe's method.[9] Bleeding scores, pain scores and health-related quality of life measures (EQ-5D and SF-12 scores) were compared using a linear regression model to estimate the mean difference between groups after adjusting for baseline values.[10] Changes in quality of life from baseline were compared using paired t-tests. Women who had had a hysterectomy at follow-up were included in all comparisons. Non-responders were assigned a negative response (that is presumed dissatisfaction) when calculating proportions for satisfaction with the procedure and willingness to recommend to a friend. The CONSORT scheme of reporting was adhered to.[11,12,13]

Results

Two hundred and seventeen of the 314 (69.1%) women originally randomised returned completed questionnaires. The baseline characteristics of the 217 women successfully followed up were very similar to those of the total trial group and not statistically significantly different between either. Mean age at follow up was 48 (SD 5.2) in both arms. The flow of participants through the trial is outlined in figure 1.

Participants

Baseline characteristics of those returning questionnaires at five years are shown in Table 1 and are comparable

There were no statistically significant differences between the two groups with respect to menstrual symptoms (Table 2). This was also the case for the number of women totally or generally satisfied with treatment MEA™ 91/157 (58.0%) and TBall 83/157 (52.9%); difference (95% CI) 5.1 (-5.9, 16.1) and those who would recommend the treatment to a friend, MEA™ 104/157 (66.2%), TBall 89 /157 (56.7%); difference (95% CI) 9.6 (-1.2, 20.3)

The amenorrhoea rates are high and comparable for both modalities for those returning questionnaires. Even if all non-responders are assumed to be failures and still bleeding (except for non-responders known to have had a hysterectomy), then this gives intention to treat amenorrhoea rates of 51% (80/157) for MEA™ and 45% (70/157) for TBall (risk difference 6.4%, 95% CI: -4.7% to 17.4%).

There were no significant differences in quality of life (mean (SD)between groups for SF-12 (physical functioning) - MEA™ 51.1% (10.1),TBall 52.6 %(8.6); difference (95% CI -0.9 (-3.4, 1.6), SF-12 (mental functioning) - MEA™49.1%(9.4),TBall 49.4 %(10.1); difference (95% CI 0.2 ((-2.4, 2.8) or EQ-5D - MEA™ 0.83 (0.26),TBall 0.83 (0.26); difference (95% CI) 0.01 (-0.06, 0.07). SF12 demonstrated significant improvement from the baseline quality of life scores for both categories ($p<0.01$ for both physical and mental functioning) and this was not altered significantly from the 12-month follow-up (figure 2).

Subsequent treatment received or continued at five years

At a minimum of five years following treatment, the majority of women had not required further gynaecological surgery. There was no statistically significant difference in women undergoing hysterectomy, with ten women (8.8%) in the MEA™ arm and seven (6.8%) in the TBall (difference of 2.0%, 95% CI: -5.1% to 9.1%). Following MEA™, of the ten hysterectomies, four were for heavy bleeding, one for cyclical pain, four for pain and

bleeding and one for prolapse In the TBall arm, one hysterectomy was for pain alone, one for heavy bleeding, four for combined pain and bleeding and one for fibroid pressure symptoms. There was one repeat ablation in the TBall arm and none in the MEA^{TM} arm.

Discussion

Main Findings: The two trial arms remained balanced at the five year follow-up despite the dropout of recruits. Those women who did not respond were analysed as treatment failures for the principal outcome measure which gives the impression of deterioration in satisfaction with treatment over time. Whilst this is the accepted method of analysis it does not lend itself to comparison with results from other trials that have not used this method.

It is more likely however given the low hysterectomy rates that satisfaction rates are higher and are likely to lie between the rates ascertained by ITT analysis and rates reported by responders (totally or generally satisfied, 91/111, 82%, for MEA^{TM} versus 83/99, 84%, for TBall). The same argument also applies to amenorrhoea rates which by ITT analysis, for MEA^{TM}, assuming all non-responders are still bleeding is 51%, but 68% for responders. For TBall the corresponding rates are 45% and 61%.

Whilst no statistically significant differences could be demonstrated between the two treatments it is important to point out that with only 219 responders there was not adequate power to detect smaller perhaps meaningful differences in clinical outcomes between the two ablative techniques. Given that hysterectomy rates were low and comparable it does support the fact that there is little difference in outcome in the long term. Subsequent operations were determined not only from the patient questionnaire but also from the hospital database. As fewer than 10% of women had left the region and this is the only hospital supplying gynaecological care, it is likely that these figures are representative of the original recruited cohort. Hysterectomy rates of around 16% have been previously reported for follow up after five years for MEA^{TM}.[5]

Women recruited had a subjective complaint of heavy bleeding and formal menstrual blood loss measurements were not performed. The majority of woman had a preoperative ultrasound and endometrial biopsy but hysteroscopy was not performed preoperatively unless clinically indicated. All cases underwent hysteroscopy immediately prior to insertion of the ablative device to ensure no false passage or perforation. This mirrors recommended clinical practice, thereby increasing the generalisibility of the results. Also, the procedures were all undertaken by a trainee and not a consultant hysteroscopic surgeon with extensive experience of both techniques. It is important to reiterate that during the treatment phase

with the thermal balloon that the pressure was maintained at between 160 -180 mmHg by injecting further dextrose solution during the treatment phase. This, along with the active impellor in Thermachoice 3™, circulating the heated fluid, may account for the better results achieved by the balloon in this study when compared to previous trials.

Heavy menstrual loss is known to cause significant deterioration in quality of life, and SF-12 and EQ-5D were used although neither has been formally validated for menstrual disorders. Neither is a condition specific QOL tool but SF-36 has been used in the past to demonstrate reduction in generic QOL values for menorrhagia[14] and also shown return to normative values following endometrial ablation for heavy menstrual loss.[3,15] Importantly normative values for the healthy female population are known for SF-12.[16] EQ-5D is used for economic calculations which were not repeated at five year follow up. The physical component of the SF-12 score demonstrated improved scores from baseline for responders and maintained at normative levels. The mental component followed a similar pattern, with an overall improvement for both arms at 12 months, maintained at the normative values (49.2) by five years. Importantly, no significant difference was noted between the groups.

Strengths and Limitations

The strength of this trial is that it was an independent, government funded, double blind randomised controlled trial and hence bias is minimised. The procedures were performed on patients with a generic complaint of heavy menstrual loss where the patients had decided upon endometrial ablation as treatment. It is entirely possible that some would not have true menorrhagia, but this reflects standard practice in the UK and through randomisation prognostic factors should be equalised. There were limited pre-selection criteria with cavities up to 12 cms treated and no exclusion of smaller fibroids which enhances generalisibility as does the fact that the procedures were all performed by a trainee.

It is unfortunate that the numbers returning questionnaires failed to meet the original power study requirements, but the number of hysterectomies performed at five years was comparable and low at under 10% in each arm, which is reassuring. An operating pressure of between 160 and 180mmHg was maintained throughout the TBall treatment phase which was not the manufacturer's recommendation. A failure to do this may lead to inferior results

Long-term follow up of interventional randomised trials are rare but offer invaluable information for the health care purchaser and potential patient. Five year follow up data are available for Novasure[6], Microwave ablation[4] and now Thermachoice 3 and are highly informative, particularly as health related quality of life data are also available in addition to

menstrual outcomes. Ten year data are also available for transcervical resection of the endometrium, microwave ablation[5] and Novasure[17], and whilst it is commendable that these data are available, it perhaps offers principally reassurance of endometrial ablation's long term safety and efficacy rather than the ability to discriminate between different techniques. This is because almost 50% of the recruits from the trials are menopausal by this stage, making menstrual status a meaningless outcome[18], and almost all repeat surgeries, including hysterectomies for treatment failure occur within the first three years of endometrial ablation.[19]

Interpretation

This trial confirms that Thermachoice 3™ achieves better results than earlier models of this balloon device[2,6]. It is simple to use requiring minimal dilatation of the cervix and has been successfully used under local anaesthetic. Whilst treatment times are slower than MEA™ and short term costs slightly higher, clinical and QOL outcomes are comparable with low hysterectomy rates. These results should be used and quoted when critically assessing Thermachoice 3™ rather than trials involving previous models which are now obsolete

Conclusion

This trial confirms that Thermachoice 3™ endometrial ablation achieves comparable long-term results to Microwave Endometrial Ablation, which is one of the most robustly evaluated second generation devices. Since MEA™ has been removed from the market in the UK by a competing company, who purchased the distribution rights, it is important to prove that another method of ablation achieves encouraging long term results. These results enhance choice for the gynaecologist and reduce the likelihood of a monopoly situation arising for the supply of endometrial ablation technology.

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Disclosure of interest

KC has received financial support to attend conferences from Microsulis PLC and Ethicon Women's Health and Urology.

Contribution to authorship

AS recruited and undertook follow-up of all patients for this study, input the data and wrote the manuscript.
AE undertook the statistical analysis and edited the manuscript.
KC designed the trial and methodology, supervised the original procedures, co-wrote the manuscript and is guarantor.

Details of ethics approval

Grampian Research Ethics Committee No. 00/0023.

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