The levonorgestrel intrauterine system: a simple and effective alternative for the management of menorrhagia?

Trial: Hurskainen R, Teperi J, Rissanen P, et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. *Lancet* 2001; 357: 273-277.

Question

What is the effectiveness of the levonorgestrel-releasing intrauterine system (IUS) compared with hysterectomy for the management of women with menorrhagia?

Trial details

Design: Randomised controlled trial, double-blind.

Setting: Five university hospitals in Finland.

Patients: Premenopausal women aged 35–49 years, with menorrhagia and no major gynaecological abnormalities were recruited to the study. Exclusion criteria were submucous fibroids, endometrial polyps, ovarian tumours or masses greater than 5 cm, cervical disease, urinary and bowel symptoms or pain resulting from large fibroids, lack of indication for hysterectomy, history of cancer, menopause, severe depression, metrorrhagia as a main complaint, previous treatment failure with levonorgestrel-releasing intrauterine system (IUS), severe acne, and uterine malformation.

Interventions: 119 patients were allocated to the IUS group and 117 were allocated to the hysterectomy (any method) group. Hysteroscopy was performed before randomisation only if clinically indicated.

Main outcome measures: Quality-of-life measures (including health-related, measured on a scale of 0–1 with the EuroQuol [EQ-5D] instrument), anxiety measures, resource use, menstrual blood loss, haematological indices.

Main results: In the IUS group, 24 women (20%) had had a hysterectomy and 81 (68%) continued to use the system at 12 months. Of the women assigned to the hysterectomy group, 107 underwent the operation (5 cancelled before surgery and 5 withdrew from the study group). Health-related quality of life improved significantly in both the IUS and hysterectomy groups (change in EQ-5D, 0.10 [95% CI, 0.06–0.14] in both groups), as did other indices of psychological wellbeing. There were no significant differences between the treatment groups except that the hysterectomy group had less pain than the IUS group at 12 months. Overall costs were about three times higher for the hysterectomy group than for the IUS group.

Conclusion: The significant improvement in health-related quality of life highlights the importance of treating menorrhagia. During the first year the levonorgestrel-releasing IUS was a cost-effective alternative to hysterectomy for treating this disorder.

Commentary

Rationale for the trial

International hysterectomy rates vary considerably; by the age of 60 years, a third of women in the United States will have undergone a hysterectomy and menorrhagia is one of the most common indications.[1] Satisfaction rates with hysterectomy have been consistently reported as 95% or higher.[2] Quality-of-life measures have also been reported to improve following hysterectomy.[3] It is perceived as a permanent solution to the problem of menorrhagia. However, short-term complications following hysterectomy are not uncommon; recent studies report rates of moderately severe complications of 16% while in hospital.[4] The IUS is an intrauterine system that can be sited during a clinic visit and its duration of action is five years. The IUS contains 52 mg of levonorgestrel which is released through a rate-limiting membrane (20 μg/24 h), resulting in endometrial shrinkage and a reduction in menstrual bleeding. As the IUS has been proposed as an alternative to hysterectomy, it was important to establish if improvements in quality of life are reported with the IUS.

Trial methods

The trial was well conducted and reported according to published guidelines.[5] Patients were allocated to the two treatment groups without the prior knowledge of the investigators, although blinding of patients and investigators was not possible in the follow-up period. An instrument measuring disease-specific QOL may have made QOL differences between the two groups more apparent; however, no disease-specific QOL measure exists. The completeness of follow-up was 97% (228/236), and an intention-to-treat analysis was done. In the IUS group, a third of devices were removed and 20% of the women underwent hysterectomy during the first year of follow-up. Reasons for removal included spotting and other bleeding disorders. This removal rate is higher than the two smaller trials comparing IUS with endometrial resection, which report a 20% removal rate, possibly reflecting the severity of symptoms among women who seek hysterectomy instead of endometrial resection.[6,7] The use of health-related quality of life (EuroQol) and other measures of psychological wellbeing was appropriate, and the measures had been validated in the population before the study. Not all women referred for menorrhagia were included. Most of those not participating either did not want to take part or did not meet the eligibility criteria for either of the two treatments. Therefore, it is likely that the study group was representative of women who were candidates for both treatments, and the results can be generalised to the population of women with menorrhagia. The planned five-year follow-up will be welcome.

New information

Two small trials had previously reported that the IUS was an alternative to hysterectomy.[8] However, this large randomised trial has improved on those studies, as it included a wider range of outcomes, and shows that, after a year, no statistically significant differences were present between the treatment groups in terms of health status, health-related quality

of life, and psychological wellbeing. Cost-effectiveness data favour the IUS.

Implications for clinical practice

This study has shown that, in women with menorrhagia, there were no statistically significant differences between IUS and hysterectomy for the outcomes of quality of life and psychological wellbeing. The quality-of-life data show that the IUS scored as well at 12 months as hysterectomy in seven of the eight areas assessed, with the only difference between the groups being pain scores, despite a 66% reduction in the IUS group. The IUS is by no means the final answer to the problem of menorrhagia — a third of women had the device removed by one year because of bleeding problems. Costs to both the healthcare system and the patient were reduced with the use of the IUS, although these cost differences may reduce with time. The costs of hysterectomy may be higher because of the 30% complication rate reported in this study — similar rates have been reported by others.[4,9] This study provides convincing evidence that the IUS is an effective alternative for women with uncomplicated menorrhagia, and should be offered as a treatment choice.

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Managing the resource demands of a large sample size in clinical trials: can you succeed with fewer subjects?

Anthony C Keech and Val Gebski

IN PLANNING CLINICAL TRIALS, it is common to find that the calculated sample size[1] (Item 7 of the CONSORT checklist; Box 1) is too large for available resources. Strategies to determine whether the trial question(s) can be answered with fewer subjects are needed. These include:

- focusing on higher-risk subjects;
- using a run-in phase before randomisation;
- "expanding" the primary study endpoint; or
- running the trial for a longer period, with an event-based, rather than a calendar-based, stopping rule.

1: CONSORT checklist of items to include when reporting a trial[1]

Section and topic	Item no.	Descriptor
Methods Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules

Choosing subjects with higher risk

If the subjects in a trial have a very low risk of the condition that the intervention is hypothesised to prevent, the trial, regardless of sample size, will not prove the value or otherwise of the intervention. For example, in the "Finnish Businessmen's Study", the efficacy of a multifactorial risk-factor intervention to prevent cardiovascular death among middle-aged men could not be proven, as only five such deaths had accrued at the end of the scheduled follow-up.[2] The proof required from trials relies on demonstrable differences in event counts between the intervention and control groups, and whether this difference could reasonably have occurred by chance alone. It matters little how many subjects produced these event counts — the evidence rests in the main with the event counts themselves and the size of the difference between them.

Consequently, if the calculated sample size of a proposed clinical trial is larger than feasible, limiting the subjects to

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