Uterine artery embolization: Long term follow-up and implementation
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Summary, general discussion and conclusion
SUMMARY OF THE THESIS

This thesis aims to determine the position of uterine artery embolization (UAE) in the spectrum of treatments for symptomatic uterine fibroids and to stimulate its implementation into daily practice. To do this, firstly the following aspects of UAE were investigated: the long-term clinical results of UAE, the summary of the body of evidence on UAE in comparison to established surgery and to other/new minimally invasive alternatives, and finally the patients’ preferences on UAE and the methods of pain management with this procedure. Herewith the position of UAE in fibroid management was established. We concluded that UAE is a valuable alternative to hysterectomy of which all women with symptomatic uterine fibroids should be counseled. We also concluded that despite this evidence UAE was not applied widely in the Netherlands. To initiate its implementation we investigated the hampering factors for the application of UAE and acted on the results of this inquiry by integrating UAE in the national guideline on heavy menstrual bleeding (HMB), thus enabling its further introduction into standard clinical practice.

The above-mentioned course of actions as described in this thesis will be summarized in the next paragraphs. Thereafter the implications of this thesis will be mentioned together with an overall conclusion and indications for future research.

LONG-TERM RESULTS OF UAE

In chapter 2 we described the 5-year follow-up results of the EMMY (EMbolization versus hysterectoMY) trial, a randomized comparison between UAE and hysterectomy. Patients suffering from symptomatic fibroids who were eligible for hysterectomy were randomized 1:1 for either hysterectomy or UAE. Endpoints after 5 years were re-interventions, effect on menorrhagia, menopause, Health Related Quality of Life (HRQOL) and patients’ satisfaction. In the EMMY trial, 177 patients were randomly assigned UAE (n=88) or hysterectomy (n=89). Five years after successful UAE, 24.7% of the patients had undergone a hysterectomy because of insufficient improvement of symptoms. HRQOL measures improved significantly and remained equally stable in both groups. UAE had a positive effect both on urinary and defecation function. We concluded that UAE avoided hysterectomy in 3 out of 4 cases after 5 years of follow-up. Based on these outcomes, UAE is a good alternative to hysterectomy and patients should be counseled on the possibility of UAE.
SUMMARY OF EVIDENCE ON UAE

Chapter 3 contains a systematic review and meta-analysis on the existing evidence on short-, mid- and long-term results up to 5 years of UAE in comparison to surgery. Four RCTs with a total of 515 patients were included in the analysis. On the short-term, UAE showed fewer blood loss, shorter hospital stay and quicker resumption of work. Mid- and long-term results showed comparable HRQOL results and a higher re-intervention rate in the UAE group, while both groups were equally satisfied. We concluded that UAE has short-term advantages over surgery in terms of shorter hospital stay and quicker resumption of daily activities. On the mid- and long-term the benefits were similar, except for a higher re-intervention rate after UAE.

PATIENTS’ PREFERENCES

The effect of treatment preference and treatment allocation on HRQOL in patients in the EMMY trial was described in chapter 4. We invited 349 eligible patients for trial participation, of whom 177 women agreed to participate (the ‘randomized group’). Within the randomized-group patients were allocated UAE (n=88) or hysterectomy (n=89). The remaining 172 patients refused randomization and received the treatment of their preference (varying from hysterectomy to no treatment at all), of which 103 patients agreed to fill in questionnaires (the ‘preference group’). Patients’ treatment preferences and HRQOL were assessed at baseline and the patients were prospectively followed to evaluate HRQOL at 12 months after treatment. At baseline, most (65%) of the patients in the randomized group preferred UAE, while in the preference group most (58%) of the patients preferred hysterectomy. At 12 months there was no effect of having had the preferred treatment on HRQOL, neither in the randomized nor in the preference group. The randomized group improved significantly in both mental and physical health, compared with baseline. In the preference-group only mental health improved compared with baseline, while physical health did not improve significantly. We concluded that the pre-randomization preference for a specific treatment did not affect HRQOL. Trial participants improved better on physical HRQOL than women who refused to participate.

PAIN MANAGEMENT

In chapter 5 we compared the costs and effects of epidural analgesia (EDA) with those of patient controlled intravenous analgesia (PCA) for post-intervention pain relief in women
undergoing uterine artery embolization (UAE) for systematic uterine fibroids. We performed a cost-effectiveness analysis (CEA) based on data from the literature by constructing a decision tree. We found that six hours after the intervention the VAS (Visual Analogue Score) was 3.56 when using PCA and 2.0 when using EDA. The costs for pain relief in women undergoing UAE with PCA and EDA were €191 and €355, respectively. The costs for EDA to reduce the VAS-score 6 hours after the intervention with one point compared with PCA were €105, and €179 after 24 hours. The risk of having a complication was 2.45 times higher when using EDA. We concluded that EDA provides superior analgesia for post UAE pain at 6 and 24 hours, at the expense of higher costs and an increased risk of complications.

OTHER MINIMALLY INVASIVE OPTIONS FOR FIBROID THERAPY

In chapter 6 we reviewed the evidence on the many non-surgical and minimally invasive therapies for symptomatic uterine fibroids that were introduced in recent years. We summarized the effect on fibroid volume, menorrhagia, HRQOL, fertility and the risk of complications of these procedures. Laparoscopic or hysteroscopic myomectomy and uterine artery embolization (UAE) were the most widely studied and all showed significantly beneficial effects on menorrhagia and HRQOL, with a low incidence of complications. For those women wishing to retain their childbearing options, myomectomy was the best-studied intervention, which was specifically indicated in submucosal fibroids with subsequently beneficial effects on fertility. The use of UAE in fertile women has not been studied extensively, but evidence points towards an increase in pregnancy-related complications after UAE. Magnetic resonance-guided high-intensity focused ultrasound (MRgFUS), myolysis/ radiofrequency ablation (RFA) and laparoscopic or vaginal occlusion of uterine vessels (L/V-OUA) are newer interventions, for which no convincing evidence is available as yet. More evidence is required before their routine use in clinical practice can be justified.

IMPLEMENTATION OF UAE IN DAILY PRACTICE IN THE NETHERLANDS

Chapter 7 describes an inventory that aimed to find out why UAE was only marginally being applied in the Netherlands despite the available evidence on its effectiveness. The inventory tried to identify factors, which either restricted or facilitated the implementation of UAE. Gynecologists and interventional-radiologists in three hospitals in Amsterdam were
interviewed by means of questionnaires. One of these hospitals had ample experience in UAE for uterine fibroids, one hospital just started providing this treatment, and one hospital did not perform UAE. Also patients with symptomatic fibroids who were scheduled for either UAE or hysterectomy were interviewed about the counseling for UAE. The following obstacles in the implementation of UAE were found: lack of knowledge about UAE, absence of a multi-disciplinary protocol, and above all, the absence of UAE as one of the presented treatment options in the Dutch national guideline on the management of menorrhagia. Our recommendations for the implementation of UAE were: 1) adding UAE to the Dutch guideline for the management of menorrhagia with clearly defined indications and contraindications; 2) educating gynecologists about UAE; 3) composing a patient information leaflet and a website, and 4) arranging a protocol in a multidisciplinary team.

GUIDELINE ON HEAVY MENSTRUAL BLEEDING

Chapter 8 summarized the new Dutch national guideline on heavy menstrual bleeding to which UAE was added. The part on the (minimally invasive) treatment alternatives addresses the counseling of patients with symptomatic uterine fibroids:

- Discuss UAE as an alternative to hysterectomy in patients with fibroids and HMB.
- Up to 5 years after intervention HRQOL has been improved equal after hysterectomy and UAE, and patients are equally satisfied; UAE patients recover faster than hysterectomy patients and return to work earlier; 5 years after successful UAE there is a chance of about 75% that no hysterectomy will take place.
- Due to insufficient evidence on pregnancy after UAE, myomectomy is preferable in women with symptomatic fibroids who still wish to conceive.
- Perform preferably a hysteroscopic resection in symptomatic submucous myomas up to 4 cm in diameter.
- For MRgFUS, myolysis/ RFA and L/V-OUA more evidence is needed, and for this reason these therapies should be carried out in the context of clinical trials only.

GENERAL DISCUSSION

In recent years, several minimally invasive treatment options in the treatment of symptomatic uterine fibroids have been developed. One of these minimally invasive options is uterine artery embolization (UAE), which was introduced in 1995 by Ravina et al (1). In the following
years, four randomized comparisons with surgery/hysterectomy have been published, demonstrating the potential of UAE in fibroid therapy on the short-term as shown in the Cochrane review on this topic (2). One of these trials is the Dutch randomized EMMY (embolization versus hysterectomy) trial. Publications of this trial reported on the follow-up until 2 years after UAE and showed, similar to the other trials, a reduction of total length of hospital stay, quicker resumption of daily activities, more minor complications and similar major complications compared with hysterectomy (3,4,5). Health Related Quality of Life (HRQOL) and satisfaction on the short-term and after 2 years were comparable to hysterectomy (6). The 2-year cumulative costs of UAE were lower compared with hysterectomy (7).

Despite this evidence UAE was hardly performed in the Netherlands. One of the reasons for the limited implementation of UAE in clinical practice was the absence of evidence on long-term outcomes. The present study anticipated on this lack, by adding the long-term follow-up of the EMMY trial and by providing a systematic review and meta-analysis on the long-term follow-up outcomes of UAE compared with surgery. The 5-year follow-up of the EMMY trial showed that in the UAE group 83% of the women reported to be symptom free or to experience improvement of heavy menstrual bleeding (HMB) (8). The Scottish REST trial (Randomised controlled trial of Embolisation versus Surgical Treatment) also reported on 5-year follow up (9). Despite the improvement that most women experienced after UAE, both studies showed a significant re-intervention-rate in these women; 28% in the EMMY trial and 26% in the REST trial. While exploring this, we found that three-quarter of these re-interventions in the UAE group took place in the first 2 years of follow-up, which indicates that not undergoing a hysterectomy in the first 2 years after UAE might be a predictor for staying long-term hysterectomy-free (10). This is in accordance with other data (11). Despite these re-interventions, patients in both groups had similar HRQOL scores after 2 and after 5 years, were similarly satisfied and in both groups an equally high percentage would recommend the received treatment to a friend. It seems as though these re-interventions did not affect the HRQOL (6,8,12).

These results are solid and determine the place of UAE in fibroid management. The fact that UAE is not being offered to women as an alternative to surgery in daily practice, was judged as substandard care by our study-group. In the pilot implementation-study as described in this thesis we found that the main obstacle for implementation was the absence of UAE in the Dutch guideline on HMB (13).

We continued where many trials stop: by incorporating this new treatment in clinical practice by adding UAE to the national guideline. While rewriting the national guideline on HMB we also systematically searched the literature for other therapeutic options for fibroids, as discussed in the review on minimally invasive treatment of fibroids in chapter 6 (14). In this
review we concluded that laparoscopic/hysteroscopic myomectomy and UAE are the best-studied minimally invasive therapies for symptomatic uterine fibroids. Both show a significant reduction of HMB and an improvement in HRQOL. On other minimally invasive fibroid therapies as magnetic resonance-guided high-intensity focused ultrasound (MRgFUS), myolysis/radiofrequency ablation (RFA) and laparoscopic or vaginal occlusion of uterine vessels (L/V-OUA) more evidence is needed.

The new guideline on Heavy Menstrual Bleeding (HMB) advises to counsel patients with symptomatic uterine fibroids on UAE as an alternative to hysterectomy. Patients need to know that HRQOL improves equally after hysterectomy and UAE while patients are equally satisfied; UAE patients recover faster than hysterectomy patients and they go back to work earlier; 5 years after successful UAE there is a chance of about 75% that no hysterectomy will be needed. Due to insufficient evidence on pregnancy after UAE, myomectomy is preferable in women with symptomatic fibroids who still wish to conceive.

FUTURE RESEARCH

As a second step in the implementation-process, the use and compliance of the new guideline on HMB will be tested by the use of indicators, one of which deals with UAE. The embolization/hysterectomy-ratio in women with symptomatic uterine fibroids in Dutch hospitals may serve as a quality of care indicator. In hospitals without facilities for UAE the referral ratio may serve this goal. This implementation research will be carried out 2 years after the publication of the new guideline on HMB and is part of the so-called ‘circle of quality’ (‘kwaliteitscirkel’ in Dutch). This circle contains 4 steps; making a guideline, implementing this guideline, checking the compliance to this guideline with the use of indicators, and finally reinforce/innovate the guideline by updating it with new evidence.

Besides this, the role of UAE in the treatment of women with fibroids that have a wish to conceive in the future deserves to be investigated. Also, other minimally invasive alternatives in the treatment of symptomatic uterine fibroids as MRgFUS, myolysis and laparoscopic or vaginal occlusion of uterine vessels need to be more extensively researched or abolished.

CONCLUSION

In conclusion, this thesis investigated and summarized the long-term evidence on UAE, and attributed to the incorporation of UAE in the new Dutch guideline on heavy menstrual bleeding. The implementation of this new guideline will hopefully ensure that patients with
symptomatic uterine fibroids will be counseled for this minimally invasive option so that UAE has a solid place in the therapeutic arsenal for the treatment of symptomatic uterine fibroids in the Netherlands.

We feel that new techniques such as UAE are exciting and indicative of innovation in the field of fibroid management. However, sometimes new techniques find their way to daily practice without any solid evidence. The introduction course of UAE demonstrates how new techniques should be introduced: first getting an indication of its effectiveness in cohort series, then evaluating it in RCTs compared with the gold standard, followed by a solid long-term follow-up. Finally introduction in the national guideline and evaluation of its compliance is compulsory. This course of action leads to a high standard of care, which is accessible for all women and identical for everyone.
REFERENCES

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