The value of pre-operative treatment with GnRH analogues in women with submucous fibroids: a double-blind, placebo-controlled randomized trial†

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BACKGROUND: Submucous fibroids are common benign tumours responsible for menorrhagia, subfertility and miscarriage. They can be readily removed by hysteroscopic transcervical resection of myoma (TCRM). To facilitate resection, pre-operative GnRH analogues have been suggested, but the value of this treatment is uncertain. Our aim was to assess the value of pre-operative GnRH analogues for the resection of submucous fibroids.

METHODS: This was a prospective, double-blind, placebo-controlled, randomized trial. Women found to have submucous fibroids on three-dimensional saline infusion sonohysterography (3D SIS) were randomized to receive GnRH or placebo. Following treatment patients underwent TCRM by a single operator blinded to the group allocation. Women were followed up 6 weeks after their operation to ascertain resolution of symptoms. The primary outcome measure of the study was completeness of fibroid resection. Secondary outcome measures included the duration of the TCRM, the fluid deficit recorded at TCRM, the resolution of symptoms post-operatively and the number of subsequent fibroid related operations.

RESULTS: Forty-seven women were randomized to GnRH or placebo. On the basis of intention-to-treat analysis, there was no significant difference in the number of complete fibroid resections between women who received GnRH analogues [14/24, 58.3% (95% CI 38.6–78.1)] and those who received placebo [16/23, 69.6% (50.8–88.4)] (RR 0.84, 95% CI 0.54–1.29; P = 0.43). Similarly there was no significant difference between the groups in any of the secondary outcome measures.

CONCLUSIONS: Our study does not support routine administration of GnRH analogues before transcervical resection of fibroid as we did not identify any benefit in such treatment.

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Key words: submucous fibroids / hysteroscopic resection / GnRH analogues

Introduction

Submucous fibroids distort the endometrial cavity and typically cause heavy or irregular menstrual bleeding (Clevenger-Hoefst, 1999). They have also been identified as a potential cause of infertility and early miscarriage (Pritts, 2001). Such fibroids can be treated effectively by hysteroscopic resection, which is a minimally invasive procedure performed as a day surgery and is associated with a rapid post-operative recovery. Complete hysteroscopic removal of submucous fibroids results in a good therapeutic effect and resolution of symptoms (Emanuel et al., 1999). However, the complete removal of fibroids becomes progressively more difficult with increasing size of fibroid and proportion of the fibroid volume confined to the myometrium (Wamsteker et al., 1993). Larger or multiple fibroids require a longer operating time, which increases the risk of excessive absorption of distension fluid into the circulation. This can cause fluid overload leading to serious complications, such as pulmonary and cerebral oedema.
Pre-operative administrations of gonadotrophin hormone releasing hormone (GnRH) analogues results in a significant reduction in size of fibroids. It has been suggested that this treatment could be used to facilitate a complete resection of fibroids and to reduce the risk of fluid overload (Mencaglia and Tantini, 1993). There is some evidence that the reduction in fibroid size results in a higher proportion of the tumour protruding into the endometrial cavity, increasing the chance of the resection being completed successfully (Donnez et al., 1990; Mencaglia and Tantini, 1993; Emanuel et al., 1997). Shortening of the operating time, due to reduced size and higher intracavitary protrusion of fibroids, lowers the risk of excessive fluid absorption and overload (Donnez et al., 1989). However, the evidence supporting pre-operative use of GnRH is limited with only a single non-randomized trial published so far (Perino et al., 1993; Parazzini et al., 1998) and although some studies have shown that operating time is reduced with the use of GnRH analogues (Perino et al., 1993) others have not confirmed these findings and have reported that operations may actually take longer to complete (Campo et al., 2005). There is no evidence to demonstrate better long-term outcomes and less need for repeated surgery with the pre-operative use of GnRH analogues (Hart et al., 1999). GnRH analogues are costly and they can cause unpleasant side-effects such as hot flushes and night sweats. Therefore they should be administered only when there is a proven clinical benefit with their use.

The aim of this study was to compare the success and complication rates in women with submucous fibroids who were treated with GnRH analogues prior to hysteroscopic resection of submucous fibroids to those in women who received only placebo.

Materials and Methods

This was a prospective randomized placebo-controlled trial performed at King’s College Hospital NHS Foundation Trust. The study was approved by the hospital Ethics and Research and Development Committees. This study was registered on the Current Controlled Trials Website: http://www.controlled-trials.com/mrct/trial/662485/ISRCTN06656076.

Patients were recruited from the Gynaecological Outpatient Clinic at King’s College Hospital. All women referred to the clinic with a history of menstrual disorders are seen by gynaecologists, who take a detailed clinical history and perform a physical examination. All women are then offered a transvaginal ultrasound scan, which is performed by trained clinicians in order to identify the cause of women’s symptoms. Submucous fibroids diagnosed on ultrasound scan are classified into three types depending on the percentage of the tumour being confined to the myometrium (Wamsteker et al., 1993): Fibroids forming a polyp-like structure within the uterine cavity are classified as Type 0, those <50% contained within the myometrium are defined as Type I and fibroids ≥50% contained within the myometrium are described as Type II. The inclusion criteria for our study were: history of heavy and/or irregular menstrual periods and diagnosis of a Type I or Type II submucous fibroid on ultrasound (Fig. 1).

Procedures

All women underwent routine two-dimensional ultrasound scans, which were performed in a standardized fashion. First the cervix and uterine corpus were identified in the transverse plane. The uterine corpus was then assessed in a systematic way by examining a series of parallel scanning planes starting from the internal cervical os to the top of the uterine fundus. Fibroids were defined as distinct, well-circumscribed heterogeneous lesions arising from the myometrium. Each fibroid was examined individually to ascertain its size and position in relation to the uterine cavity. Fibroids were classified as submucous if they caused a visible distortion of the uterine cavity. All women with evidence of a submucous fibroid were offered three-dimensional ultrasound scans with intracavitary instillation of normal saline (three-dimensional saline infusion sonohysterography, 3D-SIS) in order to assess the degree of fibroid protrusion into the cavity more accurately.

The technique for 3D-SIS has been described previously (Salim et al., 2005). Briefly, a sterile Cusco speculum was placed, the cervix visualized and cleaned with sterile chlorhexidine solution. A 3.3 mm soft plastic paediatric nasogastric suction catheter was then passed through the cervix into the uterine cavity without grasping the cervix. The speculum was removed and a 5 MHz transvaginal three-dimensional ultrasound probe was inserted into the vagina (Voluson 730; expert GE Medical Systems, Milwaukee, WI, USA). The uterine cavity was visualized and the position of the catheter within the uterine cavity was confirmed. A longitudinal view of the uterus was obtained and the catheter was withdrawn to a level just above the internal cervical os. A volume of 5 – 10 ml of sterile saline solution was then instilled into the uterine cavity. A three-dimensional volume was generated by the automatic sweep of the mechanical transducer. The acquired volume was the shape of a truncated cone, with a depth of 4.3 – 8.6 cm and a vertical angle α = 90°. The volumes were stored digitally and analysed using multiplanar visualization. With this technique it was possible to examine the uterine cavity in three orthogonal planes. The fibroid diameter was compared with the measurement of intracavitary fibroid protrusion, to calculate the percentage of fibroid volume confined to the myometrium. We recorded the number and size of uterine fibroids as well as the degree of protrusion of any submucous fibroids into the endometrial cavity in a computerized database (PIA Fetal Database, version 5.5.4.152, Viewpoint Bildverarbeitung GmbH, Munich, Germany).

All women with a confirmed Type I or Type II submucous fibroid on 3D-SIS were given an information leaflet about the study and a written informed consent was obtained from all patients who agreed to take part.

Consecutively numbered, opaque, sealed envelopes were prepared at King’s College Hospital NHS Foundation Trust using a computer-generated simple randomization sequence. The envelopes were securely kept at the nurses’ office at the Gynaecology Outpatient Clinic. Patients were randomly assigned to subcutaneous injections of placebo (5 ml of 1% Lignocaine) or Goserelin 3.6 mg (Zoladex, AstraZeneca UK, Luton, UK). Randomization of patients and administration of injections were done by staff nurses who were not part of the trial. Both patients and clinicians involved in the trial were blinded to the group allocation.

A total of three injections were given at 4 weekly intervals. The operation was scheduled to take place within 4 weeks from the last injection. Following completion of pre-operative treatment patients underwent hysteroscopic transcervical resection of myoma (TCRM) by a single experienced operator (A.D.).

TCRM was performed under general anaesthesia with a rigid 30° resectoscope with bipolar loop wire electrodes (Storz Endoscopy, Germany). Aseptic technique was observed throughout the procedure. Normal saline was used to distend the uterine cavity. Infusion pressure was elevated by a pneumatic cuff under manometric control to 100 – 120 mmHg. A high-intensity cold light source and fibre optic cable were used to illuminate the uterine cavity. The procedure was monitored using a single chip video camera and the image was displayed on a monitor visible to the operator. The approximate size of the fibroid was determined by visualization of the fibroid and comparison with the length of the hysteroscope. The protrusion into the cavity was determined by visualization of the angle between the fibroid and the uterine wall. For all fibroids, an attempt was made to resect them completely. Throughout the operation the balance between infused and collected fluid was monitored. Any fluid
deficit was recorded at the end of the procedure along with the time lapsed from the initial application of the tenaculum to the completion of resection. The procedure was stopped when all the fibroid had been removed or the resection had gone 1 cm deep into the myometrium as measured from the endometrial surface to the deepest point of the space in the myometrium from where the fibroid had been removed. The procedure was also stopped if the fluid deficit exceeded 1.5 l or it was not possible to visualize the uterine cavity due to excessive bleeding.

For women with multiple fibroids, we analysed the largest and least protrusive fibroid. The resection in these women was classified as complete when all fibroids had been removed. Six weeks after TCRM, women were followed up to review their symptoms and assess the need for further treatment.

**Statistical methods**

The aim of the study was to assess whether pre-operative treatment with GnRH analogues facilitates the complete resection of submucous fibroids at TCRM. The primary outcome measure was the completeness of resection of the submucous fibroid at TCRM. Secondary outcome measures included: the duration of the TCRM, the fluid deficit recorded at TCRM, the resolution of symptoms post-operatively and the number of subsequent fibroid related operations.

In the 1993 study of TCRM, Wamsteker et al. (1993) showed that the probability of complete resection of Type O fibroids was 92% per procedure while that of Type I and Type II fibroids was 60 and 50% per procedure, respectively (average 55%). Similar figures were also reported by Vercellini et al. (1999) and Perino et al. (1993). Given that it would be desirable to completely remove the fibroid with a single operation, our hypothesis was that pre-operative use of GnRH analogues would improve the probability of Type I and II fibroids to be completely resected to that of Type O. The study was designed to have an 80% power detect an increase in the proportion of fibroids completely resected at the first operation from 55% in the placebo group to 92% in the treatment group with a two-sided \( P \)-value of 0.05.
Pre-operative GnRH treatment for submucous fibroids

Table I Baseline characteristics of study participants.

<table>
<thead>
<tr>
<th></th>
<th>GnRH (n = 24)</th>
<th>Placebo (n = 23)</th>
<th>P</th>
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<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>38.8 (7.6)</td>
<td>44.5 (5.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median parity (range)</td>
<td>1 (0–3)</td>
<td>2 (0–3)</td>
<td>0.327</td>
</tr>
<tr>
<td>Median fibroid diameter, mm (range)</td>
<td>29.0 (24.5–40.25)</td>
<td>29.0 (21.25–35.5)</td>
<td>0.237</td>
</tr>
<tr>
<td>Mean degree of protrusion, % (± SD)</td>
<td>71 (19)</td>
<td>68 (21)</td>
<td>0.820</td>
</tr>
<tr>
<td>Multiple fibroids, n, % (95% CI)</td>
<td>4 (16.7, 1.8–31.6)</td>
<td>4 (17.4, 1.9–32.9)</td>
<td>1.0</td>
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(1/10, 10% (95% CI 0.0–28.6)) and one was abandoned because of a fluid deficit >1.5 l [1/10, 10% (95% CI 0.0–28.6)]. The logistic regression analysis identified fibroid size and degree of fibroid protrusion as independent significant predictors of completeness of fibroid resection (Table II).

On the basis of the intention to treat analysis, there was no significant difference in the number of complete fibroid resections between women who received GnRH analogues [14/24, 58.3% (95% CI 38.6–78.1)] and those who received placebo [16/23, 69.6% (50.8–88.4)] (RR 0.84, 95% CI 0.54–1.29; P = 0.43). The difference in the proportion of completely resected fibroids between the two groups was 11.3% (95% CI −15.5 to 35.7). A total of seven women did not undergo planned operation: 3/24 (12.5%, 95% CI 1.4–23.6) in the treatment group and 4/23 (17.4%, 95% CI 4.4–30.4) in the placebo group (P = 0.701). Of the three women in the treatment group who did not undergo their operation, one developed an allergic reaction, the second one opted for abdominal myomectomy and the third did not attend for her operation. Of the four women in the placebo group who did not undergo their operation, one opted for abdominal myomectomy and the remaining three did not attend for their operation.

The results in the subgroup of women who underwent surgery are shown in Table III. Again, there was no significant difference in the number of complete resections between women in the study compared with the placebo group [14/21, 66.7% (95% CI 46.5–86.8) versus 16/19, 84.2% (95% CI 67.8–100.0), respectively; RR 0.79 (0.55–1.13); P = 0.20]. The difference in the proportion of completely resected fibroids between the two groups was 17.5% (95% CI −12.9 to 43.8). The mean volume of fluid infused during hysteroscopy [7.7 (± 4.9) versus 9.3 l (± 5.7), respectively; P = 0.39], the number of women who had fluid deficit in excess of 1.5 l [12.5% (95% CI 0.0–25.7) versus 4.3% (95% CI 0.0–12.7), respectively; RR 2.71 (0.31–23.93); P = 0.38], the mean duration of the procedure [30.0 min (20.0–40.0) versus 30.0 min (21.0–31.0), respectively; P = 0.84] and complication rate [4.2% (95% CI 0.0–12.2) versus 8.7% (95% CI 0.0–20.2), respectively; RR 0.45 (0.04–4.6); P = 0.56] were also similar between the two groups (Table III).

One woman who received GnRH analogue suffered a uterine perforation and bowel injury that necessitated laparotomy and repair. She eventually made a full recovery. Two women in placebo group suffered excessive intraoperative bleeding, which was controlled by the insertion of a Foley catheter in one and by cervical suture in the other case.

Thirty-six out of 40 (90%) of women who were operated attended for a 6 week follow-up visit. Fourteen out of 20 women who had received GnRH analogues felt that their symptoms were had resolved compared with 7/16 women who were allocated to the placebo group [75.0% (95% CI 56.0–93.9) versus 43.8% (95% CI 19.4–68.1), respectively; RR 1.7 [0.39–3.2]; P = 0.084).

Until the 3rd of October 2009, 10 women had undergone a second operation for their fibroids. Four out of 20 women who had received GnRH analogues compared with 6/16 who had received placebos had a second operation [(20.0%, 95% CI 2.5–37.5) versus (37.5%, 13.8–61.2), respectively; RR 0.53 [0.18–1.57]; P = 0.25]. Of the 10 women, 8 (80%, 95% CI 55.2–100.0) had a repeat intervention because their symptoms of menorrhagia had not resolved. One woman was operated because of several non-submucous fibroids [1/10, 10% (95% CI 0.0–28.6)] and one developed a new submucous fibroid [1/10, 10% (95% CI 0.0–28.6)].

Discussion

Our study did not demonstrate a benefit of pre-operative administration of GnRH in increasing the proportion of complete resections of Type I and II fibroids at TCRM. However, the overall success rate of TCRM was 75%, which was higher than assumed in our power calculation. This could be explained by the improvements in the quality of surgical equipment and increased experience and skill of the operating surgeons, which have occurred since the original data on which we based our power calculation were published. In order to demonstrate an improvement in complete fibroid resection from 75 to 92%, we would have needed to recruit 95 women in each arm, which is difficult to achieve in a single centre. It could be argued that a potential improvement in the success of TCRM with the use of GnRH that is less than what we expected could still be clinically significant. However, despite the small sample size of our study, the result indicates that pre-operative administration of GnRH analogues is unlikely to be helpful.
The treatment and placebo groups in our study were unbalanced in terms of age as the placebo group contained no woman under 35 whereas the treatment group contained a cluster of 8 women under 35 of whom 3 were under 30. However the groups were balanced in terms of parity, fibroid size and percentage of protrusion, which should confirm the absence of selection bias. Age alone is unlikely to have influenced either main or secondary outcomes. The results of our multivariate logistic regression analysis confirmed that, of the variables analysed, only fibroid size and degree of protrusion are significant predictors of completeness of resection.

There were no differences in the success of TCRM when the analysis was limited to those women who underwent the planned surgery. The length of the procedure, fluid deficit and complication rates were similar between the treatment and placebo groups and they were also broadly in agreement with data from the literature (Perino et al., 1993). At the follow up visit 6 weeks after surgery, more women in the treatment group reported improvement in their symptoms, but the result was not statistically significant. This difference could be explained by a prolonged effect of GnRH analogues, which could still be present at 6 weeks after surgery. Long-term follow-up showed a lower number of secondary procedures in the treatment group compared with the control group (Lethaby et al., 2001). The length of the procedure, fluid deficit and complication rates were similar between the treatment and placebo groups and they were also broadly in agreement with data from the literature (Perino et al., 1993). At the follow up visit 6 weeks after surgery, more women in the treatment group reported improvement in their symptoms, but the result was not statistically significant. This difference could be explained by a prolonged effect of GnRH analogues, which could still be present at 6 weeks after surgery. Long-term follow-up showed a lower number of secondary procedures in the treatment group compared with the control group (Lethaby et al., 2001). The length of the procedure, fluid deficit and complication rates were similar between the treatment and placebo groups and they were also broadly in agreement with data from the literature (Perino et al., 1993). At the follow up visit 6 weeks after surgery, more women in the treatment group reported improvement in their symptoms, but the result was not statistically significant. This difference could be explained by a prolonged effect of GnRH analogues, which could still be present at 6 weeks after surgery. Long-term follow-up showed a lower number of secondary procedures in the treatment group compared with the control group (Lethaby et al., 2001).

Another rationale for the administration of pre-operative GnRH analogues is a reduction of fluid deficit. Emanuel et al. (1997) performed a retrospective study of factors that may influence fluid deficit at TCRM. They found that pre-operative administration of GnRH is associated with reduced fluid deficit. However, the criteria for GnRH administration were not listed and the operating surgeon was not blinded to the treatment, which may have introduced an element of bias. Donnez et al. (1994) showed that use of GnRH reduced fibroid surface area by a third and they hypothesized that this could reduce the risk of fluid overload. In another study they found that GnRH analogues reduce fluid absorption by about 400 ml (Donnez et al., 1990). Neither of these two studies was randomized or included controls. We also found a reduction in the median volume of fluid deficit in the GnRH group compared with placebo. The difference, however, was only 200 ml, which was not statistically significant. It could be argued that there are other potential benefits of pre-operative treatment with GnRH analogues apart from facilitating a complete excision of fibroids. A recent meta-analysis of randomized controlled trials comparing GnRH analogue administration before abdominal myomectomy showed that women in the treatment group had significantly higher pre-operative haemoglobin concentration compared with the control group (Lethaby et al., 2001). Similar benefits are also likely to occur in women scheduled for hysteroscopic surgery.

In conclusion, our study did not demonstrate a significant benefit of administration of GnRH analogues prior to TCRM. Our results, however, are limited by a relatively small sample size and a larger multicentre trial is required to confirm our findings. Nevertheless, our trial methodology was robust and our data could be used in a meta-analysis of studies with similar outcome measures.

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**References**


