Pertubation with lignocaine as a new treatment of dysmenorrhea due to endometriosis: a randomized controlled trial

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BACKGROUND: Endometriosis is a chronic inflammatory disease of unknown aetiology that can cause severe dysmenorrhea. Lignocaine has anti-inflammatory properties and exerts effects on nerve endings and intra-peritoneal macrophages. The objective of this study was to evaluate the effect of pertubation with Ringer–Lignocaine on dysmenorrhea in women with endometriosis.

METHODS: A double-blind randomized controlled trial (RCT) was carried out at three sites in Stockholm, Sweden. Eligible patients had endometriosis as diagnosed by laparoscopy, dysmenorrhoeic pain >VAS 50 mm (visual analogue scale) and patent Fallopian tubes. The study patients were randomized sequentially to preovulatory pertubations with placebo (n = 18) or study treatment (n = 24) during three consecutive menstrual cycles. The pertubation procedure comprised passing study solution through the uterine cavity and the Fallopian tubes via an intra-cervical balloon catheter. The effect on pain was evaluated with VAS scales before and after the treatments and up to nine menstrual cycles after the last pertubation. Success was defined as a reduction of ≥50% on the VAS scale after the third pertubation. The success rate between the treatment and the placebo group was compared with Fisher’s exact test.

RESULTS: In the intention-to-treat analysis, the success rate was 41.7% (10 of 24) in the treatment group compared with 16.7% (3 of 18) in the placebo group (P = 0.10, 95% CI = 7.3 to 36.2%). In the per protocol analysis, the success rate in the treatment group was 45% (9 of 20) compared with 7.1% (1 of 14) in the placebo group (P = 0.024, 95% CI = 2.6 to 44.8%). Of the nine patients in the lignocaine group who fulfilled the criteria for success after three pertubations, 4 (44%) had an effect persisting after nine months. The treatments were well tolerated.

CONCLUSIONS: This small RCT indicates that pertubation with lignocaine is a non-hormonal treatment option for patients with dysmenorrhea and endometriosis.

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Key words: endometriosis / lignocaine / dysmenorrhea / pertubation

Introduction

Endometriosis is defined by the presence of viable endometrial tissue outside the uterine cavity. It affects 6–10% of all fertile women and up to 35–50% of females with dysmenorrhea and/or infertility, which are the main symptoms of endometriosis (Houston, 1984; Giudice and Kao, 2004). The explanation of the increased pelvic pain caused by endometriosis is still unclear. It might involve aberrant immunologic mechanisms together with an increased density of sensory nerves fibres in the endometriotic lesions and the eutopic endometrium (Berkley et al., 2005; Christodoulakos et al., 2007; Medina and Lebovic, 2009). A local sterile inflammation occurs in the peritoneal cavity in women with endometriosis (Agic et al., 2006). All subgroups of leukocytes are represented in the peritoneal fluid; however, macrophages constitute up to 90% of the cells (Haney et al., 1981; Ho et al., 1997; Gasvani and Templeton, 2002). The numbers and activity of macrophages in the peritoneal fluid are increased in women with endometriosis and subsequently macrophage-derived cytokines are elevated (Oral et al., 1996; Wu and Ho, 2003). Macrophages and a complex network of cytokines may modulate the growth and...
inflammatory behaviour of ectopic endometrial implants (Berkkanoglu and Arici, 2003). Increased quantities of nerve fibres have also been found in peritoneal endometriotic lesions compared with normal peritoneum, and in the functional layer of the eutopic endometrium in patients with endometriosis (Tokushige et al., 2006a,b). Inflammatory substances produced by macrophages and in the endometriotic lesions can stimulate nerve endings (Tran et al., 2009). The innervation of endometriotic implants and eutopic endometrium can thus have an impact on the pathogenesis and symptoms of endometriosis.

Lignocaine is a potent drug that in high concentrations is used for anti-arrhythmic treatment and for local and regional anaesthesia. Low concentrations of lignocaine affect inflammatory cells by stabilizing the cell membrane (Hollman and Durieux, 2000). Incubations of endothelial cells have shown that the concentrations of activated endothelial IL-1β, IL-6 and IL-8 are attenuated by lignocaine (Lan et al., 2005). In studies of peritoneal macrophages in vitro, the presence of lignocaine has been shown to reduce the phagocytosis of spermatozoa (Edelstam et al., 1998).

In fertility therapy, lignocaine has increased the pregnancy rate when used in preovulatory perturbations (Edelstam et al., 2008). An unexpected positive side effect of this fertility treatment in patients with endometriosis was reduced dysmenorrhea spontaneously reported by the patients who did not achieve pregnancy (Edelstam et al., 2001). Thus the purpose of the present study was to further evaluate the effect of perturbation with Ringer-Lignocaine on dysmenorrhea in women with endometriosis.

Materials and Methods

Study design and participants

This phase II study was randomized, double-blind and controlled. The patients were sequentially randomized to receive study treatment (perturbation with lignocaine 1 mg/ml in Ringer solution) or placebo (perturbation with Ringer solution). Three treatments were to be given sequentially on cycle Day 6–12 in three sequential menstrual cycles. The Regional Ethical Review Board and the Medical Products Agency in Sweden approved the procedure.

In the power analysis using the \( \chi^2 \) test at 80% power, it was assumed that 60% of the subjects given the study treatment and 20% in the control group would improve. To achieve a statistical significance \( P < 0.05 \), using Fisher’s exact two-sided test, 20 subjects in the treatment group and 15 subjects in the control group had to be randomized. A 4:3 treatment/placebo rate was used to gain more safety data and to encourage women to participate since the chance of active treatment compared with placebo was higher.

Subjects were recruited through advertisements and from the gynaecological outpatient unit at the participating clinics. Treatments were given in Stockholm, Sweden, at three sites, i.e. Danderyd Hospital, Karolinska University Hospital and Låkargruppen Victoria. A total of 106 women with dysmenorrhea due to endometriosis expressed interest in participating in the study and 42 fulfilled all eligibility criteria. The main inclusion criteria were presence of peritoneal or ovarian endometriosis as verified by laparoscopy and dysmenorrhea with a pain score of \( > 50 \) mm on the visual analogue scale (VAS). Main exclusion criteria were reduced patency in the Fallopian tubes and intention to achieve pregnancy during the forthcoming year. Detailed eligibility criteria are presented in Table I. Written informed consent was obtained before any study-related procedures.

### Table I: Eligibility criteria for study participants.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Age &gt; 20 years</td>
<td>Continuous treatment with medication that may increase risk of infection</td>
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<tr>
<td>Endometriosis verified by laparoscopy</td>
<td>Clinical signs of pelvic inflammatory disease</td>
</tr>
<tr>
<td>Dysmenorrhea or pelvic pain defined as a pain score of ( &gt; 50 ) mm (VAS)</td>
<td>Hyperreactivity to local anesthesia</td>
</tr>
<tr>
<td>Normal Fallopian tubes</td>
<td>Fibroids ( &gt; 2 ) cm</td>
</tr>
<tr>
<td>Regular menstrual cycles 21–35 days</td>
<td>Ongoing treatment with GnRH agonist</td>
</tr>
<tr>
<td>Treatment with OC ongoing ( &gt; 1 ) month and continued during the trial</td>
<td>Ongoing continuous treatment with high-dose gestagens</td>
</tr>
<tr>
<td>Previous hormonal treatment discontinued ( &gt; 1 ) month (OC, gestagens) and ( &gt; 6 ) months (GnRH agonist)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>No wish for pregnancy during the study</td>
<td>Peritubal adhesions</td>
</tr>
<tr>
<td>Normal Pap smear, Negative chlamydia test</td>
<td>Occluded Fallopian tubes</td>
</tr>
<tr>
<td>Negative pregnancy test</td>
<td>Inability to understand information or comply with study procedures</td>
</tr>
<tr>
<td>Informed consent given and signed</td>
<td>Participation in a clinical study within one year before the present study</td>
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Procedures

At the first visit, the study patients were scrutinized concerning the inclusion and exclusion criteria. A physical examination including blood pressure, gynaecological examination including wet smear and vaginal ultrasound were performed. Chlamydia and pregnancy tests were taken and bacterial vaginosis, if present, was treated. The subjects should have had a normal Pap smear taken within the previous three years and if not, a new smear was carried out. Demographic data, concomitant medication and medical history were recorded (Table I). The patency was considered normal if the preceding laparoscopy revealed normal anatomy of Fallopian tubes. In five patients, three in the placebo group and two in the lignocaine group, information concerning patency of the Fallopian tubes was missing in the patient records or history, and therefore hysterosalpingo contrast sonography was performed prior to study entry.

At the second visit, the patients were randomized sequentially as they were eligible. The treatment was given over three sequential menstrual cycles and was considered successful if three treatments were given during a maximum of five consecutive menstrual cycles (i.e. per protocol, PP). Data from a previous study had given indications that the effect on dysmenorrhea increased after repeated treatments (Edelstam et al., 2001), hence it was decided to use three treatments. At the treatment visits, any changes in concomitant medication, medical status or presence of any adverse events (AE) since the preceding visit were recorded. Before each treatment a pregnancy test was performed and a gynaecological
examination including wet smear was performed to confirm the absence of bacterial vaginosis or signs of pelvic inflammatory disease. The pertubations were carried out on menstrual cycle Day 6–12 since some patients were in natural cycles and could possibly become pregnant. A thin plastic catheter (PBN-Medicals, Stenløse, Denmark) was inserted in the cervical canal and the small, intraluminal rubber balloon on the catheter was inflated with saline to prevent retrograde leakage. Blood pressure and heart rate were measured and recorded before and five minutes after the treatment. A 10 ml quantity of solution was infused through the uterine cavity and pertubated into the peritoneal cavity (Fig. 1).

The effect on dysmenorrhea was evaluated with a VAS scale and a pain questionnaire, initially filled out at the menstruation before the first treatment, i.e. baseline. Thereafter the VAS scale and questionnaires were completed during the second, third and fourth period, i.e. after every treatment. The final follow-up took place after the 7th, 10th and 13th menstrual period, i.e. 6, 9 and 12 months after initial treatment.

The VAS scale is a valid instrument for evaluating chronic pain during endometriosis (Price et al., 1983; Vincent et al., 2010). The maximum pain during every menstrual period was recorded and a decrease on the VAS scale of ≥50% from baseline was defined as a success.

The pain questionnaire used was a revised version derived from a validated questionnaire with a categorical scale evaluating the degree of pain from no pain to bedridden for the major part of the day (Biberoglu and Behrman, 1981). The dysmenorrhea was evaluated on menstrual cycle Day 1, 3 and 5. The sum of the pain scores from the categorical scale (0–12) was compared between the different time points and a decrease by ≥2 from baseline, was defined as a treatment success.

The time point for primary efficacy evaluation was after the third and last pertubation that corresponded to the fourth menstruation ≈3 months after the initial treatment. The secondary time points for primary efficacy evaluation were after 6, 9 and 12 months, respectively. The participating patients were also asked to estimate any changes in their overall pain level, the use of rescue medication and their need to be on sick leave, all of which were secondary end-points. Obtaining a VAS < 20 mm was also evaluated and considered a secondary end-point and an indication of a low pain level.

Randomization and masking

The patients were randomized sequentially as they were eligible. Solutions for pertubation were produced and released in a double-blinded manner (APL/Apoteket Production & Laboratories, Box 6124, SE 906 04 Umeå, Sweden). The double-blinded study solutions were delivered to the sites in blocks of treatments for seven patients: three placebo and four study treatment kits. In total six blocks were completely used. After randomization of a patient, each site assigned the patient to the next available treatment kit in the ongoing block. The randomization list remained at APL until a clean file was declared.

Statistical analysis

The success rate between the treatment and the placebo groups at different time points was compared using Fisher’s exact test. The 95% confidence interval was an exploratory analysis since the study population was too small to assume normal distribution.
Results

In total, 124 pertubations, 70 with lignocaine and 54 with placebo, were carried out from 22 March 2007 to 3 June 2009. The last follow-up questionnaire was received on 1 March 2010. In total, 42 patients were randomized, 24 to pertubation with lignocaine and 18 to pertubation with placebo (Fig. 2). The trial ended when a sufficient number of participants had been recruited, based on the power analysis and with compensation for drop-outs.

The intention-to-treat (ITT) population consisted of 42 patients, 34 of whom remained in the PP analysis (Fig. 2). The medical history and demographic characteristics of the patients in both groups were comparable (Table II). They had similar usage of concomitant medications such as analgesics, selective serotonin reuptake inhibitors (SSRI) and oral contraceptives (OC). The results of the pertubations with lignocaine or placebo were analysed in the PP and the ITT populations, respectively. For inclusion in the PP analysis, the subjects had to have a VAS score of $\geq 50$ mm, have undergone three pertubations in a maximum of five consecutive menstrual cycles and at least the primary end-point evaluation had to be completed. Eight patients were excluded from PP analysis. Four initially reported a VAS of $>50$ mm but later when the baseline questionnaire was analysed, they proved not to fulfill this inclusion criterion. One subject became pregnant immediately after the first treatment and three further patients did not undergo treatments according to the PP criteria. Thus 20 patients in the treatment group and 14 patients in the placebo group remained for the PP analysis (Fig. 2).

The time point for primary efficacy evaluation was after the third and last pertubation that corresponded to the fourth menstruation $\approx 3$ months after the initial treatment. In the ITT analysis, 10 of 24 patients (41.7%) in the treatment group compared with 3 of 18 patients (16.7%) in the control group fulfilled the criteria for success as having a decrease of $\geq 50\%$ on the VAS scale ($P = 0.10$, 95% CI $-7.3$ to $36.2\%$). In the PP analysis, 9 of 20 (45.0%) compared with 1 of 14 (7.1%) had a decrease of $\geq 50\%$ on the VAS scale ($P = 0.024$, 95% CI $-2.6$ to $44.8\%$).

When analysing the sum of scores from the categorical scales during menstruation between baseline and after the third treatment, there were no statistically significant differences between the groups.

In the PP population, nine of the patients in the lignocaine group ($n = 20$) and one in the placebo group ($n = 14$) improved by $\geq 50\%$ on the VAS scale from baseline to the first menstruation after the third treatment. In the lignocaine group, three of these nine patients improved by $\geq 50\%$ on the VAS scale after the first treatment and five improved after the second treatment. Three months after the third treatment, four of these nine patients in the lignocaine group still fulfilled the criterion of an improvement of $\geq 50\%$ on the VAS scale from baseline. This improvement persisted for 6 months after the last treatment for two patients and for nine months for four patients. The only patient in the placebo group who improved by $\geq 50\%$ after the third treatment, had not improved after the first or second treatments. She was still improved three months after the third treatment, but thereafter her pain level returned to baseline (Table III). Time-line analysis showed that the percentage of responders increased with the increasing number of lignocaine pertubations while no such trend was seen in the placebo population.

The secondary time points for primary efficacy evaluation were after 6, 9 and 12 months, respectively. On the VAS scale or when analysing the sum of scores from the categorical scales, no significant differences were found between the treatment group and the placebo group either in the ITT, or in the PP, population. The participating patients were asked to estimate any changes in their overall pain

Figure 2  Study participant flow chart. ITT, intention-to-treat; PP, per protocol.
Table III Successful treatments in the PP population after three pertubations.

<table>
<thead>
<tr>
<th>Time point for primary efficacy evaluation</th>
<th>After first treatment</th>
<th>After second treatment</th>
<th>Success, first menstrual period after third treatment</th>
<th>3rd menstrual period after third treatment</th>
<th>6th menstrual period after third treatment</th>
<th>9th menstrual period after third treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved ≥ 50% on VAS-scale from baseline</td>
<td>Lignocaine (n = 9)</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

level, and 13 of the 24 patients in the lignocaine group and 11 of 18 in the placebo group reported reduced dysmenorrhea after the third treatment. Four patients in the lignocaine group experienced no dysmenorrhea at all. The change in the use of analgesics from baseline to primary end-point was comparable between the groups, and no significant changes were found. Only half of the study population reported a need to be on sick leave. The change in work capacity was similar between the groups. In the PP analysis after the third treatment, six patients in the lignocaine group achieved the secondary end-point <20 mm on the VAS-scale compared with none in the placebo group (P = 0.031). Five of the nine subjects (56%) who responded to the treatment in the lignocaine group had no pain symptoms (VAS ≤ 4 mm). No patient in the placebo group reached VAS of ≤10 mm at the time point for primary efficacy evaluation.

Five patients became pregnant during the course of the whole study and were withdrawn from further evaluation. Two patients in the lignocaine group achieved spontaneous pregnancy after the first and third perturbation, respectively. Three patients in the placebo group became pregnant after IVF. The pregnancies were normal. One malformation was registered in the placebo group after IVF treatment and the other children were healthy.

Two patients in the lignocaine group were withdrawn because of endometriomas >25 mm diagnosed 1 and 4 months after the third treatment, respectively. They were surgically treated and withdrawn from further evaluation. Another patient in the lignocaine group discontinued 5 days after the third treatment because of such painful endometriosis that continuous OC had to be initiated. In the placebo group, three patients were withdrawn during the study. This was due to escalating pain and the need for other therapies such as high doses of gestagens or GnRH agonists. Blood pressure and heart rate recorded before perturbation were normal and did not change in either the lignocaine or the placebo group following treatment.

**Discussion**

In the current study, the PP analysis demonstrated a significant pain reduction on the VAS scale after three pertubations with lignocaine compared with placebo. Thus, perturbation with lignocaine might be developed to be a new non-hormonal treatment option for endometriosis-related menstrual pain in patients with minimal to moderate endometriosis.

Endometriosis is a chronic disease treated surgically with resection of endometriotic tissue or pharmacologically with side effects such as anovulation (Jacobson et al., 2010). Hormonal therapeutic approaches currently used for amelioration of endometriosis-associated pelvic pain include GnRH agonists, high doses of gestagens and continuous OC, all of which inhibit ovulation and do not improve subsequent fertility (Hughes et al., 2007). Perturbation with lignocaine represents an alternative treatment strategy that has previously been tried in a small study as a non-hormonal treatment with promising results. Lignocaine pertubated through the uterus and Fallopian tubes out into the peritoneal cavity might influence the endometrium during its passage. Lignocaine exerts effects on inflammatory cells such as macrophages and their activation status but might also affect sensory nerves in the peritoneum, in peritoneal lesions and in eutopic endometrium. Further studies are in progress to assess the mechanism of the clinical effect on dysmenorrhea as well as the optimal dosage and therapy intervals.

The first clinical trial of pertubations with lignocaine was carried out after an in vitro study on peritoneal macrophages (Edelstam et al., 1998). Patients with endometriosis, infertility and patent Fallopian tubes were offered preovulatory pertubations in a double-blind cross-over study and several patients who did not become pregnant reported reduced dysmenorrhea (Edelstam et al., 2001). A separate study investigated what dose was optimal for treating dysmenorrhea (submitted). This study, however, had to be terminated early due to difficulties of recruiting enough patients. Women with endometriosis and pain are hesitant to participate in a randomized study including a placebo and therefore the present study was designed with 40% placebo treatments and 60% study treatments in order to facilitate the inclusion of participants in the study.

The present PP analysis demonstrated a significant pain reduction on the VAS scale after three pertubations with lignocaine compared with placebo. The findings correspond to the effect on dysmenorrhea seen in the previous studies.

It is interesting to note the long-term effect in 10 patients in the PP population who improved by ≥50% on the VAS scale. Nine of these were in the lignocaine group and the reduced pain level lasted up to 1 year after the first treatment. There is no apparent explanation of this long-term effect; however, macrophages have a long lifespan, ranging from months to years (van Furth and Cohn, 1968) and the effect might depend on permanent effects on the cellular membranes (Hollman and Durieux, 2000; Medina and Lebovic, 2009). Several mechanisms of local anaesthetic action on inflammatory cells have been suggested, but only a few targets have been described in molecular detail (Hollman and Durieux, 2000). Macrophages can switch their activation status from a pro-inflammatory to an anti-inflammatory...
scopic uterine nerve ablation in women with chronic pelvic pain (Porcheray et al., 2005). In chronic inflammatory diseases, the inhibition of the apoptotic programme promotes monocyte survival contributing to the accumulation of macrophages and the persistence of an inflammatory milieu (Panhar et al., 2010).

No significant differences were seen on the VAS scale between the groups 3–9 months after the last treatment, which might be due to the sample size. Neither were there any significant differences between the groups when analysing the sum of scores from the categorical scales. Many patients had difficulty in grading their pain level on the categorical scales and the pain questionnaire might not adequately separate the degree of pain.

There are some studies defining criteria for relevant improvement on the VAS scale. A randomized study evaluating the effect of laparoscopic uterine nerve ablation in women with chronic pelvic pain defined improvement as >50% on the VAS scale from baseline (Johnson et al., 2004). Johnson referred to an RCT study evaluating hormonal treatment and psychotherapy (Farquhar et al., 1989). Therefore this definition of success was used in the present study. However, in 2010 Gerlinger et al. tried to define a minimal clinically important difference for endometriosis-associated pelvic pain. In this study, based on two RCTs, they found that the best separation between women rating themselves ‘minimally improved’ and ‘improved’ was a decrease of 28 mm on the VAS scale (Gerlinger et al., 2010). Such a low definition of success did not allow a distinction of treatment effect from placebo effect in our study. When analysing the present results with other definitions of success, e.g. ≥40 mm decrease on the VAS scale, similar results were obtained as with ≥50% reduction.

Overall, the pertubation treatments were well tolerated and there were no treatment related AE. Pertubation does not affect ovulation and the chance of achieving pregnancy after preovulatory pertubation with lignocaine is even increased (Edelstam et al., 2008). In the present study, two patients in the lignocaine group became pregnant spontaneously after the initiation of treatments and were withdrawn from evaluation.

Women who have severe dysmenorrhea and side effects on medical treatments, are more inclined to participate in a non-hormonal clinical trial. The fact that patients who have failed to improve on other treatments are attracted to clinical trials might constitute an attenuation biased group. In total, 106 women were interested in participating, but 53 of them were not scheduled for a screening visit since they did not fulfil the inclusion criteria or were not interested after information had been given. A forthcoming phase III study should aim to reduce the number of exclusion criteria, e.g. even patients with a present wish for pregnancy could be included to reduce the risk of bias. The study has limitations due to the small sample size but the design contributes to the strength of the study.

Pertubation treatment constitutes a non-hormonal treatment option for dysmenorrhea and maintained the possibility of pregnancy. The procedure is easy to learn and to perform for any gynaecologist.

Conclusions

Pertubation with lignocaine might be developed to be a new non-hormonal treatment option for endometriosis-related menstrual pain. During pertubation treatments, ovulatory cycles can be maintained. The treatment is easy to perform with good safety in an outpatient setting. Pertubation with lignocaine merits further evaluation in larger clinical trials.

Acknowledgements

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Authors’ roles

All the authors have participated in the study design, manuscript drafting and critical discussion and share equal responsibility for the article. K.W., G.E. and J.S. performed the applications for required approvals. K.W., G.E., A.S. and C.B. recruited and treated patients. K.W., G.E. and J.S. analysed data. K.W. and G.E. have full access to all study data and are responsible for the decision to submit for publication.

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Conflict of interest

J.S., A.S. and G.E. are minor shareholders in Isifer AB.

Details of ethics approval

The procedure was approved by the Medical Products Agency in Sweden 8 November 2006 (Dnr 151:2006/56028) and after amendment 12 December 2007 (Dnr 151:2007/76934) as well as by the Regional Ethical Review Board in Stockholm 10 January 2007 (Dnr 2006/1416-32) and after amendment 14 December 2007 (Dnr 2007/1398-32).

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