The Role of GnRH Analogues in Improving Outcome in Women Undergoing Superovulation and Intrauterine Insemination after Surgical Correction of Mild Endometriosis: A Randomized Controlled Trial

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ABSTRACT

Objective: Treatment with laparoscopic surgery, gonadotropin-releasing hormone analog (GnRHa) therapy, superovulation (SO), and intrauterine insemination (IUI) have individual benefits in improving fertility outcomes in women with endometriosis. The aim of the study was to evaluate the role of GnRHa in improving outcome in women undergoing SO and IUI after surgical correction of mild endometriosis.

Materials and Methods: This was a randomized controlled trial conducted in the Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India, over a period of 2 years and 6 months. Ninety women who were diagnosed with mild endometriosis on laparoscopy using the revised American Society for Reproductive Medicine criteria were included in the study. The patients in the study group (n=45) received a single dose of 3.75 mg GnRHa subcutaneously within 48 h of the surgery, and those in the control group (n=45) did not receive GnRHa. Thereafter, patients in both arms received SO and IUI from the next menstrual cycle. Four patients in the study group and three patients in the control group were lost to follow-up before the first cycle of ovulation induction. Primary outcomes measured in our study were live birth rates and clinical pregnancy rate. Secondary outcome measures were number of follicles>18 mm, endometrial thickness, dose and days of gonadotropin stimulation.

Results: Baseline characteristics, such as age and body mass index, were comparable in both groups. The SO and IUI cycles were comparable between the two groups with regard to the secondary outcome parameters. Pregnancy rate in the first cycle was 17.1% in the study group and 19.1% in the control group (p=0.81). The overall pregnancy rate was similar in both groups (study group=21.9%, control group=23.8%; p=1). As no patient had miscarriage or any other complication during pregnancy, live birth rate was similar to the clinical pregnancy rate.

Conclusion: Adding GnRHa for the suppression of mild endometriosis has shown no significant improvement in the surgical management of women undergoing SO and IUI.

Keywords: Mild endometriosis, GnRH analog, superovulation, intrauterine insemination

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Introduction

Endometriosis is a common condition affecting 5%–10% of the general population [1]. Approximately 30%–50% of women with endometriosis are infertile, and 50% of infertile women suffer from endometriosis [2]. It is defined as the growth of endometrium-like tissue outside the uterus, which induces a chronic inflammatory reaction [3]. In women with unexplained subfertility, its prevalence is reported to be as high as 50% [4]. Despite its high prevalence, endometriosis remains an enigmatic disease, especially the association of minimal and mild disease with infertility.

The precise physiologic mechanism involved in the development of endometriosis lesions in the pelvis and abdominal cavity has not been elucidated. Furthermore, the exact mechanism by which endometriosis impairs fertility remains speculative. There is a lack of sufficient data to establish a significant correlation between those non-anatomical alterations and reproductive failure in humans with endometriosis. This is currently attributed to the altered immunologic milieu of peritoneal fluid by cytokines, proteases, prostaglandins, reactive oxygen species, IgG, IgA, lymphocytes, and autoantibodies [2]. These may lead to impaired ovulation, fertilization, embryo development, and implantation. Moderate-to-severe disease is known to cause

anatomic distortion and hence interferes with fecundity. Surgical treatment of the lesions is proven to improve the chance of pregnancy even in minimal and mild disease [5-7]. Following surgical treatment, expectantly awaiting conception or moving to ovarian stimulation and intrauterine insemination (IUI) remains a debatable issue. However, considering improvements in surgical corrections would be best garnered with active interventions in the first few cycles including superovulation (SO) and IUI, which have shown improved live birth rates (LBRs) [8]. However, in vitro fertilization (IVF), which has the best outcome, is generally offered after failed attempts at SO and IUI, particularly in minimal and mild disease.

Gonadotropin-releasing hormone agonists (GnRHa) have an established role in pain management [9], but its role in fertility improvement is uncertain. It has shown to improve results when administered before IVF [10], but its use before ovarian stimulation and IUI has not been explored. Laparoscopic surgery, GnRHa therapy, SO, and IUI have individual benefits in improving fertility in women with endometriosis, but they have not been studied together in a prospective manner. The aim of our study is to evaluate the role of GnRHa in improving outcome in women undergoing SO and IUI after surgical correction of mild endometriosis.

Materials and Methods

The study was a randomized controlled trial conducted in the Department of Obstetrics and Gynecology at All India Institute of Medical Sciences, New Delhi, India, over a period of 2 years and 6 months. Approval for the study was obtained from the institute's ethics committee board.

Patients with unexplained infertility and suspected endometriosis were recruited from the gynecology and infertility clinic after a basic workup for infertility, which included a detailed history, examination, and investigations for the couple. Optimum investigations for the evaluation of infertility included detailed semen analysis (to exclude male factor); endometrial biopsy (to exclude tuberculosis); baseline serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH) levels on days 2–5 of the menstrual cycle (to exclude ovarian failure, hyperprolactinemia, and thyroid dysfunction); hysterosalpingogram during the follicular phase to exclude tubal and uterine factor defects; and ultrasonography (USG) of the pelvis to rule out any associated pelvic pathology. Informed written consent was obtained from the patients after thorough counseling.

Women older than 36 y who had pelvic inflammatory disease including genital tuberculosis, polycystic ovarian syndrome, diminished ovarian reserve (serum FSH level>10 mIU/mL, Antimullerian hormone <1.1 ng/mL), or factors advocating outright IVF as in moderate or severe endometriosis, and recurrent endometriosis and cases of severe male factor infertility were excluded from the study. Besides, patients with conditions that could impede implantation as in endometrial polyp or submucous myoma or thin endometrium were also excluded.

All patients underwent a standard three-port laparoscopy under general anesthesia by a single surgeon to evaluate the cause of infertility. Women who were diagnosed with endometriosis on laparoscopy were staged using the revised American Society for Reproductive Medicine (ASRM) criteria [11]. Women with ASRM stage II or mild endometriosis (score, 6–15) at laparoscopy were included in the study. These women underwent fulguration of endometriotic peritoneal implants, resection with fulguration of endometriotic nodules, and cystectomy with fulguration of endometriotic ovarian cysts. Bipolar cautery was used for fulguration.

Thereafter, patients were randomized into two groups, study (group A) and control groups (group B), based on computer-generated random numbers. Randomization was done by one of the data entry operators from the department who was not involved in the study and not by any of the clinicians involved during surgery or treatment cycles post-surgery. Patients in the study group (group A) received a single dose of 3.75 mg GnRHa–leuprolide acetate subcutaneously within 48 h after surgery, whereas the control group (group B) did not receive GnRHa. The injection leuprolide acetate (injection Leuprodex depot) was given free of cost. The pharmaceutical company Bharat Serums and Vaccines Limited, Mumbai, India, declared no conflict of interest for the same. Thereafter, patients in both arms underwent SO and IUI beginning at the next menstrual cycle.

Ovarian stimulation was performed in all women using a combination of clomiphene citrate and urinary human menopausal gonadotropin (hMG) in a sequential therapy, wherein clomiphene citrate (50 mg; Siphene, Cipla Pharmaceuticals Limited, Mumbai, India) was started on day 3 of the menstrual cycle for 5 days. hMG injection (150 IU; HUMOG, Bharat Serum and Vaccines Limited, Mumbai, India) was given intramuscularly on days 7 and 9 of the menstrual cycle. Serial transvaginal sonography was started on day 10 of the cycle to track follicular development and endometrial thickness (ET) and to check treatment response. An additional dose of hMG was given when the response on follicular tracking was sub-optimal (<10 mm follicle on day 10 scan). Once follicle size reached ≥18 mm and ET ≥7 mm, human chorionic gonadotropin injection (5000 IU; hCG, HUCOG, Bharat serum and vaccines limited, Mumbai, India) was given intramuscularly to

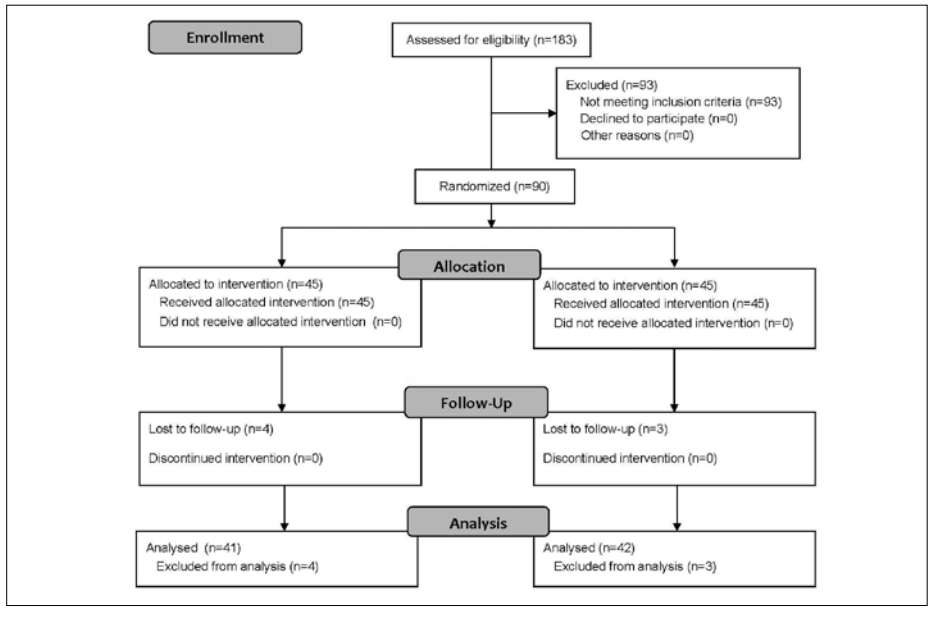

Figure 1. Flowchart of the study

trigger ovulation. IUI was performed 36 h after injecting hCG. The cycle was canceled if more than four dominant follicles developed on days 10–12 on monitoring or if there was no response with clomiphene citrate and increasing doses of hMG until day 16 of stimulation.

The outcome measures were compared between cases and controls at the end of the first cycle of SO followed by IUI, as the effects of GnRHa would prevail for approximately 4 weeks that is up to the first cycle. Subsequent cycles would not have a bearing of the GnRHa effect. However, up to three cycles of SO+IUI were given to patients in both groups as is the practice of our fertility units before moving to IVF.

Primary outcomes measured were LBRs and clinical pregnancy rate. A urine pregnancy test was performed 14 days after IUI or in case the patient missed her period. A quantitative serum beta-hCG test was performed followed by a USG at 6 weeks to confirm pregnancy. Clinical pregnancy was defined as the presence of a viable intrauterine pregnancy during scans performed at 6 weeks. All pregnant women were then further followed up during their pregnancy until delivery. A live birth was defined as the delivery of fetus after 26 weeks.

Sample Size Calculation

Using the software Stata 9.0 (Stata Corp 4905, Texas, USA) and based on the study by Rickes et al. [12], to achieve a power of 80% with an alpha error of 5%, an estimated sample size of 40 per group was established. Rickes et al. [12] only documented clinical pregnancy rates and did not measure LBRs. In women with mild endometriosis, they found higher pregnancy rate with postoperative GnRHa therapy followed by IUI than with surgery alone (86% vs. 58%). Considering 10% loss to follow-up, we recruited 45 patients per group.

Secondary outcome measures assessed were the number of follicles>18 mm in diameter, ET, dose and days of gonadotropin stimulation.

As shown in Figure 1, a total of 183 women who presented to our gynecology or infertility clinic were assessed for eligibility. Of these women, 93 (50.8%) were not eligible for the study, as they did not meet the inclusion criteria. Ninety infertile women who were diagnosed with mild endometriosis on laparoscopy were enrolled in the study. Women in group A (n=45) received GnRHa injections in the postoperative period. Four patients of group A and three patients of group B were lost to follow-up before the first cycle. Hence, 41 patients in group A and 42 patients in group B underwent SO and IUI cycles. A total of 156 treatment cycles were conducted. A maximum of three cycles was offered to the patients. The number of cycles varied from 1 to 3 in either group, with the majority of patients undergoing the first cycle (group A, 39% and group B, 43%).

Statistical Analysis

Statistical analysis was conducted using software Stata 11.0 (College Station, Texas, USA). Data were presented as number (percentage) or mean±SD/median (minimum, maximum) as appropriate. Baseline categorical variables were compared between the groups using chi-square test/Fischer's exact test, and continuous variables were compared using student's t-test

Table 1. Baseline characteristics

Variable	Group A (n=45)	Group B (n=45)	p
Age (years)	29.4+2.86	28.3+3.35	0.10
BMI (kg/m2)	25.3+3.66	25.5+2.31	0.83
Primary infertility	38 (84.4%)	28 (62.2%)	0.017
Secondary infertility	7 (15.6%)	17 (37.8%)	0.017
Duration of infertility (years)	4 (1–13)	4 (2–16)	0.78
Mild dysmenorrhea	10 (22.2%)	6 (13.3%)	0.27
Total count (million/mL)	78 (19–224)	75 (15–256)	0.92
Sperm motility (%)	67.9 (13.5)	61.1 (15.5)	0.02
Motile sperm count (million/mL)	53.2 (8.5–148)	46.8 (3.75–230.4)	0.39
Normal sperm morphology (%)	63.51 (13.9)	60.58 (17.7)	0.38
Surgical procedure performed			
• Fulguration of spots	34 (75.6%)	41 (91.1%)	0.08
• Excision+fulgration	11 (24.4%)	04 (9.9%)	

BMI: body mass index

Table 2. Secondary outcome parameters

Parameter	Group A (n=41)	Group B (n=42)	p
Dose of gonadotrophin (IU)	302.74 (17.5)	305.35 (24.2)	0.57
Duration of stimulation (days)	2 (0)	2.02 (0.11)	0.16
Number of follicles>18 mm in size	1.34 (0.36)	1.36 (0.42)	0.85
Endometrial thickness (mm)	9.7 (1.86)	9.1 (1.79)	0.13
Post-wash motile sperm count (million/mL)	46 (15–138)	40.5 (15–200)	0.42
Day of trigger	13.7 (0.92)	13.3 (1.22)	0.13
Cycle cancelation	None	None	

IU: international unit, mm: millimeter

Table 3. Primary outcome measures

Characteristic	Group A (n=41)	Group B (n=42)	p
Number of cycles	76	80	
Number of patients who conceived	9	10	
Pregnancy rate per cycle	11.8%	12.5%	0.90
Overall pregnancy rate	21.9%	23.8%	1.00
Cycle-wise distribution of pregnancies in the two groups			
Cycle 1	7/41 (17.1%)	8/42 (19.1%)	0.81
Cycle 2	1/25 (4%)	1/24 (4.2%)	1.00
Cycle 3	1/10 (10%)	1/14 (7.1%)	1.00
Live birth rate	21.9%	23.8%	1.00

for independent samples/Wilcoxon's rank-sum test, as the data were not following normal distribution. A P-value of<0.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics, such as age and body mass index, were comparable in both groups as shown in Table 1. A significant difference was found in the distribution of patients between the two groups despite randomization, with more number of primary infertility patients in group A. The baseline hormone profile was also similar in both groups (Serum FSH: p=0.63, LH: p=0.28, prolactin: p=0.21, and TSH: p=0.66).

Semen analysis in the two groups was based on the WHO 2010 criteria [13]. Overall, the count, motility, and morphology were within normal limits. Sperm motility was significantly higher in group A than in group B, but the motile sperm count between the two groups was comparable (Table 1).

The major surgical procedure was fulguration of endometriotic spots in both the groups followed by endometriotic cyst excision with or without fulguration (Table 1).

Prior to surgery, menstrual cycle characteristics were comparable in both groups with respect to cycle frequency (p=0.11) and mild dysmenorrhea (p=0.27) as described in Table 1. Post-surgery, in group A, there was a variable cessation of menses after GnRHa injection. A majority (32 of 41, 78%) of women had amenorrhea lasting for 7–8 weeks, and the rest of the women had amenorrhea for 4–6 weeks. No amenorrhea was observed in group B. There were no symptoms of acute estrogen withdrawal such as hot flushes in group A. In group B, menstrual features did not change after surgery.

Cycle Outcome (Secondary Outcome)

The SO+IUI cycles were comparable between the two groups with regard to the secondary outcome parameters, which include dose and days of gonadotropin stimulation, number of dominant follicles>18 mm in diameter, and the day of ovulation trigger (Table 2).

None of the cycles was canceled in either group.

On an average, 1–2 follicles formed in each patient per cycle in both groups. All patients developed an ET of>7 mm. The mean ET in the first cycle was significantly higher in group A than in group B (10.2 vs. 9.1 mm, respectively, p=0.009). However, it was comparable in the remaining two cycles.

No significant difference was observed in the dose of hMG used and the duration of gonadotropin stimulation between the two groups. The post-wash motile sperm count between the two groups was also similar.

Primary Outcome Measures

The overall clinical pregnancy rate and LBR was similar in both groups as summarized in Table 3. We did not find any beneficial effect of GnRHa on fertility outcome.

When analyzed over the three cycles, the maximum number of pregnancies was seen in the first cycle in both groups. In our study, participation of the patients till the end of the third cycle was not compulsory, as the analysis of the effect of GnRHa can be assessed only at the end of the first cycle. Two more cycles were offered to the patients as a part of our unit protocol. However, the participation was seen to decline after the first cycle (Table 3).

All women who conceived after SO and IUI were booked with our antenatal unit and followed for their entire gestation in the unit. All the expecting women delivered at term gestation without any miscarriage or significant complications during pregnancy, with LBR being similar to the clinical pregnancy rate.

Discussion

Infertility associated with endometriosis has been treated empirically with assisted reproductive techniques. The role of GnRHa is well-established in cases of endometriosis-associated pain [9] and prior to IVF for long-term pituitary downregulation in women with endometriosis [10]. But its use before ovarian stimulation and IUI has not been explored. Advantages associated with depot GnRHa injection include its administration as a single monthly depot increasing patient acceptability. It has no major metabolic side effects except for reduction in bone mass on long-term use for which preventive strategies have been developed. However, side effects are associated with prolonged use of GnRHa, due to the profound hypoestrogenic state that includes hot flushes, headache, decreased libido, vaginal dryness, emotional lability, and insomnia.

Marcoux et al. [5] conducted a randomized controlled trial to determine whether laparoscopic surgery enhanced fecundity in infertile women with minimal or mild endometriosis and found the cumulative pregnancy rate to be 30.7% in women who underwent resection and ablation of endometriosis and 17.7% in women who underwent only diagnostic laparoscopy (p=0.006). The findings of this study are further supported by a meta-analysis published by Jacobson et al. [6], who demonstrated an advantage of operative laparoscopy (excision or ablation of endometriosis lesions) rather than diagnostic laparoscopy in terms of clinical pregnancy rates, with an OR of 1.66 (95% CI, 1.09–2.51) in infertile women with mild endometriosis.

On the contrary, a study by an Italian group showed a small negative effect. They reported higher pregnancy rate in women who underwent diagnostic laparoscopy than in those who underwent operative laparoscopy (29% and 24%, respectively, p>0.05) [14].

However, the results of Marcoux et al. [5] appear to be more reliable due to the higher power of their study. The conclusions of these studies suggest that when ectopic endometrial tissue is no longer present, the peritoneal environment becomes more favorable for pregnancy.

Milingos et al. [7] conducted a prospective cohort study on infertile women with minimal or mild endometriosis. Of the 151 women, operative laparoscopy was performed in 49 (group 1), diagnostic laparoscopy+GnRHa therapy was given in 59 (group 2), and diagnostic laparoscopy alone was performed in 43 patients (group 3). During a 24-month period, cumulative pregnancy rates were found to be 36.7%, 30.5%, and 20.9%, respectively. They concluded that laparoscopic surgery seems to be the milestone of treatment in such cases, increasing the fecundity and involving minimal risk. Pregnancy rates were comparable in groups 1 and 2 (p=0.19). However, both these groups had statistically significant higher pregnancy rates than group 3 (p=0.0001 and 0.014, respectively; group 1 and group 2 vs. group 3).

Similarly, in our study, the addition of GnRHa after laparoscopic treatment has not shown any significant difference in changing fertility outcome and does not have any added advantage in pregnancy rates.

Thus, it can be said that both surgical treatment (by ablation/resection) and treatment with GnRHa are equally effective in improving the hormonal milieu and that there is no added advantage of supplementing GnRHa over surgical treatment in patients with infertility. Fur-

thermore, patients can try for conception in the immediate cycle after surgical treatment, whereas GnRHa delays treatment by approximately 2 months due to the amenorrhea because of ovarian suppression. Also, there is an additional cost of therapy on administering GnRHa, which can be avoided if surgical treatment is done. However, GnRHa therapy might be a better option in cases wherein the focus of endometriosis is present in critical locations as in close proximity to the ureter; in such cases, attempting surgery can be risky for both patient as well as clinician. Postoperative GnRHa has a definite role in reducing pain and increasing time to recurrence of symptoms [15].

The next debatable issue is whether to go for SO and IUI or wait for spontaneous conception following surgical treatment and/or GnRHa therapy. We preferred to advise SO and IUI for these patients, as the best results are expected in the first few cycles. This theory is supported by several studies in the literature [8, 16, 17]. Tummon et al. [8] investigated the role of SO and IUI in improving fertility outcomes in infertile women with minimal or mild endometriosis. Live birth followed 11% of SO and IUI cycles and 2% of no-treatment cycles. They did not comment on the pregnancy rates. In addition, many of the patients (almost 50%) were not treated surgically during laparoscopy; therefore, the above pregnancy outcome cannot be compared with our results, as our patients underwent surgical treatment and subsequent SO and IUI. Fedele et al. [16] conducted a randomized controlled trial among 49 women with stage I/II endometriosis and infertility and compared three cycles of gonadotropin/IUI with 6 months of expectant management. They found significantly higher pregnancy rate per cycle in the gonadotropin/IUI group (15%) than in the untreated group (4.5%) ($p<0.05$). Another study by Kemmann et al. [17] reported higher pregnancy rate in women with infertility and minimal or mild endometriosis who received gonadotropin therapy or clomiphene citrate than those who did not receive any treatment (7.3%, 6.6%, and 2.8%, respectively). To emphasize, SO and IUI should be considered in infertile women with minimal and mild endometriosis.

To assess the role of GnRHa in various stages of endometriosis, Rickes et al. [12] conducted a prospective randomized controlled study among 110 infertile women with mild, moderate, or severe endometriosis. All women underwent operative laparoscopy. After that, 55 women received GnRHa therapy for 6 months followed by artificial reproductive technique (ART), and the remaining 55 women received ART immediately after surgery. In women with mild endometriosis, the pregnancy rate was higher with postoperative GnRHa therapy followed by IUI than surgery alone (86% vs. 58%), but this benefit was not statistically significant. Whereas in patients with mild endometriosis who opted for IVF or ICSI, the pregnancy rate was slightly lower in those who received GnRHa than in those who underwent only surgery (50% vs. 56%). In patients with moderate or severe endometriosis who underwent IVF or ICSI, GnRHa treatment significantly increased pregnancy rates compared with patients with surgery alone (82% vs. 40%; $p<0.05$). They concluded that postoperative GnRHa therapy is not useful for patients with mild endometriosis. It may be beneficial for women with advanced endometriosis, especially for patients undergoing IVF or ICSI.

Randomized prospective nature with pre-calculated sample size are the strengths of this study. Moreover we followed up all the women throughout the pregnancy, LBR was one of the primary outcome measures. Although the sample size was pre-calculated, a larger sample or a multicentric study to get a larger sample would have produced more robust results. This was perhaps one of the possible limitations of our study.

There is a clinical dilemma for the management of mild endometriosis, which clinicians usually face after surgical management, as to whether they should or should not give GnRH. In our study, both clinical pregnancy rate and LBR were comparable. We did not find any benefit of adding GnRHa after surgical management in women with mild endometriosis undergoing SO and IUI over surgical management alone.

After the analysis of our data, we conclude that postoperative GnRHa is not effective in women with mild endometriosis in improving fertility outcome. Although GnRHa may be equally effective as surgery, it delays resumption of menstrual cycles, impeding the chances of pregnancy, besides adding to the cost of therapy. Long-term follow-up studies with larger sample size are required to assess whether these patients do conceive spontaneously and whether the change in hormonal milieu leads to a better pregnancy outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of All India Institute of Medical Sciences, New Delhi, India.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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