

Symptom control after different duration of triptorelin treatment following conservative surgery for deep infiltrating endometriosis

Post-hoc analysis of a multicentre, prospective, real-world study

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Abstract

Triptorelin has been used after surgery in deep infiltrating endometriosis. This post-hoc analysis aimed to evaluate symptom control between patients receiving 1–3 triptorelin injections and those receiving 4–6 injections within 24 months of conservative surgery for deep infiltrating endometriosis, in the real-world.

Included patients were divided into two groups (received up to 3 months injections in group A, 4–6 injections in group B) based on the numbers of triptorelin (Diphereline, 3.75 mg intramuscular injection once every 28 days for up to 24 weeks) administration. Evolution in score of pain intensity at 3, 6, 9, 12, 18, and 24 months after primary triptorelin administration and symptom improvement/recurrence rates between two groups were compared. Symptoms of pain intensity were assessed using a visual analogue scale (VAS) with a range from 0 to 10 cm. An improvement in symptoms was defined as a reduction of at least 3 cm or 3 units from pre-surgery levels.

156 patients in group A and 228 in group B. Pain symptom score (mean \pm standard deviation) diminished to a nadir at 3-months for group A and 6-months for group B; at 6-months nadir scores were significantly lower in group B (0.9 ± 1.7 vs 0.4 ± 1.2 respectively, $P = .002$). No significant difference for pain symptom scores between both groups at 24-months ($P = .269$). The 6-month and 24-month cumulative improvement rates of pain (80.6% vs 89.8%, $P = .014$ and 82.6% vs 90.7%, $P = .025$) and gastro-intestinal symptoms (61.0% vs 80.8%, $P = .022$ and 61.0% vs 83.3%, $P = .008$) were significantly higher in group B, whereas there was no significant difference in rates of menstrual disorders and urinary symptoms. There is no significant difference for 12-months and

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Valerie Perrot and Hongbo Li are employees of Ipsen. The other authors have stated explicitly that there are no conflicts in connection with the article.

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The study was approved by the Institutional Review Board at Women's Hospital, School of Medicine, Zhejiang University and by ethical committees of all study centres in the date of June 24, 2013 with the reference number of 2013 (0017).

Informed consent was obtained from all individual participants included in the study.

Where patient data can be anonymised, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

The first study focuses on the symptom control in comparison of different duration of post-operative triptorelin therapy in patients with deep infiltrating endometriosis conducted in multi-centres in China and suggests that treatment duration may affect the efficacy.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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24-months cumulative recurrence rates of total symptoms between both groups (11.3% vs 13.8%, $P = .568$ and 16.1% vs 26.0%, $P = .094$).

In women with deep infiltrating endometriosis, longer treatment with triptorelin following conservative surgery was associated with a decrease in symptom intensity and greater improvement of pain symptoms in the short-term and greater improvement of gastrointestinal symptoms in the long-term.

Trial registration number: ClinicalTrials.gov, NCT01942369.

Abbreviations: CI = confidence interval, DIE = deep infiltrating endometriosis, GnRH-a = gonadotropin-releasing hormone agonists, HR = hazard ratio.

Keywords: deep infiltrating endometriosis, post-operative, treatment duration, triptorelin

1. Introduction

Deep infiltrating endometriosis (DIE) as the most debilitating form of endometriosis is estimated to affect more than 20% of women with endometriosis.^[1,2] It is defined by the infiltration by endometriotic tissue beneath the peritoneum of more than 5 mm with symptoms of severe pain and infertility.^[3,4] DIE is responsible for various symptoms such as chronic pelvic pain, coital pain, dysmenorrhea, menstrual urinary and intestinal symptoms.^[3] Moreover, DIE affects several locations including uterosacral ligament, bladder and ureter, intestine, vaginal rectovaginal septum, vagina, etc.^[3] It greatly reduces the quality of life of patients, meanwhile it increases the difficulty of treatment and increases the financial burden of their families.^[5]

Surgery is often required for patients with DIE aiming at excising affected tissues to achieve symptom relief and restore fertility.^[6] Compared with radical surgical operation, conservative surgery might have a reduction of trauma and complications, so conservative surgery is also considered the preferable option aiming at complete disease excision. Conservative surgery can be appropriate for many patients with DIE and more patients may benefit from rectal sparing procedures.^[6–9] However, the rate of symptom recurrence after conservative surgical approach is very high, long-term care and medical therapy is always warranted.^[2]

Pharmacological therapy combined with conservative surgical treatment have been proved to achieve the best therapeutic effects.^[5] Medical treatments include combined oral contraceptive pills, danazol, gestrinone, progestogen, and gonadotropin-releasing hormone agonists (GnRH-a).^[10–12] It has been proved that GnRH-a have an important role in the treatment of endometriosis after conservative surgery with the aim to help relieve pain and reduce the risk of recurrence.^[5,13–15] Currently, it is widely used for the therapy of endometriosis.^[16] Moreover, GnRH-a therapy following conservative surgery is appreciated to be a good choice in the long-term care of patients with DIE. However, the use of GnRH-a is usually limited to 6 months due to risk of bone loss for longer prescription.^[13]

Triptorelin (D-Trp6-LHRH) is one of the most commonly used GnRH-a and can improve post-operative pain symptoms, such as dysmenorrhoea, dyspareunia and pelvic pain.^[17,18] A prospective observational study performed in China investigated the effects of triptorelin in the treatment of patients with endometriosis, using a 6-week versus 4-week triptorelin drug regimen.^[19] The study suggested that similar efficacy and symptom recurrence were achieved from both therapeutic regimens. However, the single-centre study was with a small sample and a narrow population. The duration and efficacy of post-operative triptorelin therapy remains the subject of debate in China.

This was a post-hoc analysis of a multicentre, prospective, real-world study whose publication were in press. The primary

objectives were to evaluate and compare the evolution of symptom score and improvement rates by the number of triptorelin injections within 24 months after surgery for DIE. The secondary objectives were to compare symptom recurrence and pain-free intervals.

2. Materials and methods

The study was approved by the Institutional Review Boards of the hospitals in which it was performed and the Institutional Review Boards of Women's Hospital, School of Medicine, Zhejiang University approved the study. It was registered at www.clinicaltrials.gov, number NCT01942369.

2.1. Participants and clinical characteristics

A prospective real-world study was performed in 18 tertiary hospitals in China. Premenopausal Chinese women aged ≥ 18 years old with a diagnosis of DIE who had undergone surgery prior to triptorelin (Diphereline, Ipsen Pharma Biotec, Paris, France) 3.75 mg intramuscular injections (every 28 days for ≤ 24 weeks; ≤ 6 injections) therapy at the participating centres and who were mentally and physically able to describe their symptoms and answer questions between September 2013 to July 2016 were included. Patients who were pregnant or lactating, who might reach menopause within 3 years after surgery, with a history of allergic reaction of triptorelin or one of the excipients, with a history of treatment of other drugs within 3 months and GnRH-a therapy within 6 months prior to the study, who were potentially non-compliant or unsuitable for the study for other reasons were excluded.

In the post-hoc analysis, patients were divided into two groups based on the duration of triptorelin administration, patients received 1 to 3 injections in group A, 4 to 6 injections in group B. Information of pain, menstrual disorders, gastro-intestinal and urinary discomfort were focused on and collected during 3-monthly (first-year follow-up) and 6-monthly (second-year follow-up) routine post-operative hospital visits. All participants were followed for a period of 24 months after surgery.

Baseline characteristics including age, body mass index, DIE lesion, history of surgical and hormonal therapy, and symptoms (i.e. pain, menstrual disorders, gastro-intestinal and urinary symptom) intensity between two groups were collected and compared.

The study was approved by the respective Ethical Committees of all participating sites. An informed consent was signed by all eligible participants.

2.2. Outcomes of interest

Primary outcomes of interest were comparisons between the two groups in evolution in score of pain intensity (visual analogue

scale) and cumulative symptom improvement rates, at 3, 6, 9, 12, 18, and 24 months after primary triptorelin therapy. The definition of symptom improvement was a reduction of at least 3 cm or 3 units from pre-surgery.

Secondary outcomes of interest were to compare symptom recurrence and time to relapse of pain between the two groups. Symptom recurrence was defined as an increase of more than 3 cm or 3 units compared to the lowest previous score. Pain-free interval is the time elapsed from date of disappearance of symptoms (at month 3 or month 6) up to the first occurrence of pelvic pain, dysmenorrhoea, pain at time of ovulation or dyspareunia (visual analogue scale > 3). Patients without occurrence of pain were censored at the date of the last study visit.

Duration of triptorelin treatment was the interval between first and last dose. The predictive factors of triptorelin duration were explored.

2.3. Statistical analysis

Continuous variables were expressed as mean \pm standard deviation and compared with F test or analysis of variance. Categorical variables are expressed as frequency/proportions and compared using a χ^2 test or Fisher's exact test or Wilcoxon rank sum test for ordinal variables. The evolution of symptom pain intensity was compared by F test or analysis of variance. The cumulative improvement and recurrence rates between the two groups were compared by univariate logistic regression. The time to relapse of pain was assessed and survival curves in the two groups were drawn using Kaplan-Meier method and compared by Log-rank test. Univariate and multivariate Cox regression models were conducted to identify the predictive factors of triptorelin duration among the demographics and clinical characteristics at baseline.

Variables included in the multivariate analysis were those with a P -value < .2 in the univariate analysis. Statistical analysis was performed using the software of SAS version 9.21 (SAS Institute, Cary, NC). P < .05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

In total, 402 patients were screened for eligibility, 2 excluded because of not meeting the inclusion criteria and 1 withdrew consent, and 399 were enrolled. Of them, 15 patients who did not receive an injection of triptorelin were excluded, therefore, 384 (96.2%) women who received triptorelin therapy with diagnosis of DIE were included in the final analysis (Fig. 1). Among them, 156 (40.6%) patients were in group A with a mean age of 32.8 ± 5.7 years and 228 (59.4%) in group B with a mean age of 33.7 ± 6.5 years ($P = .162$).

Table 1 shows demographic and clinical characteristics of participants who had up to 3 triptorelin injections versus those who had 4–6 injections. Baseline characteristics were not significantly different between the two groups except for location of DIE lesions; fewer patients in group A had intestinal (49.4% vs 59.6%, $P = .048$) or vaginal lesions (5.8% vs 12.3%, $P = .036$).

At baseline, the proportions of women reporting pain symptoms in group A and group B were respectively null (7.7%, 5.3%), mild (19.2%, 16.2%), moderate (28.2%, 28.5%) and severe (44.9%, 50.0%), the difference between two groups was without significance ($P = .601$). The proportions of pain at time of ovulation in both groups were null (72.4%, 58.3%), mild (20.5%, 24.1%), moderate (5.1%, 11.4%) and severe (1.9%, 6.1%), the difference was significant ($P = .011$). The proportions

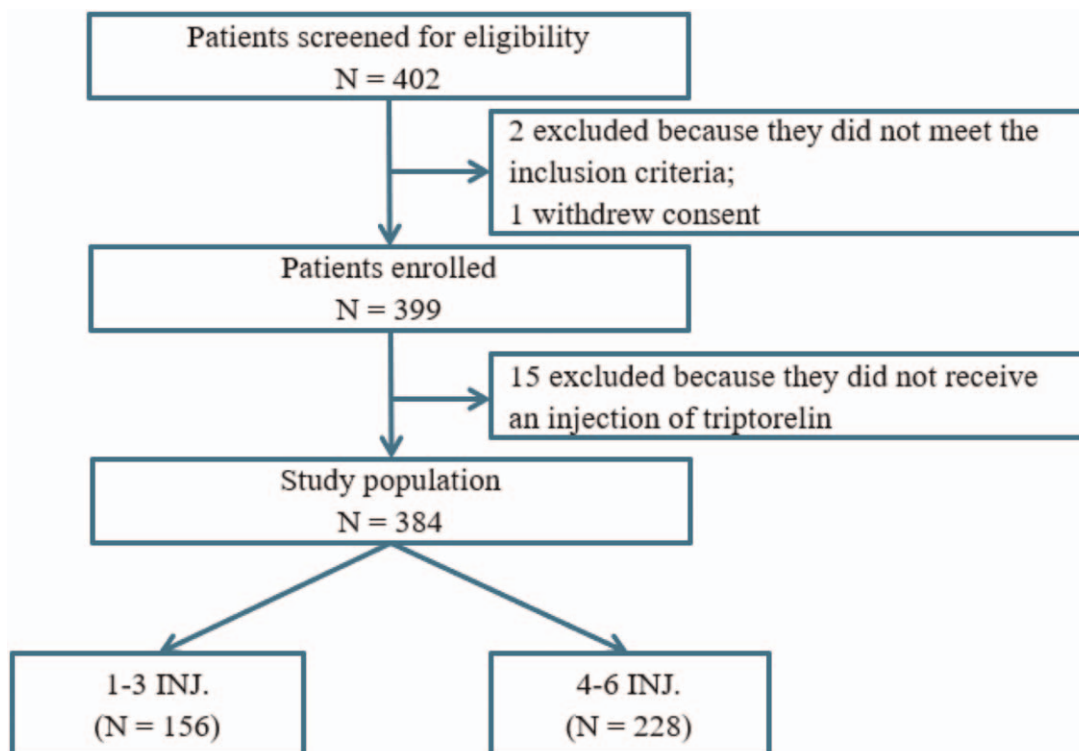


Figure 1. Flow diagram of study population.

Table 1
Demographics and baseline characteristics of study population.

Baseline characteristics	Group A		Group B		P-value
	N	mean ± SD / n (%)	N	mean ± SD / n (%)	
Age	156	32.8 ± 5.7	228	33.7 ± 6.5	.162 ^α
BMI	153	21.1 ± 2.7	226	21.0 ± 2.9	.733 ^α
Age at first endometriosis symptoms	143	30.1 ± 6.9	184	30.4 ± 7.5	.723 ^α
Age when first medical attention sought	143	30.9 ± 6.1	184	31.7 ± 6.5	.264 ^α
Age at first endometriosis surgical diagnosis	24	28.7 ± 3.2	56	30.4 ± 5.9	.175 ^α
Ever had a hormonal treatment for endometriosis	156	23 (14.7)	228	40 (17.5)	.487 ^β
Oral contraceptive pills treatment duration	5	4.6 ± 1.9	5	25.8 ± 32.4	.182 ^α
Gn-RH agonists treatment duration	3	4.3 ± 1.5	15	3.9 ± 2.0	.704 ^α
Traditional Chinese medication treatment duration	18	8.0 ± 11.5	20	12.9 ± 17.9	.328 ^α
Ovarian endometrioma	156	149 (95.5)	228	208 (91.2)	.154 ^γ
Main DIE lesions	156		228		
Ureter		6 (3.8)		4 (1.8)	.328 ^γ
Intestine		77 (49.4)		136 (59.6)	.048 ^γ
Bladder		5 (3.2)		3 (1.3)	.279 ^γ
Associated DIE lesions	156		228		
Vagina		9 (5.8)		28 (12.3)	.036 ^γ
Left uterosacral ligament		20 (12.8)		22 (9.6)	.405 ^γ
Right uterosacral ligament		12 (7.7)		19 (8.3)	.852 ^γ
Bilateral uterosacral ligament		70 (44.9)		124 (54.4)	.077 ^γ

Group A: patients received up to 3 injections of triptorelin. Group B: patients received 4–6 injections of triptorelin. ^αP-values are based on F test. ^βP-values are based on Fisher exact test. ^γP-values are based on Fisher exact test.

BMI = body mass index, DIE = deep infiltrating endometriosis, SD = standard deviation.

of dyspareunia in two groups were null (62.2%, 54.4%), mild (25.6%, 18.9%), moderate (11.5%, 17.1%) and severe (0.6%, 9.6%) with statistical significance ($P < .001$) (Fig. 2).

The proportion of previously surgically diagnosed with endometriosis in group A was significantly lower than that in group B (15.4% vs 24.6%, $P = .030$). The differences of others surgical history were not statistically significant (Table 2).

3.2. Outcomes of interest

All symptom scores decreased significantly between baseline and 3 months and remained stable until 24 months (Fig. 3). Pain symptom score (mean ± standard deviation) decreased from baseline to nadir (5.6 ± 3.2 vs 0.6 ± 1.3 , $P < .001$) at 3-months in group A, whereas the score decreased to nadir (6.0 ± 2.9 vs 0.4 ± 1.2 , $P < .001$) at 6-months in group B; at 6-months nadir scores

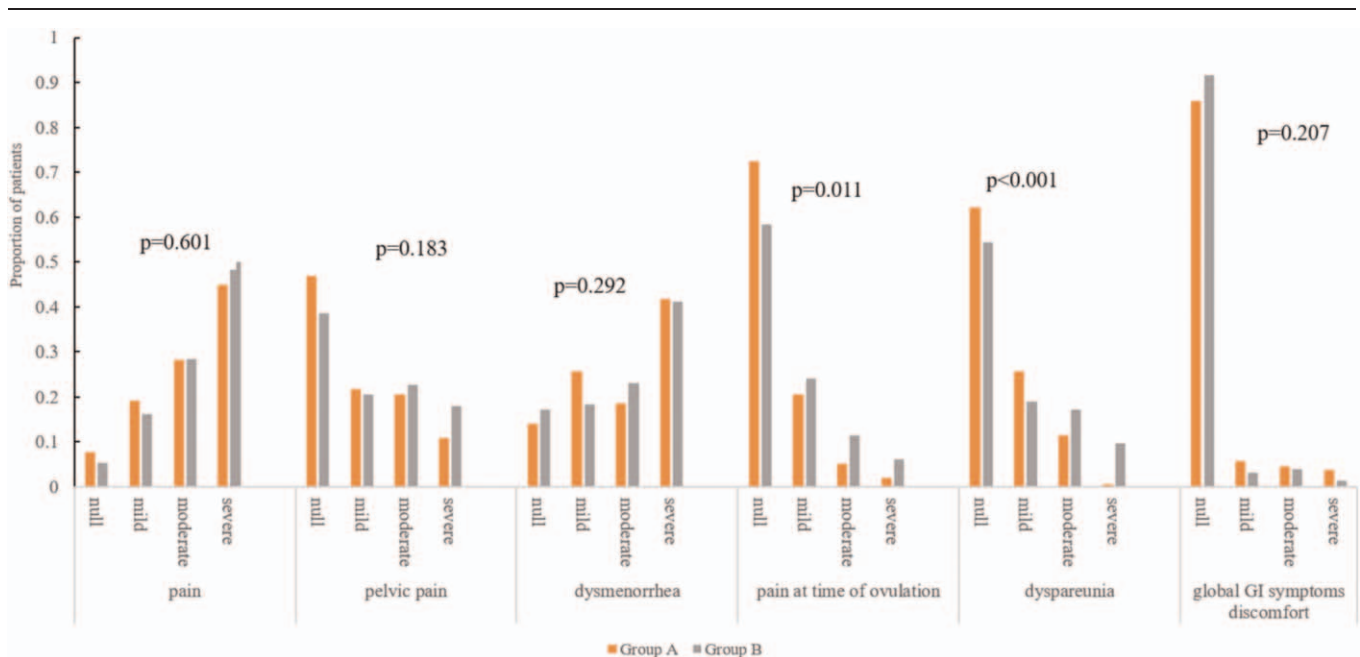


Figure 2. Proportion of patients with different symptom intensity pre-surgery.

Table 2
Surgical history of study population.

Baseline characteristics	Group A		Group B		P-value
	N	n (%)	N	n (%)	
Previously surgically diagnosed with endometriosis	156	24 (15.4)	228	56 (24.6)	.030 ^β
Ever operated for endometriosis (other than DIE)	24	10 (41.7)	56	33 (58.9)	.221 ^β
No. of previous Non DIE-endometriosis surgery-Laparoscopy	10		33		.522 ^γ
0		4 (40.0)		10 (30.3)	
1		6 (60.0)		22 (66.7)	
2		0 (0.0)		1 (3.0)	
No. of previous Non DIE-endometriosis surgery-Lower midline incision	10		33		.905 ^γ
0		6 (60.0)		21 (63.6)	
1		4 (40.0)		11 (33.3)	
2		0 (0.0)		1 (3.0)	
No. of previous Non DIE-endometriosis surgery-Pfannenstiel incision	10		33		.078 ^γ
0		9 (90.0)		33 (100.0)	
1		1 (10.0)		0 (0.0)	
Ever operated for DIE	24	1 (4.2)	56	3 (5.4)	1.000 ^β
No. of previous DIE surgery-Laparoscopy	1		3		.617 ^γ
0		1 (100.0)		1 (33.3)	
1		0 (0.0)		2 (66.7)	
No. of previous DIE surgery-Lower midline incision	1		3		.617 ^γ
0		0 (0.0)		2 (66.7)	
1		1 (100.0)		1 (33.3)	
Surgical procedure	156		228		.706 ^γ
Laparoscopy		151 (96.8)		218 (95.6)	
Laparoscopy + Laparotomy		0 (0.0)		2 (0.9)	
Laparotomy		5 (3.2)		8 (3.5)	

Group A: patients received up to 3 injections of triptorelin. Group B: patients received 4–6 injections of triptorelin. ^βP-values are based on Fisher's exact test. ^γP-values are based on Wilcoxon rank sum test. DIE: deep infiltrating endometriosis.

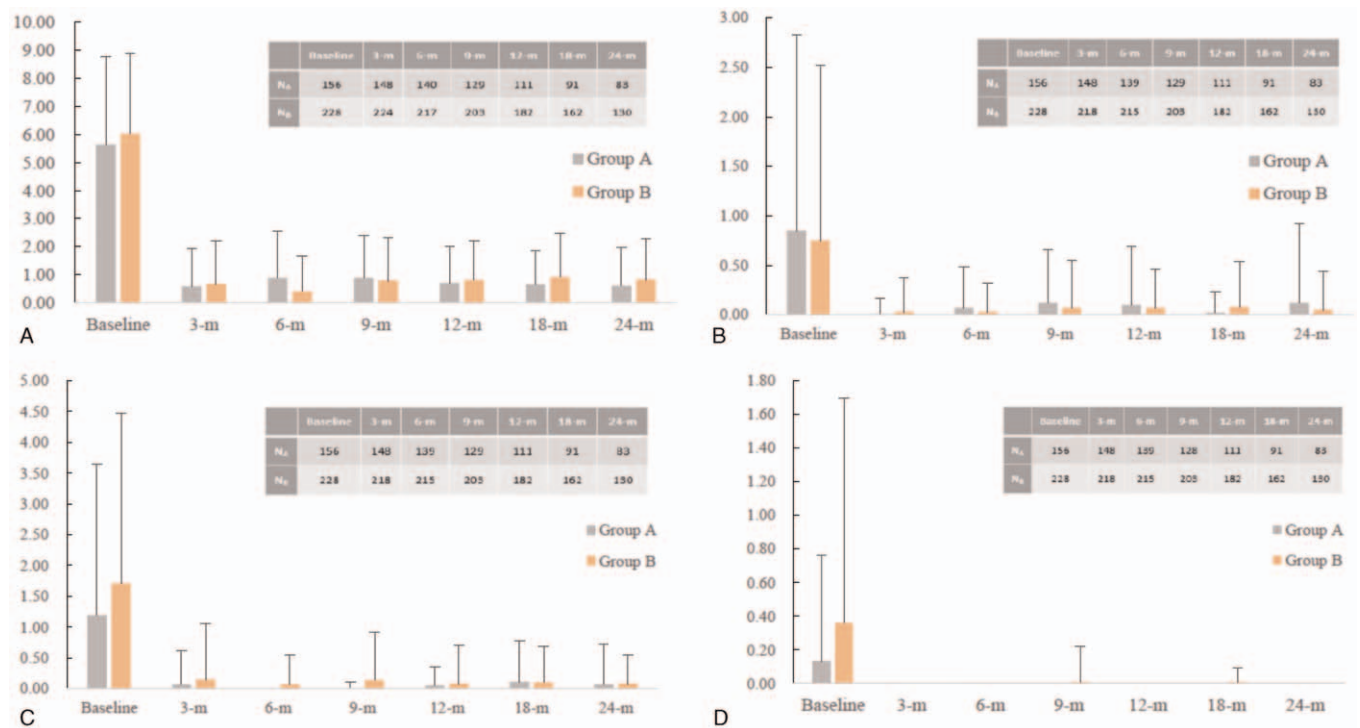


Figure 3. Summary of symptoms scores for study population in 24 months.

Table 3
Cumulative improvement rates of specific endometriosis symptoms in 24 months.

Timeline	Group A		Group B		Group A vs Group B		
	n/N	% (95%CI)	n/N	% (95%CI)	Odds ratio	95% CI	P-value
Pain symptoms							
3-mo	114/144	79.2 (71.6, 85.5)	185/216	85.6 (80.3, 90.0)	0.5	(-0.1, 1.0)	.110
6-mo	116/144	80.6 (73.1, 86.7)	194/216	89.8 (85.0, 93.5)	0.8	(0.2, 1.4)	.014
9-mo	118/144	81.9 (74.7, 87.9)	196/216	90.7 (86.1, 94.3)	0.8	(0.1, 1.4)	.016
12-mo	119/144	82.6 (75.4, 88.4)	196/216	90.7 (86.1, 94.3)	0.8	(0.1, 1.4)	.025
18-mo	119/144	82.6 (75.4, 88.4)	196/216	90.7 (86.1, 94.3)	0.8	(0.1, 1.4)	.025
24-mo ^α	119/144	82.6 (75.4, 88.4)	196/216	90.7 (86.1, 94.3)	0.8	(0.1, 1.4)	.025
Menstrual disorders							
3-mo	20/31	64.5 (45.4, 80.8)	31/42	73.8 (58.0, 86.1)	0.4	(-0.6, 1.4)	.394
6-mo	20/31	64.5 (45.4, 80.8)	33/42	78.6 (63.2, 89.7)	0.7	(-0.3, 1.7)	.187
9-mo	20/31	64.5 (45.4, 80.8)	33/42	78.6 (63.2, 89.7)	0.7	(-0.3, 1.7)	.187
12-mo	20/31	64.5 (45.4, 80.8)	33/42	78.6 (63.2, 89.7)	0.7	(-0.3, 1.7)	.187
18-mo	20/31	64.5 (45.4, 80.8)	33/42	78.6 (63.2, 89.7)	0.7	(-0.3, 1.7)	.187
24-mo ^α	20/31	64.5 (45.4, 80.8)	33/42	78.6 (63.2, 89.7)	0.7	(-0.3, 1.7)	.187
Gastro-intestinal symptoms							
3-mo	25/41	61.0 (44.5, 75.8)	61/78	78.2 (67.4, 86.8)	0.8	(0.0, 1.7)	.049
6-mo	25/41	61.0 (44.5, 75.8)	63/78	80.8 (70.3, 88.8)	1.0	(0.1, 1.8)	.022
9-mo	25/41	61.0 (44.5, 75.8)	65/78	83.3 (73.2, 90.8)	1.2	(0.3, 2.0)	.008
12-mo	25/41	61.0 (44.5, 75.8)	65/78	83.3 (73.2, 90.8)	1.2	(0.3, 2.0)	.008
18-mo	25/41	61.0 (44.5, 75.8)	65/78	83.3 (73.2, 90.8)	1.2	(0.3, 2.0)	.008
24-mo ^α	25/41	61.0 (44.5, 75.8)	65/78	83.3 (73.2, 90.8)	1.2	(0.3, 2.0)	.008
Urinary symptoms							
3-mo	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562
6-mo	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562
9-mo	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562
12-mo	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562
18-mo	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562
24-mo ^α	4/8	50.0 (15.7, 84.3)	13/21	61.9 (38.4, 81.9)	0.5	(-1.2, 2.1)	.562

Group A: patients received up to 3 injections of triptorelin. Group B: patients received 4–6 injections of triptorelin. ^α The 24-month visit data or last available data. The table presents the improvements of symptoms on patients with symptoms (intensity > 0) at baseline. Logistic regression was used for the comparison.

were significantly lower in group B (0.9 ± 1.7 vs 0.4 ± 1.2 , $P = .002$). No significant difference between both groups at 24 months (0.6 ± 1.4 vs 0.8 ± 1.5 , $P = .269$). Scores of menstrual disorders decreased from baseline to nadir at 3-months in both of group A (0.9 ± 2.0 vs 0.0 ± 0.2 , $P < .001$) and group B (0.8 ± 1.8 vs 0.0 ± 0.4 , $P < .001$). The 24-months scores were no statistical significance between two groups (0.1 ± 0.8 vs 0.1 ± 0.4 , $P = .395$). Gastrointestinal symptom scores decreased from baseline to nadir at 6-months in both of group A (1.2 ± 2.5 vs 0.0 ± 0.0 , $P < .001$) and group B (1.7 ± 2.8 vs 0.1 ± 0.5 , $P < .001$). The 24-months scores were without statistical significance (0.1 ± 0.7 vs 0.1 ± 0.5 , $P = .898$).

The 6-month improvement rate of pain symptoms in group B was significantly higher than that in group A (80.8% vs 90.2%, $P = .015$). Likewise, the 18-month and 24-month improvement rates of gastro-intestinal symptoms in group B were significantly higher than those in group A (55.6% vs 80.4%, $P = .023$ and 59.0% vs 78.2%, $P = .032$). Moreover, the cumulative symptom improvement rates of 6 follow-up visits in group B were all higher than those in group A (Table 3). The 6-month and 24-month cumulative rates of symptoms were significantly higher in group B than those in group A for pain (80.6% vs 89.8%, $P = .014$ and 82.6% vs 90.7%, $P = .025$) and gastro-intestinal symptoms (61.0% vs 80.8%, $P = .022$ and 61.0% vs 83.3%, $P = .008$), whereas there was no significant difference in rates of menstrual disorders (64.5% vs 78.6%, $P = .187$ and 64.5% vs 78.6%, $P = .187$) and urinary symptoms (50.0% vs 61.9%, $P = .562$ and 50.0% vs 61.9%, $P = .562$).

The majority (60.0%) of pain recurrence for group A occurred during 6–9 months of the treatment while the majority of recurrence (53.5%) in group B occurred during 12–24 months. Table 4 describes the recurrence rate of pain during 24-months. For study population, the 12-months and 24-months cumulative recurrence rates (11.3% vs 13.8% and 16.1% vs 26.0%) of specific symptoms in group A were lower than those in group B, albeit not statistically significant ($P = .568$ and $P = .094$). However, for patients with null or mild symptoms at 3-month, the 12-months and 24-months cumulative recurrence rates (11.9% vs 11.9% and 15.6% vs 23.8%) of symptoms between two groups were not statistically significant yet ($P = .990$ and $P = .145$). 15/148 and 43/226 patients had pain after primary symptoms disappearance in group A and group B respectively; whereas, 16/157 and 35/191 patients with null or mild symptoms at 3-months in both groups experienced pain respectively. The pain-free interval for study population between the two groups (see Figure S1, Supplemental Digital Content, <http://links.lww.com/MD2/A299>, Supplementary content, which shows the time to relapse of pain) was not statistically significant ($P = .072$). And patients with null or mild symptoms at 3-months between the two groups was not statistically significant yet ($P = .160$).

The hazard ratio (HR) of multivariate Cox regression analysis (see Table S1, Supplemental Digital Content, <http://links.lww.com/MD2/A300>, Supplementary content, which illustrates the predictive factors of triptorelin therapy duration) suggested that triptorelin treatment duration was longer for elder patients than younger at surgery (HR 0.983; 95% confidence interval [CI]:

Table 4
Cumulative recurrence rates of specific endometriosis symptoms in 24 months.

Timeline	Group A		Group B		Group A vs Group B ^α		
	n/N	% (95%CI)	n/N	% (95%CI)	Odds ratio	95% CI	P-value
Study population							
12-mo	14/124	11.3 (6.3, 18.2)	27/196	13.8 (9.3, 19.4)	0.2	(-0.4, 0.9)	.568
24-mo	20/124	16.1 (10.1, 23.8)	51/196	26.0 (20.0, 32.8)	0.6	(-0.1, 1.2)	.094
Patients with null or mild pain symptoms at 3-mo							
12-mo	16/135	11.9 (6.9, 18.5)	20/168	11.9 (7.4, 17.8)	0.0	(-0.7, 0.7)	.990
24-mo	21/135	15.6 (9.9, 22.8)	40/168	23.8 (17.6, 31.0)	0.5	(-0.1, 1.1)	.145

Group A: patients received up to 3 injections of triptorelin. Group B: patients received 4–6 injections of triptorelin. Logistic regression was used for the comparison. ^α Group B as reference for level factor.

0.968 - 1.000; $P=.044$) and also for patients who previously received hormonal treatment for endometriosis than those who did not (HR 0.724; 95% CI:0.543 - 0.950; $P=.024$), and shorter in patients who were infertile versus fertile (HR 1.401; 95% CI:1.046 - 1.844; $P=.019$).

4. Discussion

To our knowledge, this is the first prospective multicentre study to evaluate symptom control by comparing postoperative triptorelin treatment duration among Chinese patients with DIE.

The results of this study suggest that triptorelin significantly decreases pain, menstrual disorders, gastro-intestinal symptom scores irrespective of treatment duration. Pain symptoms score at 6-months in group B with 4 to 6 triptorelin injections was significantly lower than those in group A with 1 to 3 injections, while the 24-months scores were with no statistical significance between two groups. It illustrates that treatment with triptorelin following conservative surgery may associated with a decrease in the intensity of pain symptoms in the short-term, and the long-term effects of shorter or longer triptorelin therapy may depend on long-term clinical care. A published study performed in China using 4 injections (6-week per cycle for 24 weeks) versus 6 injections (4-week per cycle for 24 weeks) of triptorelin depot regimen in the treatment of patients with adenomyosis and endometriosis, which suggested that both therapeutic regimens achieved similar efficacy on decreasing dysmenorrhoea score and similar symptom recurrence.^[19] The results were also in accordance with another study by Liu et al published in China.^[20]

The 6-month and 24-month cumulative improvement rates of pain and gastro-intestinal symptoms were significantly higher in group B than those in group A in the study. Moreover, the improvement rate of pain symptoms in group B was significantly higher at 6-month than that in group A. Likewise, the 18-month and 24-month rates of gastro-intestinal symptoms in group B were significantly higher than group A. The results illustrate that longer treatment with triptorelin following conservative surgery may be associated with greater improvement of pain symptoms in the short-term and greater improvement of gastro-intestinal symptoms in the long-term.

The rates of symptom recurrence were slightly lower in group A than those in group B between 10% and 25% in 12 to 24 months which were consistent with the recurrence rate of 21% reported in previous study,^[21] even if comparison between studies has limitations due to different settings and varying designs. For patients with null or mild pain symptoms at-3month, continued use of drugs may slightly decrease the rate of recurrence. At baseline, the number of patients with mild symptoms in group A was more than those in group B, which

might be the reason for the slightly higher recurrence rate in group B. In our study, 60.0% of patients in group A experienced pain recurrence within 6 to 9 months follow-up while 53.5% in group B occurred within 12 to 24 months. Furthermore, pain-free intervals for group A were shorter than those for group B in total population and patients with null or mild symptoms at 3-months. It reveals that longer triptorelin treatment duration might lengthen pain-free interval within 24 months. Moreover, published study proved that proper lifestyle, diet rich in vegetables, omega-3 polyunsaturated fatty acids with less consumption of red meat, coffee, alcohol and trans fats play an important role in whole therapy.^[22] And published study showed that proper lifestyle, intakes of magnesium, phosphorus, calcium, and vitamin D lower the risk of occurrence and strengthen the effectiveness of treatment of endometriosis.^[23]

In our study, patients with longer triptorelin treatment duration were those who were fertile, older at surgery, previously with hormonal treatment for endometriosis. In clinical practice, the treatment duration might be concerned with patients health status, pregnancy history, the family economic revenue, history of treatment, severity of disease, and sensitivity to triptorelin injections.

The strength of this study is that it is the first study on symptom control in comparison of different duration of post-operative triptorelin therapy in patients with DIE conducted in multi-centres in China. The study suggests that the treatment duration of triptorelin following conservative surgery may affect the efficacy. Therefore, exploring predictive factors of increasing treatment duration was meaningful. A few limitations of this study must be acknowledged. The main limitation of the study may be that the baseline characteristics between two groups were not balanced and the propensity score matching method was not conducted in the study. In addition, data missing in the non-interventional observation study was inevitable. However, the observational study was performed in the real-world clinical practice, it provides guidance for clinical pharmacy. Additionally, the study was finished from multi-centres, diagnostic and therapeutic capabilities may vary from hospitals, so the central effect was considered by the post-hoc analysis. Moreover, that was an exploratory analysis with a multiplicity of test without adjustment.

5. Conclusions

In women with DIE, longer treatment with triptorelin following conservative surgery was associated with a decrease in the intensity of pain symptoms in the short-term, greater improvement of pain symptoms in the short-term and greater improvement of gastro-intestinal symptoms in the long-term, but a higher

rate of recurrence. Moreover, it might lengthen the pain-free interval. Age at surgery, previously hormonal treatment for endometriosis and infertility are the predictive factors of increased triptorelin treatment duration.

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Author contributions

WS performed the study and was a major contributor in writing the manuscript. KH, LH, JZ, MH, JW and JZ performed the study and made a contribution to the study design and manuscript draft. VP and HL analysed and interpreted clinical data, provided feedback on the manuscript. XZ designed and performed the study, was a major contributor in writing the manuscript and gave final approval of the version to be submitted. All authors read and approved the final manuscript.

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