A Prospective Observational Study to Evaluate the Efficacy and Safety Profiles of Leuprorelin 3 Month Depot for the Treatment of Pelvic Endometriosis

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Objective:
To evaluate the suppression of pituitary gonadotrophins and ovarian steroid hormones with the administration of a combination of leuprorelin depot 3.75 mg and leuprorelin depot 11.25 mg at 5 weeks apart.

Design:
Prospective open observational study.

Setting:
Gynaecology department of a public hospital under Hospital Authority in Hong Kong.

Patients:
25 consecutive symptomatic patients with laparoscopy or laparotomy proven stage III and stage IV pelvic endometriosis were recruited from February 2003 to July 2004.

Main outcome measures:
Serum levels of 17-β-oestradiol, follicle-stimulating hormone and luteinising hormone; pelvic pain scores.

Other outcome measures:
Side-effects and non-responders.

Results:
This regimen of treatment was found to significantly suppress the endogenous oestradiol level to postmenopausal range and the pain scores to a very low level. These effects were well maintained till 24 weeks after commencement of treatment. Side-effects were mainly hot flushes and sweating and were tolerable by all subjects.

Conclusion:
The combination of leuprorelin 3.75 mg and leuprorelin 11.25 mg 3 Month Depot is a safe and effective alternative to conventional monthly injection of gonadotrophin-releasing hormone agonists. It can be recommended as a more cost-effective and patient-friendly alternative in the treatment of pelvic endometriosis.

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Introduction

Endometriosis is a common benign gynaecological disease that causes infertility and intolerable clinical symptoms, such as dysmenorrhoea, dyspareunia and pelvic pain, caused by the presence of endometrial tissue outside the inner lining of the uterus. The proliferation of these endometriosis implants is totally dependant on the hormonal profile of the patients, i.e. the fluctuation of oestrogen and progesterone during the menstrual cycle[1]. Gonadotrophin-releasing hormone agonists (GnRHa) are the major choice of treatment for this disorder. GnRHa suppresses the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland and results in a hypo-oestrogenic state leading to the remission of the endometriotic lesions[1].

Commercially available GnRHa prepared in depot formulations are suitable for endometriosis management. Monthly depots of triptorelin or leuprorelin, which are administrated every month for 6 doses, have been the standard for this purpose. Recent evidence suggested that GnRHa might possess therapeutic efficacy longer than that claimed by the manufacturer[2,3]. Therefore, aiming at a cost-effective strategy, an extended-interval dosing regimen was proposed to be effective. Study with a new regimen of triptorelin (1 injection/1.5 months for 6 months) showed effective suppression of endogenous oestradiol (E_2) to post-menopausal level[4]. More importantly patients receiving this therapy reported similar pain relief and incidence of side-effect as those undergoing standard treatment regimen. It was expected that there would be reduction in drug cost with this new regimen as well. Recently leuprorelin 11.25 mg (Enantone 3 Month Depot; Takeda Chemical Industries Ltd., Osaka, Japan) is available for the treatment of endometriosis. This new long-acting drug has the advantage of fewer injections (2 doses at 3 monthly interval for a 6-month course of treatment). However there are no data on the efficacy and safety of this drug in the local population. Furthermore the effect of leuprorelin 3 Month Depot is likely to last for more than 3 months according to the previous experience with other GnRHa[4]. The use of less than 2 standard doses of leuprorelin 3 Month Depot may be a more cost-effective approach to the treatment of endometriosis.

It was postulated that the combination of 1 dose of leuprorelin 3.75 mg together with 1 dose of leuprorelin 11.25 mg at 5 weeks apart is sufficient to suppress E_2 level to postmenopausal range for 6 months and hence effective in the treatment of pelvic endometriosis.

Materials and Methods

This was a prospective open observational study. 25 consecutive symptomatic patients suffering from rAFS (revised American Fertility Society) stages III or IV (either laparoscopy/laparotomy proven) were recruited into the study from February 2003 to July 2004 following a routine physical check-up and the fulfillment of inclusion criteria (Table 1).

All recruited subjects were advised to visit the study

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Pre-menopausal women between 18-45 years of age seeking medical treatment
Patients with spontaneous and regular menses (26-32 day cycle) during the past 3 months
Surgically (laparoscopy/laparotomy) confirmed moderate to severe (rAFS stage III-IV) cases of endometriosis with symptoms of pelvic endometriosis
Body mass index between 19-22
Exclusion criteria
Patients with recurrent endometriosis
Patients who have had GnRHa, danazol or other ovarian suppression therapies e.g. hormonal contraceptive method within 3 months before the start of the study
Patients with known allergic reaction to GnRHa, danazol or otherwise contraindication for intramuscular injection
Patients suffering from any type of cancers
Patients who refuse to use any contraceptive method

Table 2. Follow-up schedule

Follow-up	Visit number							
	Pre-trial	1	2	3	4	5	6	7
Treatment day (± 2 days)*	N/A	0 (0)	35 (5)	84 (12)	126 (18)	168 (24) [end of treatment]	210 (30)	252 (36)
Enantone SR injection		√						
Enatone 3 Month Depot			√					
Laparoscopy or laparotomy	√							
Physical examination	√							
Inclusion and exclusion	√							
Blood sample for E_2, FSH, LH levels		√	√	√	√	√	√	√
Pain scores		√	√	√	√	√	√	√
Side-effects			√	√	√	√	√	√

* Weeks in brackets

centre on menstrual cycle day 7 (± 2 days) of their current or upcoming menses (Visit 1). Before the administration of any medication, blood samples from each patient were obtained for E_2, FSH and LH measurement. The patients' basal pain scores for dysmenorrhoea, dyspareunia and non-menstrual pelvic pain were evaluated and rated by the investigators according to the visual analogue scale (VAS). Each of the pain sub-scores (i.e. dysmenorrhoea, non-menstrual pelvic pain and deep dyspareunia) were graded according to the VAS 0 to 10. Total pain score was the sum of sub-scores and the maximum score was 30. The first injection of leuprorelin 3.75 mg (Enantone SR) was given at this visit after the above procedures.

For all subjects, injections of leuprorelin 11.25 mg (Enantone 3 Month Depot) were given at Visit 2 five weeks (± 2 days) from the first injection (treatment day 35). Blood samples, pain scores and side-effects experienced were obtained from each individual subject. Visit 3 was scheduled at 7 weeks (± 2 days) after the second dose of leuprorelin. Subsequent follow-up visits (Visits 4-7) were scheduled at 6-weekly interval (± 2 days) until 36 weeks from the commencement of treatment. Collection of blood samples for E_2, FSH and LH determination, recording of pain scores and side-effects were done during these visits. Table 2 shows the treatment and follow-up schedule of this study.

The Statistical Package for Social Science (Windows version 11.5; SPSS Inc., Chicago, United States) was used for data analysis. Wilcoxon signed rank sum test was used to assess the reduction in endogenous E_2 levels and pain scores after treatment.

Results

Demographic Profile

25 subjects were recruited from February 2003 to July 2004 and all completed the study. The mean age of the study sample was 33.68 (range, 22-44) years. 72% (18 of 25) of the recruited subjects were nulliparous. All subjects were suffering from rAFS stage III or IV. Their mean rAFS score were 28.64 and 75.79 respectively (Table 3).

Table 3. Study sample demographics

	No.	Mean ± SD	Range
Age (years)	25	33.68 ± 6.59	22 - 44
Parity	25	0.36 ± 0.64	0 - 2
AFS scores			
All subjects	25	55.04 ± 28.67	22 - 109
Stage III	11	28.64 ± 6.33	22 - 38
Stage IV	14	75.79 ± 20.82	42 - 109

Figure 1. Trend of mean oestradiol level by week

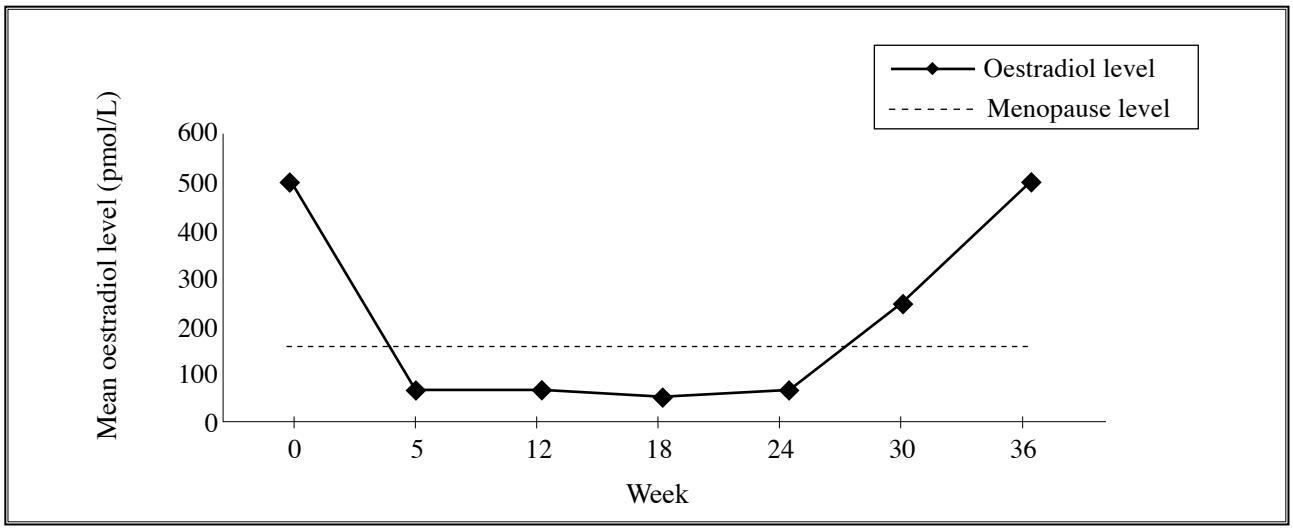
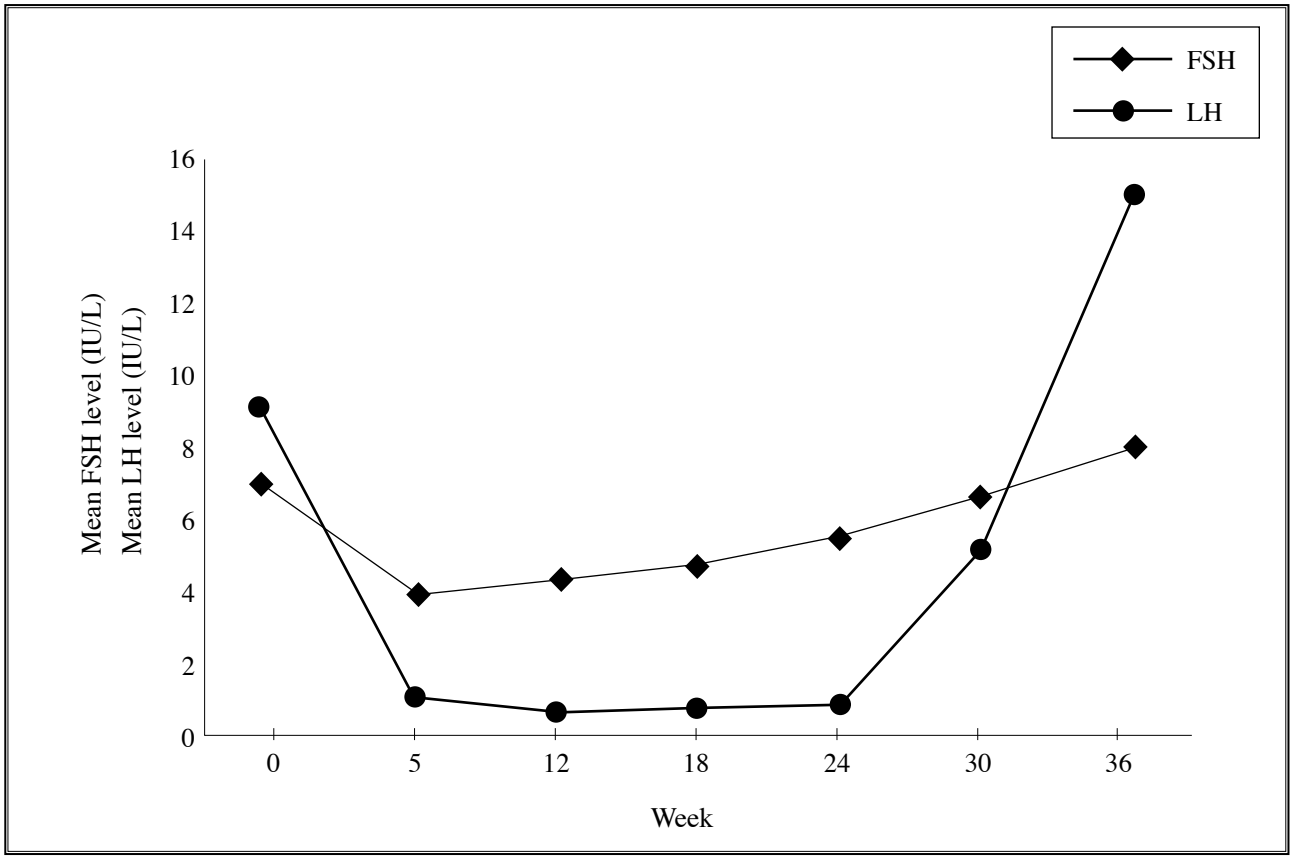


Figure 2. Mean follicle-stimulating hormone (FSH) and luteinising hormone (LH) level by week



Suppression of Oestradiol Level

Serum E_2 level was reduced significantly from baseline level of 506.5 pmol/L to 57.0 pmol/L at week 5 after 1st treatment injection. It was maintained at similar level after 2nd treatment injection (from week 12 to week 24) and reached minimum level of 48.6 pmol/L at week 18. The E_2 level gradually returned to the pre-treatment level from week 30 to week 36 (Figure 1).

Suppression of Gonadotrophin Levels

FSH level was reduced from baseline of 6.9 mIU/mL to 4.0 mIU/mL at week 5. It did not go further down after 2nd injection and gradually increased from week 12 to week 24. After week 24 the upward trend of FSH level continued and reached a maximum of 8.0 mIU/mL at week 36 (Figure 2).

Table 4. Duration of amenorrhoea

	No.	Mean ± SD	Range
Duration (days) from 1st injection	25	242.8 ± 34.5	200 - 327
Duration (days) from last injection	25	203.7 ± 29.4	165 - 292
Duration (days) after treatment completion	25	70.5 ± 29.8	31 - 158

LH level was also reduced from baseline 8.8 mIU/mL to 0.9 mIU/mL at week 5. It was maintained at low level after 2nd injection (from week 12 to week 24) and reached minimum of 0.6 mIU/mL at week 18. After the end of treatment period, LH level bounced back and reached a maximum of 15.0 mIU/mL at week 36 (Figure 2).

At week 30, the E_2 and LH level had bounced back significantly from week 24 ($p<0.001$). These hormone levels kept increasing significantly from week 30 to week 36 (both $p<0.05$). There was no significant bounce back of FSH level during the follow-up period.

Suppression of Pain Scores

Dysmenorrhoea pain score was reduced from baseline of 6.76 to 3.0 after 1st injection and down to minimum of 0 after 2nd injection. It was maintained at 0 till the end of treatment at week 24 and gradually increased during subsequent follow-up period (week 24 to week 30).

The baseline non-menstrual pelvic pain score was 1.12 and it was reduced only slightly after 1st and 2nd injection.

Deep dyspareunia pain score was reduced from baseline of 2.30 to 0.48 after 1st injection and decreased slightly after 2nd injection. The scores were maintained at low level throughout the subsequent follow-up period.

The total pain score was reduced from baseline of 10.18 to 3.96 after 1st injection and down further to 0.64 after 2nd injection. Then it maintained till the end of treatment at week 24 and increased to 2.64 at week 36.

The dysmenorrhoea pain score increased gradually (i.e. increased 14%) during the post-treatment period from week 30 to week 36 and the change was statistically significant ($p=0.004$).

The non-menstrual pelvic pain score increased gradually but it did not reach significant level during post-treatment period.

The deep dyspareunia pain score reduced further 3.2% at week 30 and then bounced back 5.2% at week 36. However, neither of these changes was statistically significant.

Figure 3. Trend of pain scores

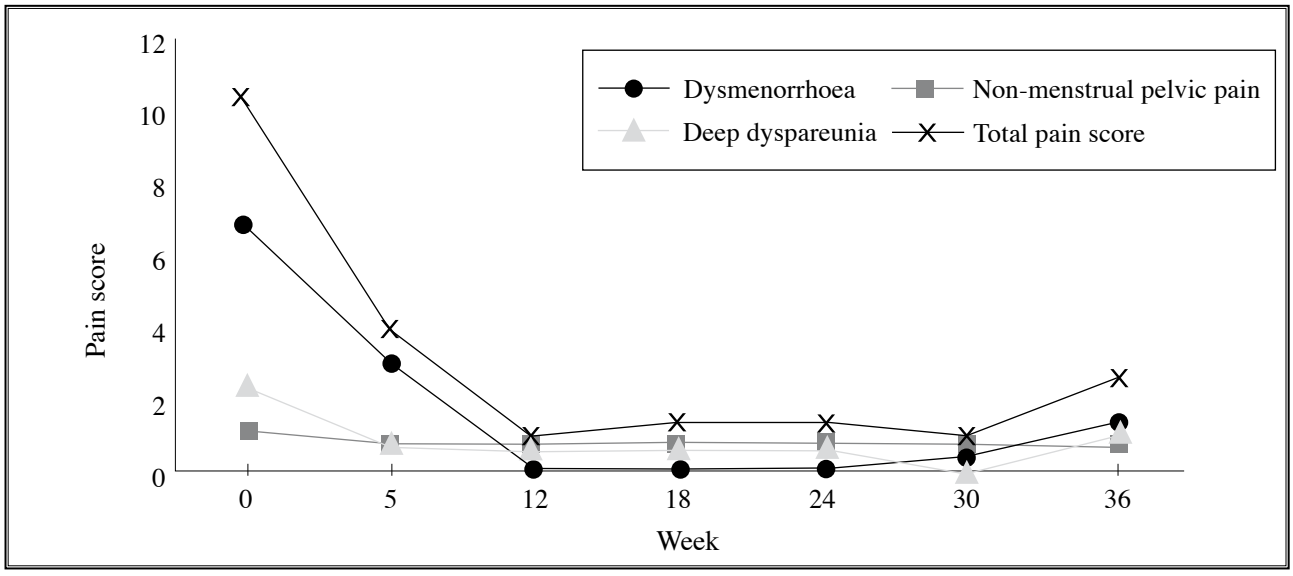


Table 5. Percentage of subjects with side-effects after treatment injection

	Week 5	Week 12	Week 18	Week 24	Week 30	Week 36
Hot flush	56%	80%	84%	64%	12%	0%
Sweating	40%	72%	72%	60%	12%	0%
Headache	28%	28%	28%	16%	4%	0%
Dizziness	12%	16%	20%	12%	12%	4%
Nausea	8%	12%	4%	0%	0%	0%
Insomnia	20%	28%	36%	24%	8%	0%
Depression	8%	20%	8%	4%	8%	0%
Vaginal dryness	24%	52%	52%	44%	12%	0%
Vaginal bleeding	16%	0%	0%	0%	0%	0%

The total pain score was reduced further by 0.7% at week 30 but was not statistically significant. At week 36, the total pain score had bounced back by 6.8% and the change was statistically significant (p=0.007).

Figure 3 summarises the trend of pain scores during the follow-up period.

Duration of Amenorrhoea

Mean durations of amenorrhoea from 1st and last injection were 242.8 days and 203.7 days respectively. Mean duration of amenorrhoea after completion of treatment (week 24) was 70.5 days (Table 4).

Non-responders to the Therapy

Non-responders to GnRHa therapy is defined as patients who cannot achieve a post-menopausal serum E_2 level (<150 pmol/L) after GnRHa therapy. The evaluation was done at treatment week 5 and there was one patient classified as non-responder after first injection, i.e. 4% of study sample. The E_2 level of this subject had maintained over 150 pmol/L at week 12 and then reduced to the post-menopausal level from week 18 to week 24.

Safety Profile

Over 80% of patients experienced hot flush during treatment period at week 12 and week 18. Moreover, over 70% of patients experienced sweating at week 12 and week 18. Other reported side-effects included headache, dizziness, nausea, insomnia, depression, vaginal dryness and vaginal bleeding. Most of these side-effects had vanished at the end of study period. No patient quitted the study because of side-effects. Table 5 summarises the side-effects experienced by patients during the study period.

Discussion

This study aims primarily at evaluating the efficacy of leuprorelin that was administered in 2 doses with different dosage: 1 injection of leuprorelin 3.75 mg (Enantone SR) and 1 injection of leuprorelin 11.25 mg (Enantone 3 Month Depot) at 5 weeks apart for the treatment of endometriosis. One dose of leuprorelin 3.75 mg was given initially so that possible non-responders, anaphylactic reactions and severe side-effects could be identified early. If 3 Month Depot injections were given initially, any severe side-effects could not be reversed. According to previous experience[4] with extended-interval dosing regimen, it is expected that the effect of leuprorelin 3.75 mg can actually last for more than 4 weeks and leuprorelin 11.25 mg can last for longer than 3 months and combination of the two is sufficient to maintain hormonal suppression for 6 months. The drug cost can be reduced by as much as one third compared to 2 standard doses of leuprorelin 11.25 mg at 3 months apart.

The standard treatment regimen of GnRHa is 6 months. Treatment lasting for longer than 6 months is associated with irreversible bone loss. It is believed that endometriotic deposits will undergo atrophy and regression after subjecting them to 6 months of hypo-oestrogenic environment. The proposed regimen of leuprorelin was shown to suppress the endogenous E_2 level to menopausal range (<150 pmol/L) and the effect lasted for more than 6 months. It should be considered as adequate treatment for endometriosis. There was only 1 case of non-responder as defined by E_2 level of less than 150 pmol/L at 5 weeks after the first injection. However the E_2 level in this patient was well suppressed to below 150 pmol/L at 18 weeks of treatment and she had good

suppression of pain symptoms. The suppression of gonadotrophin levels was also consistent with other studies[2-4].

There was marked suppression of pain symptoms after commencement of treatment. The dyspareunia score was not suppressed as much as the other pain scores. Superficial dyspareunia due to lack of vaginal secretion as a result of oestrogen deprivation after treatment was common after GnRHa treatment. It could be confused with deep dyspareunia that the study intended to investigate. Some of the subjects were not sexually active and therefore the dyspareunia score could not be assessed. Dysmenorrhoea score became zero at 12 weeks after treatment as all patients had complete amenorrhoea at that time. Non-menstrual pain score was difficult to assess as the pre-treatment level was low. All the pain scores were suppressed at week 30 (i.e. 6 weeks after completion of treatment) and were only slightly raised at week 36. However it should be noted that pain is a subjective feeling. Although the VAS was used it would still be subject to great bias due to patients' own experience.

The above findings demonstrate that the regimen was efficacious in suppressing endogenous hormone levels and reducing pain symptoms. Side-effects were similar to other regimens[3-5] of GnRHa treatment and were mainly hot flushes and sweating. All the side-effects were mild and tolerable. No anaphylactic reactions or severe side-effects were detected.

Mean duration of amenorrhoea after completion of treatment (i.e. from week 24) was 70 days and is similar to a previous local study using extended doses of triptorelin[4]. However it is longer than other overseas studies which ranges from 39 to 56 days[2,5]. The reason for delay in return of menstruation in local population is not obvious from this study.

From this small-scale observational study, this regimen of treatment seems to be safe and efficacious in the treatment of endometriosis. However subsequent recurrence of endometriosis, effect on bone loss and effect on fertility were not investigated. Larger scale prospective randomised trials are awaited.

Conclusion

The combination of leuprorelin 3.75 mg (Enantone SR) and leuprorelin 11.25 mg (Enantone 3 Month Depot) for the treatment of endometriosis significantly suppressed the endogenous E_2 levels and pain symptoms severity and the effect was maintained till the end of treatment period (i.e. week 24). There was only one subject classified as non-responder to GnRHa therapy after the first treatment injection.

Hot flush and sweating were the most common reported side-effects experienced by the subjects after the treatment. Other side-effects experienced by subjects included headache, dizziness, nausea, insomnia, depression, vaginal dryness and vaginal bleeding. However, most of these side-effects had vanished at the follow-up period.

This combination of leuprorelin could be employed as a more cost-effective and patient-friendly method for the treatment of pelvic endometriosis.

Acknowledgement

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