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Reduction of Postoperative Adhesions after Laparoscopic Surgery for Endometriosis by Using a Novel Anti-Fibrotic Drug Pirfenidone: A Randomized Double Blind Study

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Abstract

Introduction: This study was done to insight the effect of the novel anti-fibrotic drug Pirfenidone in the prevention of postoperative endometriosis induced adhesions.

Patients and methods: 210 patients were enrolled and randomly allocated into 2 groups according to sequence of computer-generated block-random numbers. Each group included 105 patients. This prospective randomized double blind controlled study was conducted at Tanta University Hospital between August 2013 and May 2016. In group A (study group) the patients after the initial laparoscopic management received Pirfenidone 200 mg (pirfinex) tablets in a dose of 3 tablets tds i.e. 1800 mg daily for 6 months while in group B (control group) the patients after the initial laparoscopy received placebo starch tablets 3 tablets tds also for 6 months.

The patients in both study groups were subjected to 2nd look laparoscopy after 6 months from the initial procedure.

The primary outcome measure of the study was the difference in the AFS scoring between the study groups during the second look laparoscopies. Secondary outcome measure was the difference between both groups regarding the rate of pregnancy before the second look.

Results: On comparing the American Fertility Society score on 2nd look laparoscopy between both groups a statistically significant lower score was found in the study group A when compared to the control group B (P=0.019). 95% CI for difference: (-8.00; -0.73).

The pregnancy rate before the 2nd look laparoscopy was 39.3% in group A and 31% in group B and this difference is statistically non-significant (P=0.215).

Conclusion: Although that from the results of this study we can conclude that Pirfenidone (Pirfenix) is an effective drug to be used in reduction of the postoperative endometriosis provoked adhesions, the actual benefit of pirfenidone is very moderate (no difference in pregnancy rates). Pirfenidone provides minor clinical added value. The use of pirfenidone should not be recommended since its use is associated with potential adverse events (side effects). Use of pirfenidone necessitates regular monitoring of tolerability and liver enzymes. The most commonly reported adverse events were gastrointestinal disorders (nausea, dyspepsia and diarrhoea), rash, photosensitivity and fatigue. Pirfenidone is an immunosuppressant. Therefore, its use should be limited to proven indications.

Keywords: Endometriosis; Pirfenidone; Laparoscopy; Adhesions

Introduction

The presence of endometrial tissue in sites other than uterine cavity is defined as Endometriosis [1]. It is a one of the main causes of pelvic pain and infertility and can affect the physical, mental, and social wellbeing of a female [2]. Endometriosis could be explained by several theories, including implantation theory, defective immune system, genetic factors, etc. As endometriosis runs in families with 51% inheritance ratio, some researches considering genetic risk factors for endometriosis-related infertility have been conducted [3,4]. Molecular evidence of the negative effect of endometriosis on the ovaries is present [5]. The negative effect on the adnexa can be directly by distorting the anatomy [6], indirectly by causing inflammation [7] or by oxidative damage with poorer-quality oocytes [8]. Negative impact of Endometriosis on pregnancy outcome after assisted reproduction techniques is also documented [9].

Because of its inflammatory nature, endometriosis is an adhesion provoking pathology. Because of its recurrent nature multiple surgeries are usually needed [10]. For these reasons adhesion prophylaxis in endometriosis treatment is mandatory [11].

The most practical classification of the disease is the one by the American Fertility Society in 1985 [12], subsequently modified in 1996 into the original revised American Society of Reproductive Medicine Classification–rASRM. The rASRM scoring system clarifies the critical role of adhesions in endometriosis. Pelvic adhesions strongly affect the total score [13].

Even after successful surgical treatment of endometriosis the postoperative course may be complicated by adhesions and their consequences [14]. Adhesions may precipitate infertility, dyspareunia,

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chronic pelvic pain, and also intestinal obstruction and complications at subsequent surgery [15].

Formation of adhesions and endometrioma formation are strongly correlated. These cysts are rarely seen in the absence of ovarian adhesions, and there is evidence that adhesions play an important role in their pathology [16].

Different methods of adhesions prevention can be classified into those associated directly with the surgical techniques and those involving the use of either drugs or the application of barrier agents [15,17,18].

Many pharmacological agents were studied as an adhesion preventing agents. They include non-steroidal anti-inflammatory drugs, corticosteroids, heparin, fibrinolytic drugs, antibiotics, colchicine, calcium channel blockers, vascular endothelial growth factor inhibitors, platelet-activating factor inhibitors, collagen α1 inhibitors, interleukin-6 inhibitors, melatonin, progestagens, and GnRH analogues. Interference with inflammation and prevention of fibrin formation is the rational for their use [15,18-20].

Prolonged contact between two areas of injury is the key point for an adhesion to form. Preventing this contact with some form of barrier or fluid agents may prevent adhesions [15,17]. Solutions tested include dextran, icodextrin (Adept; Baxter, Deerfield, IL), ferric hyaluronate gel (Intergel; Irvington, NJ), hyaluronic acid in phosphate buffered saline solution (Sepracoat; Genzyme, Cambridge, MA), auto-cross-linked hyaluronic acid, polyethylene oxide/ carboxymethyl cellulose (Oxiplex/ AP; FzioMed, San Luis Obispo, CA), spraygel, fibrin glue, heparin, and noxytioline. Barrier agents with some available scientific data include oxidized regenerated cellulose (Interceed; Ethicon Gynecare, Somerville, NJ), expanded polytetrafluoroethylene (Gore-Tex; Gore Medical, Flagstaff, AZ), hyaluronic acid/carboxymethylcellulose (Seprafilm; Sanofi, Bridgewater, NJ), fibrinogen/thrombin/aprotin/ collagen/riboflavin (fibrin sheet), and polylactic acid film [14].

Pirfenidone (PFD), or 5-methyl-1-phenyl-2-[1H]-pyridone, is a new drug developed for the management of IPF. PFD and its metabolites 5-hydroxypirfenidone (PFD-OH) and 5-carboxypirfenidone (PFD-COOH) exert antifibrotic and antioxidant effects [21].

The antifibrotic properties of pirfenidone were mainly attributed to its effects on pulmonary levels of various cytokines, growth factors and chemokines [16]. Pirfenidone reduced the production of transforming growth factor-β1 (TGF-β1), a profibrotic and pro-inflammatory cytokine, in the lungs of animal models of pulmonary fibrosis [22,23].

In vitro, pirfenidone inhibited the TGF-β1-induced differentiation of human lung fibroblasts into myofibroblasts and thereby prevented the excessive synthesis of collagen [24].

Pirfenidone is only used for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in many countries including those of the EU [25], and including the USA where it is one of two drugs approved for use in patients with IPF.

Patients and Methods

This prospective randomized double blind case controlled study was conducted at Tanta University Hospital between August 2013 and May 2016. Patients eligible for inclusion were those who referred to the laparoscopy unit to perform laparoscopy for pelvic endometriosis as a part of infertility management.

Inclusion criteria

The study inclusion criteria were: Age from 18 to 40 years, infertility (failure of conception for 1 year of regular sexual intercourse without use of any contraception) with high suspicion of pelvic endometriosis (i.e. clinical triad of pelvic pain and/or abnormal genital bleeding associated with infertility). Also Transvaginal Ultrasound with high suggestion of endometriosis e.g. endometrioma), Body mass index between 18 to 38 and the patients should not have other pelvic pathology.

Exclusion criteria

The exclusion criteria include patients with any previous ovarian surgery, suspicion of benign or malignant ovarian condition (indicated by ultrasound or proved by histopathology). Also patients with Anti Mullerian Hormone (AMH) less than 1.0 were excluded from the study. Patients with associated male sub-fertility diagnosed by failure of computer assisted semen analysis to pass the WHO criteria, were excluded from the study.

Baseline examination

All patients were assessed by history taking, clinical examinations and were investigated by routine investigation to check for general condition. Abdominal and trans-vaginal Ultrasound was done to confirm suspicion of endometriosis and to check for other adnexal lesions.

All women were thoroughly informed about the study aims and through discussion about the procedure, associated benefits and risks and assigned written consent. Patients were randomized in a 1:1 ratio. to either the study group or the control group by an administrative team according to sequence of computer-generated block-random numbers. Neither the researchers nor the participants will know their study group. In group A (study group) the patients after the initial laparoscopic management including adnexal adhesiolysis, bipolar cauterization of the endometriotic lesions in the surgical sites and excision of endometriomas received Pirfenidone 200 mg (pirfinex) tablets in a dose of 3 tablets tds i.e. 1800 mg daily for 6 months while in group B (control group) the patients after the initial laparoscopy received placebo starch tablets 3 tablets tds also for 6 months.

The patients in both study groups were subjected to 2nd look laparoscopy after 6 months from the initial procedure.

All surgeries were recorded, and the video files were forwarded to a single masked gynaecological laparoscopy expert to assess and score the adhesions after the primary surgery and at second-look surgery according to the revised American Fertility Society scoring system [13].

The primary outcome measure of the study was the difference in the AFS scoring between the study groups during the second look laparoscopies. Secondary outcome measure was the difference between both groups regarding the rate of pregnancy before the second look.

Sample size calculation

Power analysis for a dependent sample t-test was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, a small effect size (dz=0.2), and two tails [26]. Based on the aforementioned assumptions, the desired sample size is 199.

Results

Of the 105 patients allocated for each group 6 patients in group A and 5 patients in group B was excluded from the study after the initial laparoscopy because another pelvic pathology was discovered on laparoscopy like dermoid cysts and hemorrhagic non endometriotic lesions as proven by histopathology later on.

Table 1 shows a comparison between the pre-study variables between the 2 groups. There were no significant differences between the 2 groups regarding age, BMI, duration of infertility in months, Anti Mullerian Hormone (AMH) level and number of patients showing initial tubal block diagnosed by hysterosalpingography (HSG).

On comparing the initial American Fertility Society score after the initial laparoscopic surgery between both groups Table 2 no statistically significant difference was found (P= 0.372). On comparing the American Fertility Society score on 2nd look laparoscopy between both groups (Table 3) a statistically significant lower score was found in the study group A when compared to the control group B (P=0.019) (Tables 4-6 and Figures 1-4).

Discussion

Prevention of adhesions was and still a major challenge in infertility management. Endometriosis as one of the most adhesion provoking pathologies needs special attention from researchers to face this challenge. In this clinical trial we tried to evaluate the drug Pirfenidone which is a new emerging anti-fibrotic medication. Pirfenidone is used with high success in the management of idiopathic pulmonary fibrosis IPF which is a chronic and ultimately fatal disease characterized by a progressive scarring of the interstitial tissue of the lung with 20% of 5 years life expectancy. The data from the ASCEND study were also pooled with data from the two CAPACITY studies in a pre-specified analysis which showed that pirfenidone reduced the risk of death by almost 50% over one year of treatment [27].

To the best of our knowledge this is the very 1st clinical trial that tested this novel anti-fibrotic drug in the prevention of surgical and endometriosis provoked adhesions.

Statistic	Group A	Group B
Age		
Mean	29.09	29.49
SD	3.7	5.1
Minimum	22	21
Maximum	35	37
Two sample T-Test **P-value=0.534**		
BMI		
Mean	27.13	28.65
SD	6.03	5.94
Minimum	18	19
Maximum	37	38
Two sample T-Test **P-value=0.075**		
Duration of infertility in months		
Mean	35.3	38.5
SD	14.4	15.3
Minimum	13	15
Maximum	61	66
Two sample T-Test **P-value=0.130**		
AMH ng/ml		
Mean	3.9	3.7
SD	1.7	1.5
Minimum	1	1.3
Maximum	6.6	6.4
Two sample T-Test **P-value=0.561**		
Patients with uni- or bilateral tubal block on HSG		
Number	35	42
percentage	35.30%	42.00%
Chi Square test **P-value=0.336**		

Table 1: Comparison between the pre-study variables between the 2 groups.

	Number	Mean	SD
Group A (study)	99	12.9	10.9
Group B (control)	100	14.3	11.3
Two sample T-Test **P-value=0.372**			

Table 2: Comparison of the AFS score after the initial surgery between the 2 study groups.

	Number	Mean	SD
Group A (study)	60	13.8	10.9
Group B (control)	69	18.12	9.74
Two sample T-Test **P-value=0.019***		***=significant**	

Table 3: Comparison of the AFS score on 2nd look laparoscopy between the 2 study groups.

Two sample T-Test				
		Number	**Mean**	**SD**
Minimal endometriosis (Figure 1)	Group A (study)	22	3.45	1.65
	Group B (control)	20	6.55	5.8
	P-value=0.032*			
Mild endometriosis (Figure 2)	Group A (study)	2	10	5.66
	Group B (control)	6	13.83	4.26
	P-value=0.541			
Moderate endometriosis (Figure 3)	Group A (study)	6	12.67	7.35
	Group B (control)	9	15.22	3.15
	P-value=0.461			
Severe endometriosis (Figure 4)	Group A (study)	30	21.77	9.08
	Group B (control)	34	26.44	3.59
P-value=0.012*, *=significant				

Table 4: Comparison of the AFS score on 2nd look laparoscopy between the 2 study groups according to degree of endometriosis.

Baseline AFS category		**Total**	**Get pregnant**	**Second look AFS scores**			
				Minimal	**Mild**	**Moderate**	**Severe**
				(0-5)	**(6-10)**	**(11-20)**	**(21-32)**
Treatment: surgery + PFD							
Minimal	(0-5)	44	22	21	1	0	0
Mild	(6-10)	11	9	0	1	1	0
Moderate	(11-20)	11	5	1	2	2	1
Severe	(21-32)	33	3	2	3	5	20
Total		99	39	24	7	8	21
Control: surgery only							
Minimal	(0-5)	40	20	11	5	2	2
Mild	(6-10)	10	4	0	0	5	1
Moderate	(11-20)	14	5	0	0	9	0
Severe	(21-32)	36	2	0	0	1	33
Total		100	31	11	5	17	36

Table 5: Change in the degree of endometriosis in the 2nd look evaluation between the study groups.

	Pregnant	No Pregnancy
Group A (study)	39	61
Group B (control)	31	69
Chi Square test **P-value=0.215**		
Chi square test show no significant relation between drug and pregnancy rate		

Table 6: Pregnancy before the 2nd look laparoscopy.

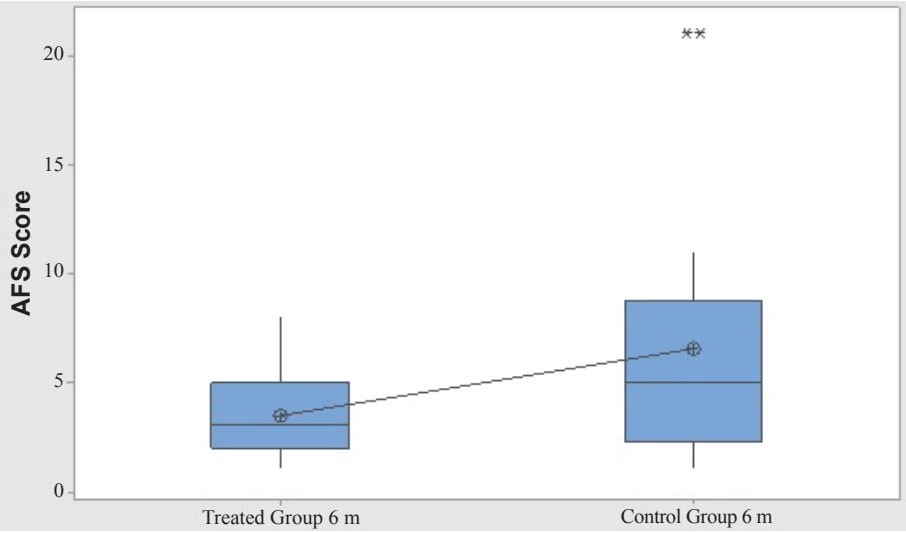

Figure 1: Comparison of AFS in the patients with minimal endometriosis.

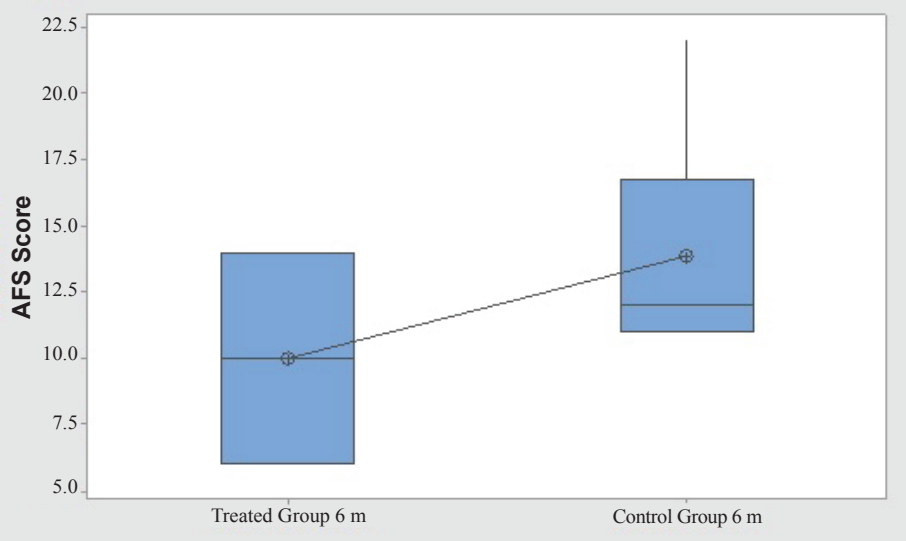

Figure 2: Comparison of AFS in the patients with mild endometriosis.

In this clinical study, 199 patients underwent surgical therapy of their adnexa to remove existing adhesions or endometriosis by surgery performed via laparoscopy. Following the primary surgical procedure(s), the treated patients received the drug pirfenidone by the same dosage used for treatment of IPF i.e. 200 mg (pirfinex) tablets in a dose of 3 tablets tds (1800 mg daily) for 6 months. Before the 2nd look laparoscopy the pregnancy rate in the treatment group A was 39.3% which is higher (although statistically non-significant P=0.215) than pregnancy rate in control group B 31%.

On comparing the AFS score on 2nd look laparoscopy between the 2 study groups a significant (P=0.019) lower score is noted in the treatment group A 13.8 ± 10.9 when compared to group B 18.12 ± 9.74. This reflects that the drug is effective in prevention of postoperative and endometriosis provoked adhesions. When we re-analyzed the 2nd look laparoscopy AFS scores according to the degree of endometriosis the difference between the study and control groups was significant only in the minimal (P=0.032) and severe (P=0.012) endometriosis subgroups and non-significant in mild (P=0.541) and moderate (p=0.461) endometriosis subgroups, but this can be explained by the small number of patients allocated in minimal and moderate subgroups, 8 and 15 patients respectively.

Twenty one out of 22 of the Pirfenidone treated adnexa continued to have minimal adhesion scores at second-look laparoscopy. By contrast, only 11/20 control adnexa with minimal adhesion scores were unchanged at the time of second look.

Ten out of 30 patients having severe endometriosis shifted to have less adhesion scores at second-look laparoscopy in the treatment group A. By contrast, only 1/34 is shifted to less adhesion score at second-look laparoscopy in the control group B.

Limitations

As pirfenidone is used in patients who are expecting pregnancy, hence emerged the question of its teratogenic effect. Fertility and

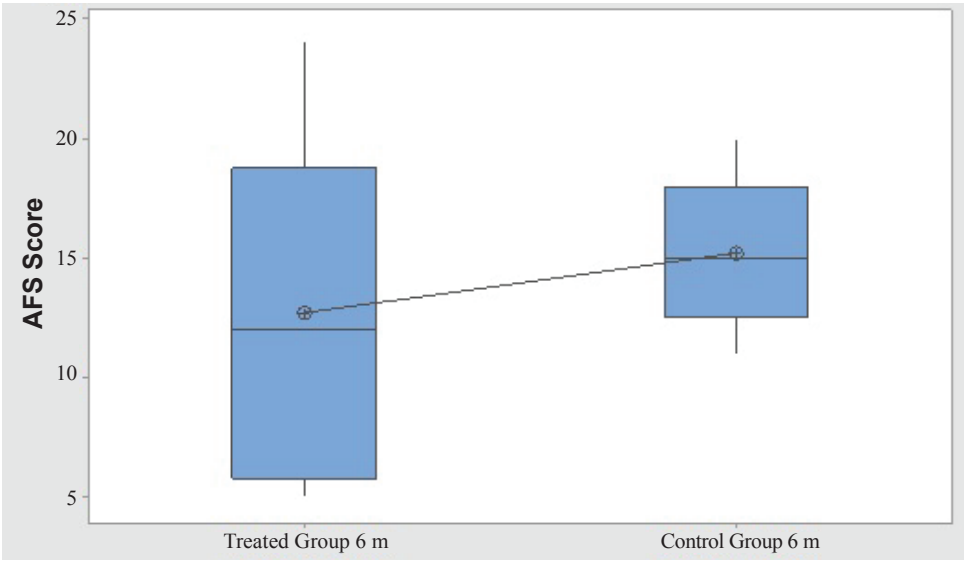

Figure 3: Comparison of AFS in the patients with moderate endometriosis.

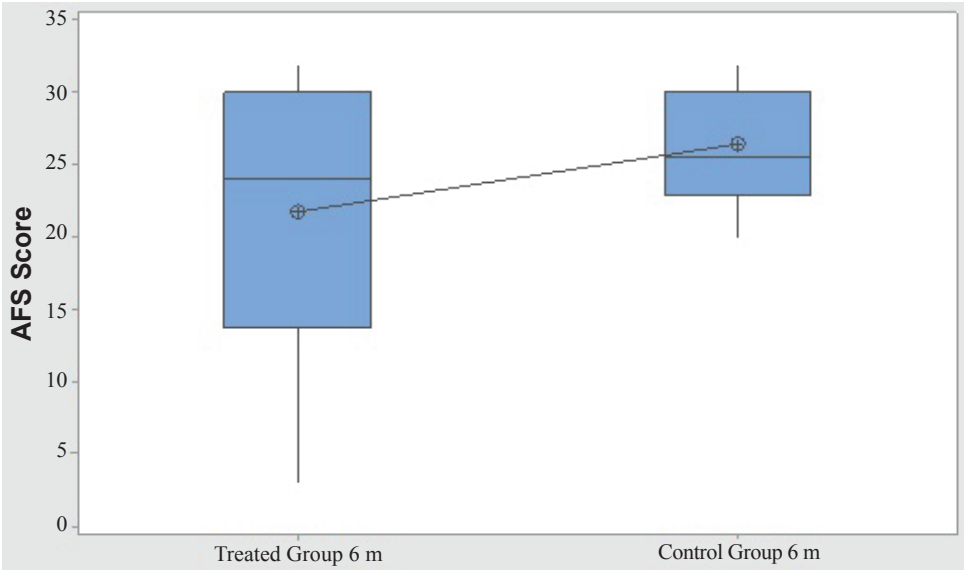

Figure 4: Comparison of AFS in the patients with severe endometriosis.

embryo-fetal development studies revealed no evidence of impaired fertility or fetal harm in rats and rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults. However, a pre- and post-natal development study showed gestation prolongation, decreased number of live new-borns, reduction in fetal viability and lower body weights in rats receiving an oral dosage approximately 3 times the MRDD in adults [28].

As there are no controlled data in human pregnancy, US FDA put pirfenidone in pregnancy category C (Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).

Conclusion

Although that from the results of this study we can conclude that Pirfenidone (Pirfenix) is an effective drug to be used in reduction of the postoperative endometriosis provoked adhesions, the actual benefit of pirfenidone is very moderate (no difference in pregnancy rates). Pirfenidone provides minor clinical added value. The use of pirfenidone should not be recommended since its use is associated with potential adverse events (side effects). Use of pirfenidone necessitates regular monitoring of tolerability and liver enzymes. The most commonly reported adverse events were gastrointestinal disorders (nausea, dyspepsia and diarrhoea), rash, photosensitivity and fatigue. Pirfenidone is an immunosuppressant. Therefore, its use should be limited to proven indications.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Declaration of Funding

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