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The Value of Using Platelet Rich Plasma after Hysteroscopic Analysis of Severe Intrauterine Adhesions (A Randomized Controlled Trial)

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ABSTRACT

Background: Office hysteroscopic examination is now an established step in the diagnostic work up of cases with abnormal uterine bleeding, infertility, and recurrent miscarriage that can be performed safely and efficiently without anesthesia in most cases. **Objectives:** This study aimed at assessment of the efficacy of the use of platelet rich plasma (PRP) in decreasing occurrence and recurrence of intrauterine adhesions after operative hysteroscopy. **Patient and Methods:** This study was conducted in Ain Shams Maternity Hospital (Early Cancer Detection and Endoscopy Unit) during the period between January 2017 and February 2018. 60 patients seeking for conception with a history of primary or secondary infertility with sever intrauterine adhesions. 30 patients (case) injected with PRP and 30 patients (control) with IU balloon. All patients had normal complete blood count, and not taking anticoagulant or NSAID in the 10 days before procedure with no active cervical or uterine infection. **Results:** It was found that the mean age in PRP group was 31.8 ± 4 years old and balloon group was 30.5 ± 4.7 range: (20-45 years old). The mean of BMI in PRP group was 24.4 ± 2.2 and balloon group was 25.1 ± 2.4. In this PRP group (13.3%) of patients were nulliparous and balloon group (10%), (86%) of PRP group are multipara and in balloon group (90%). There was no significant association between ages, parity with any possible etiology. Our study showed significant increase of menses duration among the PRP group post-operative (3.0 ±1.2) days and preoperative menses duration (1.4 ± 1.5) days. Compared to balloon post-operative (1.8 ± 1.3) and preoperative (1.3 ± 1.4) days.
Conclusion: platelet rich plasma had high efficacy and safety in improvement of menses duration, amount and adhesion score in cases of sever intrauterine adhesions and decreasing postoperative adhesions.

Keywords: Intrauterine adhesions - Platelet rich plasma

INTRODUCTION

Intrauterine adhesions may occur after intrauterine trauma. The severity of the adhesions varies: some are focal and small bands, some extensive, some even total occlusion of the uterine cavity. Uterine surgery and diagnostic curettage are common reasons of adhesions, but serious adhesions usually arise from pregnancy complications such as postpartum hemorrhage, missed or complete abortion and placental retention. Multiple curretages performed for pregnancy termination is also a risk factor and adhesion risk is more than 30% after the third curretage. Infections, especially uterine tuberculosis cause severe adhesions [(1)].

Intrauterine adhesions may be asymptomatic, but generally are related with infertility, menstrual disorders (hypomenorrhea, amenorrhea), cyclic pelvic pain or cramping around the time of period, recurrent miscarriage and endometriosis (caused by backflow of blood from the uterus). Indirect imaging methods give useful information in diagnosis as 3D ultrasound, but the gold standard diagnostic method is hysteroscopy that has the advantage of concurrent treatment [(1)]. Management and treatment strategy include hysteroscopic adhesiolysis; readhesion prevention by intrauterine device, uterine balloon stent, Foley's catheter or amnion graft; restoration of normal endometrium (hormonal treatment - stem cells) and postoperative assessment by (office hysteroscopy – ultrasound) [(2)].

Hysteroscopy is a valuable diagnostic and therapeutic modality in the management of infertility. Hysteroscopy is the gold standard procedure for uterine cavity exploration. It is widely accepted that a complete infertility workup should include an evaluation of the uterine cavity. Uterine abnormalities, congenital or acquired, are implicated as one of the causes of infertility. In fact, infertility related to uterine cavity abnormalities has been estimated to be the causal factor in as many as 10% to 15% of couples seeking treatment. Moreover, abnormal uterine findings have been found in 34% to 62% of infertile women [(3)].

The role of hysteroscopy in infertility investigation is to detect possible intrauterine changes that could interfere with the implantation, growth of the conceptus or both and to evaluate the benefit of different treatment modalities in restoring a normal endometrial environment [(3)].

Platelet rich plasma (PRP) is an autologous product derived from whole blood through the process of gradient density centrifugation. Autologous PRP has been shown to be safe and effective in promoting the natural processes of wound healing, soft tissue reconstruction, bone reconstruction and augmentation [(4)].

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Recently, PRP has been used to promote endometrial growth and improve pregnancy outcome during in vitro fertilization [5]. PRP functions as a fibrin tissue adhesive with hemostatic and tissue sealing properties, but it differs from fibrin glue and other poor tissue adhesives because its platelets provide a unique ability to promote wound healing through growth factors**.** PRP accelerates endothelial, epithelial and epidermal regeneration, stimulates angiogenesis, promotes soft tissue healing and reverses the inhibition of wound healing caused by glucocorticoids. The high leukocyte concentration of PRP has an added antimicrobial effect. Since PRP is an autologous blood product, it carries no risk of transmitting infectious disease**.** Up to70% of growth factor content from activated PRP can be released over 10 minutes [4]**.**

There are various methods of preparation of PRP, best by 2-step centrifugation: first step (1000 gravitational force for 5 minutes) and second step (1500 gravitational force for 15 minutes) then gelling by adding calcium gluconate. Gelling process by calcium only without thrombin can reduce the loss of growth factors by preventing early platelet activation and coagulopathy or immune reaction from bovine thrombin [5]**.**

AIM OF THE WORK

The aim of present study is to evaluate the effect of the use of platelet rich plasma in decreasing recurrence of intrauterine adhesions after its lysis.

PATIENT AND METHODS

Study design: prospective randomized controlled clinical trial (pilot study).
Settings: Early cancer detection and endoscopy unit at Ain Shams Maternity University Hospital.
Population: The study included 60 patients with Asherman's syndrome randomly divided into two equal groups.

Research methodology

After approval of the ethical committee, patients were enrolled in the study according to the following criteria:

Inclusion criteria: Age 18-43 years. Infertility due to Asherman's syndrome with history of hypomenorrhea or amenorrhea and infertility and evaluated by office hysteroscopy to confirm the presence of sever adhesions according to American fertility society.

Exclusion criteria: Age < 18 or > 43 years. Hb < 11 g/dL, platelets < 150.000/mm^3. Patient taking anticoagulant. Patient taking NSAID in the 10 days before procedure. Any significant comorbidity or psychiatric disorder that would compromise patient's consent. Active cervical or uterine infection.

Randomization: Patients fulfilling the inclusion criteria will be randomized into two groups.

Allocation and concealment: **S**ixty opaque envelope will be numbered serially and envelope the corresponding letter that denotes the allocated be put according to randomization table. Then all envelopes will be closed and put in one box. When the first patient arrives, the envelope will be opened and the patient will be allocated according to letter inside.

Study Group: After hysteroscopic adhesiolysis, 30 patients will undergo injection of 5ml PRP into the wall then lining the uterine cavity by 5ml platelet rich plasma gel. Finally, Foley's balloon catheter will be inserted intrauterine then inflated and cutting its stem and to be left for two weeks.

Control Group: After hysteroscopic adhesiolysis, 30 patients will undergo intrauterine insertion of inflated Foley's balloon catheter with cutting its stem only to be left for two weeks.

RESULTS

Table (1): Demographic characteristics among the studied groups

Items	Measure	PRP (N=30)	Balloon (N=30)	P
Age (years)	**Mean ± SD**	31.8 ± 4.0	30.5 ± 4.7	^0.230
	Range	22.0–41.0	21.0–39.0	
BMI (kg/m^2)	**Mean ± SD**	24.4 ± 2.2	25.1 ± 2.4	^0.257
	Range	19.2–28.5	21.2–29.0	
Parity	**Nulligravida**	4 (13.3%)	3 (10.0%)	§1.000
	Multigravida	26 (86.7%)	27 (90.0%)	
Possible etiology (n, %)	**CS**	11 (36.7%)	11 (36.7%)	§1.000
	DC	11 (36.7%)	10 (33.3%)	
	Membranectomy	2 (6.7%)	3 (10.0%)	
	Hystrotomy	2 (6.7%)	3 (10.0%)	
	TB	1 (3.3%)	1 (3.3%)	
	IUD	3 (10.0%)	2 (6.7%)	
Previous balloon		3 (10.0%)	4 (13.3%)	§1.000

Table (1) show that:
As regarding demographic data there was no statistical significance between two groups regarding (age-BMI-parity-possible etiology) P value > 0.05.

Table (2): Adhesions grades among the studied groups

Items	Grade	PRP (N=30)	Balloon (N=30)	P
Before	**Grade-III**	30 (100.0%)	30 (100.0%)	**--**
After	**Grade-I**	25 (83.4%)	18 (60.0%)	**#0.045***
	Grade-II	4 (13.3%)	6 (20.0%)	
	Grade-III	1 (3.3%)	6 (20.0%)	
Value of PRP over balloon in getting grade-I				
Items		**Value**	**95% CI**	
Rate in PRP group		83.3%	26.9%–49.8%	
Rate in balloon group		60.0%	50.2%–26.9%	
Rate elevation		23.3%	-2.8%–42.9%	
Efficacy		28.0%	-4.0%–46.0%	
Relative Rate		1.39	0.96–1.85	
Number needed to treat		4.3	2.3–Infinite	

Table (2) show that:
- **Grade-I adhesions** was higher but non-significant among PRP group than among balloon group.
- **Grade III** adhesion was non significantly less frequent among PRP group than balloon group.
- We concluded that treatment with PRP is more effective than balloon insertion (efficacy 25%).

Table (3): Menses duration (days) among the studied groups

Time	Measure	PRP (N=30)	Balloon (N=30)	^P
Ordinary¤	**Mean ± SD**	3.7 ± 0.9	3.8 ± 0.7	0.879
	Range	0.0–6.0	3.0–6.0	
Before	**Mean ± SD**	1.4 ± 1.5	1.4 ± 1.4	0.862
	Range	0.0–5.0	0.0–5.0	
After	**Mean ± SD**	3.1 ± 1.1	1.9 ± 1.2	**<0.001***
	Range	0.0–5.0	0.0–5.0	
After-ordinary*	**Mean ± SD**	-0.6 ± 0.7	-1.9 ± 1.0	**<0.001***
	Range	-2.0–0.0	-4.0–0.0	
	#P	**<0.001***	**<0.001***	
After-Before	**Mean ± SD**	1.7 ± 1.4	0.5 ± 0.7	**<0.001***
	Range	0.0–4.0	0.0–2.0	
	#P	**<0.001***	**<0.001***	
Value of PTP over balloon				
		Mean ± SE	**95% CI**	
Menses prolongation		1.2 ± 0.3	0.6–1.8	

Table (3) show that:
Our study shown significant increase of menses duration among the PRP group compared to balloon group. and there was no significant difference in menses duration between both study groups regarding #last ordinary and before intervention.
*But the menses duration is still lower than the last ordinary duration.

Table (4): Menses amount (pad) among the studied groups

Time	Measure	PRP (N=30)	Balloon (N=30)	^P
Ordinary¤	**Mean ± SD**	9.5 ± 5.2	9.9 ± 5.2	0.767
	Range	0.0–24.0	4.0–24.0	
Before	**Mean ± SD**	1.0 ± 1.0	0.9 ± 1.0	0.793
	Range	0.0–3.0	0.0–3.0	
After	**Mean ± SD**	5.9 ± 3.8	2.8 ± 2.6	**<0.001***
	Range	0.0–15.0	0.0–10.0	
After-ordinary*	**Mean ± SD**	-3.6 ± 3.2	-7.2 ± 4.8	**<0.001***
	Range	-9.0–0.0	-18.5–0.0	
	#P	**<0.001***	**<0.001***	
After-Before	**Mean ± SD**	5.0 ± 3.6	1.9 ± 2.0	**<0.001***
	Range	0.0–13.0	0.0–7.5	
	#P	**<0.001***	**<0.001***	

Value of PTP over balloon		
	Mean ± SE	**95% CI**
Menses prolongation	3.1 ± 0.8	1.6–4.6

Table (4) show that:
Our study shown significant increase of menses amount among the PRP group compared to balloon group. and there was no significant difference in menses amount between both study groups regarding last ordinary and before intervention.
* But the menses amount is still lower than the last ordinary amount.

DISCUSSION

Intrauterine adhesions (IUAs) are fibrous strings at opposing walls of the uterus. The spectrum of severity of IUAs ranges from minimal to complete obliteration of the uterine cavity. Any trauma to the endometrium can lead to formation of IUAs. In daily clinical practice, nearly 90% of all IUAs are associated with postpartum or post abortion dilatation and curettage [(6)].

Intrauterine adhesions may be asymptomatic, but generally are related with infertility, menstrual disorders (hypomenorrhea, amenorrhea), cyclic pelvic pain or cramping around the time of period, recurrent miscarriage and endometriosis (caused by backflow of blood from the uterus). Indirect imaging methods give useful information in diagnosis as 3D ultrasound, but the gold standard diagnostic method is hysteroscopy that has the advantage of concurrent treatment [(1)].

When more scarring is present, the treatment is usually less successful. Direct hysteroscopic view of the endometrial cavity is the only way to determine the degree of IUA and can easily be performed in the office. Diagnostic hysteroscopy has the fewest risks, followed by operative hysteroscopic adhesiolysis. Fluid management is critical for intraoperative safety. Meticulous detail should be paid to fluid management, and consultation sought with a critical care specialist when fluid overload or hyponatremia is suspected. Lingering pain, fever, or pelvic discomfort after surgery requires prompt evaluation [(7)]

Management and treatment strategy include hysteroscopic adhesiolysis; readhesion prevention by intrauterine device, uterine balloon stent, Folly's catheter or amnion graft; restoration of normal endometrium (hormonal treatment - stem cells) and postoperative assessment by (office hysteroscopy – ultrasound) [(2)].

Prevention of both formation and reformation of intrauterine adhesions is a challenging issue in clinical practice. Varieties of methods have been proposed including hormone treatment, intrauterine mechanical barriers, such as IUDs and intrauterine balloons, which all appear to have some benefit. Both Hyaluronic acid gel and amnion graft have promising results but further clinical trials are required to confirm their efficacy [(8)].

Platelet rich plasma (PRP) is an autologous product derived from whole blood through the

process of gradient density centrifugation. Autologous PRP has been shown to be safe and effective in promoting the natural processes of wound healing, soft tissue reconstruction, bone reconstruction and augmentation [(4)].

Recently, PRP has been used to promote endometrial growth and improve pregnancy outcome during in vitro fertilization [(5)].

This current study was held to assess the efficacy of the use of plasma rich platelet versus IU balloon in decreasing occurrence and recurrence of intrauterine adhesions after operative hysteroscopy.

We decided to design a prospective randomized clinical trial study in Ain Shams Maternity Hospital (Early Cancer Detection and Endoscopy Unit). 60 patients were recruited for the study, (30 patients in the study group underwent PRP injection and 30 patients in the control group underwent balloon insertion)

In the studies of **Amer *et al.*** [(9)], hysteroscopic adhesiolysis was followed by intrauterine application of a fresh amnion graft over an inflated balloon of a Foley's catheter for 2 weeks. Follow-up hysteroscopy was performed after 4 months.

In the study of **lin *et al.*** [(10)], Women were randomized for having either a heart-shaped intrauterine balloon or an IUD fitted after hysteroscopic adhesiolysis. The devices were removed after 7 days. A second-look hysteroscopy was carried out 1 to 2 months after the surgery. Main Outcome Measure (s): Incidence of adhesion reformation and reduction of adhesion score before and after surgery.

In the study of **Amer *et al.*** [(9)], 25 patients were recruited with moderate or severe intrauterine adhesions. Mean participant age (SD) was 30.7 ± 5.8 years old in the group of moderate intrauterine adhesions and 28.8 ± 4.2 years old in the group with severe intrauterine adhesions.

In the study of **lin *et al.*** [(10)] Initially 201 cases were recruited; 39 cases dropped out, resulting in 82 cases in the balloon group and 80 cases in IUD group. The age, menstrual characteristics, pregnancy history, and American Fertility Society score before surgery were comparable between the two groups

In our study, there was no significant difference regarding patient characteristics (age, parity, BMI and possible etiology) in the studied groups and all patients had grade III adhesions.

Our study showed significant increase of menses duration among the PRP group post-operative (3.0 ± 1.2) days and preoperative menses duration (1.4 ± 1.5) days. Compared to balloon post-operative (1.8 ± 1.3) and preoperative (1.3 ± 1.4) days.

Our study showed significant increase of menses amount among the PRP group post-operative (5.8 ± 4.0) pads, and preoperative menses duration (1.0 ± 1.0) pads. Compared to balloon post-operative (2.9 ± 2.7) and preoperative (0.9 ± 1.0) pads.

Our study showed significant increase in the improvement of menses amount and duration in PRP group (93.3%) and balloon group (80%).

Our study showed that PRP has a non-significant but higher improvement than balloon in the adhesion score. Before hysteroscopic adhesiolysis 60 patients had Grade-III adhesions, 30 patients underwent PRP injection 23/30 patients became grade I (76.7%), 5/30 patients became grade II (16.7%) and 2/30 (6.7%) still grade III adhesions. 30 patients underwent balloon 18/30 patients became grade I (607%), 6/30 patients became grade II (20%) and 6/30 (20%) still Grade III adhesions.

The study of **Amer *et al.*** [(9)] showed significant improvement in adhesion score with absence of adhesions recorded in 12/12 (100%) of group A (group with moderate intrauterine adhesions) and 1/13 (7.7%) in group B (group with severe intrauterine adhesions). There was improvement in all patients with significant increase in uterine length and duration of menstrual flow in both groups. Restoration of normal menstrual flow occurred in 80% of patients (20/25). Despite improvement, failure to achieve normal duration of menstrual flow after single surgical attack was found in 2/12 (16.7%) in group A and in 3/13 (23.1%) in group B.

The study of **Lin *et al.*** [(10)] reported adhesion reformation rate of 30% (balloon group) and 35% (IUD group). There was no significant difference between the two groups. The intrauterine balloon and IUD are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for Asherman's syndrome.

Our study showed promising results with significant improvement in using the PRP than the balloon where there was no complications recorded from using PRP. Further clinical trials are required to confirm its efficacy. We also recommend the following: other studies to compare single vs. multiple injections of PRP. Also, following the infertility and adding it to the

studies outcome. In addition to head to head studies with the other methods.

CONCLUSION

Platelet rich plasma after operative hysteroscopy has high efficacy and safety in improvement of menses duration, amount and readhesion score in cases suffering from severe intrauterine adhesions.

REFERENCES

1- **Sendag F, Dikmen A, Akman L, Oztekin K (2013):** Hysteroscopic management of intrauterine adhesion: Journal of Turkish Society of Obstetrics and Gynecology, 10(1): 21-25

2- **Conforti A, Alviggi C, Mollo A, De Placido G, Magos A (2013):** The management of Asherman syndrome: a review of literature: Reproductive Biology and Endocrinology, 11(1):118.

3- **Sahu L, Tempe A, Gupta S (2016):** Hysteroscopic evaluation in infertile patients: a prospective study: International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 1(1): 37-41.

4- **Smith RG, Gassmann CJ, Campbell MS (2007):** Platelet-rich plasma: properties and clinical applications: J Lancaster Gen Hosp., 2(2):73-8.

5- **Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, Liang X (2015):** Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization: International Journal of Clinical and Experimental Medicine, 8(1):1286.

6- **Nappi C, Di Spiezio Sardo A, Greco E, Guida M, Bettocchi S, Bifulco G (2007):** Prevention of adhesions in gynaecological endoscopy. Human Reproduction Update, 13(4):1–16.

7- **Bradley LD (2002):** Complications in hysteroscopy: prevention, treatment and legal risk. Curr Opin Obstet Gynecol., 14(4):409-15.

8- **Deans R, Abbott J (2010):** Review of intrauterine adhesions. J Minim Invasive Gynecol., 11:555–569.

9- **Amer MI, Abd-El-Maeboud KHI, Abdelfatah I, Salama FA, Abdallah AS (2010):** Human amnion as a temporary biologic barrier after hysteroscopic lysis of severe intrauterine adhesions: pilot study. Journal of Minimally Invasive Gynecology, 17(5):605–11.

10- **Lin XN, Zhou F, Wei ML, Yang Y, Li Y, Li TC, Zhang SY (2015):** Randomized, controlled trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation after hysteroscopic adhesiolysis. Fertility and sterility, 104(1):235-40.