The Therapeutic Effect of Intravesical Instillation of Platelet Rich Plasma on Recurrent Bacterial Cystitis in Women: A Randomized Clinical Trial

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Purpose: Recurrent bacterial cystitis is a common infection in women and there are concerns about its antibiotic therapy. Platelet rich plasma has antimicrobial and tissue repairing effects. We investigated the effect of platelet rich plasma as an intravesical therapy to prevent recurrence of bacterial cystitis.

Materials and Methods: Thirty women with a history of recurrent bacterial cystitis were randomly assigned into two groups: 1) platelet rich plasma and 2) control groups. The first group received 10 mL of platelet rich plasma with intravesical instillation plus 40 mL of normal saline. The control group only received 50 mL of normal saline. We did the instillation once a week for four weeks in both groups. We followed up the participants two and 12 months after the last instillation with a questionnaire (the international consultation on incontinence questionnaire in overactive bladder) and result of their urine culture.

Results: A significant decrease was observed in the number of bacterial cystitis recurrences in the platelet rich plasma group compared to the control group 12 months after the instillation (4 vs. 1, $P = 0.004$). Also, there was a significant improvement in the questionnaire's score two (3.6 ± 2.58 vs. 0.66 ± 1.63, $P = 0.002$) and 12 months (3.4 ± 2.77 vs. 0.006 ± 1.83, $P < 0.001$) after instillation in the platelet rich plasma group compared to control group. There was no adverse effect 12 months after instillation.

Conclusion: Platelet rich plasma can significantly decrease the recurrence of bacterial cystitis up to a year after instillation without any side effect.

Keywords: platelet rich plasma; recurrent cystitis; bacterial cystitis; intravesical instillation

INTRODUCTION

Urinary tract infection is the most common bacterial infection. The acute cystitis occurs about 0.5 episodes per person per year in young women[(1)]. Approximately 25% of women involved in the first episode of cystitis experience recurrent urinary tract infections in the next six months. Some of them experience this infection six or more times per year. Also, recurrence of cystitis which follows an acute cystitis is a major complaint that can affect their quality of life[(2)].

Bacterial urinary tract infection occurs with various symptoms, and many organisms can be responsible for it. *Escherichia coli* is the most common pathogen of acute cystitis[(2)]. Although its current antibiotic therapy is effective, it cannot prevent the recurrence of bacterial cystitis[(2)]. Prophylactic antibiotic regimes cannot prevent infection completely[(3)]. According to the rising uropathogens' antibiotic resistance, we will soon need new treatments for this urinary tract infectious disease[(4,5)].

There is a strong relationship between lower urinary tract symptoms such as frequency, urgency, suprapubic pain with or without hematuria and positive urine culture[(6,7)]. A symptomatic cystitis depends on a reaction between a uropathogen and the host cells[(8)]. Uropathogens can continue to expose immature urothelial cells and form quiescent intracellular reservoirs to protect themselves from the immune system and antibiotics[(9-11)]. Platelet rich plasma (PRP) is the concentrated autologous platelet in a small amount of plasma. Also, factors such as factor 7, TGF□1, TGFβ2, PDGFαβ, PDGFββ, PDGFαα, EGF and VEGF and three blood proteins (fibrin, fibronectin and vitronectin which repair lesions) can be found in PRP[(12)].

Some studies suggest the antimicrobial role of platelet with releasing antimicrobial peptides from its alpha granules. These peptides have a broad-spectrum action against gram-positive and gram-negative bacteria and fungi[(13-16).] In our study, we sought to return the bladder to a normal state in which it would be sterile for a longer period. This therapeutic idea had been suggested before[(17)]. Thus, we investigated the effect of PRP as an intravesical therapy to prevent recurrence of bacterial cystitis.

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Table 1. Comparison of bacterial cystitis episodes in the PRP and control groups

Bacterial cystitis episodes	PRP group	Control group	*P*-value*
Before treatment (mean)	5.53 ± 1.92	6.46 ± 1.64	0.13
12 months after treatment (mean)	1.88±1.59	5 ± 1.64	< 0.001

* Mann-Whitney U

PATIENTS AND METHODS

Study design and population

This was a double-blinded clinical trial with available sampling method. In this sense, 30 women older than 18 years old participated in our study. They had referred to our center with a history of recurrent cystitis in 2016. They were randomly assigned into two groups based on random table numbers (15 women in each group): 1) PRP and 2) control groups. The first group received 10 mL of PRP with intravesical instillation plus 40 mL of normal saline. The control group only received 50 mL of normal saline.

The inclusion criteria were having: 1) at least four episodes of bacterial cystitis during the previous year; and 2) positive urine culture with more than 1000 CFU/mL. The exclusion criteria were having: 1) any urologic disease history (such as ureterocele, vesicoureteral reflux, urinary stone, urethral stenosis, pyelonephritis history); 2) any history of urological surgery (such as cystocele); 3) any measurable post-void urine residue, constipation, vaginal prolapse; 4) an active infection at the time of entering the study; 5) not using any drugs and addiction history; and 6) not using spermicidal and intrauterine devices during the study.

One woman in each group was single. The rest were married and sexually active. We instilled the treatment for each participant based on her group once a week for four weeks, that is if she cooperated and based on her therapeutic responses. Then we followed them up at two and 12 months after the last instillation. They filled a questionnaire and we took their urine culture before the first instillation and in each follow-up session.

The questionnaire was the Persian (Farsi) version of international consultation on incontinence questionnaire in overactive bladder (ICIQ-OAB)[18]. This questionnaire has five questions and each question has a score of 1 to 4 according to severity of symptoms. If at any time after treatment the participants had symptoms of acute cystitis, we did urine culture and they underwent a three-day antibiotic therapy with ciprofloxacin. Informed consent was obtained from the participants before entering the study. This study was approved by the ethics committee of our university (IR.KMU.AH.REC.1396.110).

Instillation method

The instillation was done with a 10 French Nelaton catheter insertion in both groups. It was done in a sterile method and under local anesthesia with xylocain 2% gel. The participants did not void until two hours after instillation. The instillation's position was changed every 30 minutes to the sides, back and abdomen to make sure it reaches the entire bladder.

Platelet rich plasma preparation

The first 20 mL of participants' blood was collected in a dexterous citrate acid contained tube. Then it was centrifuged 10 minutes with 2400 rmp at room temperature to be divided into three layers: red blood cells, Buffy coat and platelet poor plasma. Buffy coat and platelet poor plasma were carefully transferred to another tube with micropipette. Platelet poor plasma was centrifuged 10 minutes at 3500 rmp at room temperature. PRP was extracted from it and used for instillation immediately (**Figure 1**).

STATISTICAL ANALYSIS

Mann-Whitney U test was used to compare the demographic characteristics and number of bacterial cystitis episodes. We used Wilcoxon test for comparing the bacterial cystitis episodes between patients before and after intervention. The repeated measure analysis was used to compare ICIQ-OAB scores within groups during follow up (before treatment, two and 12 mounts after treatment), respectively. The data were analyzed with statistical package for social sciences (SPSS) software version 18.

RESULTS

The means of age were 46.2 ± 10.62 and 45.06 ± 11.93 years old ($P = 0.78$) in the PRP and control groups, respectively. There was no significant difference between the two groups in the number of deliveries 2.46 ± 1.24 vs 3 ± 1.77 ($P = 0.34$) before the study. There was no significant difference in the number of bacterial cystitis episodes between the two groups ($P = 0.13$; **Table 1**)

A year after the intervention, a significant reduction was observed in the number of cystitis recurrences in both groups (5.53 ± 1.92 vs 1.88 ± 1.59, $P = 0.001$ in PRP group and 6.46 ± 1.64 vs 5 ± 1.6, $P = 0.003$ in the control group). This reduction was significantly more in the PRP group compared to the control group (3.66 ± 2.16 vs. 1.46 ± 1.59, $P = 0.004$). There was a little reduction in the control group that could be due to placebo effect (**Table 2**).

The result of the repeated measure analysis showed that ICIQ-OAB score decreased significantly in PRP group

Table 2. Comparison of bacterial cystitis episodes and the reductions before and after treatment in PRP and control groups

Bacterial cystitis episodes	Before treatment (mean)	12 months after treatment (mean)	*P*-value†	The reduction of bacterial cystitis episodes	*P*-value*
PRP group	5.53 ± 1.92	1.88 ± 1.59	< 0.001	3.66 ± 2.16	0.004
Control group	6.46 ± 1.64	5 ± 1.64	0.003	1.46 ± 1.59	

† Wilcoxon test
* Mann-Whitney U

Table 3. The comparison of ICIQ-OAB scores before, two and 12 months after treatment in PRP and control groups

ICIQ-OAB score	Before treatment	2 months after treatment	12 months after treatment	*P*-value*
PRP group	12.06 ± 2.25	8.46 ± 3.22	8.66 ± 3.61	0.001
Control group	13.06 ± 5.78	12.4 ± 2.61	13.13 ± 2.92	0.89

*Repeated Measure analysis

during follow up ($P \leq 0.001$). But there was no significant change in this score in the control group during the same period ($P = 0.89$; **Table 3**)

DISCUSSION

The recurrent bacterial cystitis is a common infection in women[1]. Its current antimicrobial therapies have problems such as increased antibiotic resistance and recurrence after discontinued treatment[2,4,5]. Therefore, we need to find new treatments for it. Platelet has an antimicrobial role with releasing antimicrobial peptides from its alpha granules[13-16]. There are studies on using PRP for tissue repair[19,20] which can be used to repair the damaged bladder mucosa in recurrent cystitis.

Dönmez and colleagues investigated the effect of PRP intravesical instillation in interstitial cystitis in rabbits. They divided the rabbits into four groups: 1) serum physiologic, 2) serum physiologic + PRP, 3) hydrochloride acid and 4) hydrochloride acid + PRP. They observed that mitotic activity increases in serum physiologic + PRP and hydrochloride acid + PRP groups compared to serum physiologic and hydrochloride acid groups[21]. They did instillation only once. They gave a 96-hour time to the agents to act on the bladder. Although the results were significant, doing more instillations and spending more time could have had better results.

Two years later, the same authors studied the effects of PRP on rabbits' bladders. This time they instilled saline, saline + PRP, hydrochloride acid, hydrochloride acid+PRP, cyclophosphamide, cyclophosphamide+PRP in six groups with six rabbits in each group. The bladder of rabbits in hydrochloride acid and saline groups were surgically removed 96 hours after the instillation. In cyclophosphamide group, they were removed 72 hours after administration. They saw that the instillation of PRP significantly increases mitotic index and significantly decreases macroscopic bleeding in these groups[22]. These results support the repairing role of PRP on bladder mucosa. So, we theoretically accepted and used it to improve the symptoms of humans with recurrent bacterial cystitis.

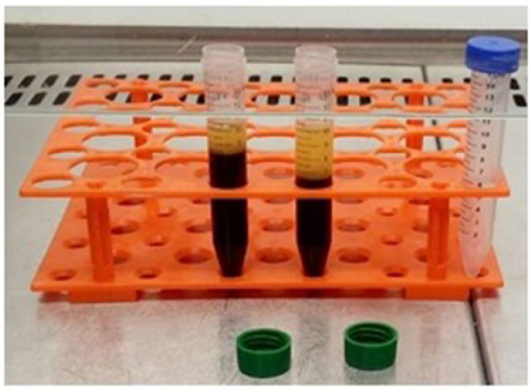

Figure 1. Platelet rich plasma

In another study, Lara Paro Dias and colleagues used PRP to treat the non-muscular invasive bladder cancer in rats. They divided the animals into four groups: 1) control, 2) Bacillus Calmette–Guérin, 3) PRP and 4) Bacillus Calmette–Guérin+PRP. They reported that animals treated with Bacillus Calmette–Guérin+PRP had less neoplastic lesion progression compared to the other groups [23]. These studies are promising, but have been done on animals. To our knowledge, there is no study on PRP intravesical instillation on humans. However, there are studies that have examined intravesical instillation therapies for recurrent bacterial cystitis with hyaluronic acid with or without chondroitin sulfate. They show the significant effect of intravesical instillation with few side effects[24-27].

In a recent study, Dutta and Lane treated 39 women with recurrent urinary tract infection by heparin intravesical instillation in six sessions, one per week. They reported that 12 patients (30.8%) had recurrence of urinary tract infection in the treatment phase. 46.2% of patients had at least one urinary tract infection and seven (17.9%) met the criteria of recurrent urinary tract infections in the six months follow up period[28]. Their study had no control group and their follow-up period was only six months. If they had a longer follow-up period or a control group, the results could have been more useful. Their study had no strong exclusion criterion that could lead to a difference in participants because of the small sample size, causing an error in the conclusion.

We examined the effect of intravesical instillation of PRP in women who suffered from recurrent bacterial cystitis. This is important because to our knowledge, it is the first study of intravesical instillation of PRP on humans. So, we should be cautious about the possible adverse effects. Although we had a small sample size, we observed a significant therapeutic effect in administering intravesical instillation of PRP. This seems promising. Although recurrence happened in all of our participants, the number of occurrences had decreased compared to the year before doing the intervention. We observed a partial improvement in the control group, which was the placebo effect in our study.

CONCLUSIONS

PRP seems to have a therapeutic effect. Fortunately, we have not seen any adverse effect up to 12 months after instillation. PRP can significantly improve the symptoms and decrease recurrence of cystitis up to a year after instillation. More studies with larger sample sizes should be done until we can present the intra-vesical instillation of PRP as an available non-antibiotic therapy for recurrent cystitis.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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