Intravesical Injections of Platelet-Rich Plasma

Subjects: Allergy

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Intravesical instillations are based on two fundamental assumptions: restoration of the urothelial barrier or topical anti-inflammatory action. One of the drugs used for topical anti-inflammatory action is Dimethyl Sulfoxide (DMSO). This substance has proven to be useful due to its anti-inflammatory, analgesic and muscle relaxant properties and is also able to block mast cell degranulation.

Keywords: platelet-rich plasma ; interstitial cystitis ; bladder pain syndrome ; primary bladder pain syndrome ; recurrent urinary tract infections

1. Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) or primary bladder pain syndrome (PBPS) is a chronic inflammatory disorder characterized by pelvic pain for at least 6 months due to increased bladder pain and increased urination frequency, which worsens the quality of life of affected patients [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35]. The incidence of PBPS is approximately 52–67 per 100,000 cases in the United States of America [2]. Chronic inflammation can cause urothelial dysfunction with edema, the presence of neurogenic inflammatory infiltrates, and ulceration formations [3]. Studies have documented that there is an increase in both tissue and urinary expression of certain neurotrophins, such as the nerve growth factor (NGF), which may indicate a hyperactivation of sensory nerves and increased neuronal plasticity that would lead to the typical sensation of pain present in this pathology [4]. Additionally, there has been a reported increase in inflammatory cytokines, such as tumor necrosis factor- alpha and interleukin (IL)-6 and 8 [5]. These events could lead to a malfunction of urothelial tight junctions with loss of urinary blood barrier integrity and subsequent loss of potassium within the interstitium [6]. Overexpression of some angiogenic growth factors, such as vascular endothelial growth factor (VEGF), has also been demonstrated, which can induce the formation of immature vasculature easily demonstrated during the hydrodistension procedure with the formation of typical glomerulations [7]. Moreover, in patients with BPS/IC, there is a decreased bladder capacity due to the process of organ fibrosis that is generated after chronic inflammation. In these patients, there is an increase in transforming growth factor (TGF)-beta 1 and hyperactivation of matrix metalloproteinases (MMPs) [8].

Intravesical instillations are based on two fundamental assumptions: restoration of the urothelial barrier or topical anti-inflammatory action [3]. One of the drugs used for topical anti-inflammatory action is Dimethyl Sulfoxide (DMSO) [3]. This substance has proven to be useful due to its anti-inflammatory, analgesic and muscle relaxant properties and is also able to block mast cell degranulation. The main problem of this substance is that it can initially worsen the symptomatological picture and therefore patients are forced to suspend it.

It has been hypothesized that within the PRP, there are some growth factors, such as the platelet-derived growth factor (PDGF), TGF, and epidermal growth factor (EGF), that stimulate mitogenesis, chemotaxis, and cell differentiation [11]. Specifically, it has been hypothesized that PRP injected within the bladder may promote repair of urothelial defects and regeneration of the epithelium that is damaged in patients with IC/BPS [12]. Therefore, the purpose of this review was to discuss the clinical and preclinical evidence published to date regarding the use of PRP in the treatment of IC/BPS.

The therapy currently approved for this pathology is essentially based on the aforementioned elements [14]. In fact, the substances that are used can restore the endothelial barrier, and they try to “turn off” the neurogenic inflammation and block the uncontrolled mast cell activation [14]. Following a bladder insult, a vicious circle is generated in which the damage is perpetuated, and in this way, bladder pain syndrome associated with urination disorders develops [15]. Subsequently, bladder fibrosis can be generated, and through the process of neuronal plasticity, chronic neuropathic pain can be established [15].

2. Development and Findings

Donmez et al. [16]. evaluated the early histological effects of intravesical PRP instillation in rabbit models of interstitial cystitis and hemorrhagic cystitis (**Table 1**). They divided 36 rabbits into six groups according to the substances injected intravesically: saline solution (S), S + PRP, hydrochloric acid (HCl), HCl + PRP, cyclophosphamide (CyP), and CyP + PRP. At 48 h after induction by HCl, which mimicked the presence of interstitial cystitis, and CyP, which mimicked the presence of hemorrhagic cystitis, the preparation containing PRP was instilled. They found that the mean mitotic index and profiling index were higher in the S + PRP group than in the S group ($p = 0.004$ and $p = 0.009$, respectively). In addition, the mean mitotic index increased ($p = 0.002$) in the HCl + PRP group compared to the HCl group. Furthermore, in the Cyp + PRP group, there was a significant reduction in intravesical bleeding ($p = 0.006$) and an increase in leukocyte infiltration ($p = 0.038$) and the mitotic index ($p = 0.002$). They concluded that intravesical injection of PRP increased the mitotic index and decreased bladder bleeding [16].

Table 1. Main features of the preclinical studies analyzed.

Study	Donmez et al., 2016 [16]	Chen et al., 2020 [17]
Purpose	**To investigate the early histological effects of intravesical instillations of PRP**	**To investigate whether the intravesical instillation of PRP could be ameliorate urothelial injury**
Animal model used	**36 rabbits**	**30 virgin female rats**
Design	**Experimental**	**Experimental**
Investigated variables	**Histopathology of the bladder sections, mitotic index**	**Histopathology of the bladder sections, ZO-2 expression, IL-6 expression, voiding intervals value**
Significant results	**In the PRP-treated groups, there was an increase in the mitotic index, reduction in hemorrhage, and an increase in leukocyte infiltration**	**In the PRP-treated groups, there was an increase in HFCs, an increase in the interval between micturitions, an increase in ZO-2 expression, and a decrease in IL-6 expression**

PRP: platelet-rich plasma; ZO-2: zonula occludens 2; IL-6: interleukin 6; HFCs: human skin fibroblast cells.

Jhang et al [19]. investigated the clinical efficacy of intravesical PRP injections in IC/BPS (**Table 2**). The authors performed four intravesical injections of PRP (volume of 12 mL extracted from 50 mL of the patient's own blood) at monthly intervals in 15 patients with IC/BPS and analyzed the O'Leary-Sant symptom (OSS) score, as the primary endpoint, at baseline and at 30 days and 4 months later. In addition, they analyzed pain perception using the visual analog scale (VAS), urination frequency, functional bladder capacity, maximum flow rate, post-urination residual (PVR), and global response assessment (GRA), which is a symmetric seven-point scale; the result was considered excellent when patients reported improvement in the score by >2, and the result was considered improved if there was an improvement of >1. They also investigated urinary cytokine levels at baseline and 1 month and 4 months later.

Table 2. Main features of the clinical trials analyzed.

Study	Jhang et al., 2017 [19]	Jhang et al., 2018 [20]	Jiang et al., 2020 [21]
Purpose	**To investigate the clinical efficacy of intravesical injections of PRP**	**To investigate the clinical efficacy of intravesical injections of PRP**	**To investigate the changes in urinary markers after PRP treatment**
Design	**Prospective clinical trial**	**Prospective clinical trial**	**Prospective clinical trial**
Subjects	***N* = 15 women, but 13 completed the 4 injections and follow-up visits**	***N* = 40 (37 women and 3 men)**	***N* = 40 (37 women and 3 men)**
Protocols	**4 PRP endovesical injections monthly**	**4 PRP endovesical injections monthly**	**4 PRP endovesical injections monthly**
Primary outcome	**Change in the OSS index from baseline to 1 month after the 4th PRP injection**	**GRA score at 3 months after the 4th PRP injection**	**Urinary levels of cytokines, functional proteins, and growth factors**

Study	Jhang et al., 2017 [19]	Jhang et al., 2018 [20]	Jiang et al., 2020 [21]
Secondary endpoints	VAS score, daily urination frequency, nocturia, FBC, maximum flow rate, voided volume, PVR, GRA score, IL-2 expression, and IL-8 expression	OSS index, VAS score, daily urination frequency, nocturia FBC, maximum flow rate, voided volume, PVR	OSS index, VAS score, daily urination frequency, nocturia FBC, maximum flow rate, voided volume, PVR
Significant results	OSS index and VAS score decreased, FBC and GRA score increased after the 1st PRP injection until 1 month after the 4th PRP injection, no change in PVR	GRA score improved after the 1st PRP injection until 3 months after the 4th PRP injection, OSS index and VAS score decreased, FBC decreased and urination frequency and nocturia decreased, no change in PVR	GRA score improved; VAS score, urination frequency, and nocturia decreased; urinary levels of NGF and VEGF decreased; urinary level of PDGF increased

PRP: platelet-rich plasma; *N*: number; OSS: O'Leary-Sant Symptom index; GRA: global response assessment; VAS: visual analog scale; FBC: functional bladder capacity; PVR: post-void residual; NGF: nerve growth factor; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor.

The results of this study at 1 month after the last treatment were as follows. In total, 13 of 15 patients completed the course of intravesical injections with PRP. The VAS and OSS scores decreased significantly ($p < 0.05$) after the first PRP injection, and there was an increase in the GRA score ($p < 0.05$) and an increase in bladder capacity ($p < 0.05$). In addition, there were no changes in post-micturition residual or micturition difficulties ($p > 0.05$), but there was an increase in the expressions of IL-2 ($p = 0.028$) and IL-8 ($p = 0.019$), suggesting an immunomodulatory response following the PRP injections [19].

An endoscopic procedure consisting of 20 suburothelial injections of PRP was performed in patients with IC/BPS. Each injection corresponded to 0.5 mL of PRP. A 23-gauge needle was inserted 1 mm inside the bladder wall (the lateral and posterior walls were involved), and then hydrodistension was performed up to a bladder capacity of 500 mL to activate the injected substance.

3. Conclusions

Intravesical treatment with PRP, according to the studies published in the literature, could be an innovative treatment, albeit minimally invasive, with efficacy in terms of improving clinical symptoms, and preclinical and clinical evidence suggests that PRP can change the natural history of the disease, leading to its clinical and pathophysiological improvement. However, further studies are needed to demonstrate its true clinical efficacy. In addition, studies indicate that PRP can also be used to treat BPS/IC-like urologic conditions such as rUTI.

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