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Restoration of the pubourethral ligament with platelet rich plasma for the treatment of stress urinary incontinence

Kostis I. Nikolopoulos [a,b,*], Vasilios Pergialiotis [a], Despina Perrea [a], Stergios K. Doumouchtsis [c]

[a] Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, University of Athens, Greece
[b] Department of Obstetrics and Gynaecology, Queen's Hospital, Rom Valley Way, Romford, Essex, United Kingdom
[c] Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust/St George's University of London, United Kingdom

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ABSTRACT

Stress urinary incontinence (SUI) is a major health problem, which affects nearly 20% of adult women and has a detrimental impact on their daily activities and quality of life. Several surgical techniques have been proposed for the treatment of SUI including the Burch colposuspension, retropubic mid-urethral slings (TVT), trans-obturator tapes (TOT), trans-obturator tapes inside out (TVT-O), bladder neck injections and the insertion of an artificial urethral sphincter. All of these treatments aim to either restore the urethral support, which is naturally preserved by the pubourethral ligament (PUL) or to increase the urethral resistance at rest. Most surgical techniques are associated with a variety of intraoperative and postoperative complications. Platelet rich plasma (PRP) is extremely rich in growth factors and cytokines, which regulate tissue reconstruction and has been studied extensively among trauma patients and trauma experimental models. To date, however, there is no evidence to support or oppose its use in women who suffer from SUI due to PUL damage. PRP is an easily produced and relatively inexpensive biologic material. It is produced directly from the patient's blood and is, thus, superior to synthetic materials in terms of potential adverse effects such as from foreign body reaction. In the present article we summarize the existing evidence in the field, which supports the conduct of animal experimental and clinical studies to elucidate the potential role of PRP in treating SUI.

Introduction

The reported prevalence of stress urinary incontinence (SUI) can be as high as one in five adult women and approximately half of all incontinent women are affected by this type of incontinence [1]. It is estimated that 120,000 women undergo surgery for urinary incontinence each year in the USA [2]. Since the introduction of tension-free vaginal tape (TVT) in 1995, more than 1,200,000 procedures have been performed worldwide [3].

Midurethral sling procedures, the most commonly performed ones for SUI nowadays, were designed based on studies of the female pelvic anatomy and function. According to the integral theory, the most important defect in cases of female stress urinary incontinence is a pubourethral ligament (PUL) defect [4–6]. The PUL anchors the anterior wall of the bladder and proximal urethral descending like a fan from the lower part of the pubic bone. It consists of vaginal and urethral parts, joined together by thin fibrous threads. The urethral part inserts into the mid-part of the urethra. The vaginal part, enters posterolaterally into the vagina forming a hammock, close to the bladder neck. Histologically the ligaments consist of smooth muscle, elastin, collagen, nerves and blood vessels [6,7].

Childbirth, aging, and congenital collagen defects are major causes of uterovaginal prolapse and stress incontinence [8]. The fundamental principle of the integral theory is that structure and function are intimately related, "Restore the structure, and you will correct the function" [6,8].

The hypothesis

Several surgical techniques have been proposed for the treatment of SUI. Among them, Burch colposuspension, autologous fascia slings, retropubic mid-urethral slings MUS (TVT), trans-obturator tapes (TOT), trans-obturator tapes inside out (TVT-O), bladder neck injections and artificial urethral sphincters, are the most commonly used [9].

The midurethral sling (MUS) represents a common surgical option for the treatment of women with stress urinary incontinence (SUI), with reported long-term success rates that reach 90% [10,11]. While generally well tolerated and safe, these operations are not free of complications. Intraoperative complications

* Corresponding author at: Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, University of Athens, Greece.

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such as bleeding, bladder and urethral injuries as well as postoperative complications, such as pain, voiding dysfunction, infection and tape erosion, are the most commonly reported ones [12].

Periurethral and transurethral bulking injections are less invasive procedures for the treatment of SUI. They seem to be accompanied by lower rates of intra- and postoperative complications; however, the reported cure rates with this type of treatment seem to be low (up to 53%) [13,14]. The main objective of injectable biomaterials is to provide mechanical support to the bladder neck in order to increase urethral resistance, at rest, in patients with SUI, and not to restore the PUL.

To date the clinical thinking in the field of SUI has been limited in the field of synthetic implants which partially mimic the mechanism of the PUL. An alternative approach for the treatment of SUI, could be the implementation of an injectable agent which could primarily restore the PUL's structure and function. This regenerative principle with autologous substances could potentially limit the side effects of synthetic materials. Interestingly, despite the widespread use of fibrin adhesives and plasma rich plasma in various fields the past 30 years [15], these substances have not been used for the treatment of female SUI. Research projects investigating the regenerative abilities of plasma (platelet-rich or platelet-poor fractions) offer opportunities of using an autologous substance with adhesive, healing, and hemostatic properties at a low cost [16–18]. In this context, injecting an autologous adhesive factor to the PUL, might have promising results in the treatment of the SUI by re-approximating the urethra and the bladder neck to the pubic bone, a mechanism which could correct urethral hypermobility, restore the normal anatomy in the region with minimal, if any, complications. The purpose of the present article is to summarize all available evidence in the field and to construct a robust medical hypothesis, which would potentially drive the research agenda toward conducting experimental and clinical studies in this field.

Current evidence

PUL defects in experimental animal models

Studies in animal experimental models have shown that the transection of the PUL is associated with long-term stress urinary incontinence [7,19,20]. Specifically, Kefer et al. reported that the leak point pressure (LPP) of female rats with an incised PUL was significantly lower compared to those with an intact PUL (15.75 ± 6.46 H_2O, vs 42.56 ± 11.58, $p < 0.001$) [20]. Sajadi et al. commented that the neurologic effects of PUL transection remain unknown and suggested that further studies should be implemented in this field [21].

Plasma-derived ligament-regenerative growth factors

Preclinical studies have suggested that PRP might serve as a growth factor vehicle which could accelerate the restoration of ligaments and tendons [22]. It has been demonstrated that platelets exhibit the ability to promote angiogenesis, which is induced after proliferation and migration of endothelial cells from a pre-existing vascular network [23]. To date, several platelet derived fractions have been described. Among them pure platelet rich plasma (PRP) is the most widely investigated in tissue regeneration [24]. PRP contains several growth factors that contribute to the pathophysiology of ligament reconstruction including vascular endothelial growth factor (VEGF), insulin growth factor I (IGF-I), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor beta (TGF-β) and fibroblast growth factor (FGF) [9,14,25,26].

It seems that PDGF is initially released from platelets shortly after the ligament damage in the inflammatory phase and induces angiogenesis, fibroblast mitogenesis, and macrophage activation [27,28]. Its release, triggers a cascade which eventually leads to the production of several other growth factors including the VEGF, TGF-β, IGF-1 as well as that of several cytokines (IL-1, IL-6, IL-8). VEGF is a potent angiogenic factor, which seems to influence the regenerative process at its last steps during the proliferative phase, after the inflammatory process has been completed [29]. Its importance during this step has been previously examined by researchers who suggested that blocking of VEGF results in reduced biomechanical strength of ligament grafts [30].

The proliferative phase of ligament-tendon healing is also regulated by IGF-1, bFGF and PDFG, whereas TGF-β, bFGF and PDGF trigger collagen synthesis and extracellular matrix deposition [25]. Specifically, TGF-β seems to be active in every stage of tendon healing as it stimulates cell migration, regulates the production of proteinases and collagen. The expression of TGF-β mRNA rapidly increases shortly after tissue injury and seems to suppress matrix metalloproteinases production and to increase the synthesis of extracellular matrix [31]. However, its overexpression seems to result to adhesion formation and decreased range of motion in experimental studies of tendon and ligament healing [32]. To date, it remains unclear, whether its increased expression in PRP would result in the formation of adhesive tissue in PUL, which could worsen SUI.

bFGF also increases the production of collagen. Chan et al., suggested that a single injection of PDGF significantly enhanced tendon, repair [33]. These results have been also confirmed in recent studies [34,35]. Fukui et al. suggested in 1998 that increased doses of locally applied recombinant bFGF could reduce repair tissue maturation [36]. However, this information has not been confirmed from recent studies.

IGF-I is crucial for wound healing and tissue repair. Provenzano et al. in 2007 suggested that systemic administration of IGF-I with or without growth hormone (GH) enhances healing of collagenous tissue [37]. This results in increased values of maximum force, ultimate stress, and elasticity in biomechanical tests.

A previous study suggested that the implementation of TGF-β and IGF significantly enhances collagen synthesis (5.2-fold) and tensile strength (5.7-fold) in engineered human ligaments [38]. Given this information we strongly believe that PRP deserves further research in the field of SUI, because it contains an abundant amount of these factors and it could enhance PUL healing, thus partially (or even completely) diminishing the symptoms.

The use of autologous fibrin adhesive in PRP preparations (PRFG)

Fibrin glue (FG) is a topical biological adhesive. It mimics the final stages of coagulation, wherein thrombin splits off fibrinopeptide A and B from the fibrinogen chain to form a monomer, which polymerizes to form a fibrin clot at the site of application [39]. Its surgical use was first described in 1970 by Matras [40], but interest in FG as a surgical adhesive or sealant began in the early 1990 s [15]. The mixture of PRP with FB (PRFG) produces a colloid structure which easily remains in the site of application as previously described by Shirvan et al. [41] and Messora et al. [42].

Implications for future research

Platelet rich plasma contains several growth factors which have been implicated in collagenous tissue healing. Previous studies suggested that PRP may actually enhance tendon and ligament healing. To date, it has not been used in SUI. Future studies in animal experimental models and consecutively in humans will shed

more light on the role of platelet rich plasma as a potential treatment option for stress incontinence. It is our belief that platelet rich plasma has a key role to the regeneration of the PUL, because it contains several growth factors and cytokines, which modulate tissue healing. Animal experimental models have been already studied in research protocols on stress urinary incontinence after PUL damage [20]. Further experimental work with PRP in these models will yield sufficient results to support or oppose the conduct of clinical trials.

Conclusion

As PUL defects lead to SUI, restoration of the anatomy of this ligament could have a curative effect on this condition. The contribution of growth factors seems to be crucial during this process and PRP is an easily prepared, relatively inexpensive solution, which could serve as a vehicle for the administration of these proteins. However, currently, evidence is lacking and further research will evaluate the safety and efficacy of this potential therapeutic strategy for SUI.

Conflict of interest

None of all authors.

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