The efficacy of platelet rich plasma in pelvic organ prolapse surgery : A protocol for scoping review

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Study Protocol

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The efficacy of platelet rich plasma in pelvic organ prolapse surgery: A protocol for scoping review

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Abstract

Background : Platelet-rich plasma (PRP) is an autologous, self-blood product, anticoagulated blood product generated by centrifugation method of whole blood that primarily contains platelets at amounts up to 5 times those found in physiologic platelet concentrations. PRP contains multiple growth factors such as transforming growth factor (TGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor-1 within the alpha granules of platelets (IGF-1). Platelets also contain antibacterial and fungicidal proteins, metalloproteinases, coagulation factors, and membrane glycoproteins, which can regulate inflammation by promoting the production of various integrins, interleukins, and chemokines. Pelvic organ prolapse occurs when the genitalia organ, bladder, rectum, and intestine protrude into the vaginal canal or even out of it due to the weakening of ligaments and muscles that serve as suspensors for the pelvic organs. Surgery is one of the treatment options for pelvic organ prolapse. The use of platelet rich plasma in pelvic organ prolapse surgery is becoming much more common. The goal of this procedure is to reconstruct the anatomical components of the pelvic supporting tissues and increase the healing process. To determine the efficacy of PRP on pelvic organ prolapse surgery, we will synthesize the available research on the use of platelet rich plasma for pelvic organ prolapse surgery. The goal of this study is to conduct a scoping study of the published research on the efficacy of platelet rich plasma for the surgery procedure of female pelvic organ prolapse.

Methods/design : This review was conducted on research articles in PubMed, Proquest, EBSCO, ScienceDirect databases published between January 2010 – Desember 2021 regarding the use of platelet rich plasma for pelvic organ prolapse surgery. All primary research in human, case reports and case series will be included to evaluate the outcome of platelet rich plasma as an adjunct to conventional surgery in the treatment of pelvic organ prolapse.

Discussion : This review will offer actual evidence of PRP's efficacy for pelvic organ prolapse surgery. This is a new approach, and the findings of this study are expected to inform clinical practice and ongoing research focused on improving outcome of pelvic organ prolapse surgery.

Trial registration number : osf.io/gyr72

***Keywords**:* Pelvic organ prolapse, Platelet rich plasma, Scoping review, Surgery

Introduction

Pelvic organ prolapse (POP) is a serious health disease that affects many women and can have a significant physical and psychological impact on their daily activities and quality of life [1]. Pelvic organ prolapse occurs when the genitalia organ, bladder, rectum, and intestine protrude into the vaginal canal or even out of it. Urinary and bowel impairment, incontinence, and sexual dysfunction are the symptoms commonly develop [2]. Although pelvic organ prolapse can not result in major death or disease severity, it can reduce a woman's quality of life. Pelvic organ prolapse is a prevalent gynecological problem, with roughly 37% of patients seeking treatment in a clinic and a lifetime risk of 11-19% in the population for surgical operations. [3][4].

Prolapse is a frequent condition caused by the weakening of the uterus supporting structures. The uterosacral (USL) and cardinal ligaments (CL) support the uterus and pelvic organs, while the round ligaments (RL) keep the uterus and pelvic organs in place. The connective tissue, smooth muscle, vascular, and innervation of the pelvic support systems are changed in women with pelvic organ prolapse (POP) [5]. The ECM (extracellular matrix) in connective tissue is primarily responsible for the supporting role of structures. The majority of the ECM is composed of fibrillar components including collagen and elastin, as well as non-fibrillar components such proteoglycans, hyaluron, and glycoproteins. Within this matrix, fibrillar components predominate over non-fibrillar elements, and collagen plays a significant role in the supporting function [6][7]. According to a recent study, patients with POP had an inherent deficiency of a gene involved in the development of the USL [8]. Collagen III and matrix metalloproteinase 1 (MMP-1) are overexpressed in the USL of women with POP [9] [10], meanwhile there were decreased expression of collagen type 1 in uterosacral ligaments of women with POP [10].

There are various surgical management options are available to assist surgeons in repairing pelvic organ prolapse (POP). POP surgery options include native tissue restoration, mesh augmentation, and minimally invasive procedures [11]. The type of surgical intervention performed is determined by the type of prolapse identified during the evaluation and the related symptoms. Surgery for pelvic organ prolapse is usually successful in managing the main symptoms of prolapse (vaginal bulge). Although the impact of pelvic organ prolapse surgery on certain bowel, bladder, and sexual functions can be predicted, individual women should be aware that the procedure can sometimes exacerbate existing symptoms or cause new ones, such as urine leakage or issues with sexual intercourse [12]. Surgery techniques also have high frequency of postoperative complications and high recurrence rates, about 30% of patients require further surgery [13]. Furthermore, when POP is treated without grafting, recurrence is common. Although the use of synthetic mesh or biological grafts provides structural reinforcement to POP weakened tissue, complications such as foreign body reaction, excessive fibrotic response, would infections, and vaginal erosion are too common, necessitating surgical revision and, in some cases, mesh removal [14]. These issues occur more frequently with vaginal mesh than with abdominal mesh, prompting two FDA warnings about the use of vaginal mesh in 2008 and 2011 [15]. As a result, new therapy strategies must be investigated as soon as possible. Implementation of an injectable drug, which would primarily strengthen the ligaments and speed up the healing process, could be an alternate technique for the therapy of prolapse.

Platelets are nucleated discoid cellular elements of various sizes with a density of about 2-4 μm in diameter, the minimum density of all blood cells includes megakaryocytes as their stem cells, perform a number of important functions such as blood clotting, inflammation, antimicrobial host immune, angiogenesis, and tissue repair, and are exposed to daily consumption of up to 25% in physiologically normal settings [16]. Platelets produced by bone marrow and have a number of secretory granules that are essential for platelet function. Dense granules, o-granules, and lysosomes are the three types of granules. The most abundant of the three types of granules, there are roughly 50–80 granules in each platelet [17]. Platelets are the first to arrive at the site of tissue injury and initiate the early inflammatory phase of the healing process [18] . They aid in homeostasis by promoting tissue repair and influencing the reactivity of blood vessels and blood cell types involved in angiogenesis and inflammation through cell membrane adherence, aggregation, clot formation, and the release of substances that affect the reactivity of blood vessels and blood cell types involved in angiogenesis and inflammation [19]. Platelets contain therapeutically active proteins such mitogenic, chemotactic, adhesive, angiogenic and antiangiogenic proteins, as well as neurotrophic factors [16].

Platelet-rich plasma (PRP) is currently commonly used as a growth factor pool for promoting tissue regeneration in a variety of clinical settings, including orthopedics, ophthalmology, and healing therapies [20]. Platelet-rich plasma is defined as plasma with a platelet count of more than 1.000.000/l in every 5 mL of plasma, as well as a variety of cytokines and growth factors [21]. Platelet-rich plasma can be created using recently developed techniques . PRP is extracted from the blood of patients prior centrifugation. The separation of blood components (red blood cells, PRP, and platelet-poor plasma [PPP]) occurs after centrifugation and according to their distinct density gradients [22]. There are a variety of procedures for collecting platelet concentrates, each of which might result in a different product with varied biology and applications [16].

PRP is a natural source of signaling molecules, and when platelets in PRP are activated, the P-granules degranulate and release growth factors and cytokines, which alter the pericellular milieu [17]. Through growth factors and chemical mediators generated by platelets, platelet-rich plasma (PRP) can stimulate cell migration, proliferation, differentiation, angiogenesis, and tissue debris elimination. As a consequence, PRP may help improve tissue healing, regeneration, and repair [23]. VEGF, IGF-I, PDGF, HGF, TGF-, and FGF are some of the growth factors (GFs) found in PRP, and they all have a role in the pathophysiology of ligament restoration and that have been associated to the regeneration of collagenous tissue [1]. During the early stages of tissue repair, these substances primarily stabilize the damaged tissue and direct local mesenchymal and epithelial cells to migrate, divide, and increase collagen and matrix synthesis, ultimately leading to fibrous connective tissue and scar formation [24]. VEGF and FGF-2 are necessary for encouraging the development of new blood vessels to transport nutrients and progenitor cells to the damage site; although, neo-vascularization needs other substances [25]. Overexpression of IGF-1 in PRP is thought to improve early healing of ligament damage [24].

PRP is a viable therapeutic method for future regeneration treatments due to its relative ease of preparation, clinical application, favorable safety profile, and potential beneficial effect [24]. PRP warrants proper consideration as an additional therapy for particular purposes due to its function in multiple healing pathways. A previous studies suggested that platelet rich plasma is a promising technique for tissue repair and regeneration but studies into its clinical efficacy are not conclusive especially in pelvic organ prolapse field. Looking at the bioactivity properties of PRP, we believe that PRP could provide a minimally invasive, low-risk, and

effective treatment for pelvic organ prolapse. To find primary studies on the use of PRP for pelvic organ prolapse, a search will be conducted in the PubMed, Proquest, EBSCO and ScienceDirect databases. The findings of this study are expected to inform clinical practice and continuing research focused on improving pelvic organ prolapse treatment

Methods and Analysis

Study design

This scoping review will be carried out according to the Joanna Briggs Institute scoping review methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) standards [26] [27]. Scoping review is a method that addresses the underlying concepts surrounding the phenomenon of interest, offering a comprehensive overview that can be used as a foundation for systematic studies. Scoping reviews also show the depth and breadth of research on a topic, allowing for a better understanding of the phenomenon under study [28][29]. A scoping review, besides a systematic review, aims to map "important concepts, forms of evidence, and gaps in the research relevant to a given topic or field by systematically finding, identifying, and summarizing existing knowledge," as opposed to a systematic review [30]. The six-stage framework suggested by Arksey and O'Malley (2005) and developed by Levac et al. (2010) and Daudt et al. (2013) is one formal technique to guide a scoping review for broad research questions (see Table 1). This framework is described as "an interpretative scoping literature review methodology" by Davis et al., (2009) [29] [30] [31]. Stage 6 was actually designed to be an optional stage in which experts in fields related to the research topic are invited to analyze and advise on the study's stages to ensure that it is being carried out efficiently and objectively. This scoping review will be conducted using the Arksey and O'Malley methodology, with the optional sixth step omitted. The six processes are: 1. defining a research topic; 2. locating relevant studies; 3. study selection; 4. data charting; 5. data collection, summarization, and reporting; and 6. consultation exercise (optional step).

Stage 1 : identifying a research question

The scoping review will systematically search the literature across the breadth and character of platelet rich plasma for pelvic organ prolapse, as well as the factors associated with these interventions. Following this, the proposed scoping review's questions are as follows: what is known about the use of platelet rich plasma in pelvic organ prolapse surgery based on existing literature? and How the efficacy have been linked to using this intervention for pelvic organ prolapse surgery in the literature?

Stage 2 : identifying relevant studies

Four databases will be used to find studies that are eligible: PubMed, Proquest,EBSCO and ScienceDirect databases. From January 2010 through December 2021, the search will be limited. A combination of medical search headings and free text words will be used to develop the literature search. Keywords will be selected and extracted from similar publications that are relevant to the study's population, topic, and setting. According to the database, the whole search will be performed using Boolean operators and proximity operators, including Medical Subject Headings (MeSH) terms, wildcards, AND, OR, parentheses, quotes, and more. The proposed search method for searching PubMed is shown in Table 1. This technique will be modified to fit the criteria of the other databases.

Table 1. Proposed search strategy to search PubMed

	Search terms
#1	"Pelvic Organ Prolapse"[MeSH] OR pelvic-organ-prolapse*[tiab] OR urogenital- prolapse*[tiab] OR vaginal- vault-prolapse*[tiab] OR cystocele[tiab] OR cystocoele[tiab] OR "urinary bladder prolapse"[tiab] OR rectal- prolapse*[tiab] OR anus-prolapse*[tiab] OR uterine-prolapse*[tiab] OR vaginal-prolapse*[tiab] OR "genital prolapse"[tiab] OR "genito- urinary prolapse"[tiab] OR "genitourinary prolapse"[tiab] OR "pelvic descent"[tiab] OR "pelvic organ descent"[tiab] OR "pelvic prolapse"[tiab] OR "vaginal descensus"[tiab] OR "vaginal descent"[tiab] OR "vaginal wall prolapse"[tiab]
#2	"Hysterectomy, Vaginal"[Mesh] OR "Hysterectomy, Vaginal"[tiab] OR "anterior colporrhaphy"[tiab] OR "posterior colporrhaphy"[tiab] OR "sacrocolpopexy"[tiab] OR "sacrohysteropexy"[tiab] OR "vesicovaginal fistula repair"[tiab] OR rectovaginal fistula repair"[tiab]
#3	"Platelet-Rich Plasma"[Mesh] OR "Platelet-Rich Plasma"[tiab] OR "Platelet-Rich Fibrin"[Mesh] OR "Platelet-Rich Fibrin"[tiab]
#4	#1 OR #2
#5	#3 AND #4

Stage 3 : study selection

A two-stage procedure will be used to identify studies. After eliminating duplicate records, the titles and abstracts will be reviewed for potential eligibility by two reviewers using pre-specified screening criteria. Following that, papers that have been selected as relevant will be subjected to full-text review by both reviewers. Disagreements among the reviewers will be addressed through discussion or referral to a third reviewer. As recommended in the PRISMA extension for Scoping Reviews extension checklist, this information will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, a schematic draft of which is presented as figure 1 [27].

Inclusion criteria

All primary studies (including of case reports, case series, randomised controlled trials, cohort, case–control, quasi-experimental, cross-sectional), all human studies evaluating the outcome of PRP as adjunct to conventional surgery in the treatment of pelvic organ prolapse will be included. Only article published in English language will be included.

Exclusion criteria

Studies that are irrelevant (including systematic, narrative and other review as well as conference abstracts, textbooks, posters and editorials) and not available in English language, it will be eliminated from selection.

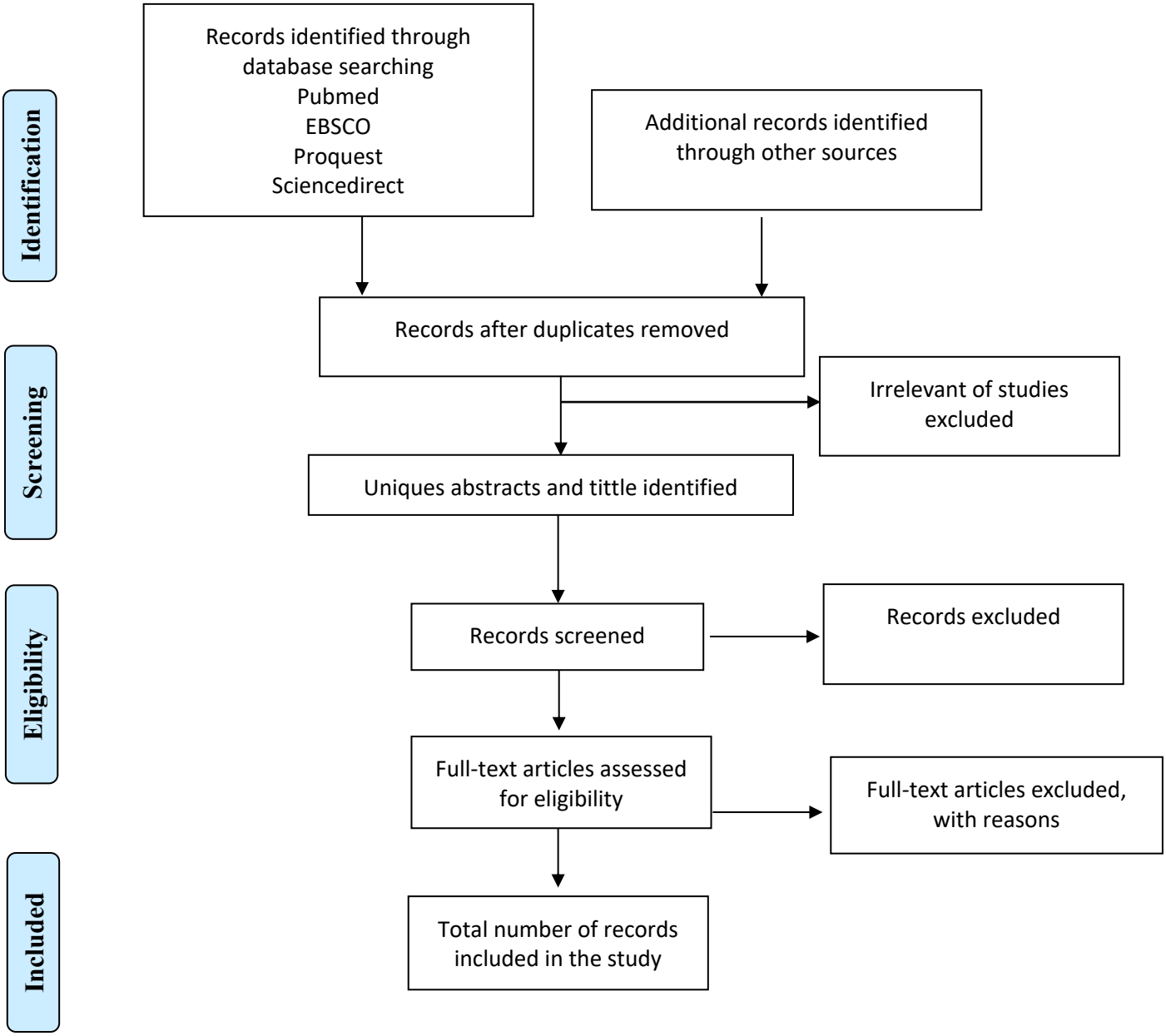

Fig.1 : Flow diagram research procedure

Stage 4 : charting the data

Using a data extraction tool built by the reviewers based on scoping review instructions, data will be extracted from publications included in the scoping review [26]. The extracted data will be electronically entered into the program using Microsoft Excel. The author(s), year of publication, subject investigated, context, methodology used, and important findings pertinent to the study will all be included in the data extraction form. Two authors will independently

extract information from all full-text papers selected for the final analysis. Discussion or referral to a third reviewer will be used to settle any disagreements or inconsistencies. The following is a list of fields that should be filled out in the data charting form: Title, first author, patients/ model, year of publication, country, study type, preparation method and doses of PRP, complications, results, follow up, other important information.

Stage 5: collating, summarising and reporting the results

Because this study is likely to produce both qualitative and quantitative data, data synthesis and analysis will be done using both a descriptive numerical summary and a theme analysis to characterize the current evidence base, including the scope of identified literature and the context of included research. The review will not comprise a meta-analysis, nor will the quality of evidence from included research be appraised. As a main purpose of this review, this will provide a scope of the existing evidence relevant to cell therapy in pelvic organ prolapse. The results of the ScR will be published in a separate publication and submitted to a peer-reviewed open-access journal. The findings of this paper will serve as a summary of the literature, which will be utilized to guide future study.

Stage 6 : consultation exercise (optional step)

This review will not include a consultation exercise since its relevance to the review question and objectives is questionable. As a result, there will be none.

Ethics approval and consent to participate

There is no need for ethical approval for this review. However, every step must be taken to ensure that the study is conducted in a transparent manner.

Consent for publication

Not required

Availability of data and material

Data findings are available from corresponding author upon reasonable request.

Competing interests

We have no competing interests.

Funding

Not applicable.

Author's contribution

ANDS contributed to the study design, conseptualisation and drafted the protocol; manuscript writing

DMR and NP contributed to the supervisory overview and feedback on the methodology and the manuscript review;

SA contributed to manuscript writing, review and editing;

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