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**Platelet-Rich Plasma for Muscle Injuries: A Systematic Review of the Basic Science Literature
The World Journal of Orthopedics**

Dear Dr. Bao-Gan Peng, Dr. Jin-Lei Wang, and reviewers,

Thank you for taking the time to read the manuscript titled above and for providing thoughtful comments. We have addressed all the comments below to the best of our abilities.

Sincerely,

The authors

Reviewer's code: 01220036

SPECIFIC COMMENTS TO AUTHORS

accepted

Author response: Thank you.

Reviewer's code: 02444715

SPECIFIC COMMENTS TO AUTHORS

the paper: Platelet-Rich Plasma for Muscle Injuries: A Systematic Review of the Basic Science Literature is well written The limitations of the paper are explained the authors explained the technique used for preparation in each paper reviewed

Author response: Thank you

Responses to Dr. Jin-Lei Wang:

- (1) Added "Hannon CP conceived the study idea and designed the research with Kunze KN. Kunze KN wrote the manuscript and analyzed the data. Kunze KN and Fialkoff JD collected the data. Kunze KN, Hannon CP, Frank RM, and Cole BJ



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edited and revised the manuscript.”

- (2) Added “Dr. Cole reports personal fees from Arthrex, personal fees from Geistlich Pharma, personal fees from Smith & Nephew, personal fees from Bioventus, personal fees from Vericel, personal fees from Zimmer Biomet, personal fees from Anika Therapeutics, personal fees from Pacira Pharmaceuticals, personal fees from Isto Technologies, personal fees from DJO, personal fees from Encore Medical, personal fees from LifeNet Gealth, personal fees from Carticept Medical, personal fees from GE Healthcare, personal fees from Aesculap Biologics, personal fees from DePuy Synthes, personal fees from Genzyme, during the conduct of the study; . Dr. Frank is a paid presenter for Arthex, Inc.; reports personal fees from Elsevier, during the conduct of the study.”
- (3) Added “Telephone: (609) 214-9245 and Fax: (708) 409-5179”
- (4) Added “BACKGROUND Platelet-rich plasma (PRP) is an increasingly used biologic adjunct for muscle injuries as it is thought to expedite healing. Despite its widespread use, little is known regarding the mechanisms by which PRP produces its efficacious effects in some patients.”
- (5) Added “Core tip: PRP has gained much attention in the treatment of muscle injuries for its potential beneficial effects in both operative and non-operative settings without knowledge of its mechanism of action. The current systematic review synthesizes the effects of PRP at the basic science level. PRP was found to induce cellular proliferation and differentiation, production of various growth factors, muscle regeneration, and changes in gene expression. Only one study reported a complete PRP cytology. This study highlights the underlying mechanisms of PRP in muscle pathology at the basic science level and emphasizes the need for standardization in PRP preparation and reporting.:



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(6) Added "ARTICLE HIGHLIGHTS

Research background

Platelet-rich plasma (PRP) is a biological adjunct derived from autologous blood which is thought to aid healing of various bone, ligament, cartilage, and muscle injuries. PRP is composed of various cytokines, growth factors, and concentrations of leukocytes and platelets. PRP is often used clinically to expedite healing as a non-operative treatment or operative adjunct. However, studies have reported mixed effects of PRP and clinicians continue to employ this adjunct despite little understanding of its mechanism of action.

Research motivation

The main topics of the current study are (1) the various mechanisms of action of PRP at the molecular and tissue levels for muscle injuries and (2) reporting patterns of PRP preparations in these studies. The current study seeks to clarify the underlying mechanisms of action of PRP in terms of its ability to induce cellular changes and changes at the histologic and tissue levels which are not well described.

Research objectives

The main objective of the current study is (1) to clarify the effects of PRP at the cellular and tissue levels through synthesizing its mechanisms of action from available basic science studies on muscle injuries. A secondary objective that was realized was that it is important to understand PRP preparations across multiple studies to allow for standardization of study protocols and better comparisons.

Research methods

A systematic review of basic science studies from the Pubmed/MEDLINE and



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EMBASE databases was conducted as these studies would allow for the best understanding of the mechanism of action of PRP at the cellular and tissue levels. Using a custom pre-determined spread sheet of a wide variety of growth factors, cytokines, and other molecular markers, each study was analyzed and subsequently these variables were extracted. The PRP preparation methods were also extracted.

Research results

A total of 23 articles were identified. PRP conferred multiple beneficial effects on muscles both in vitro and in vivo through the upregulation of genes beneficial to healing and muscle regeneration, increasing cellular proliferation and differentiation, and producing superior tissue quality and biomechanical properties in comparison to placebo. However, this study also identified the lack of PRP cytology reporting among these studies, of which only one study reported a full cytology.

Research conclusions

PRP confers multiple beneficial effects at the basic science level in models of muscle injury where compared to placebo through changes at the cellular level including gene expression, growth factor and cytokine concentrations, increased angiogenesis, and cellular differentiation and proliferation. PRP also mediates increased muscle regeneration at the gross level and superior histologic quality when compared to placebo in few studies. There was significant variability in both PRP preparation and reporting among the included studies.

Research perspectives

This study highlights the importance of understanding processes at the basic science level in order to provide better insight into clinical practice. Future research is needed to determine the optimal cytology, dosing, timing, and delivery method of



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PRP for in muscle injuries. Higher level randomized studies will need to be performed in order to determine these factors. Furthermore, it will be essential for future studies to use standardized protocols such that outcomes and practices with PRP become reproducible.

(7) Reformatted references accordingly