Platelet-rich plasma application in experimentally-induced skin wounds in animals: protocol for a systematic review and meta-analysis

Adolfo Maria TAMBELLA,Anna Rita ATTILI

Abstract

Objective

To determine whether the topical application of platelet-rich plasma (PRP) promotes healing in experimentally-induced full-thickness skin wounds in animals, a systematic review and meta-analysis will be performed.

Methods

Web of Science, Cochrane Library, PubMed, Research Gate, Cochrane Wounds Group, and Veterinary Information Network will be searched to identify randomised and not randomised controlled clinical trials comparing PRP with placebo or with other treatments in animals. Primary outcome: reduction of open wound area; secondary outcomes: healing time and number of healed cases. Effect sizes: Hedges' g; odds ratio.

Citation: Adolfo Maria TAMBELLA,Anna Rita ATTILIPlatelet-rich plasma application in experimentally-induced skin wounds in animals: protocol for a systematic review and meta-analysis. **protocols.io**
dx.doi.org/10.17504/protocols.io.k5rcy56
Published: 05 Dec 2017

Protocol

Planning to write systematic review

1.

Background
The wound healing process is regulated by a complex interaction of molecular signals involving mediators, primarily cytokines and growth factors (GFs) [1-5]. Platelets play a fundamental role in the healing process of skin wounds. The platelet-derived GFs are involved in the recruitment of mesenchymal cells, and in the synthesis of the extracellular matrix [4-8]. Platelet-Rich Plasma (PRP) is a platelet concentrate that is applied locally at the injury site, upon activation. In the recent years the positive effect of PRP for healing enhancement has been reported in many applications of human medicine: skin ulcers, plastic-reconstructive and cosmetic surgery [1,8-13]; oral-maxillofacial surgery [9,12]; cartilage and tendon repair [9,12]; orthopaedic surgery and bone reconstruction [9,12,14,15]; and ophthalmology [9,12]. Despite the growing interest, the scientific literature is still limited in veterinary medicine, where a paucity of randomised clinical trials can be observed [16-25].
Why it is important to do this review
Before designing clinical studies on large human and animal populations with spontaneous disease, there is the need to assess the evidence of the literature regarding the application of PRP in experimentally-induced wounds in animals.
Objectives
To determine whether topical application of PRP promotes the healing process in experimentally-induced full-thickness skin wounds in animals a review of current literature will be performed.

Guidelines

2. The principles of the PRISMA guidelines (Preferred Reported Items for Systematic Review and Meta-analyses) [26,27] and the Cochrane Handbook for Systematic Reviews of Interventions [28] will be followed.

Eligibility criteria

Primary studies eligibility criteria

A structured approach type PICOS (Population, Intervention, Comparison, Outcomes, Study design) will be used.

Types of studies: randomised and non-randomised controlled clinical trials (CCTs) that compared PRP with other treatments or placebo.

3. **Types of participants**: animals of all species, breed and age, on which full-thickness skin wounds were experimentally induced, and left to heal by secondary intention.

Types of interventions and control group: studies that compared PRP with placebo or with other topical therapies such as standard care or biomaterials.

Report eligibility criteria

No restriction will be placed regarding language and publication date. Only studies published on indexed, peer-reviewed journals will be considered.

Types of outcome measures

Primary outcome:

Size reduction of open wound area in the PRP treated wounds compared to the size reduction in control wounds.

Secondary oucomes:

4. -healing time (time needed to obtain the complete healing of the wound) in PRP treated wounds compared to controls;

-number of healings (proportion of wounds showing complete healing) in PRP treated wounds compared to controls.

Any reference to the assessment of wound complications, wound pain, quality of life and adverse events related to the intervention was also sought.

Search methods for identification of studies

Electronic searches

The electronic search will be undertaken on the following databases: Web of Science, Cochrane Library, PubMed, Research Gate, Cochrane Wounds Group, and Veterinary Information Network (VIN).

5. The search will be done using the following keywords, combined using the Boolean operators AND, OR:

-platelet / platelet-rich / platelet-rich plasma / platelet gel;

-wound / skin / ulcer;

-animal / dog (canine) / horse (equine) / pig (swine) / goat (caprine) / sheep (ovine) / cow (cattle, bovine) / cat (feline) / rabbit (cunicola) / mouse (mice, murine) / rat.

Data collection

Selection of studies

Two independent reviewers will perform the screening. Any discrepancies will be resolved by discussion among all members of the review team.

All identified studies will be assessed by the inclusion/exclusion criteria then subjected to the screening phase. Duplicates emerging from one or more search strategies and databases will be excluded.

The *records screened* will be selected using a two-step approach, first by analyzing the title and abstract (with identification of the # of *records excluded*), then by analyzing the full-text (with identification of the # of *full-text articles assessed for eligibility*). The reason for exclusion will be specified for each of the excluded references (# of *full-text articles excluded, with reasons*).

The identified studies will be classified as included in the systematic review (# of *studies included in the qualitative synthesis*) and in the meta-analysis (# of *studies included in the quantitative synthesis - meta-analysis*) thus completing the PRISMA flow diagram.

6. **Data extraction and management**

The following data from each included primary study will be extracted and recorded in a data extraction form:

-study characteristics (name, design, country, funding source);

-publication characteristics (year, language, type);

-participants' characteristics (number, species);

-characteristics of induced lesions (size and number of wounds, induction mode);

-intervention characteristics (PRP production technique, platelet concentration);

-treatment protocol (division into groups and groups description, randomisation, number of PRP applications, frequency of applications, bandage);

-assessments carried out in primary studies (outcome measures, the presence of multiple time points or waves);

-main results of primary studies.

Analysis of meta-data

Assessment of risk of bias in included studies

The risk of bias assessment will base on the guidance in the Cochrane Handbook of Systematic Reviews of Intervention [28]. The adequacy of the method used to generate the allocation sequence (random sequence generation, selection bias), the method of allocation concealment (allocation concealment, selection bias), the level of blinding (blinding of outcome assessment, detection bias), the presence of incomplete outcome data (attrition bias), and the defect in the reproduction of results (selective reporting, reporting bias) will be examined.

Measures of treatment effect (effect size)

For the outcomes "size reduction of the wound area" and "healing time" the Hedges' g will be used.

Hierarchical scale for data entry format from primary studies:

1. mean values, standard deviations, sample size (gold data entry format);
2. mean values, t-value (result of t-test), sample size;
3. mean values, statistical significance (p-value), sample size;
4. t-value, sample size;

7.

5. p-value, sample size.

For the outcome "number of healings" the odds ratio (OR) will be used. To calculate the OR for each study, the number of subjects healed (event) and the total sample size of each group will be used as gold data entry format.

Unit of analysis

The unit of analysis will be the single wound.

Dealing with missing data

The authors of primary studies will be contacted in order to obtain additional information where data will be missing or unclear.

Management of complex meta-analytical databases

In case of detection in primary studies of complex meta-analytical databases, such as independent subgroups, multiple outcomes, multiple comparisons, multiple time points (waves), the complexity of data will be maintained in the analysis wherever possible. Otherwise, the possibility of performing a pre-analysis for each complex database will be considered.

Assessment of heterogeneity

8. The presence of heterogeneity will be assessed with the Q homogeneity test. The impact of heterogeneity was statistically quantified using the I^2. The I^2 value will be interpreted on the basis of the cut-off proposed by Higgins et al. (25%, low; 50%, moderate; 75%, high level of heterogeneity) [29,30,31].

Assessment of reporting biases

9. The publication bias will be assessed by Funnel Plot method, Egger's linear regression method, and Trim and Fill method.

Analysis of the moderators and evaluation of heterogeneity

10. Potential moderators of possible heterogeneity will be considered and analyzed, in particular: country; animal species; initial wound size; funding source; number of spinning cycles for PRP production; activation procedures; platelet concentration in PRP; number of treatments. When necessary, a recodification of moderators will be considered.

Sensitivity analysis

11. For each meta-analysis project, a sensitivity analysis will be carried out.

Data synthesis

12. Any statistical analyses of metadata will be performed with software ProMeta version 2 (Internovi, Cesena, Italy).

References

[1] Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986; 204(3):322-330.
[2] Mast BA, Schultz GS. Interaction of cytokines, growth factors, and protease in acute and chronic wounds. Wound Repair Regen. 1996; 4:411-420. doi: 10.1046/j.1524-475X.1996.40404.x.
[3] Tarnuzzer RW, Schultz GS. Biochemical analysis of acute and chronic wound environments. Wound Repair Regen. 1996; 4:321-325. doi: 10.1046/j.1524-475X.1996.40307.x.
[4] Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg (Suppl 2A). 1998; 176:26S-38S.
[5] Rožman P, Bolta Z. Use of platelet growth factors in treating wounds and soft-tissue injuries. Acta Dermatovenerol Alp Pannonica Adriat. 2007; 16(4):156-165.
[6] Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003; 83:835-870. doi: 10.1152/physrev.00031.2002.
[7] Robson MC. The role of growth factors in the healing of chronic wounds. Wound Repair Regen. 1997; 5(1):12-17. doi: 10.1046/j.1524-475X.1997.50106.x.
[8] Crovetti G, Martinelli G, Issi M, Barone M, Guizzardi M, Campanati B, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci. 2004; 30:145-151. doi: 10.1016/j.transci.2004.01.004.
[9] Anitua E, Alkhraisat MH, Orive G. Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release. 2012; 157:29-38. doi: 10.1016/j.jconrel.2011.07.004.
[10] Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. Diabetes Care. 1992; 15:1598-1604. https://doi.org/10.2337/diacare.15.11.1598.
[11] Mazzucco L, Medici D, Serra M, Panizza R, Rivara G, Orecchia S, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. Transfusion. 2004; 44:1013-1018. doi: 10.1111/j.1537-2995.2004.03366.x.
[12] Borzini P, Mazzucco L. Tissue regeneration and in loco administration of platelet derivatives: clinical outcome, heterogeneous products, and heterogeneity of the effector mechanisms. Transfusion. 2005; 45:1759-1767. doi: 10.1111/j.1537-2995.2005.00600.x.
[13] O'Connel SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. Wound Repair Regen. 2008; 16:749-756. doi: 10.1111/j.1524-475X.2008.00426.x.
[14] Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg, Oral Med, Oral Pathol, Oral Radiol Endod. 1998; 85:638-646. doi: http://dx.doi.org/10.1016/S1079-2104(98)90029-4.
[15] Mei-Dan O, Carmont MR. Novel applications of platelet-rich plasma technology in musculoskeletal medicine and surgery. Oper Tech Orthop. 2012; 22:56-63. http://dx.doi.org/10.1053/j.oto.2011.10.005.
13. [16] Carter CA, Jolly DG, Worden CE Sr, Hendren DG, Kaneb CJM. Platelet-rich plasma gel promotes differentiation and regeneration during equine wound healing. Exp Mol Pathol. 2003; 74:244-255. http://dx.doi.org/10.1016/S0014-4800(03)00017-0.
[17] Kim JH, Park C, Park HM. Curative effect of autologous platelet-rich plasma on a large cutaneous lesion in a dog. Vet Dermatol. 2009; 20(2):123-126. doi: 10.1111/j.1365-3164.2008.00711.x.
[18] Rabillard M, Grand JG, Dalibert E, Fellah B, Gauthier O, Niebauer GW. Effects of autologous platelet rich plasma gel and calcium phosphate biomaterials on bone healing in a ulnar ostectomy model in dogs. Vet Comp Orthop Traumatol. 2009; 22:460-466. doi: 10.3415/VCOT-09-04-0048.
[19] Fresno L, Fondevila D, Bambo O, Chacaltana A, García F, Andaluz A. Effect of platelet-rich plasma on intestinal wound healing in pigs. Vet J. 2010; 185:322-327. doi: 10.1016/j.tvjl.2009.06.009.
[20] Sardari K, Emami MR, Kazemi H, Movasagi AR, Goli AA, Lotfi A, et al. Effects of platelet-rich plasma (PRP) on cutaneous regeneration and wound healing in dogs treated with dexamethasone. Comp Clin Pathol 2011; 20:155-162. doi:10.1007/s00580-010-0972-y.
[21] Visser LC, Arnoczky SP, Caballero O, Gardner KL. Evaluation of the use of an autologous platelet-rich fibrin membrane to enhance tendon healing in dogs. Am J Vet Res. 2011; 72:699-705. doi: 10.2460/ajvr.72.5.699.
[22] Iacopetti I, Perazzi A, Ferrari V, Busetto R. Application of platelet-rich gel to enhance wound healing in the horse: a case report. J Equine Vet Sci. 2012; 32:123-128. http://dx.doi.org/10.1016/j.jevs.2011.08.012.
[23] Maciel FB, DeRossi R, Módolo TJC, Pagliosa RC, Leal CRJ, Delben AAAST. Scanning electron microscopy and microbiological evaluation of equine burn wound repair after platelet-rich plasma gel treatment. Burns. 2012; 38:1058-1065. doi: 10.1016/j.burns.2012.02.029.
[24] Suaid FF, Carvalho MD, Ambrosano GMB, Nociti FH Jr, Casati MZ, Sallum SA. Platelet-rich plasma in the treatment of class II furcation defects: a histometrical study in dogs. J Applied Oral Sci. 2012; 20:162-169. http://dx.doi.org/10.1590/S1678-77572012000200007.
[25] Tambella AM, Attili AR, Dini F, Palumbo Piccionello A, Vullo C, Serri E, et al. Autologous platelet gel to treat chronic decubital ulcers: a randomized, blind controlled clinical trial in dogs. Vet Surg. 2014; 43:726-733. doi: 10.1111/j.1532-950X.2014.12148.x.
[26] Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009; 6:e1000097. doi:10.1371/journal.pmed.1000097.
[27] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6(7):e1000100. doi:10.1371/journal.pmed.1000100.
[28] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration; 2011. Available from: www.cochrane-handbook.org.
[29] Crocetti E. Rassegne sistematiche, sintesi della ricerca e meta-analisi. North Charleston, SC, USA: CreateSpace; 2015.
[30] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21:1539-1558. doi: 10.1002/sim.1186.
[31] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J. 2003; 327(7414):557-560. doi: 10.1136/bmj.327.7414.557.