LITHUANIAN UNIVERSITY OF HEALTH SCIENCES
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DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY

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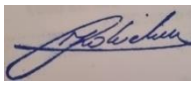
INFLUENCE OF PLATELET-RICH PLASMA, PLATELET-RICH FIBRIN, PLATELET RICH WITH GROWTH FACTORS, ON POSTEXTRACTIVE ALVEOLUS REGENRATION AND POST-OPERATIVE PAIN ON MOLAR TEETH

The master's thesis of the master's degree study program "Odontology"

Supervisor of the Master's thesis

Dr. Jan Pavel Rokicki 

Kaunas, 2023

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The Master's thesis of the Master's degree study programme "Odontotogy"

The thesis was done by graduate student

(signature)

Alon Weisman, 5th year, group 12

2023 .....

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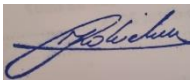
Supervisor



Dr. Jan Pavel Rokicki

2023 .....

(Month, day)

Kaunas, year 2023

EVALUATION OF THE SCIENTIFIC LITERATURE REVIEW MASTER'S THESIS REVIEWER'S FORM

Evaluation: .....

Reviewer: .....

(Scientific degree, full name)

Reviewing date: .....

Thesis volume no. of pages: _____; no. of sources in the list of references: _____;

no. of tables: _____; no. of figures: _____; no. of annexes: _____.

No.	MT parts	Evaluation criteria for the Master's thesis structural and methodological requirements	Evaluation* (1-10 points)
1	Summary	Is summary informative and in compliance with the thesis content and requirements? Do the keywords match the essence of the thesis?	
2	Introduction	Are the novelty, relevance and significance of the work justified in the introduction of the thesis?	
3	Aim and objectives	Are the aim and objectives formulated properly and clearly? Are the aim and objectives interrelated?	
4	Criteria for articles selection	Were the eligibility criteria of articles determined? Are all the information sources (databases with dates of coverage, contact with the authors of article) described and is the last search day indicated? Is the electronic search strategy described in such a way that it could be repeated?	
5	Search methods and strategy	Is the selection process of articles (screening, eligibility for systematic review or, if applicable, for meta-analysis) described? Is the process of data selection from articles described (types of research, participants, interventions, factors analyzed, and indicators)? Were all the variables, for which data were searched and described, listed and described? What assumptions or simplifications were made? Were the key measurement indicators (relative risk, mean differences) identified?	
6	Systemization and analysis of data	Is the number of checked articles given: included (after their eligibility evaluation), and rejected (with reasons at each stage of rejection indicated)? Are the characteristics of the described studies (from the included articles according to which the data were taken) provided (e.g., study sample, observation period, type of subjects)? Are systemized publication data presented in tables according to individual objectives?	

7	Discussion	Are the main findings summarized and is their significance indicated? Are the limitations of the performed systematic review discussed? Does author present the interpretation of the results?	
8	Conclusions	Do the conclusions reflect the topic, aim and objectives of the Master's thesis and are they based only on the analyzed material? Are the conclusions clear and concise? Suggestions and practical recommendations (optional).	
9	List of references	Is the references list compiled according to the requirements and are the references to the text correct? Do the cited sources not older than 10 years compose at least 70% of the references, and the sources not older than 5 years make up at least 40%?	
10	General requirements	Do the presented annexes help to understand the analysed topic? Are the volume, structure, language, layout and quality of the text appropriate? Is the amount of plagiarism at work not exceeded> 20% (not assessed)?	
		*Final evaluation (average score of 1 to 10 sections)	

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TABLE OF CONTENTS

What are the effects of Plate-rich plasma, Platelet-rich fibrin and Platelet-rich in growth factors on postextractive alveolus regeneration after extraction of molar teeth and what is their influence on postoperative pain?

SUMMARY

Introduction: The purpose of this study was to evaluate the effects of Plate-rich plasma, Platelet-rich fibrin and Platelet-rich in growth factors on postextractive alveolus regeneration after extraction of molar teeth and their influence on postoperative pain

Materials and methods: The systematic literature review search of publications was conducted in scientific databases Cochrane, PubMed/Medline, Google Scholar, and manual search in the Journal of Oral & Maxillofacial Research. Study selection and extraction of data were performed according to the PRISMA guidelines. Reports included studies published in English from January 2013 until February 2023.

Results: A total of 35 articles were screened and 7 publications were included in the final data synthesis according to inclusion criteria. Included publications represented results of 284 patients presenting for molar extractions.

Conclusions:

Platelet-rich with growth factors showed the best ability to regenerate hard tissue and prevent postoperative pain as shown throughout the included studies. Plate-rich fibrin showed positive ability to regenerate the soft tissue and decrease postoperative pain to some extent. Its ability to heal soft tissue was superior to its counterparts, however its effect on hard tissue remains in question. Platelet-rich plasma shown that it has the ability to decrease postoperative pain and promote both hard and soft tissues regeneration, however not as good as its counterparts.

Keywords: PRP, PRGF, PRF, Postoperative pain, hard tissue healing, soft tissue healing

Koks poveikis plazmos, praturtintos augimo faktoriais (PRGF), plazmos, gausios trombocitais (PRP), ir plazmos praturtintos fibriniu tinklu (PRF), alveolių kaulo kokybei, minkštiesiems audiniams ir skausmui?

SANTRAUKA

Įvadas: Šio tyrimo tikslas buvo įvertinti PRF, PRGF ir PRP įtaką poekstrakcinės alveolės kaulinio audinio, minkštųjų audinių regeneracijai ir skausmui.

Medžiagos ir metodai: Sisteminis publikacijų paieška buvo atlikta Cochrane, PubMed/Medline, Google Scholar moksliniuose duomenų bazėse ir rankiniu būdu - Oral & Maxillofacial Research žurnale. Tyrimo atranka ir duomenų įtraukimas buvo atlikti remiantis PRISMA gairėmis. Ataskaitose buvo įtraukti tyrimai, publikuoti anglų kalba nuo 2013 m. sausio mėn. iki 2023 m. vasario mėn.

Rezultatai: Buvo patikrinta 35 publikacijos, o pagal įtraukimo kriterijus į galutinį duomenų sintezę buvo įtrauktos 7 publikacijos. Įtrauktose publikacijose tirta 284 pacientai, kuriems buvo pašalinti protiniai dantys

Išvada:
PRGF parodė geriausią gebėjimą regeneruoti kaulinį audinį ir užkirsti kelią pooperaciniam skausmui, PRF - parodė teigiamą gebėjimą regeneruoti minkštuosius audinius ir tam tikru mastu sumažinti pooperacinį skausmą. Jo gebėjimas išgydyti minkštuosius audinius buvo pranašesnis už kitus autologus, tačiau jo poveikis kietiesiems audiniams išlieka abejotinas. Trombocitais praturtintos plazma (PRP) gali sumažinti pooperacinį skausmą ir skatinti kietųjų ir minkštųjų audinių regeneraciją, tačiau ne taip gerai, kaip PRF ir PRGF.
Raktiniai žodžiai: PRP, PRGF, PRF, pooperacinis skausmas, kietųjų (kaulinių) audinių gijimas, minkštųjų audinių gijimas**.**

01. INTRODUCTION

Regenerative dentistry is a relatively new aspect of medicine involving stem cell technology, tissue engineering and dental science. It investigates biological mechanisms to enhance regeneration, or simply regenerate damaged oral tissues and restore their functions [2]. Platelet-rich plasma (PRP), Plasma rich with growth factors (PRGF, also known as CGF – Concentrated growth factors) and Platelet rich fibrin (PRF) are biological products that are defined as the portion of plasma fraction of autologous blood with a concentration of biologically functional substances above that of the original whole blood. The substances are of common origin, however produced via different techniques and also vary in their applications and features.

PRP promotes healing in many different surgical applications and can be used not necessarily in association with the field of oral surgery or dentistry. It can also be used in neck surgery, otolaryngology, cardiovascular surgery, and maxillofacial surgery. Usually, after its centrifugation the PRP is made into a jelly consistency by adding thrombin or calcium chloride into the test tube containing the material. The addition of the additives activates alpha granules which release the following substances which participate in the healing process: platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-b), vascular endothelial growth factor (VEGF), insulin- like growth factor I, epidermal growth factor (EGF) and epithelial cell growth factor [3]. The main advantages of PRP are associated with PDGF, which is considered a protein with a positive effect on healing of both hard and soft tissues by stimulating chemotaxis, mitogenesis, replication of stem cells, and promotion of adhesion of adjacent tissues and cells. VEGF is also considered an important participant in PRP's function by increasing angiogenesis. Other factors related to PRP are TGF-b1 and TGF-b2 which participate in connective tissue repair. PRP has been shown to release regenerating factors mostly within the first day of implementation [4].

Tooth extractions are a common procedure in which PRP can be used, as it is a way of obtaining a high concentration of substances which aid in would healing and regeneration. Periodontal surgery is another field in which it can be used, as PRP promotes formation of fibrin clot thus increasing collagen synthesis and proliferation of fibroblasts. In the oral surgery field, PRP has shown its ability to enhance healing of fractures as it promotes the healing of hard tissues.

Unlike PRP which requires the use of additives as anticoagulants, PRF is a genuine autogenous material and is obtained by centrifugation without additions. It contains platelets, leukocytes as well as growth factors and cytokines including (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), interleukin (IL)-1β, IL-4, and IL-6 [4]. It is highly biocompatible, and enhances regeneration via osteoblasts, endothelial cells, chondrocytes, and fibroblasts. PRF retains larger amounts of cytokines and growth factors, and it dissolves relatively slowly, showing a persistent release of factors within the first 10 days until it eventually remodels to heal similarly to a natural blood clot. It must be

mentioned that due to the lack of anticoagulant factors the obtained blood tube must be immediately centrifuged to avoid initiation of coagulation cascade. This process gives rise to a fibrin clot rich in platelets, trapped between an acellular plasma layer and erythrocytes. The solid fibrin clot is found between the most superior layer and the red background formed by red blood cells. The clot may then be removed immediately and condensed in a metal box to obtain a solid covering membrane or a filling substance (e.g., for bone augmentation). The resultant material of this procedure is called PRF, and it can be used in addition to graft material, as it will moisturize it and enhance its incorporation [4]. PRF can be used in many procedures of the dental and oral-facial fields – as in onlays and inlays grafts, ridge augmentation procedures, closure of cleft lip and palate defects, and sinus lift procedures [5].

PRGF, much like the aforementioned, is obtained through phlebotomy of the patient. The tubes containing the blood are added with amounts of sodium citrate corresponding to the products' indications and centrifuged to produce two separate layers, of which the most superior layer is called PRGF. It differs from PRP and PRF in that it contains significantly less white blood cells which are thought to be counterproductive locally and contains significantly more platelets which aid in healing and regeneration [6].

Aim: To overview the efficacy of treatment of postextractive alveolus with autologous blood concentrates

Tasks:

1. To evaluate PRP, PRF and PRGF hard tissue regeneration capabilities in alveolar socket after extraction of molar teeth.
2. To evaluate PRP, PRF and PRGF soft tissue regeneration capabilities after extraction of molar teeth.
3. To evaluate PRP, PRF and PRGF effect on postoperative pain

Hypothesis: This systemic literature review hypothesizes that PRP and PRF would be superior to PRGF regarding their soft tissue healing potential, but PRGF would be most valuable when relating to hard tissue regeneration and preservation of the alveolar socket bony structure. Moreover, it is anticipated that PRGF would show the best results regarding reduction of postoperative pain.

02.SEARCH METHODS AND STRATEGY

02.1.Protocol and registration

The systematic literature review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) protocol [14]. The study was approved by the local bioethics committee (No. BEC-OF-81) (Annex 1)

02.2.Focus Question:

The focus question was developed according to the PICO framework, which is presented in Table 1:

Table 1. PICO framework of the framed clinical question.

Full Review Question *Provide the full review question in sentence format, and then break up the question according to the PICO framework (or other frameworks as appropriate).*	
What are the effects of Plate-rich plasma, Platelet-rich fibrin and Platelet-rich in growth factors on postextractive alveolus regeneration after extraction of molar teeth and what is their influence on postoperative pain?	
Population	Patients whose molar teeth present hopeless prognosis and are destined for extraction.
Intervention	Placement of Plate-rich plasma, Platelet-rich fibrin or Platelet-rich in growth factors
Comparison	Patients treated with one of the aforementioned autologous blood concentrates compared with another, and how pain experience was different based on the blood concentrate used.
Outcome	Healing of the postextractive alveolus

02.3.Types of Publications

The review included studies on humans published in the English language.

02.4.Types of Studies

The systematic literature review included randomized controlled clinical trials and retrospective cohort studies of patients treated with autologous blood concentrates, published between 2013 and 2023, which reported on hard and soft tissue postextractive alveolus regeneration as well as pain perception of patients whose molars were extracted.

02.5.Information Sources

The information sources were searched on Cochrane, PubMed/Medline, Google Scholar, and manual search in the electronic Journal of Oral & Maxillofacial Research from January 2013 until February 2023. In addition, the bibliography of the selected articles was manually searched in order to identify additional relevant studies.

02.6.Type of population

Patients over the age of 18 presenting with molar teeth destined for extraction.

02.7.Literature Search and screening

The electronic databases used for literature search are Cochrane, PubMed/Medline, Google Scholar, and manual search in the electronic Journal of Oral & Maxillofacial Research. Relevant studies were selected according to the inclusion & exclusion criteria. First, the titles and abstracts were analyzed, following evaluation of chosen full-text papers.

02.8.Selection criteria

Clinical studies assessing the influence of PRP, PRF or PRGF on hard tissue and soft tissues regeneration, as well as their effects on postoperative pain were analyzed in this systematic literature review. Also, clinical studies comparing the use of more than one of the aforementioned blood concentrates in the same individual study and comparison of their effects.

Articles were selected according to the following inclusion criteria:

- English language studies conducted on humans.
- Male and female patients ≥ 18 years old.
- Healthy patients without systemic diseases.
- At least one extraction is indicated for each patient participating.
- Studies published from January 2013 until February 2023.
- Randomized Clinical Trials including 6 individuals or more.
- Retrospective/ Prospective Cohort studies

Articles were selected according to the consequent exclusion criteria:

- Patients younger than 18 years.
- Medically compromised patients
- Patients actively prescribed medications capable of interfering with bone healing metabolism.
- Pregnant or breastfeeding women.
- In vitro and laboratory studies.
- Abstracts, discussions, literature reviews, and case studies.
- Unclear or incomplete data on PRP, PRF or PRGF protocol used.

02.9.Data extraction

The data was extracted independently from studies in the form of variables, according to the aims and tasks of the present review.

02.10. Data items

Data from the included studies was collected and presented according to the following fields:

- "Author" – reveals the author of publication.
- "Year" – reveal the year of publication.
- "Study Design" – reveal the type of study.
- "Inclusion Criteria" – indicate the inclusion criteria compatible with the chosen article.
- "Groups" – Indicate the test group, control group, sample size
  - "Test group" – patients treated with PRF, or PRGF, or PRP.
  - "Control group" – patients treated conservatively with minimal intervention during healing.
  - "Sample size" – indicates the number of patients who participated in the study.
- "Age & Gender" – indicate the gender distribution, sample age, and mean age.
  - "Gender Distribution" – male & female distribution within the research.
  - "Sample Age" – age range of sample size. Youngest to oldest patients.
  - "Mean Age" – indicates the average age of the participants in each group in the study.
- "Treatment Protocol" – Which group received which kind of treatment.
- "Observation Period" – indicates the amount of time during which patients were followed upon.
- "Conclusions" – short description of each article's conclusions
- "Assessed postoperative pain" – Description of the pain experienced by the patients post-operatively.

02.11. Statistical analysis

Meta-analysis was not performed.

02.12. Search strategy

To identify the appropriate studies, a detailed electronic search was conducted according to PRISMA protocol[14] within Cochrane, PubMed/Medline, Google Scholar, and additional records identified via manual search in the electronic Journal of Oral & Maxillofacial Research. The following keyword combinations were used for the electronic search:

#1 'PRP AND extraction' [All fields] OR 'PRF AND extraction OR PRGF AND extraction' [All Fields]; #2 'socket AND PRP' [All Fields] OR 'socket AND PRF' [All Fields] OR 'socket AND PRGF' [All Fields]; #3 alveolar socket preservation' [All Fields] OR 'PRP OR PRF OR PRGF AND socket' [All Fields] OR 'PRP AND dent'' [All Fields] OR 'PRF AND dent'' [All Fields] OR 'PRGF AND dent'' [All Fields].

The search was limited to articles published in the English language, published from January 2013 until March 2023.

02.13. Selection of Studies

The resulting articles were independently subjected to coincide with the inclusion and exclusion criteria. Firstly, titles and abstracts were analyzed to identify full articles considered adequate for inclusion in this review. Then, the full text of chosen studies were evaluated.

02.14. Results

The electronic database search presented 1491 articles in PubMed, 408 articles in ScienceDirect and 10 articles in additional records in ResearchGate. Additionally, more articles were present in Google Scholar platform. A synopsis of the article's selection process is described in Figure 1 according to the PRISMA flow diagram.

After the removal of duplicate articles, 19 articles remained, and 16 more articles which were identified through Google Scholar and screened. During the preliminary step of the screening process, most of the articles were excluded because they were irrelevant based on the exclusion criteria or did not meet the inclusion criteria. As a result, seven studies were included in this systematic literature review as they were relevant for the topic and met inclusion and exclusion criteria (Figure 1). Two randomized controlled trials, including 136 patients, divided into test (PRP, PRGF or PRF) and control groups (left to heal with minimal involvement), and five retrospective cohort studies including 148 patients were included in this study. In total, 284 patients were examined and reviewed.

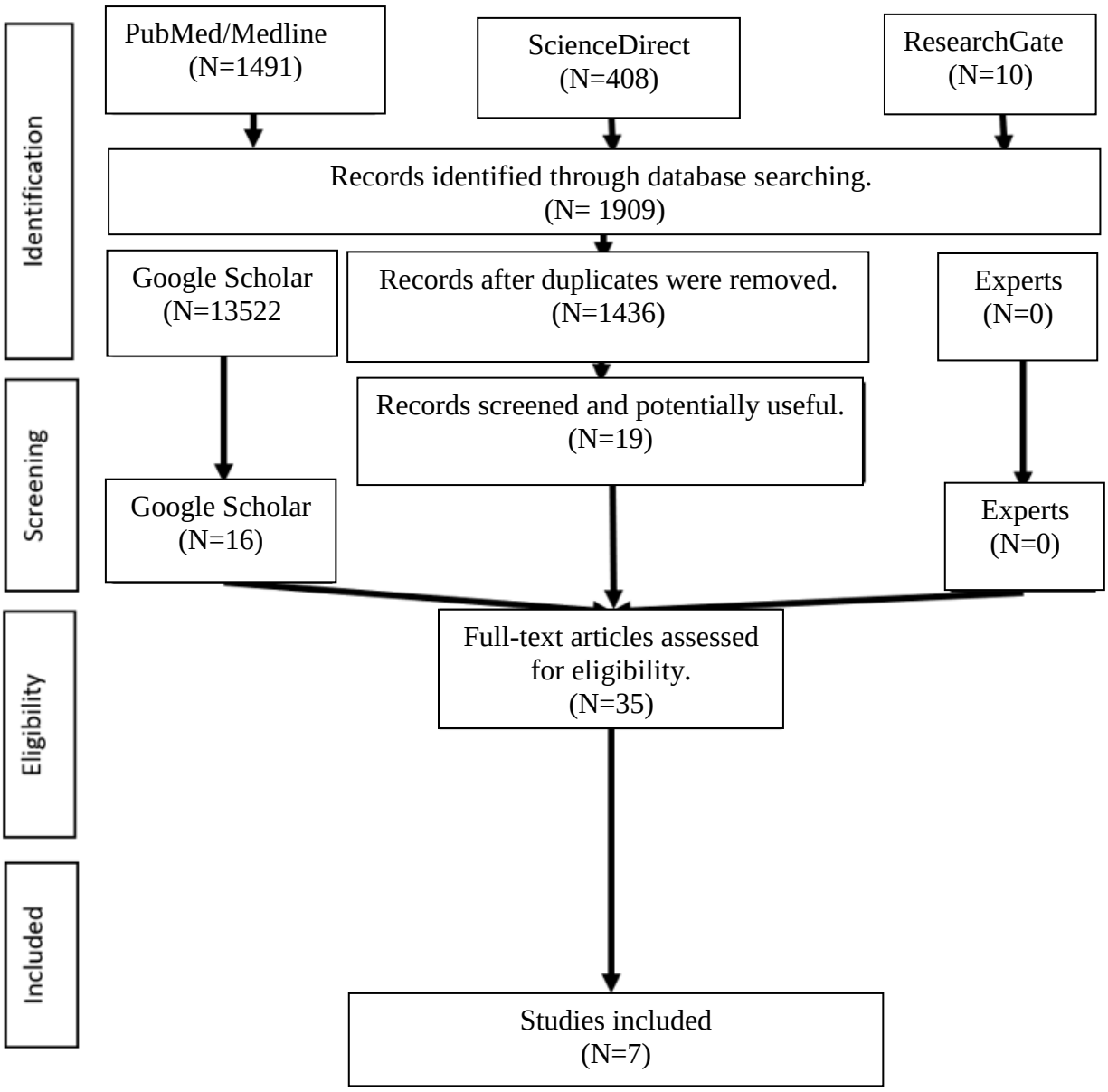

Figure 1. PRISMA flow diagram.

02.15. Risk of bias assessment

The seven studies included in this review were assessed for methodological quality using the Joanna Briggs Institute (JBI) critical appraisal checklist for randomized controlled trials (Annex 02), & JBI Critical Appraisal Checklist for Cohort Studies (Annex 03).

In this systematic literature review, both RCTs [9,12,13], and all cohort studies [7,8,10,11] had presented an average risk of bias, as the treatment assignment could not be concealed from either the patients, treating surgeons, nor outcome assessors. The risk of bias assessment results is presented in Table 2A and Table 2B. Systematization of data of included studies is presented in Tables 3.

Table 2A. JBI critical appraisal checklist for randomized controlled trials.

Study	Year	Study design	Checklist											
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q 10	Q 11	Q 12	Q 13
Eduardo Anitua et al. [9]	2014	RCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Valdonė Brazdeikytė et al. [13]	2021	RCT	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y

RCT = randomized clinical trial, Y = yes, N = no, ? = unclear

Table 2B. JBI Critical Appraisal Checklist for Cohort Studies.

Study	Year	Study Design	Checklist										
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Amol M Doiphode et al. [7]	2016	Retrospective Cohort	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Yingdi Zhang et al [8]	2018	Retrospective Cohort	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Shubha Ranjan Dutta et al. [10]	2015	Retrospective Cohort	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Ankit Sharma et al. [11]	2020	Retrospective Cohort	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yuvika Raj Kumar et al. [12]	2015	Retrospective Cohort	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

Y = yes, N = no, ? = unclear

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03. SYSTEMIZATION AND ANALYSIS OF DATA

CHARACTERISTCS OF INCLUDED STUDIES

Amol M Doiphode et al. 2016 [7] Is a split-mouth study for patients requiring bi-lateral molar extractions where patients were divided into a control group and an experimental group. The experimental group further divided into two subgroups Group IIa and Group IIb (split mouth method was used on one side of each patient as a control group and another side as intervention group). One subgroup was treated with PRP on one side and conservatively on the other side, while the other subgroup was treated similarly with PRF instead of PRP. Soft tissue recovery of the experimental group was better than the control group, and PRF proved to be superior to PRP in this category. The experimental group showed higher quality of bone formation than the control group. Yingdi Zhang et al. 2018 [8] compared postextractive alveolus healing between an experimental PRF group and a control group. The study reported better quality bone healing in the experimental group, better soft tissue healing in the experimental group. The experimental group's bone formation was quicker. Eduardo Anitua 2014 [9] compared the healing of postextractive alveolus between a PRGF experimental group and a control group. The experimental group showed better hard tissue regeneration, less pain, less inflammation, better soft tissue healing than the control group. Shubha Ranjan Dutta et al. 2015 [10] compared the healing of postextractive alveolus between a PRP experimental group and a control group. The experimental group showed earlier formation of bone, better soft tissue healing, better hard tissue healing, and less pain and discomfort compared to control group. Ankit Sharma et al. 2020 [11] compared the healing of postextractive alveolus between an experimental PRF group, and a control group. The experimental group reported better soft tissue healing, and better-quality bone formation. The latter could not be proved significant. Yuvika Raj Kumar et al. 2015 [12] compared the healing of postextractive alveolus between an experimental PRF group and a control group. The experimental group showed better soft tissue healing, an improvement in bone quantity and reduced postoperative pain compared with the control group. Valdonė Brazdeikytė et al. 2021 [13] compared the healing of postextractive alveolus between 3 groups: one receiving PRGF, other receiving PRF, and a control group. The study found that PRGF was the best regarding preservation of the socket in all dimensions, much better than the two other groups. The PRGF group reported the least amount of postoperative pain, followed by the PRF group and then the control group.

Table 3. Data analysis of included studies:

Author & Year	Study Design	Inclusion Criteria of Study	Groups	Age & Gender	Treatment protocol	Observation Period	Assessed postoperative pain	Results	Conclusions
Eduardo Anitua 2014 et al. [9]	A randomized controlled trial (RCT)	Patients over 18 years of age, only a single mandibular molar involved for each patient, patients must have consented to the study.	N: 60 T: 36 C:24 **Note:** T: 6/36 did not attend final checkup. C: 2/24 did not attend final checkup	**C:** MA: 53 SA: 18-67 G: 10 (M) 14 (F) **T:** MA: 57 SA: 29-74 G: 19 (M) 17 (F)	**T:** socket filled with PRGF and then sutured **C:** socket sutured to heal naturally.	3,7,15 days and 10-12 weeks after procedure	Control group reported higher pain values until the 15th day than the experimental group.	Test group shown better hard tissue regeneration, less pain, less inflammation, better soft tissue healing then the control group.	the use of PRGF promotes bone and soft tissue healing as well as reduced postoperative pain and inflammation
Shubha Ranjan Dutta et al. 2015 [10]	Retrospective cohort study	Patients between ages 18-50, patients who require mandibular molar extractions.	N: 60 T: 30 C:30	SA: 18-50 MA: not mentioned **C:** G: 16 (M), 14 (F). **T:** 13 (M), 17 (F)	**T:** PRP is placed in socket before closure **C:** Socket closure is done without any intra socket medicaments.	3,7,14 days, soft healing assessment. 3 weeks, 2,4 months for hard tissue assessment	Test group showed decreased amount of pain during the procedure.	Test group showed earlier formation of bone, better soft tissue healing, better hard tissue healing, less pain and discomfort compared to control group.	PRP causes significant improvement in soft tissue healing, bone regeneration, and increase in bone density in extraction sockets.

Author & Year	Study Design	Inclusion Criteria of Study	Groups	Age & Gender	Treatment protocol	Observation Period	Assessed postoperative pain	Results	Conclusions
Yuvika Raj Kumar et al. 2015 [12]	Retrospective cohort study	Healthy patients between the ages 18-40 requiring bilateral	NP: 34 N: 68 C: 34 T: 34	SA: 18-40 MA: Not mentioned. G: Not mentioned.	**T:** alveolar socket filled with PRF **C:** alveolar socket left to heal spontaneously	Pain assessment at 1,3 days, 1,4 weeks. Radiographic assessment at same day,	The results of the pain score showed that patients in the experimental group	Favorable effect on soft tissue, increase in the complexity of the trabecular bone,	Both soft tissue and hard tissue healing was enhanced by platelet-rich fibrin. Although there was no difference in osseous healing between the groups, the experimental group had greater

		mandibular third molars removal.		G: 19 (M) 17 (F)			experienced less pain.	increased the osseous healing.	soft tissue healing and better pain scores.
Amol M Doiphode et al. 2016 [7]	Retrospective Cohort Study	patients having bilateral mandibular third molar impaction (fully/partially erupted with all type of angulations), aged 18-30, generally healthy patients with no systemic diseases.	PN: 30 N: 30 C: 15 T: 15 (Note: T2 divided to two: T2a Was the one in which left extraction socket was filled with PRP gel Group T2b - In which the right extraction socket was filled with PRF.	SA: 18-30 G: not mentioned MA: not mentioned	T2a: Left socket filled with PRP. T2b: Right socket filled with PRF C: spontaneous healing. .	1,2,4,6 months after procedure.	Not measured	The least amount of post-operative alveolar bone resorption was recorded with group T2b (PRF), then group T2a (PRP gel), and the most significant bone resorption recorded in the control group.	This study indicates an improvement in the periodontal health distal to second molar after third molar surgery in cases treated with PRF as compared to the PRP group and control group. PRP and PRF have demonstrated good results, and both can be incorporated as an adjunct to promote wound healing and osseous regeneration in human mandibular third molar extraction sites.
Yingdi Zhang et al. 2018 [8]	Retrospective cohort study	Patients aged 20-40, the extracted teeth had hopeless prognosis, patients have a normal health status without systemic diseases, compliant patients.	PN: 28 N: 28 C: 14 T: 14	SA: 20-40 MA: not mentioned **T:** G: 6 (F), 8 (M) **C:** G: 8 (F), 6 (M)	T: socket filled with PRF C: socket left to heal spontaneously	Soft tissues observation at 7 days, 1 month and 3 months. Hard tissues observation after 3 months.	C: painful for 3 days, pain-free after 1 week T: Mild pain on same day, dull pain 1 day after, and no pain after 3 days.	Healing of soft tissues was better at test group and the formed bone was of higher density. Bone reformation was faster in test group.	PRF membrane used in the extraction sockets was demonstrated to promote local soft tissue healing of gums and reduce postoperative pain response. The effect of PRF to reduce alveolar bone resorption was not significant. PRF was able to increase the quality of the novel bone and enhance the rate of bone formation.
Ankit Sharma et al. 2020 [11]	Retrospective cohort study	healthy patients of age group between 18- and 45-years requiring	N: 30 C:30 T:30	SA:18-45 MA: 23.9 G: 14 (M), 16 (F),	**T:** alveolar socket filled with PRF.	3,7,14 days, for soft tissue assessment,	Pain not measured	The test group had better soft tissue healing when compared to the control group	PRF is better in promoting soft tissue healing and hastens bone formation in extraction socket.

		extraction of bilateral mandibular molars except third molars.			**C:** alveolar socket left to heal spontaneously.	1 day, 4 months for radiographic assessment.		on the 3rd day, 7th day, 14th day. The rise in radiopacity at the end of 16th week for PRF group was higher as compared to control group but did not differ significantly.	
Valdonė Brazdeikytė et al. 2021 [13]	A randomized controlled trial (RCT)	Patients aged 18 to 50 years of age, not smoking, no systemic diseases.	**N**: 43 **C**:21 **T1**: 11 **T2**:11	G: 33 (F), 10 (M) SA: 18-48 MA: 28.6 **C:** MA=30.29 **T1:** MA=27.7 **T2:** MA=26.73	**C:** mandibular molar is extracted, and the alveolus is filled with hemostatic sponge containing gentamicin. **T1:** postextraction alveolus filled PRGF. **T2:** postextraction alveolus filled with PRF.	Pain assessment after 1,7 days and assessment of bone regeneration after 1 month.	The group treated with PRGF experienced less postoperative pain 1 day after the procedure.	Lowest pain 1 day after the surgery reported in PRGF group, PRGF had the best results regarding vertical and diagonal volume regeneration, one month after surgery the age of the control group was inversely proportionally correlated with the height and diagonal dimension of callus.	In the PRGF group, the first day following surgery, the least amount of pain was seen. Better osteoblastic characteristics were a feature of PRGF. Age-related decline in bone tissue regeneration was stopped by PRF and PRGF, hence older patients are strongly advised to use blood concentrates.

T = test group, C = control group, N = sample size, G = gender distribution, SA = sample age, MA = mean age, PRP= Platelet-rich plasma, PRF= Platelet-rich fibrin, PRGF= Plasma-rich in growth factors, NP= Number of patients included

04. DISCUSSION

The purpose of this systematic literature review was to overview recent studies on the regeneration of hard and soft tissues at postextractive alveolus of molar teeth and the assessed pain with association to the use of PRP, PRF and PRGF in the sockets. The general review was conducted by including recent RCTs and non-randomized general observational studies. Case reports and case series were not included in the review. The terms platelet-rich growth factors (PRGFs), platelet-rich fibrin (PRF) matrix, PRF, and platelet concentrate are also used to refer to platelet-rich plasma (PRP). Hematology is where PRP's idea and definition first emerged [15]. To refer to plasma with a platelet count above peripheral blood, which was initially utilized as a transfusion product to treat patients with thrombocytopenia, hematologists coined the term PRP in the 1970s [16]. PRP was first used as PRF in maxillofacial surgery ten years later. Fibrin may have adhesion and homeostasis-promoting capabilities, while PRP's anti-inflammatory qualities promote cell proliferation [17]. Platelet-rich plasma was originally used in oral surgical operations by Whitman et al. [18], who reported significant benefits due to its enhancement of osteoprogenitor cells in the host bone and bone transplant. However, there is risk involved with utilizing it since bovine thrombin, which is used to treat PRP, can produce antibodies against factors V, XI, and thrombin, which can result in coagulopathies that can be fatal [19]. On the other hand, PRF is regarded as a new generation of platelet concentrate and was initially employed in 2001 by Choukroun et al. [20], specifically in oral and maxillofacial surgery. It is composed of an autologous fibrin matrix [21] and offers several advantages over PRP, such as simpler preparation and no need for chemical treatment of the patient's body. Over the past 20 years, a variety of procedures and preparations have been developed to increase the body's endogenous repair capacity through the targeted injection of autologous growth factors. The first fully autologous platelet-rich plasma (PRP) was a growth factor-rich plasma (PRGF) [22]. The BTI Biotechnology Institute created the PRGF®-Endoret Technology to concentrate autologous whole blood into a plasma enriched in growth factors. Growth factors found in PRGF contribute to undifferentiated stem cells' recruitment to the location and promote their proliferation [23]. Furthermore, mesenchymal stem cells may proliferate and differentiate because of PRGF, which can speed up bone healing [24]. The development of platelet concentrates was intended to accelerate the healing process, raise the standard of care, and enhance patients' surgical dental treatment experiences. Moreover, PRGF has been associated with better pain relief for patients after surgical procedures [25]. In the study by Valdonė Brazdeikytė et al. [13] Patients presented to the clinic for extraction of mandibular molars and their post-surgical alveolar socket was randomly filled with either PRF, PRGF, or a hemostatic sponge with gentamycin as a conservative form of treatment to be utilized as a control group. One of the focus points of the study was the effect of the applied treatment on the postoperative pain felt by the patients, using visual analog scale (VAS). VAS gauges postoperative discomfort. The VAS is composed of a 10-cm line with the

labels "no pain" and "worst possible pain" anchored at either end [26]. The pain was assessed after 1 and 7 days and it showed that the patients treated with PRGF experienced the least amount of pain after 1 day, followed by the group treated with PRF and then by the control group which experienced the most amount of discomfort. However, the study found no pain assessment differences between the groups after the 7 days period. This finding is partially supported by another study, performed by Eduardo Anitua et al. [9]. This study compared patients' healing process of postextractive alveolar socket treated with PRGF to a control group of which alveolar socket was left to heal with a blood clot in the socket. This study similarly reported decreased postoperative pain in patients treated with PRGF, and it also used VAS as the indication for pain assessment. However, it was also concluded that PRGF postoperative pain reduction capabilities are reliable for up to the 7 days period. The study also assessed the postoperative pain after 15 days, but then it could not be concluded that there was significant difference in pain assessment between the study's groups. The study by Valdonė Brazdeikytė et al. [13] showed that PRGF had the best outcomes regarding its ability to preserve the hard tissue structure of postextractive alveolus, while PRF demonstrated minimal activity in this aspect, and the control group showed the worse ability to preserve the bony structure of the alveolus. However, the effect of PRF is anticipated to be mostly on the soft tissue's ability for regeneration and wound healing, which were not profoundly measured in this specific study. It can be anticipated that PRGF's hard tissue regeneration capabilities shown in the study may be related to its ability to enhance osteoblastic function. Evidence to PRGF's hard tissue healing abilities is also to be found in a study by Eduardo Anitua et al. [9]. Clinical, radiographic, and histological evaluations of bone healing have been conducted. All three of these methods demonstrated that PRGF was much more effective at promoting bone regeneration than traditional therapy. The autologous fibrin scaffold, which is loaded with growth factors and cytokines found in plasma and produced by platelets, is responsible for this improvement. In addition to mediating cell proliferation, dissemination, and adhesion, fibrin also acts as a conductive scaffold for defect bridging. Furthermore, the study also explored PRGF's soft tissue healing capabilities according to score by Landry et al. [27]. Higher scores were recorded in the PRGF group at 3, 7, and 15 days compared to the group receiving conventional therapy.A study by Yuvika Raj Kumar et al. [12] also assessed pain in patients going through treatment of postextractive alveolus. This study focused on patients requiring bi-literal 3rd mandibular molar extractions, and as for being a split-mouth study concept, one alveolus was filled with PRF and the other left to heal spontaneously. The study reported that the patients felt less pain at the extraction site treated by PRF during the 1st, 3rd, and 1-week periods after the procedure. The pain score reflected the healing of soft tissues, which was better in the experimental group. It was found that PRF gradually increases the osseous healing during each period and that bone quality and quantity was better in the experimental group. PRF bone healing capabilities are not a consensus, and studies like Manzoor Mohammad et al. [28] and Richard J Miron et al. [4] question the consistency and quality of bone produced

at site treated with PRF. A study by Yingdi Zhang et al. [8] which also compared the healing of alveolar socket treated with PRF to a control group, found that the bone volume of the alveolar socket was not enhanced at the site of the PRF, but the quality of the bone was better, and the rate of its formation was faster. Local soft tissue's healing ability was better in the experimental group than in the control group. Although the assessment of postoperative pain was not broadly discussed in the article, it was clearly shown by the study that the experimental group reported less discomfort during the 1st and 3rd day after the procedure compared to the control group. Both groups showed similar pain measurements at the 1-week mark, unlike the study by Yuvika Raj Kumar et al. [12] which reported noticeable pain measurements between the groups even at the 1-week period. Another study which evaluated soft and hard tissue properties of PRF is a split-mouth study by Ankit Sharma et al. [11]. Extractions of molars from both sides of the mouth were performed during the same day, and one socket was filled with PRF while the other left to heal naturally. This study used Landry et al. [27] index for measurement of soft tissue healing during the 3rd day, 1-week, and 2-week follow-up periods and radiographic assessment 1 day and 4 months after the procedure. The study reported better soft tissue healing throughout its whole assessment period. Sided with all studies included in this review concerning PRF, the study also reported an increase of the rate of bone formation, however an increase in bone quality was not significant in the experimental group and remains controversial. In a split-mouth study by Amol M Doiphode et al. [7] patients requiring bi-lateral molar extractions were divided into a control group and an experimental group. The experimental group further divided into two subgroups Group IIa and Group IIb (split mouth method was used on one side of each patient as a control group and another side as intervention group). One subgroup was treated with PRP on one side and conservatively on the other side, while the other subgroup was treated similarly with PRF instead of PRP. The study investigated the effect of PRP and PRF on bone density compared to the control group and found out the PRP and PRF do promote better bone quality formation than the control group, but no major differences were measured between the subgroup treated with PRP to the subgroup treated with PRF in terms of bone quality. The assessment of soft tissue showed that PRF and PRP ability to heal soft tissue was superior to that of the control group, but overall, the PRF showed the best healing properties regarding soft tissues, supporting many other studies claim. A study by Shubha Ranjan Dutta et al. [10] compared the healing of mandibular molar sockets treated with or without PRP post-extraction, and investigated soft and hard tissue healing, as well as postoperative pain. The study reported faster regeneration of bone formation in the experimental group, an improvement in soft tissue healing measured with the use of index by Landry et al. [27]. PRP's capacity to create a biologic gel that promotes clot stability and serves as an adhesive was recognized in the study as an additional benefit. The experimental group has also reported less post-operative pain; however, it was not discussed broadly and was not profoundly evaluated as reflected by the study report. The effects of PRP are backed by other studies like Eitan Mijiritsky et al. [29] and by N B Nagaveni

et al. [30]. When considering what kind of applications would be the most suitable to produce the best results in vivo in the field of oral and maxillofacial surgeries, many additional properties of each material should be considered e.g., the time required for the preparation of each material, its cost of production. According to many articles including Rachita Dhurat and MS Sukesh [31] and Önder Solakoglu et al. [22] both PRP and PRGF require more than a single spin of centrifugation while also requiring the addition of substitutes in order to acquire the materials. Therefore, the patient would need to be available in the clinic for longer time, which consumes more time from the dentist and also consumes more energy and resources, because PRP and PRGF protocols require the addition of non-autologous materials. In contrary, according to Voja Pavlovic et al. [1] and many more studies, the production of PRF does not require the addition of non-autologous substitutes and produced via a single round of centrifugation and therefore allowing more available time for the dentist to spend productively. Other considerations regarding deciding the use of which material would be the most appropriate may depend on the concentrates' reported healing ability. PRF, for example, shown in many reported studies that it has a superior ability to heal soft tissue of a postextractive molar, and therefore would be suitable for procedures involving extensive injury to the soft tissues. PRGF has shown that it has the ability to preserve the volume and quality of bone of postextractive alveolar socket. It can be utilized in place where the preservation of the bone volume is of additional significance, e.g., if a patient requires an implant placement but has a slim alveolar ridge which is barely thick or deep enough to go through the procedure. PRP may be suggested as a balanced option between those three, as it effects are well both on hard and soft tissue healing. In terms of postoperative pain, all concentrates have shown an advantage over traditional therapy, however PRGF shown the most promising ability to minimize postoperative pain, which can be valuable for patients fearing the discomfort they would experience after the procedure.

05. CONCLUSIONS

1. PRP and PRGF's ability to regenerate the bony alveolar socket was superior to that of the PRF. PRGF's ability to preserve the alveolar structure, hasten bone formation and improve bone quality makes it the most suitable in terms of best clinical results. PRGF lack of leukocyte content minimizes inflammatory response.
2. PRF and PRP's ability to heal the soft tissues in the place of extraction was better than that of the PRGF. PRF is associated with especially good recovery of the soft tissues, better than that of the PRP.
3. PRGF's ability to decrease pain is the best out of the three blood concentrates investigated in this study. However, all three proved to be efficient in reducing postoperative pain after molar extractions.

06. PRACTICAL RECOMMENDATIONS

1. PRF is valuable in the daily routine work of a dentist, as it offers increased healing rate, better soft tissue healing and decreased post-operative pain while the treatment protocol is relatively easy and completely autogenous.
2. PRGF would be the better choice if the patient is planned to make an implant in the same area. It offers a good ability to preserve the existing bone volume and improve bone quality, which may affect positively implant placement.

07.ACKNOWLEDGEMENT

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09.ANNEXES

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS

BIOETIKOS CENTRAS

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Medicinos akademija (MA) 2023.03.15 Nr. BEC-OF-81
Vientisųjų studijų programa – Odontologija
V k. studentui Alon Weisman
Darbo vadovas lekt. Jan Pavel Rokicki
LSMUL KK Veido ir žandikaulių chirurgijos klinika

DĖL PRITARIMO TYRIMUI

LSMU Bioetikos centras, įvertinęs Alon Weisman pateiktus dokumentus, studento tiriamajam darbui tema „Influence of Platelet-rich plasma, Platelet-rich fibrin, Plasma-rich with growth factors on postextractive alveolus regeneration and post-operative pain of moral teeth“ pritaria*.

dr. Eimantas Peičius

* Pastaba: šis pritarimas neatleidžia tiriamąjį mokslinį darbą vykdančių asmenų nuo prievolės laikytis Bendrojo duomenų apsaugos reglamento nuostatų ir nuo atsakomybės gauti nacionalinio arba regioninio bioetikos komiteto leidimą, jei toks leidimas būtinas pagal LR Biomedicininių tyrimų etikos įstatyme numatytus reikalavimus.

Annex 01. Bioethics Center Approval Form

Annex 02. JBI critical appraisal checklist for randomized controlled trials.

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____Date_____

Author _____Year_____Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2.	Was allocation to treatment groups concealed?	☐	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☐	☐	☐	☐
4.	Were participants blind to treatment assignment?	☐	☐	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7.	Were treatment groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	☐	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
12.	Was appropriate statistical analysis used?	☐	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Annex 03. JBI critical appraisal checklist for cohort studies.

JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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