UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE ODONTOLOGÍA

DEPARTAMENTO DE MEDICINA Y CIRUGÍA BUCOFACIAL

“Eficacia del plasma rico en plaquetas en el control del postoperatorio de la cirugía del tercer molar inferior retenido. Informe de resultados del estudio piloto”.

Trabajo de investigación

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IX. ANEXOS

a. Anexo 1: Información para el paciente y consentimiento informado.

Hoja de información y consentimiento para los pacientes voluntarios

Introducción

Este documento contiene información sobre un estudio clínico en el que se le ha propuesto participar, para comparar el efecto antiinflamatorio y cicatrizante del plasma rico en plaquetas durante el postoperatorio de la cirugía del tercer molar inferior.

Lea detenidamente la información que le detallamos, consulte con quien crea necesario y pregunte cualquier duda.

Antecedentes y objetivos

La cirugía del tercer molar inferior retenido conlleva habitualmente en su postoperatorio la aparición de dolor, inflamación y trismo. Aunque son numerosos los estudios realizados intentando minimizar esta sintomatología todavía no se ha conseguido una terapia totalmente efectiva. En el presente estudio se propone la aplicación intralesional de plasma rico en plaquetas (PRGF-Endoret ®).

Recientemente, algunos estudios han demostrado que la aplicación de plasma rico en plaquetas contribuye a reducir el dolor, la inflamación y el trismo.

Se proponen como objetivos de este trabajo:

1) Evaluar la presencia de dolor, inflamación y trismo tras la aplicación de PRGF-Endoret ® en la cirugía del tercer molar inferior, en relación a un grupo control.

Riesgos y precauciones

Se ha relacionado la sobreexposición de factores de crecimiento y sus receptores en tejidos tumorales y displásicos. Por lo tanto, se recomienda:

1. Realizar técnicas de obtención de plasma rico en plaquetas de una sola centrifugación.
2. Evitar la utilización de plasma rico en plaquetas en pacientes con condiciones precancerosas orales y en la proximidad de lesiones precancerosas (leucoplasia oral, eritroplasia o queiltis actínica) y de tejidos con displasia epitelial oral.
3. Evitar la aplicación de plasma rico en plaquetas en el "campo de cancerificación" de pacientes con exposición previa a carcinógenos o antecedentes de COCE (carcinoma oral de células escamosas) primario.

Descripción del estudio

En el estudio van a participar 15 pacientes que precisen exodoncia quirúrgica de cordales retenidos mandibulares bilaterales, y será desarrollado en el Servicio de Cirugía Bucal e Implantología del Hospital

Virgen de la Paloma de Madrid. Su participación en el estudio se llevará a cabo de la siguiente manera:

Antes de comenzar se realizará una historia clínica y farmacológica. Previamente a la realización de la intervención quirúrgica se procederá a la extracción de sangre de cara a la obtención del plasma rico en plaquetas del propio paciente.

Durante su participación en el estudio se realizarán las maniobras habituales para la extracción quirúrgica del tercer molar inferior:

Anestesia: Con la técnica convencional de anestesia, se administrarán 1,8 ml de articaína. Una vez que aparezcan los primeros signos de adormecimiento labial, se complementará con la anestesia del nervio bucal.

Incisión y despegamiento: Se realizará el despegamiento de la mucosa que rodea el molar a extraer.

Ostectomía y odontosección: se eliminará la superficie del hueso que recubre al tercer molar inferior, facilitando su posterior extracción. En esta fase quirúrgica se realizara la sección del diente en los casos que así lo requieran.

Revisión de la herida y sutura: en el lado correspondiente al grupo de plasma rico en plaquetas (PRP) se colocará el coágulo de plasma en el lecho alveolar previamente a la sutura.

Tras la cirugía se le entregará una hoja de recogida de datos para que anote si siente dolor o no los días 1, 2 y 3 tras la intervención, cuantos analgésicos ha necesitado tomar, y si ha notado cualquier otra molestia.

Deberá acudir de nuevo a la consulta a las 48 horas de la intervención para una primera revisión y entrega de la hoja de recogida de datos y a los nueve días de la intervención para la retirada de la sutura y el último control.

Participación/retirada voluntaria del estudio

Su participación es voluntaria y en el caso de que se decida suspenderla, no va a suponer ningún tipo de penalización en su asistencia médica. Asimismo, los pacientes podrán ser retirados del estudio, sin su consentimiento, si el investigador considera que es preferible para su salud o bienestar.

Preguntas e información

Cualquier nueva información referente a la medicación recibida que se descubra durante su participación, le será debidamente comunicada y se le dará la oportunidad de interrumpir el estudio. En cualquier momento usted podrá realizar cualquier consulta o duda al investigador.

Alternativas a la participación

Debido a que el tratamiento que se propone en este estudio clínico comprende las mismas maniobras y medicación que se emplean en la práctica habitual de extracción de las muelas del juicio, la alternativa es

recibir un tratamiento similar, pero sin incluir los datos que se generan en el mismo, en los resultados del estudio.

Publicación de los resultados

Los resultados del estudio se harán públicos, según alguno de los cauces aceptados por la comunidad científica, manteniendo en todo momento la confidencialidad y derechos de los participantes.

Permiso de revisión de historia clínica, confidencialidad y acceso a datos

Con el fin de garantizar la fiabilidad de los datos recogidos en este estudio, será preciso que eventualmente las autoridades sanitarias y/o miembros del Comité Ético de Investigación Clínica, tengan acceso a su historia clínica comprometiéndose a la más estricta confidencialidad, de acuerdo con la Ley 41/2002.

Al firmar el consentimiento de participación en el estudio se permite que un representante de las Autoridades Sanitarias o del Comité Ético de Investigación Clínica que ha evaluado el estudio clínico (CEIC), revisen la historia clínica. Esto no afectará la confidencialidad de los datos que se manejarán siguiendo lo establecido en la Ley Orgánica de Protección de Datos de Carácter Personal 15/1999.

De acuerdo con la Ley 15/1999 de Protección de datos de Carácter Personal los datos personales que se le requieren (por ejemplo: edad, sexo, datos de salud) son los mínimos para cubrir los objetivos del estudio.

En ninguno de los informes del estudio aparecerá su nombre y su identidad no será revelada a persona alguna salvo para cumplir con los fines del estudio, y en el caso de urgencia médica o requerimiento legal.

Sus datos se transferirán de forma codificada. Le será asignado un número que sólo el equipo médico del estudio podrá conectar con su nombre. Los datos podrán también ser utilizados con otros fines de carácter científico.

Los resultados del estudio podrán ser comunicados eventualmente a la comunidad científica a través de congresos y/o publicaciones.

De acuerdo con la Ley vigente tiene usted derecho al acceso de sus datos personales; asimismo, y si está justificado, tiene derecho a su rectificación y cancelación. Si así lo desea, deberá solicitarlo al médico que le atiende en este estudio.

Revisión ética

El ensayo se llevará a cabo de acuerdo a las recomendaciones para Ensayos Clínicos y evaluación de fármacos en el hombre, que figuran en la Declaración de Helsinki, revisada en las sucesivas asambleas mundiales, y actual Legislación Española en materia de Ensayos Clínicos.

CONSENTIMIENTO INFORMADO POR ESCRITO

Título del Ensayo: “Eficacia del plasma rico en plaquetas en la cicatrización y el control del postoperatorio tras la cirugía del tercer molar inferior”.

Yo (nombre y apellidos) D./Dña _____

en pleno uso de mis facultades, libre y voluntariamente, DECLARO que he sido debidamente informado/a por el Facultativo/a y considero que he comprendido la naturaleza y propósito del procedimiento y el estudio.

Comprendo que mi participación es voluntaria y que puedo retirarme del estudio sin que esto repercuta en mis cuidados médicos.

Estoy satisfecho/a con la información que se me ha proporcionado y, por ello, DOY MI CONSENTIMIENTO para mi inclusión en este estudio.

FIRMA DEL PARTICIPANTE FIRMA DEL INVESTIGADOR

DNI DEL PACIENTE

Madrid,…….de…….. de 201….

b. Anexo 2: Hoja de recogida de datos para el investigador.

Protocolo Código _____ Investigador_____

Nº Paciente:	**Iniciales:**	**Fecha: / / .**

HOJA DE RECOGIDA DE DATOS PARA EL INVESTIGADOR

INFORMACIÓN CONFIDENCIAL

Instrucciones para rellenar este cuadernillo:

- Como nombre del paciente, solamente deben figurar las tres iniciales: la primera del nombre y de los dos apellidos, aunque sean compuestos.
- Cada vez que se realice una corrección se debe poner la fecha y las iniciales del investigador que la realiza.
- Por favor, compruebe que las hojas de recogida de datos están completas y firmadas.
- La información contenida en este cuadernillo es confidencial.

PERIODO DE SELECCIÓN

Fecha de nacimiento: / /	Sexo:	Raza:

Anamnesis y antecedentes personales:

Antecedentes familiares:

Historia farmacológica: anotar las alergias medicamentosas:

¿Existen alteraciones clínicamente relevantes? **SI** ☐ **Especificar:**

NO ☐

Criterios de selección

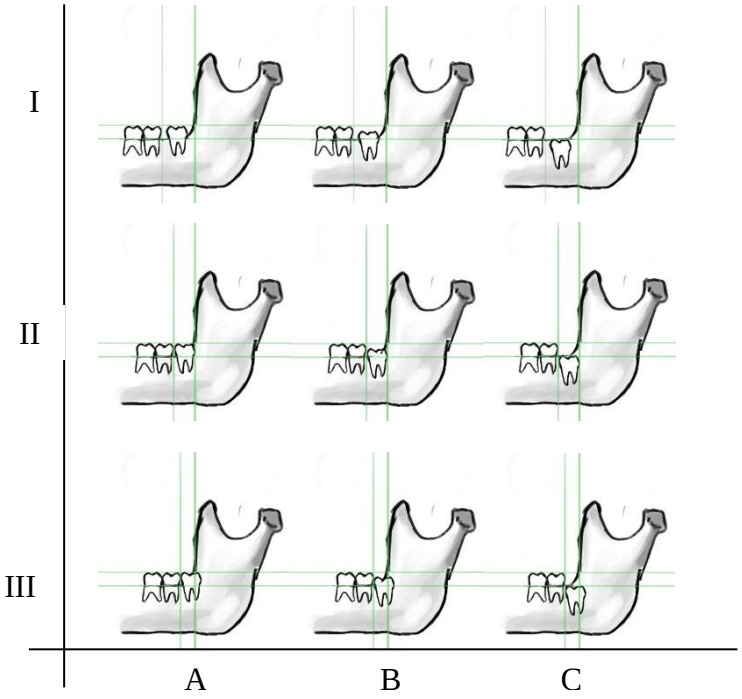
Criterios de inclusión		
	SI	NO
Sujetos de ambos sexos mayores de edad que tras haber recibido información sobre el diseño, los fines del estudio, los posibles riesgos que de él pueden derivarse y de que en cualquier momento pueden denegar su colaboración, otorguen por escrito su consentimiento para participar en dicho trabajo.		
Pacientes que presenten cordales mandibulares bilaterales incluidos con un grado de dificultad quirúrgica Tipo III, Clase C, verticales o mesioangulados y que demanden tratamiento quirúrgico en ambos lados.		
Pacientes capaces de comprender y llevar a cabo las instrucciones dadas.		
Pacientes con buen estado de salud, ASA I o II.		

Para la selección de este voluntario todas las respuestas deben ser AFIRMATIVAS.

Criterios de exclusión		
	SI	NO
Menores de 18 años.		
Pacientes ASA III y ASA IV.		
Pacientes fumadores.		
Mujeres embarazadas o en periodo de lactancia.		
Enfermedades sistémicas.		
Inmunosupresión. Pacientes tratados con cortisona en los últimos 12 meses.		
Pacientes que hayan recibido tratamiento con AINEs, anticoagulantes o ácido acetil salicílico.		
Pacientes que hayan recibido tratamiento con bifosfonatos.		
Pacientes con signos de displasia o lesiones precancerosas.		

Para la selección de este voluntario todas las respuestas deben ser NEGATIVAS.

Calcular índice de dificultad quirúrgica.



Diente nº	Clase	Tipo	Posición
38			
48			

Se seleccionarán aquellos pacientes con dificultad Tipo III Clase III, y posición vertical o mesioangular.

Duración de la intervención (en minutos):

PERIODO DE VALORACIÓN.

Mediciones sobre el paciente para valorar la inflamación y el trismo

Medidas basales.	
Medición **"A"** (Trago-Pogonio):	
Medición **"B"** (Trago-Comisura labial):	
Medición **"C"** (Gonion-Canto externo del ojo):	
Apertura bucal (Distancia interincisiva):	
48 horas de la intervención.	
Medición **"A"** (Trago-Pogonio):	
Medición **"B"** (Trago-Comisura labial):	
Medición **"C"** (Gonion-Canto externo del ojo):	
Apertura bucal (Distancia interincisiva):	
Día de la retirada de la sutura (9 días de la intervención).	
Medición **"A"** (Trago-Pogonio):	
Medición **"B"** (Trago-Comisura labial):	
Medición **"C"** (Gonion-Canto externo del ojo):	
Apertura bucal (Distancia interincisiva):	

Valoración de acontecimientos adversos:

¿Presentó el paciente algún acontecimiento adverso? (Márquese lo que proceda)

Sí ☐

No ☐

En caso de respuesta afirmativa, por favor, complete las siguientes tablas:

	INICIO		FINAL	
	Fecha	**Hora**	**Fecha**	**Hora**

(1) Leve, moderada, grave y mortal. (2) Definida, probable, posible, condicional. (3) Si precisa tratamiento concomitante, anotar en tabla inferior.

		INICIO		FINAL		
TRATAMIENTO	**PAUTA**	**Fecha**	**Hora**	**Fecha**	**Hora**	**MOTIVO DEL TRATAMIENTO**

¿El paciente ha completado el estudio?(Táchese lo que proceda)

Sí ☐

No ☐

En caso de no haber completado el estudio, anotar las causas y la fecha de abandono o retirada:

El investigador certifica que ha examinado cada página de este cuadernillo y que la información contenida es una reproducción completa y veraz de los datos del sujeto, que el estudio se ha realizado de acuerdo con el protocolo, y que antes de empezar el estudio todos los voluntarios otorgaron su consentimiento informado por escrito.

En Madrid a día……de……..de 201…

FIRMA DEL INVESTIGADOR

c. Anexo 3: Hoja de recogida de datos para el paciente.

Protocolo Código _____ Investigador_____

Nº Paciente:	Iniciales:	Fecha: / / .

HOJA DE RECOGIDA DE DATOS PARA EL PACIENTE

INFORMACIÓN CONFIDENCIAL

Instrucciones para rellenar este documento:

- Por favor, rellene los datos solicitados en este cuaderno con la mayor claridad posible.
- Anote en cada hoja sus iniciales y la fecha. El nº de paciente será anotado por su doctor.
- Cuando realice una corrección escriba con claridad el dato correcto.
- Firme todas las hojas de este cuaderno.

Nº Paciente:	**Iniciales:**	**Fecha: / / .**

Marque en la línea la intensidad del dolor, teniendo en cuenta que el **10** corresponde al dolor **<u>más intenso</u>** y el **0** a la **<u>ausencia de dolor</u>** **(realice este registro a la misma hora todos los días).**

- Día 1 tras la intervención:

- Día 2 tras la intervención:

- Día 4 tras la intervención:

¿Ha necesitado tomar analgésicos (***Metamizol magnésico***) para aliviar el dolor? Anote el día, la hora y el número de veces que ha necesitado tomar analgésicos para aliviar el dolor.

Fecha	Nº cápsulas	Hora (hh:mm)

¿Ha notado alguna molestia después de la intervención que no se le hubiera avisado? Descríbala y anote la hora de aparición, y la hora en que desapareció.

Firma del Paciente

d. Anexo 4: Datos basales y tablas de recogida de datos.

DATOS BASALES DE LA MUESTRA

	Edad	Sexo	Raza	Antecedentes Médicos	Alergias
1	26	2	Caucásica	0	0
2	18	1	Caucásica	0	0
3	19	1	Caucásica	0	0
4	21	2	Caucásica	0	0
5	27	2	Caucásica	0	0
6	22	2	Caucásica	0	0
7	21	1	Caucásica	0	0
8	23	1	Caucásica	0	0
9	23	2	Caucásica	0	0
10	19	2	Caucásica	0	0
11	19	1	Caucásica	0	0
12	21	2	Caucásica	0	0
13	24	1	Caucásica	0	0
14	19	1	Caucásica	0	0
15	26	2	Caucásica	0	0

1= sexo masculino; 2= sexo femenino; 0=ausente.

EDAD

Edad	
Media	21,86666667
Error típico	0,748755581
Mediana	21
Moda	19
Desviación estándar	2,899917897
Varianza de la muestra	8,40952381
Curtosis	-0,976133285
Coeficiente de asimetría	0,456678925
Rango	9
Mínimo	18
Máximo	27
Suma	328
Cuenta	15

SEXO femenino 1,14:1 masculino

TIEMPO medio de la intervención:

	Tiempo de intervención	
	Grupo control	Grupo PRP
1	14	17
2	19	19
3	21	15
4	16	16
5	19	16
6	16	15
7	15	17
8	15	16
9	9	15
10	10	15
11	13	13
12	13	17
13	14	19
14	16	16
15	13	14

Media:

Grupo control	
Media	14,8666667
Error típico	0,83304757
Mediana	15
Moda	16
Desviación estándar	3,22637937
Varianza de la muestra	10,4095238
Curtosis	0,07119922
Coeficiente de asimetría	0,09405888
Rango	12
Mínimo	9
Máximo	21
Suma	223
Cuenta	15

Grupo PRP	
Media	16
Error típico	0,42538498
Mediana	16
Moda	15
Desviación estándar	1,64750894
Varianza de la muestra	2,71428571
Curtosis	0,19838057
Coeficiente de asimetría	0,33174855
Rango	6
Mínimo	13
Máximo	19
Suma	240
Cuenta	15

TABLAS DE RECOGIDA DE DATOS

Grupo Control

	Día de la intervención				48 h tras intervención				7 días tras intervención			
	A	B	C	Apertura bucal	A	B	C	Apertura bucal	A	B	C	Apertura bucal
1	147	101	102	51	159	113	109	46	150	110	106	49
2*	145	105	101	53	157	113	104	46	150	107	102	50
3	149	104	101	47	-	-	-	40	156	109	102	48
4	147	101	104	51	154	112	106	38	150	105	104	46
5	149	100	106	52	157	110	112	26	152	103	110	35
6	142	108	103	51	153	118	107	40	150	110	104	49
7	150	108	100	47	158	111	111	40	150	109	103	45
8	147	111	100	51	152	115	109	40	151	110	101	50
9	140	103	104	53	149	110	110	40	146	106	105	44
10	136	100	102	47	150	105	108	35	146	101	104	43
11	146	104	101	53	155	109	103	46	151	105	102	48
12	150	100	106	50	160	112	105	40	155	106	105	48
13	150	110	101	45	159	115	107	30	157	109	103	39
14	148	105	101	48	156	109	105	40	150	106	102	48
15	145	109	102	62	151	115	104	40	148	110	103	46

*El paciente 2 tomó paracetamol con codeína en lugar de metamizol.
Los números marcados en rojo corresponden a las medidas en los tiempos 48 horas y 9 días con valores mayores a la inicial y en el caso de apertura bucal, mayor.

Grupo PRP

	Día de la intervención				48 h tras intervención				7 días tras intervención			
	A	B	C	Apertura bucal	A	B	C	Apertura bucal	A	B	C	Apertura bucal
1	140	101	102	51	151	111	108	42	142	109	104	49
2	147	105	101	53	153	113	103	49	152	106	101	52
3	147	104	101	47	154	111	103	41	150	107	101	44
4	140	101	103	51	150	110	105	40	143	103	103	47
5	139	100	105	52	163	109	110	25	145	101	109	39
6	141	109	104	51	150	118	109	43	142	109	105	50
7	150	108	101	47	156	113	104	42	151	109	103	46
8	147	112	100	51	150	114	101	43	149	113	100	51
9	139	103	105	53	145	109	109	39	143	106	104	49
10	136	101	101	47	143	113	105	35	140	103	101	43
11	147	104	101	53	153	110	107	48	149	104	103	51
12	150	101	105	50	159	109	110	43	153	102	106	49
13	150	112	103	45	155	114	109	33	152	113	103	41
14	147	105	101	48	155	112	104	40	149	106	101	48
15	144	109	101	52	149	116	104	46	144	110	103	49

En rojo: paciente 1, caso en que el PRP estuvo contaminado con elementos celulares.

e. Anexo 5: Publicaciones.

Journal section: Oral Surgery
Publication Types: Research

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Efficacy of platelet-rich plasma applied to post-extraction retained lower third molar alveoli. A systematic review

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Abstract

Dental retentions have a high prevalence among the general population and their removal can involve multiple complications. The use of platelet rich plasma has been proposed in an attempt to avoid these complications, as it contains high growth factors and stimulates diverse biological functions that facilitate the healing of soft and hard tissues.

Objectives: To evaluate the available scientific evidence related to the application of platelet-rich plasma in the post-extraction alveoli of a retained lower third molars.

Material and Methods: A systematic review of published literature registered in the Medline, EMBASE, Cochrane and NIH databases. The following categories were included: human randomized clinical studies. Key search words were: platelet rich plasma; platelet rich plasma and oral surgery; platelet rich in growth factors and third molar.

Results: Of 101 potentially valid articles, seven were selected, of which four were rejected as they failed to meet quality criteria. Three studies fulfilled all selection and quality criteria: Ogundipe et al.; Rutkowski et al.; Haraji et al. The studies all measured osteoblast activity by means of sintigraphy, and also registered pain, bleeding, inflammation, temperature, numbness as perceived by the patients, radiological bone density and the incidence of alveolar osteitis.

Conclusions: Scientific evidence for the use of PRP in retained third molar surgery is poor. For this reason randomized clinical trials are needed before recommendations for the clinical application of PRP can be made.

Key words: *Platelet rich plasma, lower third molar surgery, postoperative.*

Introduction

The use of platelet-rich plasma (PRP) is one recently proposed approach to managing complications in retained/impacted lower third molar surgery. Various authors have described PRP as an effective means for improving the healing of both hard and soft tissues, resulting in reductions in pain, inflammation and trismus, as well as an acceleration of the bone regeneration process. However, there is some controversy in the literature, which might be due to differing protocols for obtaining PRP (centrifugation) and the low numbers of systematic studies carried out to date (1,2).

PRP contains high concentrations of growth factors that stimulate different biological functions such as chemotaxis, angiogenesis, cell proliferation and differentiation, all of which facilitate healing (1-3); so when the platelets release growth factors, they trigger a process of tissue regeneration. In addition to growth factors, granulation tissue in wounds treated with PRP contains intra- and extra-platelet components that could also contribute to tissue regeneration (4,5).

PRP presents a low risk of infection or immunological reactions, as the platelets play an important role in host defense mechanisms at the wound site, due to a signal peptide release that attracts macrophages. The antimicrobial activity of platelet concentrates on the various bacteria species involved in oral infection has also been cited (1-5).

Recently, several randomized clinical trials (RCT) have been performed with small sample sizes and short follow-up periods, which have shown the results of PRP application to third molar surgical sites in the short term (6-12). The aim of the present study was to evaluate the scientific evidence in support of PRP application to retained lower third molar post-extraction alveoli.

Material and Methods

*Bibliography Search

A search was made for articles on platelet-rich plasma among the published biomedical literature included in the following databases: Medline (via Pubmed); EMBASE (via Ovid); NIH; and the Cochrane Central Register of Controlled Trials. The search was extended to include systematic literature reviews in the Medline database and the Cochrane Database of Systematic Reviews. The search was limited to randomized clinical studies of human, regardless of study duration or the language of publication.

*Search Strategy

The search covered all literature published up to and including June 30th 2013. The search parameters were "randomized clinical trials on humans". The key search words used were:

- In the Medline database: platelet-rich plasma and oral surgery; plasma rich in growth factors and third molar.
- In the EMBASE database: platelet rich plasma and oral surgery.
- In the Cochrane database: platelet rich plasma.
- In the NIH database: platelet rich plasma and oral surgery.

*Article Selection Criteria

-Inclusion criteria

Studies with the following characteristics were included:

Population: studies of humans that included adult patients who had undergone extractions of one or more retained lower third molars.

Intervention: application of platelet-rich plasma to post-extraction lower third molar alveoli.

Comparison: application of a placebo to post-extraction retained lower third molar.

Result variables assessed: pain, inflammation, bleeding, degree of healing, incidence of alveolar osteitis, degree of radiological bone regeneration and osteoblast activity.

Study design: only randomized clinical trials (RCTs) were included of parallel groups or split-mouth, one group having received an application of PRP and the other a placebo, with the two applications distributed randomly.

-Exclusion criteria

- Articles dealing with platelet-rich plasma applications to extraction sites of teeth other than retained lower third molars.
- Randomized clinical trials combining platelet-rich plasma application with other bone regeneration materials.
- Articles duplicating the same trial or study population as another, obtaining the same results, but using different study periods, or published in more than one journal.

*Data extraction

Relevant data were extracted from the studies that met the inclusion criteria and collated in tables of scientific evidence that registered the following data:

- Authors and year of publication.
- Study design: clinical trial of parallel groups or split mouth.
- Patient selection criteria.
- Sample size.
- Protocol for obtaining PRP.
- Initial patient characteristics.
- Result variables.

Quality evaluation and synthesis of scientific evidence

A critical assessment of the selected studies was performed, evaluating their internal and external validity. This was done by means of the Jadad scale (13), which awards a score of zero to five according to whether or not the following criteria were met:

- Whether or not the study was randomized.
- Whether or not it was double blind.
- Whether or not it listed patients lost or retired from the study procedure.

- Whether or not the method for generating the randomization sequence (if described) was adequate.

According to the Jadad scale, a clinical trial is considered of poor quality if it scores less than three. On the basis of the information extracted and collated in tables of scientific evidence and having assessed the quality of the clinical trials, the evidence identified as being of adequate quality was then organized, synthesized, and structured.

*Classification of scientific evidence

The quality of scientific evidence was classified by means of the GRADE system (14).

Results

1- Search Results. Flow diagram

a) Systematic reviews and meta-analyses

Five systematic reviews were found (1,2,5,15,16), all of which were excluded because: one (1) included clinical trials that had combined PRP with other bone regeneration materials, and had applied these to not only retained lower third molar post-extraction alveoli; another review (15) included clinical studies in which bone defects were treated by means of periodontal defect regeneration or maxillary sinus elevation; two (2,16) analyzed the characteristics of platelet-rich plasma, techniques for obtaining it and its possible applications, rather than treating lower third molar sites; the last (5) did not fall within the field of oral surgery but applied PRP to chronic cutaneous wounds.

b) Randomized clinical trials

The search identified 101 articles, of which 16 were duplications. Of the remaining 85, 72 were discarded on the basis of the title, as it was clear that they did not correspond to the application of platelet rich plasma in retained lower third molar surgery.

In this way, 13 articles were identified that were potentially adequate for inclusion. Having reviewed the abstracts, seven articles that met all the proposed inclusion criteria were selected and their complete texts were read; all were randomized clinical trials (6-12).

After evaluating the quality and potential for bias by means of the Jadad scale (13), four were eliminated as they failed to achieve the minimum score required (6-9) (Table 1). Figure 1 is a flow diagram describing the RCT selection process.

2- Qualitative Synthesis

The results extracted from the RCTs selected are shown in table 2.

Gürbüzer et al. (10) is a split-mouth study of 12 patients with bilateral retained lower third molars. The study objective was to investigate the short-term effects of PRP on osteoblast activity during the alveolar healing process after retained mandibular third molar extraction. Osteoblast activity was measured in alveolar neoformed bone by means of scintigraphy, one and four weeks after surgery.

16 ml of blood were extracted in two 8.5 ml tubes with citrate phosphate dextrose as anticoagulant; double-centrifugation was performed, with an initial ten-minute centrifugation at 2400 rpm and a final centrifugation at 3600 rpm for 15 minutes. The PRP obtained was diluted in saline solution at a concentration of 1:5. Lastly, the patients own blood and 0.5 ml of calcium chloride were added.

Bone scintigraphy with technetium-99 was performed one and four weeks after surgery. No statistically significant differences were found between groups.

Rutkowski et al. (11) carried out a split-mouth study of six patients. Only non-smokers took part, who had bilateral retained lower third molars in similar states of

Table 1. Results of quality evaluation generated by the Jadad scale (13) for RCTs initially selected.

Author and year	Sammartino et al. (6)	Mozzati et al. (7)	Ogundipe et al. (8)	Célio-Mariano et al. (9)	Gürbüzer et al. (10)	Rutkowski et al. (11)	Haraji et al. (12)
Randomized study	1	1	1	1	1	1	1
Double blind	0	0	0	0	1	1	1
Study describes patients lost or retired	1	0	0	1	0	1	0
Method for generating randomization sequence described and found adequate	0	0	1	0	0	0	0
Adequate blinding conditions	0	0	0	0	1	1	1
Total	2	1	2	2	3	4	3

Table 2. Results of studies included for analysis. (VAS = visual analogue scale; N.E. = not evaluated; N.D.P. = no data provided; PRP = platelet-rich plasma).

Author and year		Gürbüzer (10)	Rutkowski (11)	Haraji 2012 (12)
Pain (VAS)	Day 1	N E	N.D.P.	
	Day 2	N.E.	N.D.P.	PRP group: mean = 2.77 control group: mean = 3.97 p < 0.00
	Day 3	N.E.	N.D.P.	PRP group: mean = 2.09 control group: mean =3.82 p < 0.00
	Day 4	N.E.	N.D.P.	PRP group: mean = 1.69 control group: mean = 2.19 p < 0.00
	Days 5-9	N.E.	N.D.P.	N.E.
Inflammation (VAS)	Days 1-9	N.E.	N.D.P.	N.E.
Bleeding	Days 1-9	N.E.	N.D.P.	N.E.
Numbness	Days 1-9	N.E.	N.D.P.	N.E.
Temperature	Days 1-9	N.E.	N.D.P.	N.E.
Dehiscence	Days 1-9	N.E.	N.D.P.	N.E.
Variations in healing	Day 3	N.E.	N.E.	PRP group: mean = 2.52 control group: mean =4.07 p<0.00
	Day 7	N.E.	N.E.	PRP group: mean = 0.66 control group: mean = 0.95 p < 0.00
Incidence of alveolar osteitis		N.E.	N.E.	4 cases in PRP group 18 cases in control group p < 0.05
Radiological bone density	1 week	N.E.	N.D.P.	N.E.
	2 weeks	N.E.	N.D.P.	N.E.
	3 weeks	N.E.	N.D.P.	N.E.
	4 weeks	N.E.	N.D.P.	N.E.
	6 weeks	N.E.	N.D.P.	N.E.
	8 weeks	N.E.	N.D.P.	N.E.
	12 weeks	N.E.	N.D.P.	N.E.
	16 weeks	N.E.	N.D.P.	N.E.
	20 weeks	N.E.	N.D.P.	N.E.
	24 weeks	N.E.	N.D.P.	N.E.
	Media	N.E.	N.D.P.	N.E.
Osteoblast activity ratio	1 week	PRP group (2.61±0.53) control group (2.51±0.46) p> 0.05	N.E.	N.E.
	4 weeks	PRP group (3.88±0.51) control group (3.61±0.44) P > 0.05	N.E.	N.E.

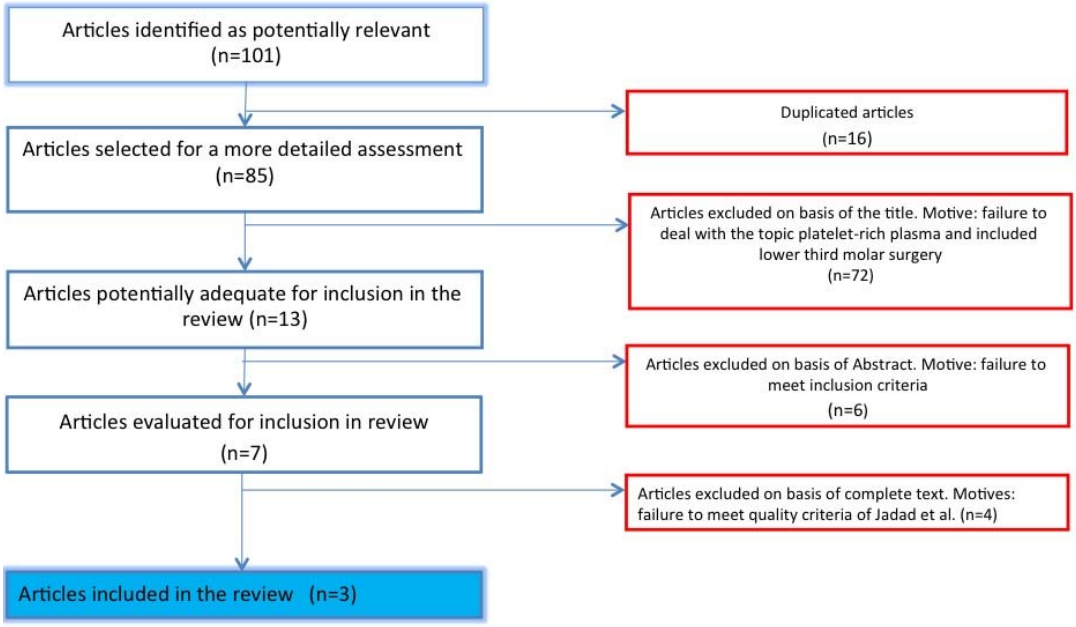

Fig. 1. Flow diagram of randomized clinical trial selection process.

eruption and without medical antecedents.

Two tubes of 4.5 ml of blood were obtained with sodium citrate as anticoagulant. These were centrifuged for 10 minutes at 1150 g. The plasma was aspirated with a pipette, 3mm above and 2 mm below the interface between plasma and the red blood cell layer. Extraction of the lower third molars was performed, after which Gelfoam® was applied to a control group and Gelfoam® together with PRP to the study group.

The study measured pain, inflammation, bleeding and temperature perceived by the patient, using a visual analogue scale nine days after surgery. No statistically significant differences were observed between the PRP group and the control group for any of the parameters analyzed.

The study also evaluated dehiscence, bleeding, inflammation and intraoral swelling perceived by an observer. A significant difference was observed in favor of PRP in relation to facial swelling.

Digital periapical radiographs were made using VinWix Pro® software to determine bone density by means of gray scales. The mean radiological bone density was significantly greater in the group treated with PRP than in the control group (Student t test for paired samples: $p<0.05$).

Haraji et al. (12) set out to evaluate the prophylactic effect of PRP against alveolar osteitis, as well as its effect on pain management and the acceleration of the healing process. Forty patients were selected with bilateral maxillary or mandibular third molars that presented similar levels of surgical difficulty and similar risk factors for alveolar osteitis: antecedents of pericoronaritis, treatment with oral contraceptives, smoking, bruxism or antecedents of dry alveolitis.

10 ml. of blood were extracted in 1 ml tubes with sodium citrate at 3.8% as anticoagulant and centrifuged at 460 g for 8 minutes. The portion of platelet-rich plasma was separated from the red blood and calcium chloride was added (0.05 ml. per ml of plasma). It was placed in an oven and heated at 37º for 5-8 minutes.

After surgery, pain was evaluated by means of a visual analogue scale; healing was evaluated by means of observation of coagulate degeneration, wound dehiscence with suppuration, wound dehiscence without suppuration (or non-healing). It was found that the intensity of post-operative pain was significantly less ($p<0.00$) and healing better ($p<0.00$) in the PRP group than in the control group. Incidence of post-operative alveolar osteitis on the side treated with PRP was significantly less ($p<0.05$) than on the conlateral side.

Discussion

Platelet-rich plasma is used in a variety of clinical situations in the field of oral surgery, ranging from filling post-extraction alveoli to more complex surgery involving bone regeneration or sinus elevation (17-19). It is claimed that its use reduces pain and inflammation, accelerates the epithelialization of soft tissues and promotes bone regeneration (20-21). The objective of this systematic literature review was to analyze the scientific evidence available for PRP application in retained lower third molar surgery.

Although there are many authors who extol the virtues of PRP use, there are few randomized clinical trials that have studied this topic. The present review could only

find seven clinical trials on the subject, of which four failed to meet Jadad criteria (13) for avoiding bias.

The three remaining studies included for review - Gürbüzer et al. (10), Rutkowski et al. (11), and Haraji et al. (12) - did not present any bias in relation to the clinical trial procedure, but two did present problems when it came to communicating the results.

Haraji et al. (12) affirm that pain and inflammation levels in the study group treated with PRP were lower than in the control group with statistically significant difference ($p<0.00$). However, the article did not include any values (mean, standard deviation or any numeric value) deriving from the trial. This article also determined the incidence of osteitis but failed to specify the method employed for its diagnosis. Furthermore, 80 third molar extractions were performed – 40 maxillary and 40 mandibular – all of which were included in the results. This represents an important fault in methodology, given that, from a clinical point of view, the post-operative conditions of a lower third molar cannot be compared with those of an upper third molar.

Similarly, Rutkowski et al. (11) state that there were no differences between groups for the incidence of pain but a statistically significant reduction in inflammation in the PRP group. They found differences in the degree of ossification using digital radiography in favor of PRP. However, they fail to provide objective data for any of the variables studied and limit their results to the statistical analysis applied to generate p-values. In addition, the patient sample was small, only six patients and twelve lower third molars. As these two published studies failed to provide any data on pain or inflammation, and furthermore, their sample sizes were small, it is impossible to carry a synthesis of these results by means of meta-analysis.

The third clinical trial included for analysis, published by Gürbüzer et al. (13), measured osteoblast activity one week and four weeks after surgery. The study does communicate the results clearly but fails to find statistically significant differences between groups. No other study of this type can be found that would allow a comparison with these results.

Another feature of the trials was the method employed for obtaining the platelet concentrate. None of the studies analyzed used the same method, a key factor given that the concentration of growth factors will differ depending on the method used. It is even possible that some of the less rigorous protocols may have allowed the inclusion of red cells or white cells, which would produce a stronger inflammatory response than expected (11).

Recently, the Spanish Agency of Medicines and Medical Products has published a report that considers PRP application a medication fit for human use. Authorization of any medication implies that it meets the required criteria of quality, safety and efficacy. However, the report states that clinical trials of sufficient quality are yet to be carried out before firm conclusions can be drawn as to its application and urges researchers to carry out clinical trials of adequate design in order to establish an adequate body of evidence for each pathology, type of PRP and application (Alonso C, Baró F, Blanquer M, de Felipe P, Fernández ME, Gómez-Chacón C, et al. INFORME/ V1/23052013, Spanish Agency of Medicines and Medical Products on the use of platelet-rich plasma, Ministry of Health, Social Services and Equality, available at: http://www.aemps.gob.es/vigilancia/medicamentosUsoHumano/docs/notificacion-SRA.pdf.).

When the Grade system guidelines were applied (14), the quality of published evidence for PRP application in lower third molar post-extraction alveoli was found to be poor and so recommendations for its clinical use cannot be made.

Clearly, randomized clinical studies are needed that investigate the safety and efficacy of PRP post-operative treatments for lower third molar alveoli and compare PRP applications with a placebo. Result variables should include its influence on pain, inflammation and trismus, bone and soft tissue healing and reduction of the periodontal sac distal of the adjacent second molar. Publication of the results of such trials should follow the Consort Declaration guidelines (22) in order to ensure the external validity of the results obtained.

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