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CENTRO NAZIONALE SANGUE
Istituto Superiore di Sanità

L'approccio metodologico: l'analisi della qualità metodologica degli studi

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Roma, 21-01-'20

Conflitto di interessi

Il sottoscritto, MARIO CRUCIANI, in qualità di Relatore,

dichiara che

- nell'esercizio della sua funzione e per l'evento in oggetto, **NON È** in alcun modo portatore di interessi commerciali propri o di terzi;
- dichiara inoltre che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali **non sono tali da permettere a tali soggetti di influenzare** le sue funzioni al fine di trarne vantaggio.

Revisioni sistematiche e meta-analisi

Una revisione sistematica sintetizza i risultati della ricerca disponibile e risponde a un quesito clinico specifico in modo strutturato e riproducibile.

Spesso, ma non necessariamente, la revisione sistematica è accompagnata da una **metanalisi**, cioè un'aggregazione statistica di risultati di studi diversi per fornire una singola stima degli effetti.

L'utilità delle revisioni sistematiche è nella constatazione che gli studi singoli possono non essere rappresentativi dell'insieme delle evidenze e possono risultare fuorvianti.

Le revisioni sistematiche includono un numero più ampio di pazienti (di fatto, la somma dei pazienti arruolati nei singoli studi inclusi nella revisione) e ciò potenzialmente aumenta la precisione dei risultati ottenuti.

Vi sono vari tipi di RS:

- ***interventi***
  - ***RCTs***
  - studi di coorte
- accuratezza di test diagnostici
- Studi epidemiologici
- ***Overview di revisioni sistematiche***

Punti chiave per una RS/MA

- Obiettivi chiari
- Ricerca della letteratura esaustiva
- Metodologia per la conduzione rigorosa
- ***Valutazione della qualita' metodologica degli studi essenziale***
- ***Il GRADE – (Grading of Recommendations, Assessment, Development and Evaluation) è oggi lo strumento di riferimento per la valutazione della affidabilità delle prove scientifiche e per la formulazione di raccomandazioni cliniche basate sulle evidenze***.
- Analisi statistica subordinata alla valutazione della qualita' metodologica degli studi disponibili

Il metodo GRADE

Fattori che influiscono sulla valutazione della qualità degli RCT

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Da: Amato et al. Il Metodo GRADE. http://bal.lazio.it/wp-content/uploads/2017/05/Il-metodo-GRADE.pdf

Cosa valuta il GRADE

Utilizzando il metodo GRADE si valutano due componenti:

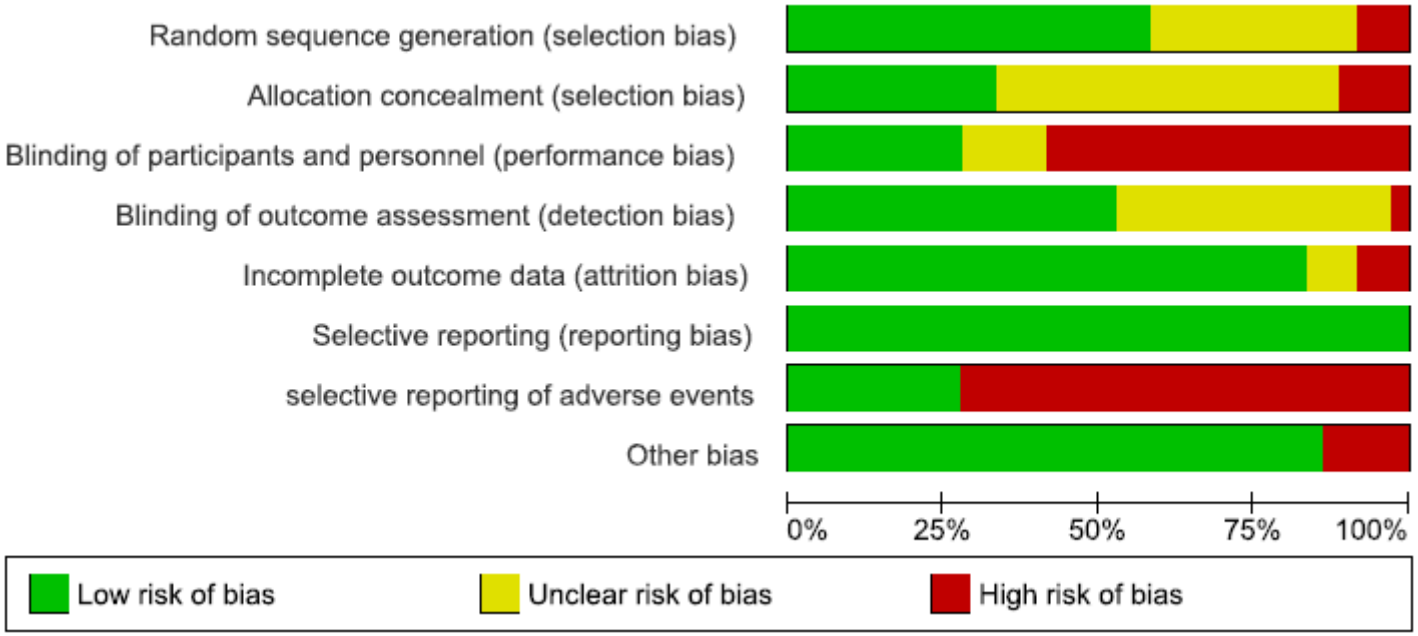
- la qualità complessiva di tutto l'insieme delle prove, cioè il **grado di fiducia** con cui si giudica la causalità di una associazione (la qualità può essere alta, moderata, bassa o molto bassa);
- la **forza della raccomandazione** (forte o debole).

Risk of Bias Assessment (ROB) in RCTs

Per gli studi randomizzati e controllati i principali rischi di bias sono:

- la modalità con cui è stata eseguita la randomizzazione cioè l'assegnazione dei pazienti ai bracci di trattamento;
- la mancanza o i problemi di mascheramento nell'assegnazione al braccio di trattamento o di controllo (*allocation concealment*);
- la mancanza o la presenza di problemi nella cecità dei pazienti e/o del personale (*performance bias*);
- la mancanza o la presenza di problemi nella cecità per esiti influenzabili dal giudizio dell'*outcome assessor* (chi valuta gli effetti del trattamento) (*detection bias*);
- le ampie perdite al follow-up o le perdite al follow-up asimmetriche nei due gruppi (*attrition bias*);
- le interruzioni precoci per vantaggio del trattamento, la mancanza dell'analisi *intention to treat* e le analisi condotte considerando solo coloro che hanno aderito al trattamento e non tutti i pazienti per i quali sono disponibili dati sui risultati (*attrition bias*);
- la relazione incompleta o assente in merito ad alcuni risultati e non altri (*reporting bias*).

ROB: review authors' judgements about each risk of bias item presented as percentages across all included studies.



The use of PRP in oral surgery... Franchini et al. Blood Transfusion, 2019, 17: 357

Costruire il GRADE: Inconsistenza: si misura con i test di eterogeneita'

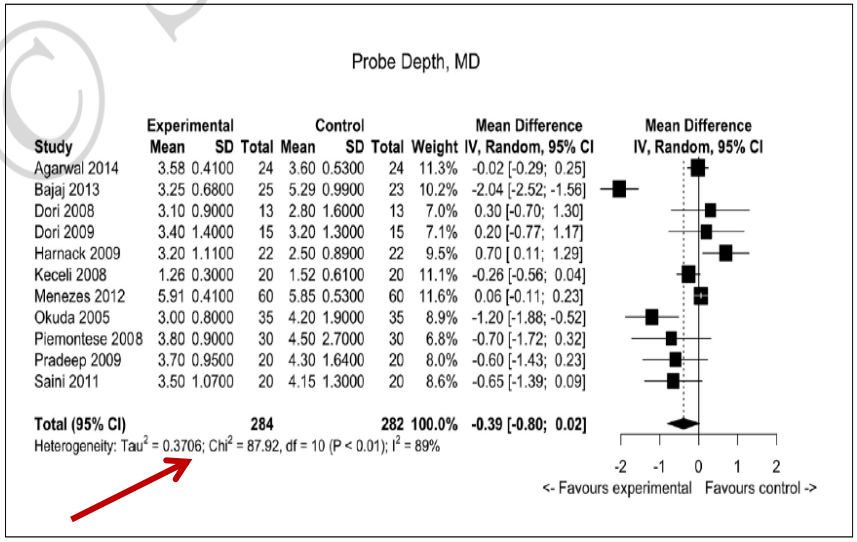
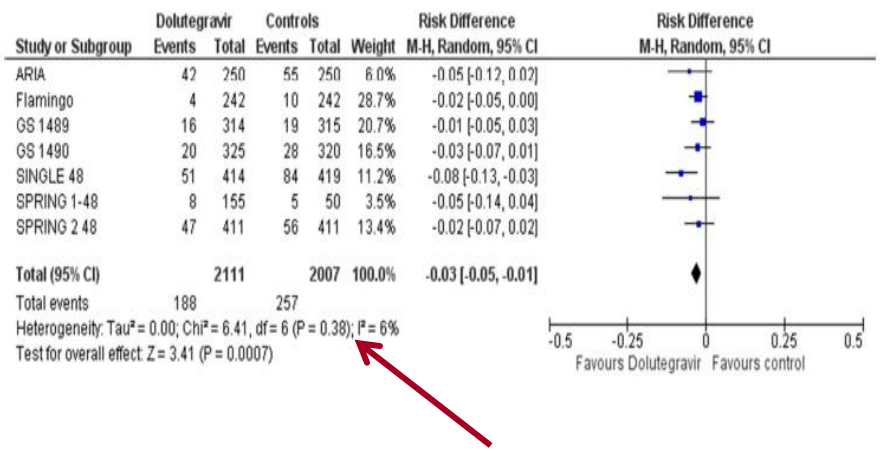


Figure 4 - Periodontal defects: forest plot for probing depths.
MD: mean difference; 95% CI: 95% confidence interval.

Fig 5. Forest plot of comparison: Dolutegravir vs comparators, outcome: Overall rate discontinuation.



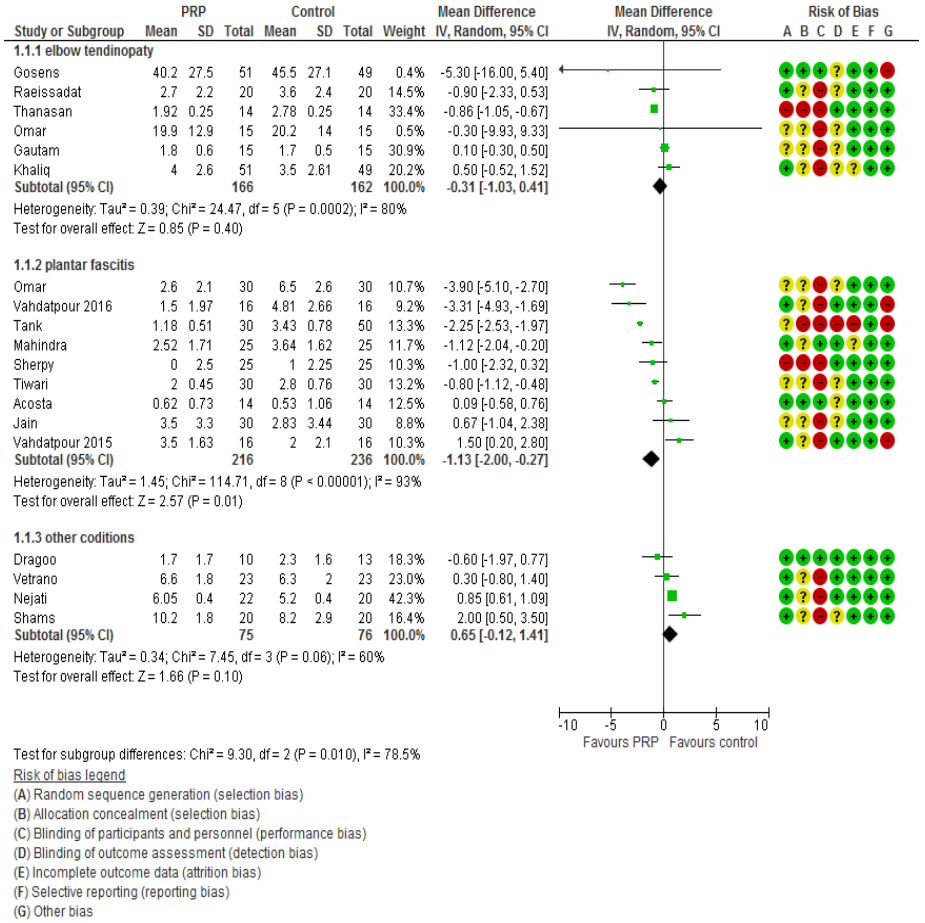
Down-graded

Non necessita' di down-grading

Costruire il GRADE: IMPRECISIONE

I risultati possono essere «imprecisi» quando gli studi includono pochi pazienti e/o si verificano **pochi eventi**, producendo così stime con intervalli di confidenza molto ampi.
Alcuni esempi per i quali è possibile decidere di ridurre la considerazione in merito alla qualità delle prove per questo fattore sono:

- il campione totale (cumulativo) è minore del teorico campione informativo ottimale;
- il numero totale di eventi è basso;
- l'intervallo di confidenza al 95% intorno alla stima dell'effetto include anche il non effetto.



Franchini et al, BT 2018

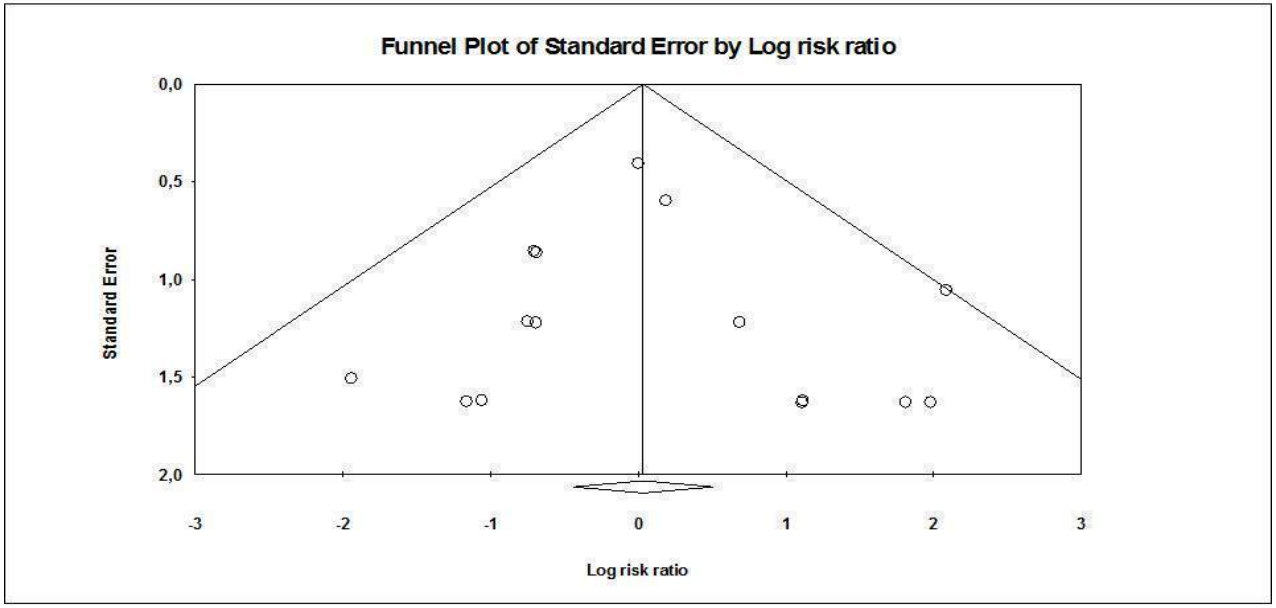
Indirectness

La *indirecteness* riguarda la non diretta trasferibilità dei risultati al contesto di interesse per la scarsa aderenza degli studi individuati al nostro PICO.

Questo problema si può manifestare in tre modi:

- **confronto indiretto**: non si hanno studi che confrontano direttamente A con B ma solo studi che confrontano A con C e B con C. I dati estratti da questi studi permettono un confronto indiretto di A e B, ma la qualità della prova sarà ridotta;
- **popolazione, intervento, controllo o esiti indiretti**: il quesito per il quale si deve produrre la raccomandazione si riferisce a una popolazione, un intervento, un controllo o considera esiti diversi da quelli per i quali sono disponibili prove di efficacia. Ad esempio, dobbiamo fare una raccomandazione per l'età pediatrica ma tutti i trial sull'intervento specifico sono stati svolti solo su soggetti adulti;
- ricorso a **esiti surrogati**.

Publication Bias



GRADE working group: gradi di evidenza ed interpretazione

ALTA	⊕⊕⊕⊕	Sicuramente l'effetto reale è vicino a quello espresso dalla stima dell'effetto
MODERATA	⊕⊕⊕◯	La stima dell'effetto è abbastanza affidabile: l'effetto reale sembra vicino a quello della stima ma potrebbe anche essere sostanzialmente diverso
BASSA	⊕⊕◯◯	L'affidabilità della stima dell'effetto è scarsa: l'effetto reale potrebbe essere sostanzialmente diverso dalla stima
MOLTO BASSA	⊕◯◯◯	La stima dell'effetto è inaffidabile: è verosimile che l'effetto reale sia sostanzialmente diverso dalla stima

*www.GradeWorking-Group.org

PRP a scopi non-trasfusionale: le RS del CNS

REVIEW

Efficacy of platelet-rich plasma as conservative treatment in orthopaedics: a systematic review and meta-analysis

Massimo Franchini[1,2], Mario Cruciani[1,3], Carlo Mengoli[1], Giuseppe Marano[1], Simonetta Pupella[1], Eva Veropalumbo[1], Francesca Masiello[1], Ilaria Pati[1], Stefania Vaglio[1], Giancarlo M. Liumbruno[1]

Blood Transfus 2018; 16: 502-13

REVIEW

Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis

Blood Transfus 2019; 17: 200-9

Massimo Franchini[1,2], Mario Cruciani[1,3], Carlo Mengoli[1,4], Giuseppe Marano[1], Enrico Capuzzo[2], Ilaria Pati[1], Francesca Masiello[1], Eva Veropalumbo[1], Simonetta Pupella[1], Stefania Vaglio[1,5], Giancarlo M. Liumbruno[1]

The use of platelet-rich plasma in oral surgery: a systematic review and meta-analysis

Blood Transfus 2019; 17: 357-67

Massimo Franchini[1,2], Mario Cruciani[1,3], Carlo Mengoli[1,4], Francesca Masiello[1], Giuseppe Marano[1], Ernesto D'Aloja[5], Cristina Dell'Aringa[6], Ilaria Pati[1], Eva Veropalumbo[1], Simonetta Pupella[1], Stefania Vaglio[1,7], Giancarlo M. Liumbruno[1]

Platelet-rich plasma for sports-related muscle, tendon and ligament injuries: an umbrella review

Blood Transfus 2019; 17: 465-78

Mario Cruciani[1,2], Massimo Franchini[1,3], Carlo Mengoli[1,4], Giuseppe Marano[1], Ilaria Pati[1], Francesca Masiello[1], Samantha Profili[1], Eva Veropalumbo[1], Simonetta Pupella[1], Stefania Vaglio[1,5], Giancarlo M. Liumbruno[1]

SOT: PRP in ortopedia

Table II - Platelet rich plasma (PRP) compared with control intervention for tendinopathies: summary of findings§.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	N. of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk Control	*Corresponding risk* PRP				
PAIN score: Visual Analogue Score (VAS)	Various controls, including local steroids injection					VAS 0-100 (higher scores = worse pain)
VAS - short-term follow-up (1-3 months) - Elbow tendinopathy	Mean VAS score across control groups ranged from 17 to 45.5 in control groups	Mean VAS score in the intervention groups was 2.86 lower (8.57 lower to 2.85 higher)	MD −2.86 (95% CI: −8.57 to 2.85)	6 studies (328 participants)	⊕⊖⊖⊖ very low[1,2,3]	On average, it is unclear whether or not use of PRP compared to controls reduces pain score at short-term follow up. The between group differences were small and unlikely to be clinically important
VAS - medium-term follow up (4-6 months). - Elbow tendinopathy	Mean VAS score across control groups ranged from 25 to 55.8 in control groups	Mean VAS score in the intervention groups was 12.97 lower (5.34 to 20.61 lower)	MD −12.97 (95% CI: −20.61 to −5.34)	3 studies (158 participants)	⊕⊖⊖⊖ very low[1,2]	Marginal clinical benefit of PRP at medium-term follow up. The between group differences were small and unlikely to be clinically important
VAS - short-term follow up (1-3 months) - Plantar fasciitis	Mean VAS score ranged across control groups from 5 to 65 in controls groups	Mean VAS score in the intervention groups was 2.86 lower (8.57 lower to 2.85 higher)	MD −2.86 (95% CI: −8.57 to 2.85)	8 studies (420 participants)	⊕⊖⊖⊖ very low [1,2,3]	On average, it is unclear whether or not use of PRP compared to controls reduces pain score at short-term follow up. The between group differences were small and unlikely to be clinically important
VAS - medium-term follow up (4-6 months) -Plantar fasciitis	Mean VAS score across control groups ranged from 5 to 48 in controls groups	Mean VAS score in the intervention groups was 7.87 lower (14.9 lower to 0.85 lower)	MD −7.87 (95% CI: −14.9 to −0.85)	6 studies (300 participants)	⊕⊖⊖⊖ very low[1,2]	Marginal clinical benefit of PRP at medium-term follow up. The between group differences were small and unlikely to be clinically important
Serious adverse events (0-6 months) - Elbow tendinopathy, plantar fasciitis, Achilles tendinopathy, rotator cuff tendinopathy	0 events	0 events	Not estimable	22 studies (1,265 participants)	⊕⊖⊖⊖ very low[1,2,3]	There were no reports of serious adverse events (e.g. injection site infection, plantar fascia rupture) during the follow-up period (1.5-24 months) of 22 trials
Function score: American Orthopedic Foot and Ankle Society Score (AOFAS)	Controls were represented only by local steroids injection					AOFAS 0-100 (higher score=better function)
AOFAS - short-term follow up (1-3 months) - Plantar fasciitis	Mean AOFAS score across control groups ranged from 81 to 96.8 in control groups (steroids)	Mean AOFAS score in the steroids groups was 4.26 higher (3.96 lower to 12.47 higher) than in intervention group	MD 4.26 (95% CI: −3.96 to 12.47)	4 studies (188 participants)	⊕⊖⊖⊖ very low[1,2,3]	On average, it seems that the use of PRP compared to local steroids injection does not increase function score at short-term follow-up
AOFAS - medium-term follow up (4-6 months) - Plantar fasciitis	Mean VAS score across control groups ranged from 74 to 97.2 in controls groups (steroids)	Mean AOFAS score in the steroids groups was 4.25 higher (5.92 lower to 14.42 higher) than in intervention group	MD 4.25 (95% CI: −5.92 to 14.42)	5 studies (218 participants)	⊕⊖⊖⊖ very low[1,2,3]	On average, it seems that the use of PRP compared to local steroids injection does not increase function score at medium-term follow-up

[1]Down-graded once for inconsistency, due to substantial heterogeneity (I2>80%). [2]Down-graded twice because of high risk of bias or unclear risk of selection bias, and at high risk of other bias (unbalance at baseline between groups) in several of the selected studies. [3]Down-graded once for imprecision (95%CI includes line of no effect). [4]Down-graded once due to serious risk of bias (especially reporting bias) and twice for very serious imprecision (no events). CI: confidence interval; MD: mean difference.

SOT: Autologous serum eye drops for xerophtalmia

Patient or population: individuals with dry eye (xerophthalmia); *settings*: eye clinic; *intervention*: autologous serum ; *comparison*: artificial tears.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect: mean difference (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	*Corresponding risk*				
	Artificial tears	*Autologous serum*				
Schirmer test Score <4 mm indicates severe dry eye. Follow up: 2-6 weeks.	The mean score ranged across control groups from 4.00 to 10.10	The mean score in the intervention groups was 1.05 higher (0.17 lower to 2.26 higher)	1.05 (−0.17-2.26)	496 (5 studies, 7 data sets). Two studies used a cross-over design.	⊕⊖⊖⊖[1] very low	On average, it is unclear whether or not use of AS compared to AT increases the score at short-term follow up. The between group differences were small and unlikely to be clinically important.
Tear film break-up time (TBUT) A TBUT <10 seconds is considered abnormal. Follow-up: 2-6 weeks.	Mean score range across control groups: 3.00-12.50 seconds	Mean score in the intervention groups was 2.68 seconds higher (1.33-4.03 higher)	2.68 seconds (1.33-4.03)	544 (6 studies, 8 data sets). Three studies used a cross-over design and paired data were available from two of these.	⊕⊕⊖⊖[2] low	On average, compared to AT, at short-term follow up AS increases in TBUT of 2.68 seconds.
Fluorescein staining Range of scale: 0-9, where a higher score is worse. Follow-up: 2-6 weeks.	The mean score ranged across control groups from 2.00 to 8.00	The mean score in the intervention groups was 0.61 lower (1.50 lower to 0.28 higher)	−0.61 (−1.50-0.28)	400 (4 studies, 5 data sets). One study used a cross-over design.	⊕⊖⊖⊖[1] very low	On average, it is unclear whether or not use of AS compared to AT decreases the fluorescein staining score at short term follow up. The between group differences were small and unlikely to be clinically important.
Ocular surface disease index (OSDI) Participant- reported symptoms. Range of scale: 0-100, with scores 0 to 12 representing normal, 13 to 22 representing mild DES, 23 to 32 representing moderate DES, and greater than 33 representing severe DES. Follow-up: 2-4 weeks.	The mean score ranged across control groups from 24.90 to 30.00	The mean score in the intervention groups was 11.17 lower (16.58 to 5.77 lower)	−11.17 (−16.58 - −5.77)	224 (3 studies; 4 data sets).	⊕⊕⊖⊖[3] low	On average, compared to AT, at short-term follow up AS decreases OSDI of 11.17.

[1]Down-graded because of imprecision (95% CI includes line of no effect), for inconsistency (due to substantial heterogeneity, I^2>80%), and because of high risk of bias or unclear risk of bias in some of the included studies.
[2]Down-graded because of inconsistency (due to substantial heterogeneity, I^2>80%) and because of high risk of bias or unclear risk of bias in some of the included studies.
[3]Down-graded because of inconsistency (due to substantial heterogeneity, I^2>80%) and for imprecision (studies include relatively few patients and thus have a wide CI around the estimate of the effect).

SOT: PRP in pazienti con difetti periodontali

Patient or population: with periodontal defects; ***Settings***: outpatient; ***Unit of analysis***: periodontal defect; ***Intervention***: regimens containing PRP; ***Comparison***: regimens not containing PRP.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect: mean difference (95% CI)	N. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	*Corresponding risk*				
	PRP	*Controls*				
Probing depth (PD) in mm Follow-up: 6-48 months	The mean score PD ranged across control groups from 1.52 to 5.85	The mean score in the intervention groups was 0.39 lower (0.80 lower to 0.02 higher)	−0.39 (−0.80/0.02)	566 (11 studies)	⊕⊖⊖⊖[1] very low	On average, it is unclear whether or not use of PRP compared to controls affects the PD at long-term follow-up. Between group differences were small and unlikely to be of clinical importance.
Clinical attachment level (CAL) Follow-up: 3-48 months	The mean score ranged across control groups from 2.02 to 11.81	The mean score in the intervention groups was 0.57 lower (0.93 to 0.20 lower)	−0.57 (−0.93/−0.20)	566 (11 studies)	⊕⊕⊖⊖[2] low	Very marginal clinical benefit of PRP compared to controls. On average, compared to controls, PRP decreases CAL by 0.57.
Gingival recession (GR) Follow-up: 6-48 months	The mean score ranged across control groups from 0.76 to 4.75	The mean score in the intervention groups was 0.46 lower (0.77 to 0.15 lower)	−0.46 (−0.77/−0.15)	482 (9 studies)	⊕⊕⊖⊖[2] low	Very marginal clinical benefit of PRP compared to controls. On average, compared to controls, PRP decreases GR by 0.57.
Bone defect (BD) Follow-up: 9-12 months	The mean BD ranged across control groups from 1.90 to 3.78	The mean score in PRP group was 0.67 lower (1.19 to 0.15 lower)	−0.67 (−1.19/−0.15)	306 (6 studies)	⊕⊕⊖⊖[2] low	Very marginal clinical benefit of PRP compared to controls. On average, compared to controls, PRP decreases BD by 0.67.

[1]Down-graded for imprecision (95% CI includes line of no effect), for inconsistency (due to substantial heterogeneity, I^2 =80-89%) and because of high risk of bias or unclear risk of bias in some of the included studies. [2]Down-graded for inconsistency (due to substantial heterogeneity, I^2=80-89%) and because of high risk of bias or unclear risk of bias in some of the included studies.

PRP in sport medicine: an Umbrella review

- 22 revisioni sistematiche—176 RCTs
  - 5 RS di lesioni muscolari sport-related
  - 17 RS di lesioni tendinee e legamentose sport-related

- Qualità metodologica delle RS
  - Checklist del Joanna Brings Institute
  - GRADE assessment

PRP in sport medicine

Conclusions

Implications for clinical practice

In the treatment of acute muscle injuries, PRP does not seem to be superior to usual care. These findings are based on low/very low quality evidence. In the treatment of tendon and ligament injuries, there is little evidence to favour PRP compared to controls. Most of the observed differences were small and, even if statistically significant, are unlikely to be of clinical significance. Moreover, the level of certainty of the evidence was low/very low. Overall, there is currently insufficient evidence to support the use of PRT for treating these injuries.

GRADE working group: gradi di evidenza ed interpretazione

ALTA	⊕⊕⊕⊕	Sicuramente l'effetto reale è vicino a quello espresso dalla stima dell'effetto
MODERATA	⊕⊕⊕◯	La stima dell'effetto è abbastanza affidabile: l'effetto reale sembra vicino a quello della stima ma potrebbe anche essere sostanzialmente diverso
BASSA	⊕⊕◯◯	L'affidabilità della stima dell'effetto è scarsa: l'effetto reale potrebbe essere sostanzialmente diverso dalla stima
MOLTO BASSA	⊕◯◯◯	La stima dell'effetto è inaffidabile: è verosimile che l'effetto reale sia sostanzialmente diverso dalla stima

*www.GradeWorking-Group.org

GRADE working group: Definizione della forza e direzione della raccomandazione

Determinate in base a

- Qualita' prove
- Rischio/beneficio
- Preferenze paziente
- Utilizzo delle risorse

- ***Forza***: Forte o debole (condizionata)
- ***Direzione***: a favore o contro

Conclusioni: PRP in ortopedia, medicina dello sport, e periodontopatie

- ***Livello di affidabilita' delle prove****: bassa/molto bassa*
- ***Efficacia degli interventi****: assente o limitata, e comunque clinicamente modesta*
- ***Raccomandazione GRADE****: si suggerisce di non utilizzare i PRP per queste indicazioni non trasfusionali.*

ONLY ONE

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Rome

13 and 14 June 2020

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Istituto Superiore di Sanità

Grazie per l'attenzione!