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Abstract

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used over the counter analgesics for the management of post-operative pain following dental surgery, including dental implant placement. NSAIDs work through inhibition of the cyclo-oxygenase (COX) enzyme, in particular the isoform COX-2.

COX-2 has been shown to induce new bone formation with upregulation of COX-2 demonstrated following bony fractures. The aim of this systematic review was to determine if NSAID use affects bone healing and osseointegration following dental implant placement.

Methods: Electronic databases (Medline and Embase) were searched in addition to hand searches from reference lists of selected papers. Only randomised control trials were included in this review.

Results: Three studies were included and data provided on bone healing and osseointegration following dental implant surgery (with and without NSAID use) were analysed. The Cochrane risk of bias tool (2.0) were used to assess risk of bias.

Two randomised control trials were conducted on animal subjects and one on human participants. One animal study reported significantly reduced bone healing around dental implants following the use of prolonged subcutaneous NSAIDs. No other studies reported any significant findings. There was considerable heterogeneity between included studies.

Conclusion: There is limited evidence exploring the relationship of NSAIDs and dental implant osseointegration and bone healing to draw definitive conclusions. Further research is required in this area.

Key Words:

Dental Implants

Anti-Inflammatory Agents, Non-Steroidal

Surgery, Oral

Osseointegration

Introduction

There are a number of options available to patients for the fixed replacement of missing teeth. Over the last twenty years, dental implants have been an ever increasing and popular choice to restore edentulous spaces ranging from a single tooth to full arch prosthesis.

Numerous studies have investigated dental implants in different clinical situations, reporting success rates over 94%. [1-3] Nonetheless, there are local and systemic risk factors that can lead to unsuccessful osseointegration and failure of the implant (table 1). Additionally, operator factors such as site selection, implant dimensions (length/width) and technique can affect the overall success of the procedure. [4]

Bone undergoes continual remodelling through life to maintain the integrity of the skeleton. This is primarily achieved through the cellular mechanisms of osteoblasts, which produce organic bone matrix, and osteoclasts that break down bone mineral. [5] Dental implant placement produces physiological similarities with bone fracture injury through initiation of a regenerative process. Initially, the fracture ruptures blood vessels resulting in haematoma formation and the release of pro-inflammatory cytokines such as tumour necrosis factor, transforming growth factor β and interlukin-6 amongst many others. [6] These generate a chemotactic gradient facilitating cellular infiltration, inducing the release of inflammatory mediators such as cyclo-oxygenase enzyme isoform 2 (COX-2) and progression through the reparative phase of the inflammatory process. [7, 8] An initial haematoma is formed and a fibrin clot, protecting the exposed underlying tissue. Proliferation of periosteal cells is followed by its differentiation into a number of cell types, notably chondroblasts and osteoblasts that produce hyaline cartilage and osteoid (woven bone) respectively. In addition, mechanical stress stimulates the activation of osteoclasts, which resorb damaged bone. Osteoblasts migrate into the site and produce osteoid which forms a scaffold and together with the

hyaline cartilage results in a fracture callus. This tissue is replaced through endochondral ossification into lamellar bone. [9-11] The fracture healing process results in bone deposition around the implant hence implant topography that favours osseointegration and long-term maintenance of bone to implant contact are important in stability and resistance to forces. [11, 12] The cellular mechanism of bone remodelling is summarised in figure 1.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics which can often be obtained by patients in the United Kingdom without a prescription, summarised in table 2.

They are effective in reducing post-operative pain from dental surgical procedures (compared to acetaminophen (paracetamol) alone). [13] The mechanism of action of NSAIDs works through inhibition of the COX enzyme, in particular the isoform COX-2. This in turn reduces prostaglandin production and other mediators of acute inflammation, producing their antipyretic, anti-inflammatory and analgesic properties. [14-16] COX inhibition is also responsible for a number of side effects including gastro-irritation, interstitial nephritis, reduced glomerular filtration rate and prolonged bleeding time amongst many others. [17] NSAIDs have also been documented to increase the risk of acute myocardial infarction with the risk greatest in the first month of treatment especially with high doses. [18, 19]

COX-2 (and its associated mediators) have been shown to induce bone formation, however as these enzymes are inhibited by NSAIDs, it has been postulated that their use could affect bone healing and dental implant osseointegration. [20-23] Furthermore, COX-2 knockout mice demonstrate significantly delayed fracture repairs in comparison to COX-1 knockout and wild type mice. [20]

Key factors in dental implant osseointegration include primary stability which is immediate stability following surgery whereas secondary stability follows bone remodelling around the

implant interface. [24] Bone quality varies according to site such as the posterior maxilla where reduced bone density can compromise implant stability. [25] In such instances, techniques such as immediate loading need to be approached with caution. Studies have shown conditions that affect bone quality such as osteoporosis to also pose similar challenges for implant stability. [26]

Success of dental implants are measured through a range of parameters well defined by Smith and Zarb (1989). [27] These include no adverse patient symptoms, immobility of the implant, no radiographic evidence of peri-implant pathosis and stability in bone levels. [27] There are a range of implant success criteria that are well evaluated by Papaspyridakos *et al* (2012). [28]

As NSAIDs are common forms of pain relief following dental implant placement and have been shown to affect the physiology of bone remodelling, it is of interest to investigate whether they have an impact on bone healing, osseointegration and success rates following dental implant placement. Therefore, the aim of this systematic review was to evaluate the current evidence basis for NSAIDs affecting bone healing and osseointegration following dental implant placement.

Methods

A preliminary search was conducted to determine the highest quality of evidence to help inform the search strategy. It was determined that there were a limited number of studies exclusively assessing NSAID use and dental implants hence search criterion were kept broad to include as many studies as possible (table 3). In addition, no language restrictions were placed.

Inclusion criteria

The following inclusion criteria were applied to search results:

- Randomised control trials only.
- Human and animal studies.
- Titanium implants only.
- Implant surgery must have been the first implant surgery in the site of placement (inclusive for local anaesthetic, intravenous sedation, general anaesthetic and primary or secondary care). Single and multiple implants placed were allowed.
- NSAID use must be clearly documented and administered either pre, peri or post operatively (no restrictions on mode of delivery or dose were placed).
- At least one of the success criteria defined by Smith and Zarb (1989) must be recorded in the study. The criteria have been adapted to include quantitative bone analysis without a specified follow up duration. No limiting timeframe was set to account for animal based studies.
- Immediate placement, delayed placement with all loading protocols were acceptable. Implants loaded following three months were defined as delayed.

Exclusion criteria

Guided bone regeneration procedures would influence the physiological process of healing and act as a potential confounder, hence studies including patients who had undergone such procedures either prior to or during the time of implant placement were excluded. [29] In addition, patients with medical conditions that could affect bone healing such as those immunocompromised, with metabolic bone disease or malignancy were excluded. Studies where it was not possible to differentiate the results between smokers and non-smokers were also excluded. It was determined that a large number of NSAIDs are available 'over the counter', hence it would not be possible to exclude patients who had previously taken NSAIDs accurately however patients taking NSAIDs for ongoing medical conditions would not be included as this may influence overall COX expression.

An electronic search was conducted from databases Medline (1946 to December 2018) and Embase (1980 to December 2018). In addition, hand searching from reference lists of selected papers were also conducted. Titles of identified papers were initially screened by both authors and all identified studies included for full text review. Both authors (MD and NP) independently reviewed all studies using the search protocol and inclusion and exclusion criteria to determine studies for inclusion in this systematic review. Any issues were discussed by both authors until an consensus was reached. The search strategy and results are presented in table 4. The Cochrane risk of bias tool for randomised control trials (RoB 2) was used to assess risk of bias for included studies.

Results

The initial search provided 99 studies with 33 duplicates that were identified and removed. Additional manual searches were performed which identified one further study. The remaining 67 studies had their titles and abstracts evaluated and excluded if they were not relevant, did not meet the inclusion criteria or fulfilled the exclusion criteria. If there were any ambiguity at this point, the studies were included for full review. Seven articles were selected and following full text analysis, four were excluded. [30, 31] The flow of studies through the review process is shown in the PRISMA flow diagram (figure 2). Three randomised control trials were included for review (summarised in table 5).

Risk of bias assessment

All included studies were assessed using the Cochrane risk of bias tool (2.0) independently by both authors and results compared to ensure accuracy (table 6). Only one included study had a low overall risk of bias. Two studies did not provide sufficient detail on the randomisation process, specifically there was missing information on the random sequence generation process and concealment (for the investigators only as both are animal based studies). Consequently, both studies were determined to have an overall uncertain risk of bias. [32, 33]

Key Findings

Three randomised control trials were included in this review, of which two were animal studies. [32-35] Ribeiro *et al*. (2006) conducted a randomised control trial (with animal subjects) and reported a significant difference in bone healing around dental implants for the group

administered subcutaneous Meloxicam (versus saline) for 60 days. [33] The other two randomised control trials included in this review used oral and subcutaneous NSAID delivery modes and did not find any significant differences with the use of NSAIDs and post-surgery bone healing or dental implant osseointegration.

Animal studies utilised the tibiae (rats) and calvaria (rabbits) for the site of implant placement. The human study used dentoalveolar bone and included both the maxillae and mandible. Methods of implant surgery were documented in detail in all studies. Outcomes measures included quantitative analysis using micro-CT, histological analysis (following sacrifice of animal subjects) and radiographic analysis. There was a lack of homogeneity in the results hence it was not possible to conduct a meta-analysis or other forms of quantitative analysis. A summary of the key findings are presented in table 5.

Discussion

Parallels can be drawn between dental implant surgery in the craniofacial skeleton and bone fracture repair. Firstly, there is (iatrogenic) blood vessel damage causing haemorrhaging of blood products. This causes platelets and inflammatory cells to release of a number of factors such as platelet derived growth factor, vaso-endothelial growth factor, transforming growth factor β and bone morphogenic protein (BMP). [36] Inflammatory mediators released at the fracture site produce a chemotactic gradient resulting in migration of mesenchymal cells (stromal stem cells) into the site. In addition, tissue injury causes release of phospholipase A2 which catalyses the formation of arachidonic acid (from membrane phospholipids) into a number of constituents such as prostacyclin, prostaglandins, thromboxane and leukotrienes modulated by the cyclo-oxygenase enzyme. [37]

There are two forms of the cyclo-oxygenase enzyme (COX1 and COX2). COX-1 is constituently active in most cells for physiological processes however is converted to COX-2 in states of inflammation, stress and other pathological conditions. [8, 38] COX-2 has been shown to potentiate the inflammatory process, mainly through the production of prostaglandins. Prostalgandin E2 (PGE2) is key compound that induces differentiation of mesenchymal cells into osteoblasts resulting in bone formation, initially as woven bone before a hard callus is formed. [39, 40]

NSAID interference in bone healing has been postulated to be due to COX and BMPs inhibiting local release of prostaglandins (mainly PGE2) through the blockage of the COX enzyme. There is some suggestion that mechanical loading on bone can stimulate bone formation, which can be inhibited by NSAIDs. Conversely, prostaglandins have also been shown to stimulate cyclic AMP causing bone resorption through osteoclast stimulation. [38, 41]

The three randomised control trials included in this review provided their subjects (both animals and humans) with NSAIDs post operatively. Cai *et al*. (2015) conducted a randomised control trial on rabbits with a control (no pain relief), oral NSAID (Diclofenac Sodium) and subcutaneous selective COX-2 inhibitor (Parecoxib) groups. [32] Drug administration was only continued for one week post dental implant surgery with the rabbits from each group sacrificed at set time intervals (weeks four and twelve). All dental implants were titanium and none were loaded. No significant histological changes were observed in the implant bone interface. Alissa *et al*. (2009) conducted a double-blinded randomised control trial with (human) patients receiving NSAIDs (ibuprofen) and placebos post implant placement for a one week duration. [35] The implants were submerged and undistributed for a three to six month duration following which they were loaded with a prosthesis. This study radiographically measured marginal bone levels at three and six months (with respect to baseline at two weeks) and did not find any significant differences. In addition, implant

stability was manually checked for all cases. However, the authors did not differentiate patients who had their implants loaded when reporting on marginal bone levels.

A similar non-randomised study were conducted by Sakka and Hanuneh (2013) whereby patients were allocated to a NSAID (Ibuprofen) or non-NSAID group. Similarly, NSAID use were continued for one week. [34] Their study was similar to Alissa *et al*. (2009) where marginal bone levels were compared and no significant differences found at three monthly and six monthly intervals.

In vitro studies have shown an increased expression of COX-2 mRNA up to two weeks following a bony fracture. Hence, longer exposure to NSAIDs for its COX-2 inhibitory effect may be required to reduce osteoblast activity and record a measurable difference in osseointegration. [20]

Ribeiro *et al*. (2006) conducted a randomised control trial on rats that were divided into a control group (subcutaneous saline) and intervention group (subcutaneous NSAID - Meloxicam). [33] The use of saline or NSAIDs were continued for 60 days at which point the subjects were sacrificed. All dental implants were titanium and none were loaded. Histological analysis showed the NSAID group to have significantly reduced bone healing around the implants as defined through bone to implant contact and bone density. This study suggests that the long-term use of NSAIDs post-operatively could result in adverse bone healing however, caution must be exercised when interpreting these results. This is because, firstly, it is unlikely that any patient would continue pain relief for such a duration post-dental implant surgery, coupled with the mode of subcutaneous delivery. In addition, there are inherent challenges in translating the findings of animal-based studies into human applications.

The mode of delivery of NSAIDs will impact on its bioavailability, tissue concentration and efficacy in blocking the expression of the COX enzymes. The studies included in this review utilised oral and subcutaneous forms of NSAID delivery with the latter an uncommon route for human patients for post dental implant surgery pain relief. Differences in NSAID delivery methods created challenges in making direct comparisons of the studies included in this review.

There are limitations of this systematic review, notably the inclusion of animal studies and their subsequent generalisability with human physiology. In addition, it was not possible to conduct quantitative analysis because of the heterogeneity of the results with respect to differences in NSAID delivery methods, bone measurements, species and implant surgery techniques. Therefore, the conclusions of the included studies were not suitable for further analysis.

Conclusion

There is limited evidence exploring the relationship of NSAIDs and dental implant osseointegration and bone healing with the studies included in this review using different NSAIDs, delivery methods and different species. This systematic review determines that there is insufficient evidence to draw conclusions on the impact NSAIDs have on dental implant osseointegration and bone healing. There was a significant difference found with long term (60 days) NSAID use and bone healing following dental implant placement however more research is required to translate this to human findings with respective changes in dose and delivery. It would be interesting to observe dental implant success rates on patients who are on long-term NSAIDs for various medical conditions, such as patients taking prophylactic Aspirin for the prevention of cardiovascular disease. [42] Long-term

NSAID use may have a greater effect in reducing overall COX-2 expression, which could affect bone healing and osseointegration. This systematic review does not recommend any changes to current practice and clinicians may continue to recommend and prescribe NSAIDs to patients for post-operative pain relief following dental implant surgery.

Conflict of interests

The authors have no conflicts of interest or funding to declare for this article.

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Tables and Table Legends

Table 1 – Local and systemic patient risk factors for implant failure. [30, 43-46]

Table 2 – Summary of common NSAIDS, their acquisition and COX selectivity.

Table 3 – PICOS format which formed part of the search strategy.

Table 4 – Key words used for each database and search results.

Table 5 – Summary of the studies included in this review.

Table 6 – Cochrane risk of bias (RoB 2.0) assessment.

Local Factors	Systemic Factors
Periodontitis	Age
Premature/excessive loading	Smoking status
Unfavourable microbiome	Diabetes
Poor bone quality	Head and neck radiotherapy
	Hormone replacement therapy
	Medications such as bisphosphonates and anti-angiogenics

Table 1 – Local and systemic patient risk factors for implant failure. [30, 43-46]

NSAID	Acquisition	COX selectivity
Ibuprofen	Over the counter	COX-1 and COX-2
Naproxen	Over the counter	COX-1 and COX-2
Aspirin	Over the counter	COX-1 and COX-2
Mefenamic acid	Over the counter	COX-1 and COX-2
Diclofenac sodium	Prescription only	COX-1 and COX-2
Celecoxib	Prescription only	COX-2
Etoricoxib	Prescription only	COX-2

Table 2 – Summary of common NSAIDs, their acquisition and COX selectivity.

Population of interest	**Intervention**	**Comparison Intervention**	**Outcome**	**Study**
Any age, gender or species with dental implant surgery.	Use of NSAIDs for any specified duration pre, peri or post-operatively.	No NSAIDs used.	Primary criteria: Dental implant osseointegration and success. Success as defined by one of Smith and Zarb's (1989) [21] adapted key criteria: 1. The implant is immobile when clinically tested. 2. No radiographic evidence of any peri-implant radiolucency. 3. Mean vertical bone loss is less than 0.2mm annually after the first year of service. Quantitative bone analysis with no specified time point 4. No persistent pain, discomfort or	Randomised control trials.

			infection (attributed to the implant) 5. Implant design does not preclude placement of a crown or prosthesis with an appearance satisfactory to both patient and dentist.	
			Secondary criteria: Post-operative complications: implant failure, delayed healing.	

Table 3 – PICO format which formed part of the search strategy.

Number	Searches	Results
1	Dental implants	34353
2	Implant surgery	5734
3	1 or 2	38979
4	Non steroidal anti inflammatory drugs	24088
5	NSAIDS	47655
6	Cyclooxygenase	131497
7	COX	338392
8	4 or 5 or 6 or 7	452818
9	Osseointegration	18487
10	Healing	425823
11	Success	543474
12	9 or 10 or 11	970727
13	3 and 8 and 12	99

Table 4 – Key words used for each database and search results.

Study	Study Design	Patient Details (Species, age, sex)	Number of participants	Participant Distribution	Intervention Details	Follow up	Outcomes Assessed	Key Results
Cai *et al.* (2015) [32]	Randomised control trial.	Rabbits, 6-9 months old, sex not specified.	18	Randomised into three groups: 1. Control group with no post-operative pain relief. 2. Group with Diclofenac Sodium 2mg/kg/day orally. 3. Group with	All rabbits underwent insertion of a dental implant into the calavarial bone. Post-operative pain relief was continued for	At weeks 4 and 12 post surgery, three rabbits from each of the groups were sacrificed.	Micro-CT analysis to investigate bone volume ratio, trabecular thickness, mean trabecular number and separation. Histomorphometric analysis to quantitatively assess the	Micro-CT analysis: no significant differences found. Histomorphometric analysis: no significant differences found.

				Parecoxib 1.5mg/kg/day subcutaneously injected.	one week.		percentage of bone to implant contact.	
Ribeiro *et al*. (2006) [33]	Randomised control trial.	Rats, 10 weeks of age, sex not specified .	31	Randomised into two groups: 1. Administration of subcutaneous 1ml/kg of saline solution for 60 days. 2. Administration of subcutaneous 3mg/kg of	Dental implants were inserted into the tibiae of all rats. Continuation of anti-inflammatory or saline medicaments	All rats were sacrificed at 60 days.	Histological analysis to determine bone to implant contact, bone area and bone density for both cortical and cancellous bony regions.	Meloxicam significantly reduced bone healing arounds implants. This included bone to implant contact, bony area and bone density for cortical and cancellous bone.

				Meloxicam for 60 days.	until sacrifice.			
Alissa *et al*. (2009) [35]	Randomised control trial.	Humans, age range 17-87 years. 37 females and 24 males.	61	Patient randomly allocated to the Ibuprofen or placebo group (oral administration).	Dental implants placed in all patients. Ibuprofen or placebo were continued for one week post operatively.	Follow up at 2 weeks (baseline), 3 months and 6 months.	Radiographic examination to determine marginal bone levels at the 3 month and 6 month recall examinations.	There were no statistically significant differences between groups for marginal bone level changes at 3 months or 6 months compared to baseline.

Table 5 – Summary of the studies included in this review.

	Cai *et al*. (2015) [29]	Ribeiro *et al*. (2006) [30]	Alissa *et al*. (2009) [32]
The randomisation process	?	?	+
Deviations from intended interventions	+	+	+
Missing outcome data	+	+	+
Measurement of the outcome	+	+	+
Selection of the reported result	+	+	+
Overall risk of bias	?	?	+

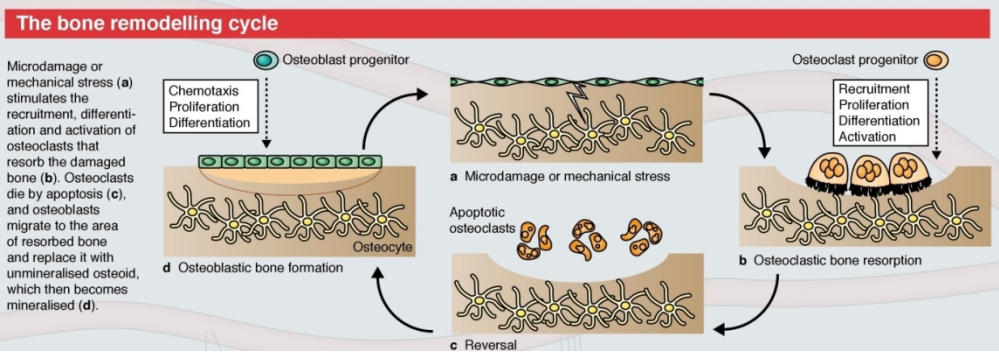
Table 6 – Cochrane risk of bias (RoB 2.0) assessment.

Figure Legends

Figure 1 – Summary of the cellular mechanism of bone remodelling during fracture injury. Adapted with permission from Journal of Cell Science (DOI: 10.1242/jcs.063032). [5]

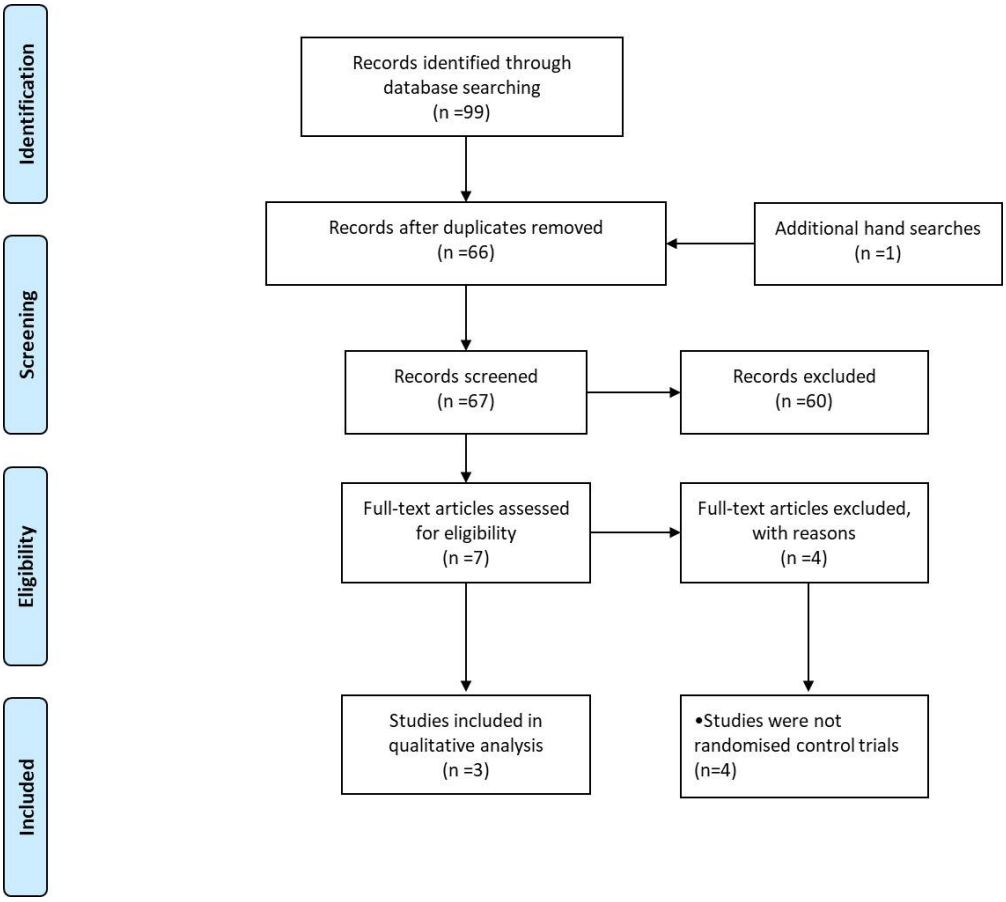
Figure 2 – PRISMA flow diagram showing the flow of studies through the review process.

Figure 3 – Overall risk of bias (assessed with the Cochrane RoB 2.0 tool) for randomised control trials included in this review.



Summary of the cellular mechanism of bone remodelling during fracture injury. Adapted with permission from Journal of Cell Science (DOI: 10.1242/jcs.063032). 5

159x55mm (220 x 220 DPI)



PRISMA flow diagram showing the flow of studies through the review process.

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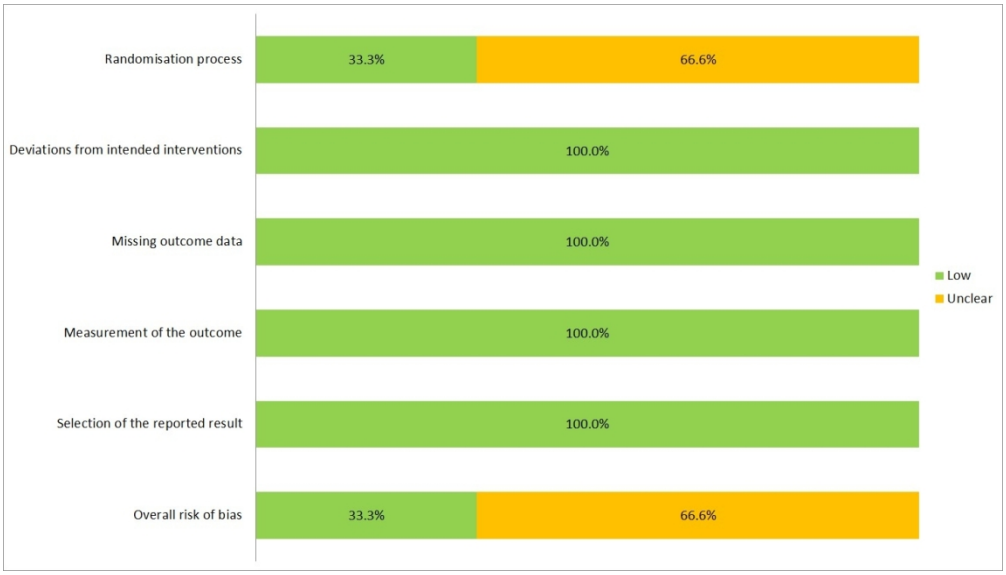

Overall risk of bias (assessed with the Cochrane RoB 2.0 tool) for randomised control trials included in this review.

387x219mm (96 x 96 DPI)