

## Comparison Of Autogenous Iliac Bone Grafting with PRP And Conventional Iliac Bone Grafting In Alveolar Bone Grafting - A Systematic Review

Research Article

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### Abstract

**Background:** Clefts of the lip, palate and alveolus are the most commonly seen congenital deformities which affect the maxillo-facial region. Efforts have been made to classify and repair, since the time of Veau (1931). Repair of cleft alveolus is an adjunctive procedure to further improve the functional and esthetic rehabilitation of patient with unilateral or bilateral cleft lip and palate, and to provide bone for eruption of the canine so that the canine teeth will erupt into the mouth with good bone support and remain healthy during the mixed dentition period.[1] Currently, the use of platelet rich plasma (PRP) in alveolar bone grafting procedures is of greater interest to enhance bone formation and specifically to enhance the bone healing.[2] Use of PRP is based on the theory that its platelets release statistically significant quantities of growth factors to facilitate the maturation of the bone graft. Also, PRP acts as a fibrin adhesive.[3] The adhesive property of PRP helps in haemostasis and flap adaptations. PRP also reduces the chances of infection, due to its acidic nature,. The chances of infection are further reduced, as PRP concentrates WBC's and platelets to cause early neovascularization, bring in circulating macrophages and neutrophils and create a more oxygen rich environment. The current concept of growth factor-aided tissue engineering with regard to reconstruction of the cleft alveolus is to use bone morphogenetic protein (BMP), transforming growth factor beta, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, vascular endothelial growth factor and PRP.[4] It is interesting to know that biphasic calcium phosphate (BCP) mixed with autologous bone has not been found to interfere with dental eruption or maxillary growth.[5] Closure of wide alveolar clefts using mid face distraction has been reported as an alternative treatment modality.[6] This systematic review is to compare the efficacy of alveolar bone reconstruction for alveolar cleft patients surgically treated with the traditional iliac graft and the iliac bone graft with PRP. Electronic databases, relevant journals, and reference lists of the included studies were searched till the end of OCT 2019 with an aim to evaluate the efficacy of PRP for secondary alveolar bone graft procedure.

**Objectives:** The objective of this systematic review is to analyze the comparison of autogenous iliac bone grafting with PRP and conventional iliac bone graft in alveolar bone grafting.

**Data Sources:** The Data Bases of PubMed, Cochrane and Google scholar were searched for the related topics along with a complimentary manual search of all oral surgery journals till October 2019. Articles were selected based on the inclusion criteria, which included all RCTs.

**Results:** From this study we conclude that PRP in addition to autogenous iliac bone graft is effective in early bone formation and reduction in bone resorption rate.

**Conclusion:** The addition of PRP to autogenous iliac bone grafts helps in early bone formation, reduces postoperative bone resorption, PRP may preserve the width, height of the graft, low infection rate and least post operative complications that makes autogenous cancellous bone grafting with PRP useful for alveolar bone grafting in cleft patients.

### Introduction

Clefts of the lip, palate and alveolus are the most commonly seen congenital deformities which affect the maxillofacial region. Efforts have been made to classify and repair, since the time of Veau (1931)[1] alveolar bone grafting has become accepted as a means

of uniting and stabilizing the segments of the maxilla prior to definitive orthodontic and restorative dental treatment [7].

In some cleft patients, the bone defect is due to the width between the maxillary segments, or as a result of bone resorption [8-10]. A method for reducing bone resorption in alveolar cleft

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**Received:** May 04, 2021

**Accepted:** July 09, 2021

**Published:** July 19, 2021

**Citation:** Ashutosh Deshpande, Hemavathy OR, Sneha Krishnan. Comparison Of Autogenous Iliac Bone Grafting with PRP And Conventional Iliac Bone Grafting In Alveolar Bone Grafting - A Systematic Review. *Int J Dentistry Oral Sci.* 2021;8(7):3323-3329. doi: <http://dx.doi.org/10.19070/2377-8075-21000677>

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bone grafting has been used for some time. In 1998, platelet-rich plasma (PRP) was reported to promote new bone formation in mandibular continuity defects and to cause faster maturation of autologous bone grafts.[11] Also, PRP acts as a fibrin adhesive.3 The adhesive property of PRP helps in haemostasis and flap adaptations. PRP also reduces the chances of infection, due to its acidic nature. The chances of infection are further reduced, as PRP concentrates WBC's and platelets to cause early neovascularization, bring in circulating macrophages and neutrophils and create a more oxygen rich environment. The current concept of growth factor-aided tissue engineering with regard to reconstruction of the cleft alveolus is to use bone morphogenetic protein (BMP), transforming growth factor beta, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, vascular endothelial growth factor and PRP.[4]

It is interesting to know that biphasic calcium phosphate (BCP) mixed with autologous bone does not interfere with dental eruption or maxillary growth.[5] Closure of wide alveolar clefts using mid face distraction has been reported as an alternative treatment modality.[6]

This systematic review is to compare the efficacy of alveolar bone reconstruction for alveolar cleft patients performed with the traditional iliac graft and the iliac bone graft with PRP. Electronic databases, relevant journals, and reference lists of the included studies were searched to the end of OCT 2019 with an aim to evaluate the efficacy of PRP for secondary alveolar bone graft procedure.

## Aim

The aim of this systematic review was to analyse the existing literature to assess the efficacy autogenous iliac bone graft with PRP in comparison to iliac bone graft alone in case of alveolar bone grafting.

## Structured Question

Does PRP in combination with autogenous iliac bone graft enhance the bone regeneration in comparison with iliac bone graft alone?

## PICO Analysis

Population: Patients undergoing alveolar grafting surgery  
Intervention: PRP in combination with autogenous iliac bone graft.  
Comparison: Conventional iliac bone graft.  
Outcome: Quantitative bone regeneration.

## Materials And Methods

### Inclusion Criteria

Criteria for considering studies for the Review -

Types of studies -

- Randomized controlled trials
- Clinical trials.

- Longitudinal studies

### Types of Participants –

- Patients undergoing Alveolar bone grafting surgery

### Types of Intervention

- PRP with autogenous bone graft in alveolar bone grafting surgery

### Types of Comparison

- Conventional autogenous bone graft alone.

### Types of Outcome Measures

- Quantitative Bone formation assessed on the basis of CT or CBCT or Computer Aided Engineering evaluation.

### Exclusion Criteria

The following studies were excluded,

- Review articles
- Animal studies
- Invitro studies
- Studies not meeting inclusion criteria
- Languages other than English

### Sources Used

The Data Bases of PubMed, Cochrane and Google scholar were searched for the related topics.

We used free-text terms to search the following journals”

- British Journal of Oral and Maxillofacial Surgery.
- International Journal of Oral and Maxillofacial Surgery.
- Journal of Oral and Maxillofacial Surgery.
- Journal of Cranio Maxillofacial Surgery.

Only articles in English and human species were applied during the electronic search to include all the possible clinical trials that are relevant for the search phase of the systematic review. Reference list of the identified randomized trials were also checked for possible additional studies.

### Search Flow Chart

Flow Chart

## Data Collection And Analysis

### Screening and Selection

Electronic search was carried out using the keywords in the Search engines- PubMed, Cochrane and manual search which yielded a total of 5 articles. Based on pre-set inclusion and exclusion criteria, the titles of the studies identified from the search were assessed independently by two review authors (Dr. Ashu-

tosh Deshpande, Dr.Hemavathy .O R) Conflicts concerning inclusion of the studies were resolved by discussion. Seventy three articles were excluded after reading titles. Two titles were identified from the search after excluding Four duplication. Abstracts of selected articles were reviewed independently. No articles were excluded after reading abstract. Full text articles were retrieved for two relevant studies.

The reference list of the full text articles were reviewed for identifying additional studies. Titles of articles relevant to the review were selected by discussion. Quality Assessment criteria to evaluate the studies were decided by two review authors in accordance with CONSORT guidelines. The risk of bias for each study was independently assessed by the review authors and conflicts concerning risk of bias were sorted by discussion.

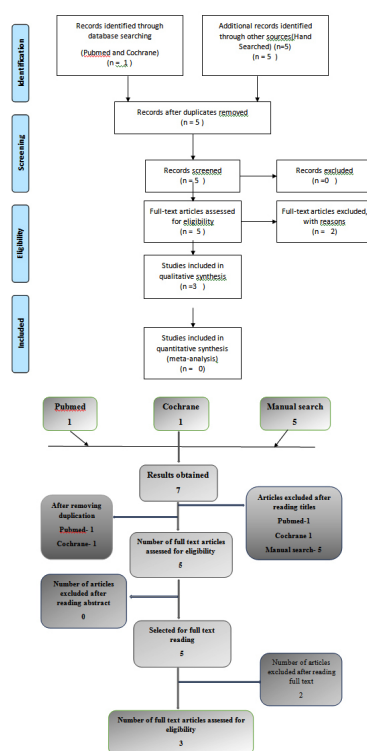
**Data Extraction**

Data extraction for general characteristics of studies and variables of outcome was done.

For each trial the following data were recorded:

- Author and Journal
- Study Design
- Sample Size
- Participants and Group
- Methodology
- Outcome measures
- Results
- Conclusion

**PRISMA Flow Diagram.**



**Table 1. Variables Of Interest.**

S.No	VARIABLES OF INTEREST
1	Quantitative evaluation of bone formation

**Table 2. General Characteristics Of The Studies.**

S.No	Author	Year	Study design	Sample size	Age	Technique Used	Method of Evaluation
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki Oyama et al	2004	Randomized controlled trial	N=12	16-18 yrs	One group receiving PRP with iliac bone graft and another iliac bone graft alone	Quantitative bone formation was evaluated by CT evaluation
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al	2013	Randomized controlled trial	N= 20	9-29yrs	One group receiving PRP with iliac bone graft and another iliac bone graft alone	Quantitative bone formation was evaluated by cbct evaluation
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al	2016	Randomised double blinded clinical study	N=29	7-9yrs	One group receiving PRP with iliac bone graft and another iliac bone graft alone	Quantitative bone formation was evaluated by computer-aided engineering.

**Table 3. Data Extraction Table.**

Sr.No	Author and year	Technique used	Method of evaluation	Statistics	Outcomes
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki Oyama et al, 2004	Alveolar bone grafting using iliac bone graft with and without PRP	Quantitative bone formation was evaluated by CT evaluation	The ratio of volume of alveolar cleft to volume of regenerated bone was PRP:80.19% ± 6.77% [SD] Non- PRP: 63.67% ± 13.94% [SD]	PRP was a safe and cost-effective source for growth factors and was easy to extract. It could enhance the osteogenesis of alveolar bone grafting in cleft lip and palate patients and may useful for subsequent orthodontic therapy
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al, 2013	Alveolar bone grafting using iliac bone graft with and without PRP	Quantitative bone formation was evaluated by cbct evaluation	The mean bone density after 6 months PRP :1028.00 _ 11.30 HU Non PRP: 859.50_27.73HU	A statistically significant improvement in the density was found.
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al, 2016	Alveolar bone grafting using iliac bone graft with and without PRP	Quantitative bone formation was evaluated by computer-aided engineering.	The mean volume of bone formation @ 1year PRP: 0.55_0.44 Non PRP: 0.59_0.28 cm3,	No significant difference was found

**Table 4. Evidence Level Of Selected Articles.**

SI No	Author and year	Study design	Level of Evidence
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki Oyama et al, 2004	Randomized controlled trial	1
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al, 2013	Randomized controlled trial	1
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al, 2016	Randomized controlled trial	1

**Table 5. Risk Of Bias- Major Criteria.**

S.No	Study	Randomization	Allocation concealment	Assessor Blinded	Drop outs described	Risk of Bias
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki Oyama et al, 2004	yes	Yes	Yes	None	Moderate
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al, 2013	Yes	yes	Yes	None	Low
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al, 2016	Yes	yes	yes	None	Low

**Table 6. Risk Of Bias-Minor Criteria.**

S.No	STUDY	SAMPLE JUSTIFIED	BASELINE COMPARISON	I/E CRITERIA	METHOD OF ERROR
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki Oyama et al, 2004	Yes	Yes	Yes	No
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al, 2013	Yes	Yes	Yes	No
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al, 2016	Yes	Yes	Yes	No

Table 7. Summation Table For Individual Parameter.

S.No	Author	Year	Evaluation period	Outcome
1	Efficacy of Platelet-Rich Plasma in Alveolar Bone Grafting by Tomoki	2004	1 month, 6 months	There was significant difference between two groups, results are in favour of PRP group
2	Alveolar bone graft with Platelet Rich Plasma in cleft alveolus by Chandan Gupta et al, 2013	2013	1 month, 3 months, 6 months	There was significant difference between two groups, results are in favour of PRP group
3	Effect of Platelet-Rich Plasma on Bone Grafting of Alveolar Clefts by Reiko Sakio et al, 2016	2016	1 month, 12 months	No statistically significant difference

## Quality Assessment

(Higgins and Green. Cochrane reviewer's hand book 2009)

The quality assessment of included trials was undertaken independently as a part of data extraction process. Four main quality criteria were examined.

### 1. Method of Randomization, recorded as

- YES- Adequate as described in the text
- NO- Inadequate as described in the text
- Unclear in the text

### 2. Allocation Concealment, recorded as

- YES- Adequate as described in the text
- NO- Inadequate as described in the text
- Unclear in the text

### 3. Outcome assessors Blinded to intervention, recorded as

- YES- Adequate as described in the text
- NO- Inadequate as described in the text
- Unclear in the text

### 4. Completeness of Follow up (was there a clear explanation for withdrawals and dropouts in each treatment group) assessed as

- YES- Dropouts were explained
- NO- Dropouts were not explained
- None- No Dropouts or withdrawals.

Other methodological criteria examined included:

- Presence or Absence of sample size calculation.
- Comparability of Groups at the start.
- Clear Inclusion or Exclusion criteria.
- Presence or Absence of estimate of measurement error.

## Risk Of Bias In Included Studies

The study was assessed to have a "High risk" of bias if it did not record a "Yes" in three or more of the four main categories, "Moderate Risk" if two out of four categories did not record a "Yes", and "Low Risk" if all the four categories recorded if randomization assessor, Blinding and Completeness of follow up were considered Adequate. In case of non-randomized and clinical trials without control group, it is recorded as not applicable.

## Results

Tables.

## Discussion

Alveolar bone grafting is a definitive treatment in case of Alveolar clefts. It may not only bring about eruption of the tooth but also plays an important role in stabilizing the maxillary arch. Also provides the bone for the dental implants in patients with missing teeth.[12-15] Iliac cancellous bone is the graft of choice, because it is easy to harvest and provides sufficient amount of bone required for alveolar bone grafting and shows better osteoinduction as compared to other grafts. However, partial absorption and shortage of reconstructed alveolar height or width may develop postoperatively in case of conventional iliac graft.

It is believed that PRP has osteogenic growth potential and could promote the formation of bone in alveolar bone grafting, reduce resorption of graft in cleft lip and palate patients, and may be useful for further orthodontic treatment. It is said that PRP might enhance the osteogenesis of autologous bone and lessen postoperative bone resorption.[15]

According to Oyama et al, 2004, PRP might increase the osteogenic potential of autologous bone and reduces the postoperative resorption of the bone. In this study, Seven patients in tertiary stage, were grafted with PRP, acquired a markedly high capacity rate of regenerated bone, which was significantly different from controls. Schmitz and Hollinger [16] doubt the effects of PRP because platelet-derived growth factor is inhibitory to osteoblastic cells if delivered in a continuous form and increases bone resorption. In this study, PRP could enhance the bone formation more than the bone resorption in a phase of bone remodeling within 6 months postoperatively. However, it is not known for how long (>6months) PRP exerts an influence on the bone volume in this study. Without functional stress in the graft, atrophic bone resorption would occur in the long term.[17]

Marx et al [11] reported successful results of the mandibular segment reconstruction with PRP.

In that article bone density was measured with the help of x-ray films and a quantitative analysis was done. Oyama et al, have measured the volume of regenerated bone (VRB) with 3D CT. However, in his study, they have not assessed the bone density. A standard method of alveolar bone grafting evaluation has not been established as yet which includes both qualitative and quantitative evaluation. According to Oyama et al, the biologically appropriate concentration of growth factors involved in PRP is still

unknown.

In the study by C. Gupta et al, 2013, 20 patients with alveolar cleft, in the age group of 8 to 30 years, with unilateral or bilateral cleft lip and palate were selected for the study. The patients were randomly divided into two groups, the test group A (10 patients) received cancellous bone graft from the anterior iliac crest mixed with PRP, while the control group B (10 patients) received the same without PRP. Alveolar bone grafting was performed under GA using standard surgical methodology for secondary alveolar bone grafting. Bone density of the grafted bone was assessed with Dentascan, using pixel tools image analyzer software, at regular postoperative follow up of 1, 3 and 6 months.

PRP primarily has acidic pH (6.5 to 6.7) inhibits bacterial colony growth. Secondly, PRP concentrates WBCs and platelets to cause bacterial inhibition by greater number of functionally viable leucocytes. Thirdly, rapid development of granulation tissue by early in-growth of capillaries prevents bacterial growth by bringing in circulating macrophages and neutrophils. Thus, creating an oxygen rich environment suppresses the growth of anaerobic micro-organisms. In our study, bone chips were harvested from the anterior iliac crest using trephine method and none of the patients reported any complications. Bone graft studies using autogenous marrow from the ilium have shown capillary in-growth within 5 to 6 days without PRP versus 3 days with PRP and complete revascularization by 20 days without PRP versus 14 days with PRP.

Studies by Marx [11] provide evidence that PRP added to ground bone graft obtained from posterior iliac crest showed increase in the rate of bone formation. Results suggest that growth factors are helpful in accelerating and intensifying regeneration of the alveolar bone. Luaces-Rey [21] found no significant differences between both therapeutic groups on bone regeneration based on digital orthopantomogram, 1 to 6 months after surgery. It has been reported that there is increase in bone mineral density grafts combined with PRP ranging from 1.6 to 2.2 times that of a grafts without PRP, as seen in our study. However, Lee [22] suggested that PRP may cause increase in the bone remodeling in the initial phase, it seems to be insufficient as a counter measure against bone resorption following secondary bone graft in the long term. Macisaac used supplemental demineralized bone matrix and allograft, and observed complete canine eruption in 71.4%, partial in 21.4, and unerupted in 3.5% [23].

The limitation of this study was a short follow up of 6 months, hence only the early results could be compared.

In a study by Sakio et al, 2016, they analyzed the regeneration of the bone using computer aided engineering by 3D CT. In this study they have assumed that the osteogenic activity of the autologous bone graft increases with the help of PRP and there is reduction in post operative bone resorption; However, But there results of the quantitative analysis of the graft sites show that the mean remaining bone was no significant difference between with and without PRP groups at 1 year after surgery.

Recent meta-analysis literatures described about the effect of PRP based on human studies was said that there was a scientific evidence regarding favorable outcomes of the use of PRP for the treatment of diabetic ulcer.[25]; However, tendon healing and

bone graft for cleft lip and palate was inconclusive of the effect of PRP for the maxillary sinus lift [26-28].

Osteoprotegerin which is a soluble receptor secreted by many cell types including osteoblasts. This factor is an inhibitory factor for the osteoclastogenesis[24]. To consider about the osteoregeneration, new bone formation at bone resorption sites in each cycle of bone remodeling to maintain the micro-architecture required for bone's mechanical properties. The platelet-derived growth factor causes stimulation of osteoprotegerin which is an inhibitor of osteoclast and produced in osteoblastic cells. It seems that inhibition of osteoclast will inhibit the resorption of the bone. TGFb-1 is activated in response to osteoclastic bone resorption. [29] But the osteoclast is inhibited by the osteoprotegerin. So not only the bone resorption does not occur but also the TGFb-1 cannot be activated. This can be one reason that the remaining bone ratio was not significant in both the groups. One of the important technologies is to achieve the controlled release of growth factors at the necessary site for clinical applications of growth factors present in PRP. In an animal study it was stated that gelatin hydrogel is needed to achieve the controlled release of bioactive factors from PRP;[30] However, can not be applied clinically.

PRP gel provides both valuable growth factors and haemostatic adhesion to the wound, which does not enhance the healing process by the postoperative bone resorption directly, but minor wound dehiscence which influenced the bone infections and resorption could be closed early. This indirectly results into prevention of the bone resorption. The biological mechanism of the PRP is still unknown[16] and more studies have to be conducted.

### Interpretation Of Results

In the study conducted by Oyama et al,2004, of bonegrafting added with PRP, the minimum percentage of VRB/VAC was 71.27% (patient 6) and the maximum was 87.32% (patient 2) (average, 80.19%  $\pm$  6.77%[SD]). In control group the minimum percentage of VRB/VAC was 47.47% (patient 9) and the maximum was 77.97%(patient 10) (average, 63.67% - 13.94% [SD]). Mann-Whitney U test revealed statistical significance (P-.05) between the groups of PRP patients and controls. There was no correlation between Volume of Alveolar Cleft (VAC) and Volume of Regenerated Bone (VRB) in either group. Therefore, even if the cleft was wide, the result was not necessarily poor in this study.

In the study by C Gupta Primary healing using PRP in our study was similar to other reported studies [11-13]. Although, the rate of graft rejection was more in group B than A, the difference was not statistically significant.

Primary healing using PRP in this study was similar to other reported studies [11-13] Although, the rate of graft rejection was more in group B than A, the difference was not statistically significant.

In the study conducted by Sakio et al, 2016 out of the 29 patients, 26 (control group: 4; PRP group: 22) had an uneventful course postoperatively. In the 3 remaining patients (control group: 2; PRP group: 1), wound dehiscence developed with minor bone exposure. However, these exposures closed during the follow-up period. No other complications were observed. One year postoperatively, the canine was exposed and orthodontically guided into

an ideal arch relation. The concentrations of platelets of each PRP preparation and whole blood were 262.5\_48.5(\_103/mL) and 1514\_507(\_103/mL), respectively. The concentration ratio was ranged from 1.60 to 9.77 and the meaning 5.9\_1.8. One month postoperative bone volume with or without PRP were 1.00\_0.53 and 1.29\_0.33 cm<sup>3</sup>, respectively (P¼0.13). And 1 year postoperative bone volume with or without PRP were 0.55\_0.44 and 0.59\_0.28 cm<sup>3</sup>, respectively (P¼0.26) (Fig. 4). The mean resorption ratio was 49.9\_17.2% and 44.9\_14.4% with no significant difference (P¼0.60). The correlation coefficients between the PRP concentrations and resorption ratio demonstrated a weak correlation of 0.35 (P¼0.08).

## Summary

The aim of this systematic review is to assess the efficacy PRP added with the autogenous iliac bone graft in comparison with iliac graft alone. Two randomized controlled trials and one longitudinal study were included in this review. All studies have compared the iliac graft with PRP and without PRP and the quantitative bone formation was evaluated with the help of CT scans CBCT and Computer Aided Engineering.

Studies by Oyama et al, 2004 and C. Gupta et al, 2011 have found a significant difference in the PRP group and the control group; However, Sakio et al, 2016 did not find significant difference in both the groups.

More studies have to be conducted to get the significant results.

## Conclusion

In this systematic review after reviewing 3 articles we have concluded that, the addition of PRP to autogenous iliac bone grafts appears to significantly leads to early bone formation, reduce postoperative bone resorption, preservation the width and height of the graft, low infection rate and least post operative complications which makes the autogenous cancellous bone grafting with PRP useful for alveolar bone grafting in cleft patients.

However, studies with more sample size should be carried out. A standard method should be developed for the evaluation of the bone regeneration.

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