



Lateral Window Maxillary Sinus Augmentation Adding rhBMP-2 without an Absorbable Collagen Sponge: A Case Report

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Abstract:	<p>Recently, biologic agents have been added to bone graft materials in sinus augmentation surgeries to accelerate the rate of regeneration. One such agent is recombinant human bone morphogenetic protein-2 (rhBMP-2) using an acellular collagen sponge (ACS) as a carrier. Researchers have previously shown that not only can rhBMP-2 be successfully be added to an allograft, but that the amount of ACS used is directly related to an increase in future graft shrinkage. However, the authors could not find any reports of adding rhBMP-2 to an allograft mixture without the use of any ACS. The objective of this case report was to provide histomorphometric analysis to assess whether rhBMP-2 could be added directly to an allograft mixture without the recommended ACS in an effort to reduce graft shrinkage while producing viable new bone. A patient presented requiring implants in the right posterior but maxillary sinus pneumatization and ridge resorption resulted in inadequate bone height. A sinus augmentation procedure was completed using the aforementioned technique; bone core biopsies were trephined at implant placement 6 months later and underwent histological analysis. The graft had regenerated as viable, mature, mineralized bone, implying it regenerated at an accelerated rate.</p> <p>This case study is the first report indicating that directly adding rhBMP-2 to an allograft mixture without the aid of an ACS carrier is a viable supplementation to a sinus augmentation procedure. However, long-term randomized controlled trials are needed for proper quantitative analysis and to determine its long-term predictability and efficacy.</p>

Lateral Window Maxillary Sinus Augmentation Adding rhBMP-2 without
an Absorbable Collagen Sponge: A Case Report

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Running title: Sinus Augmentation with rhBMP-2 and allograft

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3 **One sentence summary:** Directly adding rhBMP-2 to the mixture of human allografts is
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5 capable of promoting graft healing and producing high bone quality.
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8 **Word count:** 984
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14 **Tables and figures:** 0 tables and 17 figures
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20 Abstract
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22 Recently, biologic agents have been added to bone graft materials in sinus
23 augmentation surgeries to accelerate the rate of regeneration. One such agent is
24 recombinant human bone morphogenetic protein-2 (rhBMP-2) using an acellular
25 collagen sponge (ACS) as a carrier. Researchers have previously shown that not only
26 can rhBMP-2 be successfully be added to an allograft, but that the amount of ACS used
27 is directly related to an increase in future graft shrinkage. However, the authors could
28 not find any reports of adding rhBMP-2 to an allograft mixture without the use of any
29 ACS.
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32 The objective of this case report was to provide histomorphometric analysis to assess
33 whether rhBMP-2 could be added directly to an allograft mixture without the
34 recommended ACS in an effort to reduce graft shrinkage while producing viable new
35 bone. A patient presented requiring implants in the right posterior but maxillary sinus
36 pneumatization and ridge resorption resulted in inadequate bone height. A sinus
37 augmentation procedure was completed using the aforementioned technique; bone core
38 biopsies were trephined at implant placement 6 months later and underwent histological
39 analysis. The graft had regenerated as viable, mature, mineralized bone, implying it
40 regenerated at an accelerated rate.
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3 This case study is the first report indicating that directly adding rhBMP-2 to an allograft
4 mixture without the aid of an ACS carrier is a viable supplementation to a sinus
5 augmentation procedure. However, long-term randomized controlled trials are needed
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10 for proper quantitative analysis and to determine its long-term predictability and efficacy.
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14 **Keywords / MeSH terms:** Bone Morphogenic Protein 2, Bone Morphogenic

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16 Proteins/administration & dosage, Bone Morphogenic Proteins/pharmacology*, Maxillary
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18 Sinus/surgery*, Bone Regeneration/drug effects*, Humans, Collagen, Bone
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20 Transplantation/physiology*, Drug Carriers, Graft Survival.
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23 Background

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25 The restoration of the posterior maxilla can often be complicated by the maxillary sinus.
26
27 Accelerated bone resorption and sinus pneumatization following tooth loss may result in
28
29 insufficient native bone height to allow for the proper placement of an implant without
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31 compromising its length. Although the current success rates of implants placed in
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33 previously augmented maxillary sinuses is already high (90%¹ to 91.5%²), the addition of
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35 biologic agents with bone graft materials has been investigated.³⁻⁸
36
37 Bone Morphogenic Proteins (BMP's) belong to the transforming growth factor- β (TGF- β)
38
39 superfamily of growth factors and are osteoinductive.⁹ When added to sinus
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41 augmentation procedures, they have been shown not only to improve the quality of the
42
43 bone graft significantly, but also accelerate the healing process^{5, 10-12} in a dose-
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45 dependent manner.^{13, 14} Of concern, rhBMP-2 is FDA approved for use with an ACS.
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47 However, researchers have found a direct relationship between the number of sponges
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49 used and the degree of shrinkage of the graft material.⁵
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51 As such, we hoped to optimally reduce the degree of shrinkage by completely forgoing
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53 the use of an ACS and directly adding the rhBMP-2 solution to the allograft mixture. The
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3 following is a case report using this proposed technique in a lateral window maxillary
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5 sinus augmentation.
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9 10 Patient Presentation

11 The patient was a 63 year-old male who presented to restore the edentulous space in
12
13 his posterior upper right sextant. His medical history was significant for osteoarthritis in
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15 his hands and a systemic allergy to penicillin. His current medications were daily doses
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17 of: 20mg atorvastatin, 325mg aspirin, and 800mg ibuprofen. The patient was classified
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19 as ASA II.
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25 Relevant Dental History

26 At the initial appointment, the patient presented with a fixed partial denture #2 – #5 with
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28 #2, #4, and #5 serving as abutments and #5 connected through a semi-rigid connector.
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30 Tooth #2 had fractured 3mm subgingivally and was deemed non-restorable. The bridge
31
32 was sectioned distal to #4 and #2 was extracted with no complications; no ridge
33
34 preservation was performed at this time. The right sinus demonstrated significant
35
36 pneumatization and ridge resorption as demonstrated in the pre-treatment panoramic
37
38 radiograph (figure 1); in the area of #2–#3, mean ridge width was 9.6mm and mean
39
40 ridge height was 3.8mm.
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46 Surgery

47 Seven weeks following extraction, the patient was scheduled for surgery. On the day of
48
49 surgery, the patient took Azithromycin 500mg, Ibuprofen 800mg, and Pseudoephedrine
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51 180mg. Patient was placed under moderate intravenous sedation. Local anesthesia
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53 was achieved using 3 carpules of 2% lidocaine with 1:50,000 epinephrine for local
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55 infiltrations. A full-thickness flap was raised, and circular lateral window 10mm in
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3 diameter was created using highspeed electric and piezoelectric handpieces 3mm apical
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5 to the estimated floor of the right maxillary sinus. The Schneiderian membrane was
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7 elevated and an absorbable collagen membrane^δ was placed against it to: 1. protect the
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9 membrane during bone graft placement, 2. seal any membrane perforations that may
10
11 exist, and, 3. allow for better viewing for graft placement (figures 2 &3).

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16 A 4:1 ratio of mineralized human allograft^ε cortical (large particle 1-2mm): cancellous
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18 (small particle 250-850µm) mixture (figure 4) were hydrated with 1.05mg of recombinant
19
20 bone morphogenetic protein-2 (rhBMP-2)^φ mixed with 1ml sterile water. The bone graft
21
22 mixture was lightly packed into the sinus cavity (figure 5). Small-particle mineralized
23
24 cancellous allograft was used on the most lateral portion of the window to allow for
25
26 optimal healing (figure 6). An absorbable collagen membrane^δ was trimmed to cover
27
28 the outside window overlapping the edges by at least 2-3mm and was fixated under the
29
30 palatal flap (figures 7 & 8).

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36 Following surgery, the patient was prescribed Azithromycin 250mg 6 tablets, s.i.g 2# for
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38 the first day then 1# for the remaining 4 days, Ibuprofen 800mg dispense 20#/ s.i.g 1#
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40 q.i.d PRN pain, Dexamethasone 2mg dispense 9#/ s.i.g 4 tablets on first day, 2 tablets
41
42 on second and third days, and 1 tablet on fourth day, and Hydrocodone/Acetaminophen
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44 10/1000mg dispense 25#/ s.i.g 1# t.i.d PRN pain. Healing was uneventful and sutures
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51 ^δ BioMend collagen membrane, Zimmer Dental INC., Carlsbad, CA.

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53 ^ε Puros human allograft, Zimmer Dental INC., Carlsbad, CA

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55 ^φ Infuse[®], Medtronic, Memphis, TN.

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57 ^δ BioMend collagen membrane, Zimmer Dental INC., Carlsbad, CA.
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3 were removed 2 weeks later. Panoramic radiograph were taken at the 2-week and 4-
4
5 month post-operative visit (figures 9 & 10).
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8 9 10 Implant Placement

11 Six months following the sinus augmentation, implant surgery was performed under local
12 anesthesia. Flap was reflected showed good bone formation (figure 11). Trephine bone
13 core biopsies were collected (figure 12), and two implants^γ were placed at #2 and #3
14 (5.0x13mm and 4.3x13mm respectively) achieving excellent primary stability. The
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16 patient was placed on a similar regimen of Azithromycin and Ibuprofen as with the sinus
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18 augmentation surgery.
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27 Histological Analysis

28 Both core biopsies underwent histological analyses. Masson's Trichome method stains
29 demonstrated the maturation process of the graft (Figures 13 & 14). Immature osteoid is
30 stained red while mature mineralized bone is stained blue. As there is a significantly
31
32 greater proportion of mineralized bone, it can be inferred that the graft has undergone
33
34 accelerated regeneration and maturation. H&E staining (Figures 15 & 16) revealed
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36 osteocytes within lacunae of the mineralized bone, indicating the viability of the mature
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38 bone.
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47 Finalization of Treatment

48 Second stage surgery was performed after five months with sound stability of both implants. A
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50 subsequent 3 months later, splinted PFM crowns were cemented on #2 and #3,, a PFM
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52 crown was cemented on #4, and #5 was restored with a composite restoration. Final
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56 ^γ Nobel Biocare Replace Select® implants, Nobel Biocare USA.
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3 restoration and periapical radiographs 6 months after implant placement (figure 17; a, b,
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5 c & d)
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7 8 Conclusions

9
10 Comparing panoramic radiographs at 2 weeks and 6 months after the sinus
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12 augmentation procedure reveals minimal density change. Histological analysis showed
13
14 significant graft maturation. As such it appears as though adding rhBMP-2 directly to the
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16 allograft mixture is a viable method for maxillary sinus augmentations. However, long-
17
18 term randomized controlled trials are needed for proper quantitative analysis and to
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20 determine its long-term predictability.
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25 Summary

26 27 a) Why is this case new information?

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29 This is the first documented case demonstrating the addition of rhBMP-2 directly to an
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31 allograft mixture while foregoing the use of the ACS, especially with concurrent
32
33 histological analysis of the graft.
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36 b) What are the keys to successful management of this case?

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38 Patient case selection, surgical experience of the operator, avoiding any perforations of
39
40 the Schneiderian membrane during surgery, adequate graft isolation, and maintaining
41
42 primary closure post-operatively are the keys for the successful management of this
43
44 case.
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46 c) What are the primary limitations to success in this case?

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48 The primary limitation of this case report is the lack of a control to generalize the
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50 approach. To truly claim the graft regenerated at an accelerated rate due to the rhBMP-
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52 2, the biopsies would have been taken sooner.
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For Peer Review

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Figures Legend:

Figure 1: Pre-treatment panoramic radiograph showing right maxillary sinus pneumatization and ridge resorption.

Figure 2: Dimensions of the lateral window opening and measurement.

Figure 3: Collagen membrane was placed against Schneiderian membrane.

Figure 4: Adding rhBMP-2 to hydrate of 4:1 human cortical:cancellous allograft mixture

Figure 5: Placement of allograft/rhBMP-2 mixture into sinus cavity..

Figure 6: Placement of small-particle cancellous allograft to seal the lateral window to promote smooth healing.

Figure 7: Placement of the second absorbable collagen membrane to cover the window and protect the grafts placed.

Figure 8: Primary flap closure with adequate passivity was achieved using with 4.0 Vicryl sutures.

Figure 9: Panoramic radiograph at the 2-week post-operative visit.

Figure 10: Panoramic radiograph at 4-month post-operative visit demonstrating the graft maturation.

Figure 11: Flap was reflected and indicated good bone formation..

Figure 12: Bone core biopsy was obtained using 2.8mm diameter trephine.

Figure 13: Histological analysis using Masson's Trichome method stains depicting a greater proportion of mineralized bone (in blue) compared to immature osteoid (red).

Figure 14: Higher magnification (20x) of Masson's Trichome method shows mineralized bone (in blue) compared to immature osteoid (red).

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3 Figure 15: Histological analysis using H&E staining depicting viable osteocytes in newly formed
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5 bone.
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8 Figure 16: Higher magnification (20x) of H&E staining shows viable osteocytes in newly formed
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10 bone.
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12 Figure 17: Final restoration 6 months after implant placement.
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- 14 a. Buccal view with occlusion
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16 b. Occlusal view
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18 c. Buccal maxillary restoration view
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20 d. Final peri-apical radiograph after crown cementation.
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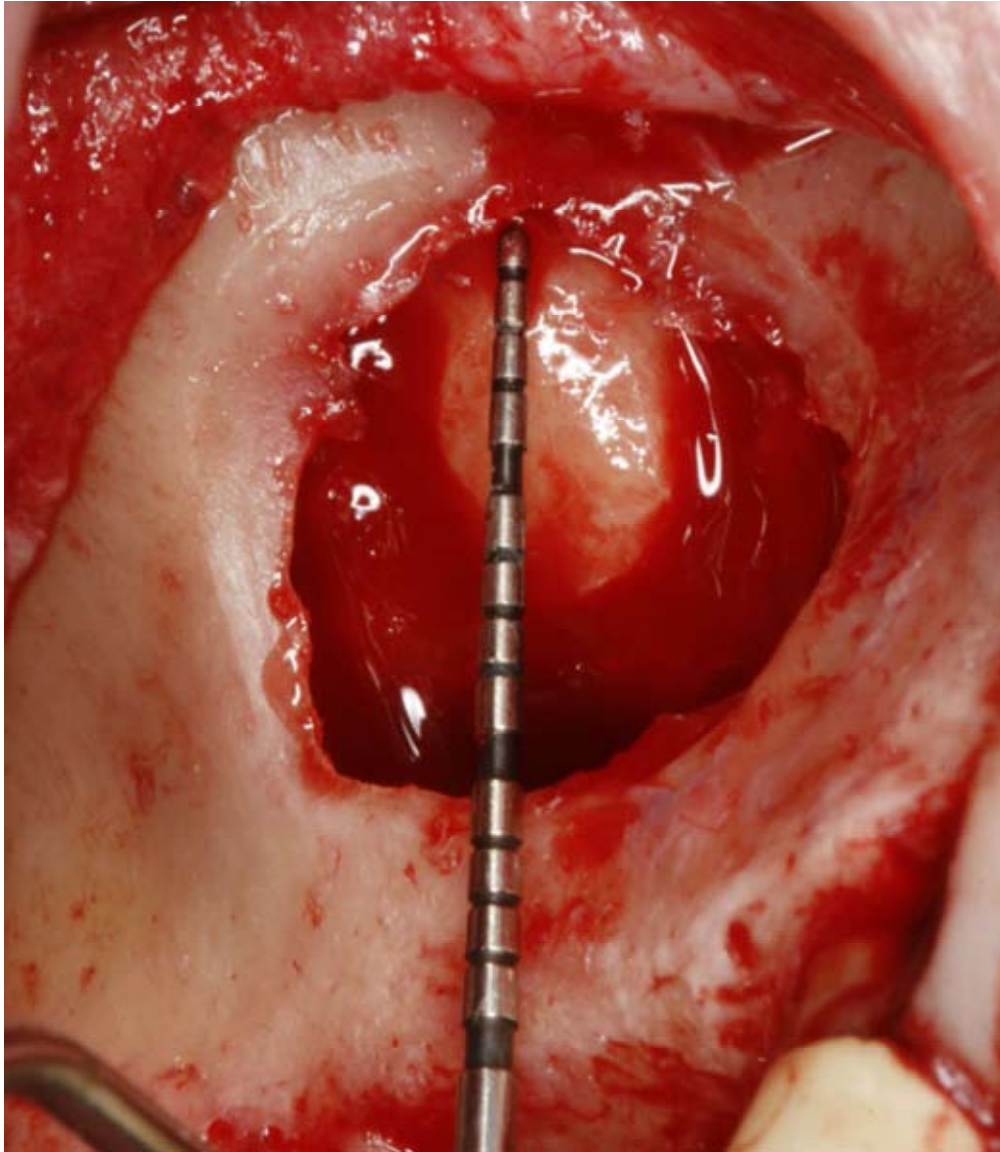
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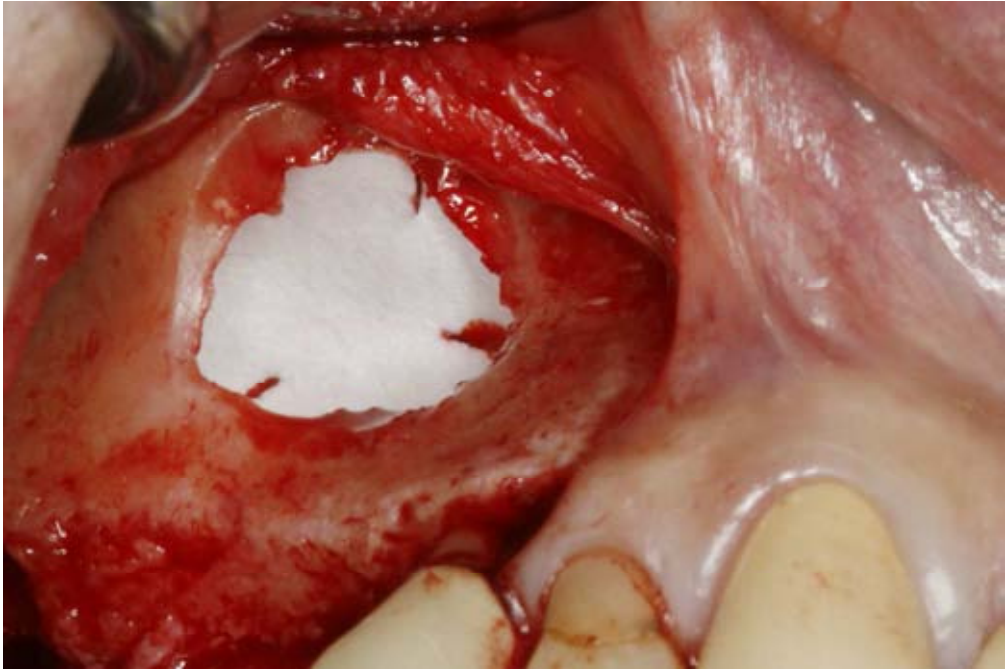
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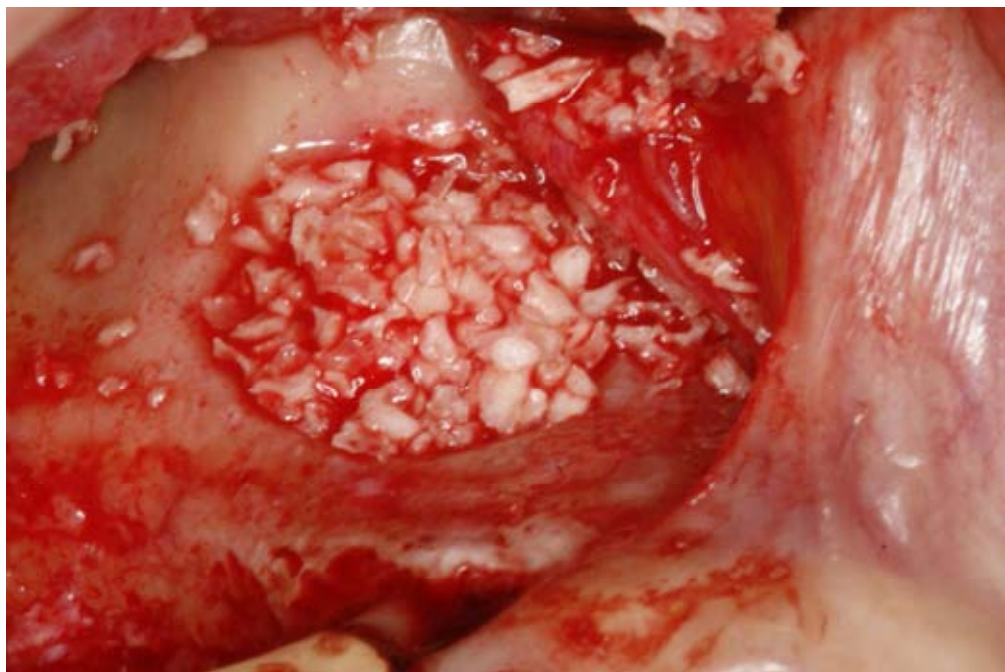
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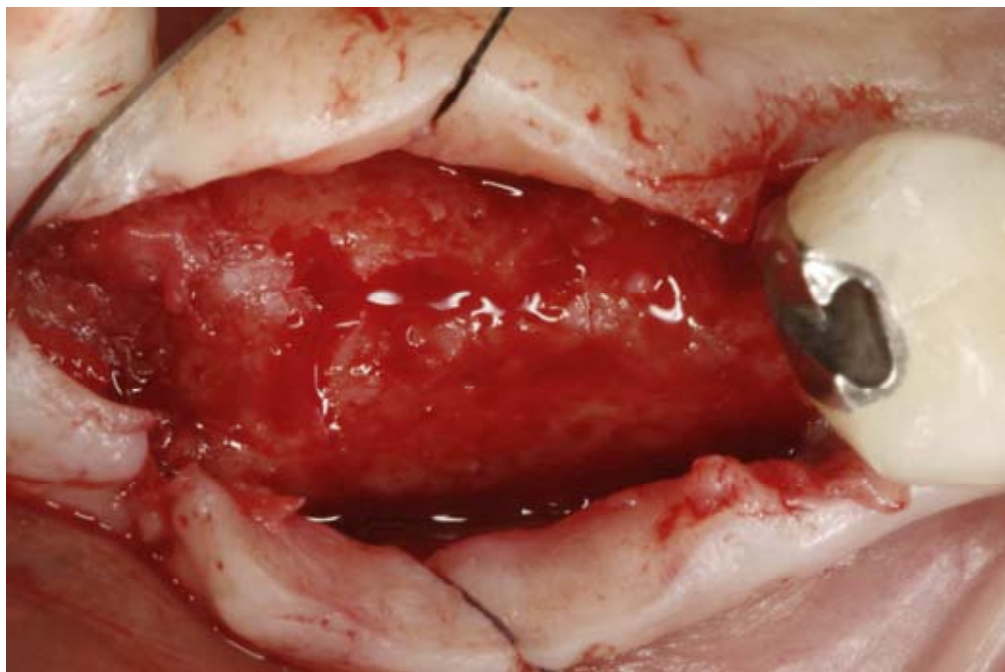
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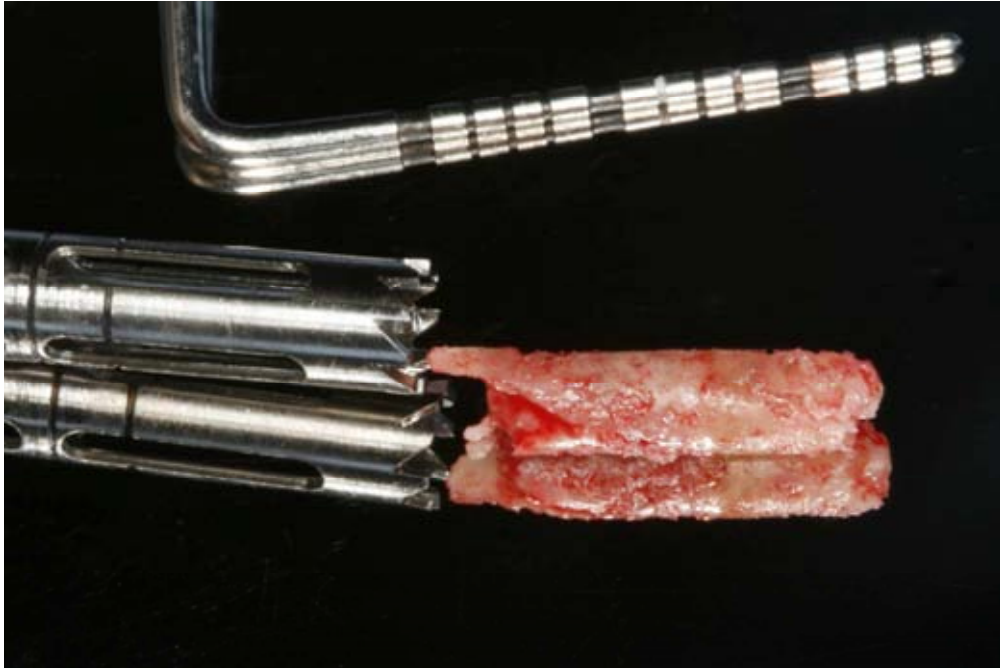
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304x203mm (100 x 100 DPI)

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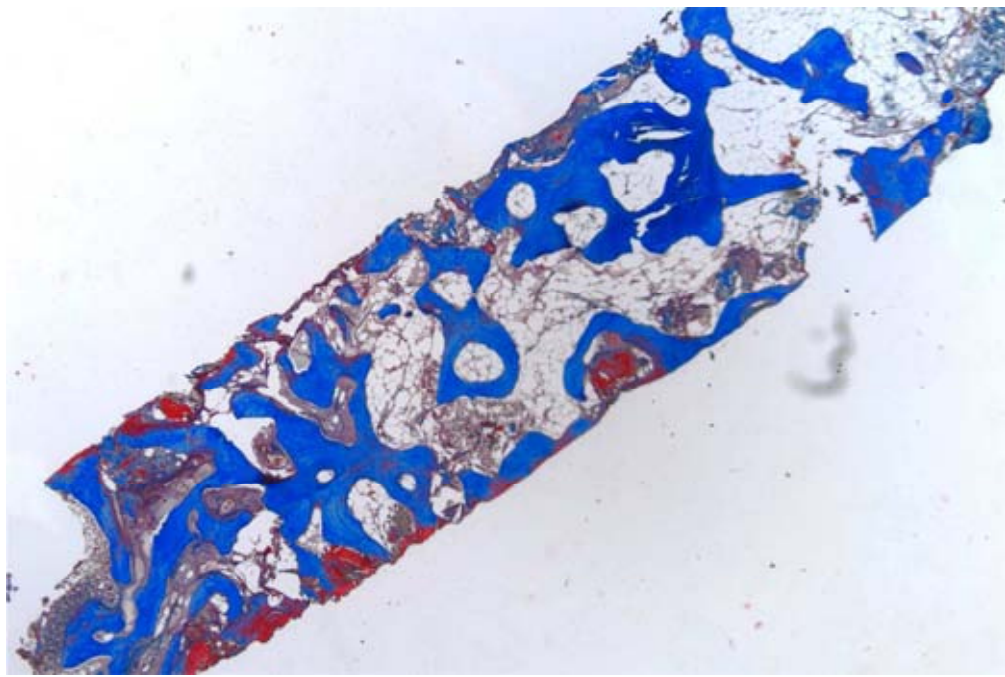
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304x203mm (100 x 100 DPI)

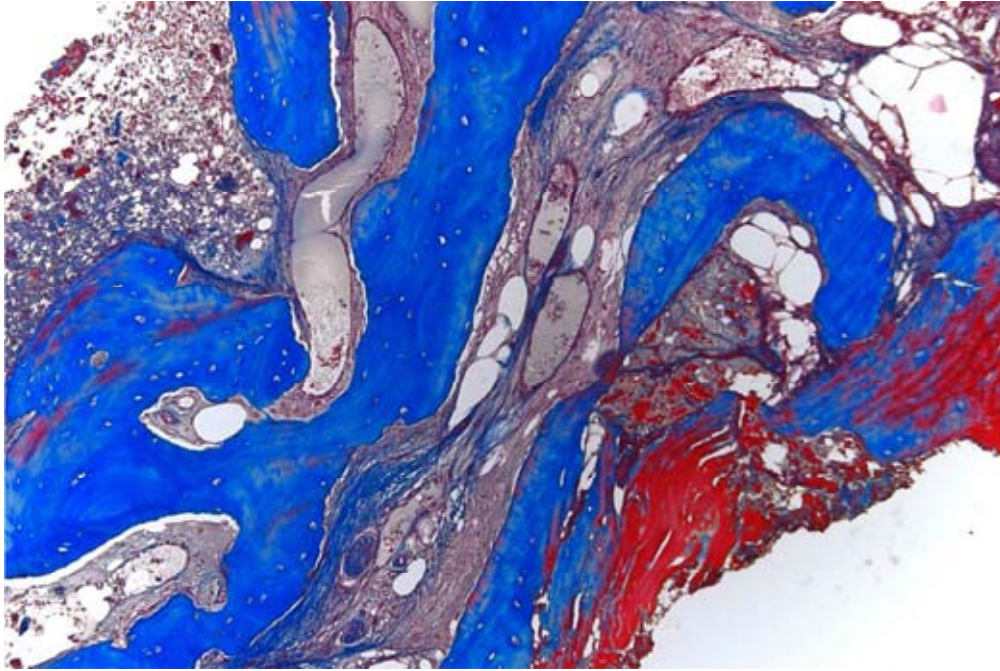
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203x135mm (150 x 150 DPI)

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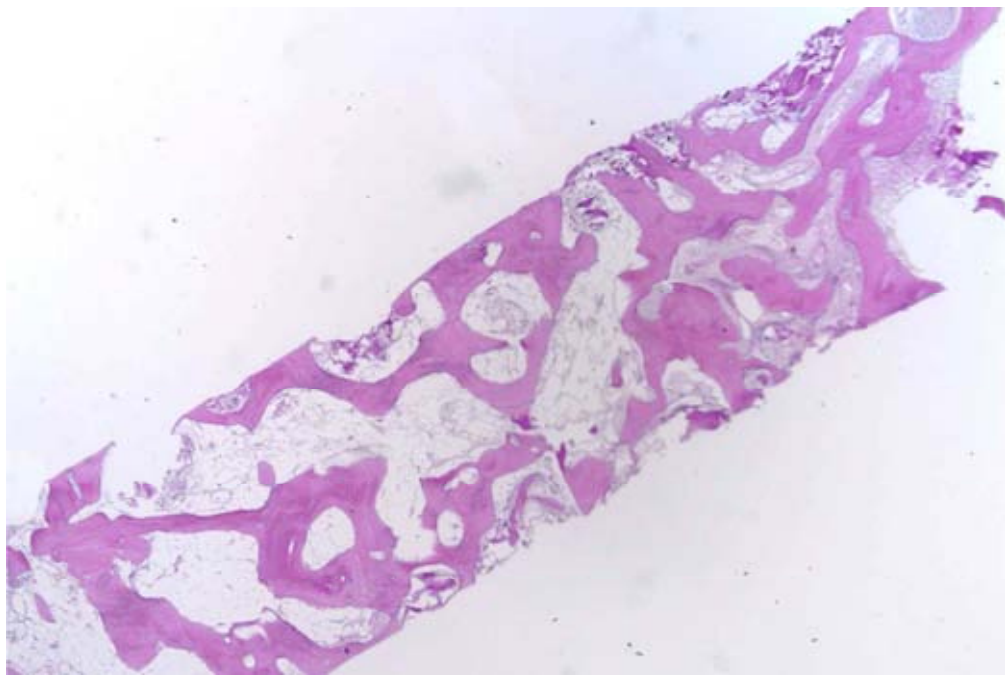


203x135mm (150 x 150 DPI)

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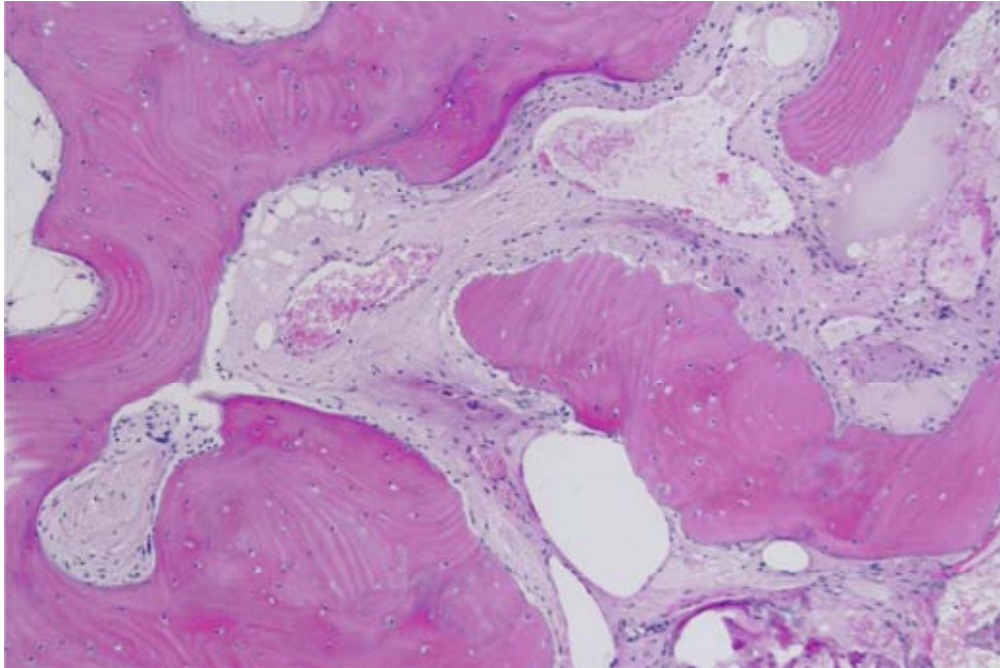
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203x135mm (150 x 150 DPI)

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203x135mm (150 x 150 DPI)

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304x203mm (100 x 100 DPI)

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304x203mm (100 x 100 DPI)

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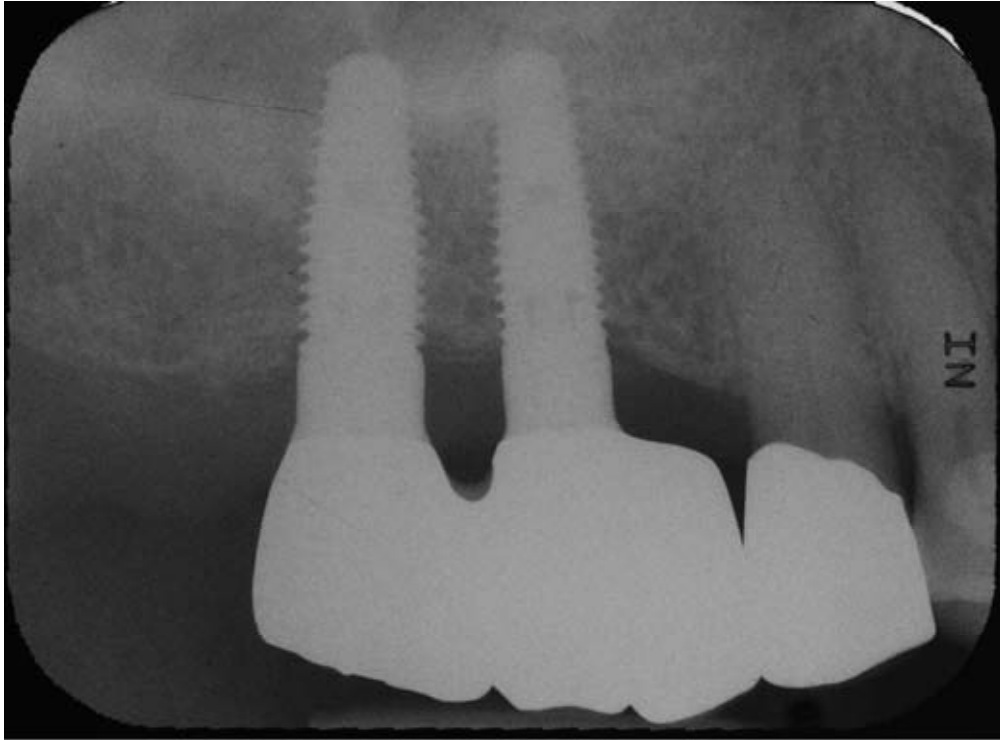
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304x203mm (100 x 100 DPI)

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423x312mm (72 x 72 DPI)

Review