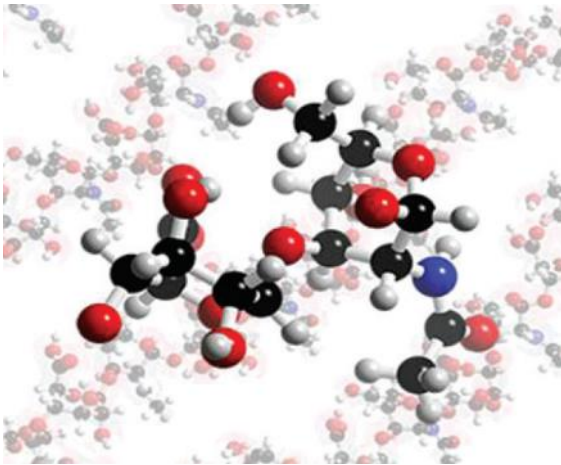


HYADENT BG

What is hyaluronic acid

Hyaluronic acid is an key element of the human body

- Extra cellular matrix is mainly composed of HA
- HA binds water and allows the transport key metabolites
- Active inhibition of the metalloproteinase and thus avoiding tissue degradation.

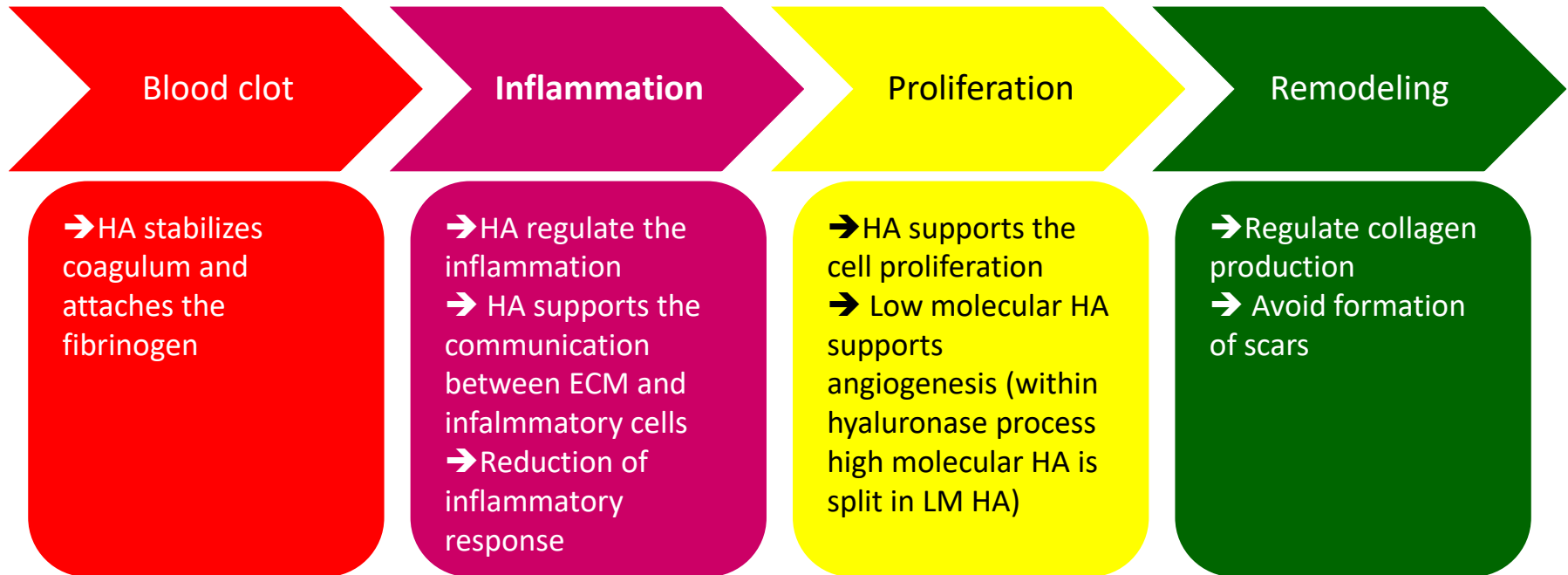


1) Olczyk P. et al. 'Hyaluronan: structure, metabolism, functions, and role in wound healing.' Postepy Hig Med Dosw (Online) , 2008; 62:651–659 4

2) Salbach J et al. 'Regenerative potential of glycosaminoglycans for skin and bone' J Mol Med (2012) 90:625–635

HYADENT BG

Hyaluronic acid regulates tissue healing



HYADENT BG

The natural promoter of regeneration



ACCELERATED TISSUE HEALING

- Coordinates the post-operative inflammation process and accelerates neoangiogenesis ^{1,2}

IMPROVED OUTCOME

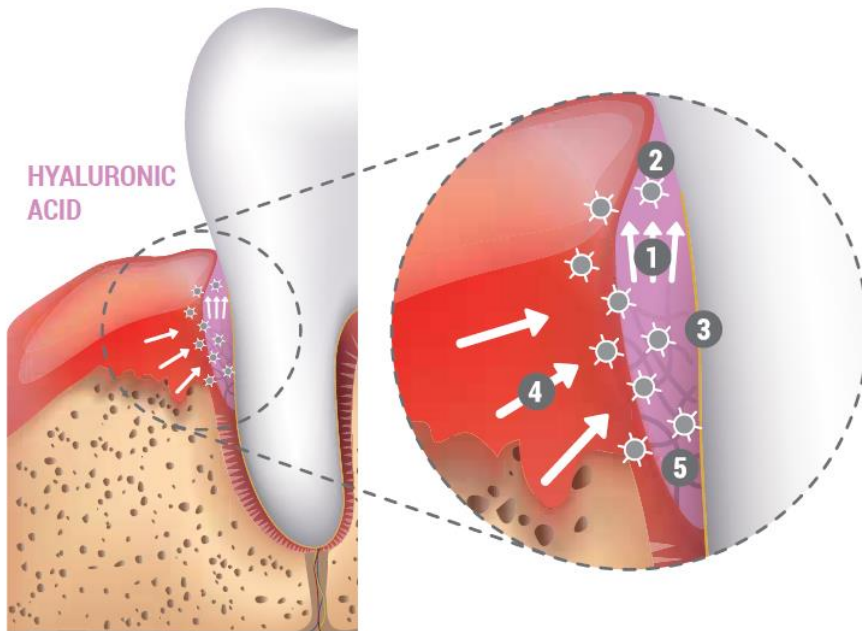
- Stabilizes coagulum and support tissue regeneration ^{1,2,3,4}

IMPROVED PREDICTABILITY

- Bacteriostatic action and reduced pathogen penetration⁵

HYADENT BG

Mode of action



- 1 ATTRACTS BLOOD
- 2 STABILIZES COAGULUM AND SUPPORTS TISSUE REGENERATION
- 3 BACTERIOSTATIC EFFECT PROVIDES PROTECTION
- 4 GROWTH FACTORS ATTRACTED BY HYALURONIC ACID
- 5 COORDINATES INFLAMMATION AND ACCELERATES NEO-ANGIOGENESIS

HYADENT BG

What

HYADENT BG

- Cross linked HA
- Concentration 1.6% CL + 0.2% NCL
- Synthetic origin completely free of endotoxins
- Resorption time: 4-6 weeks
- Package: 2 cartridges, 1.2ml each

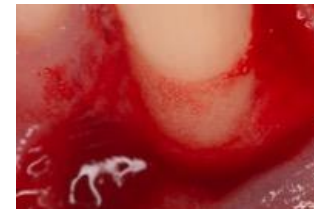
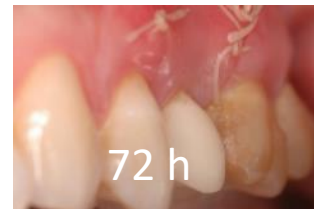
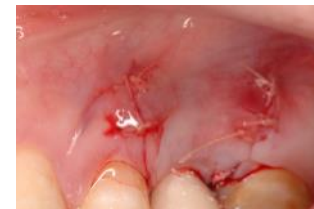


HYADENT BG

Application

HYADENT BG

- **Supporting periodontal regeneration after surgical treatment**
- **Activates bone regeneration material accelerating bone formation and bone quality**
- **Accelerates healing after (large) surgical treatment**



HYADENT BG

In vitro study – Effect of HYADENT on PDL cells

Scope

- Examine morphological changes of dentin surfaces following HA coating and thereafter investigate the influence on periodontal ligament (PDL) cell

Method

- Medium: Bovine dentin discs
- Test 1: Coating HYADENT on dentin discs
- Test 2: Coating HYADENT BG on dentin discs
- Control: Uncoated dentin discs
- Concentrations: 1:100 / 1:10 / 1:1
- Measurements: Morphological surface structure
PDL cell survival, attachment and spreading

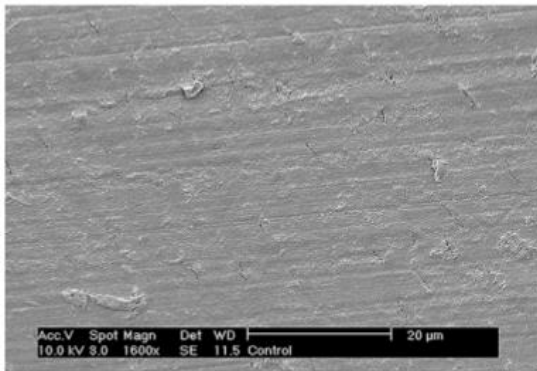


HYADENT BG

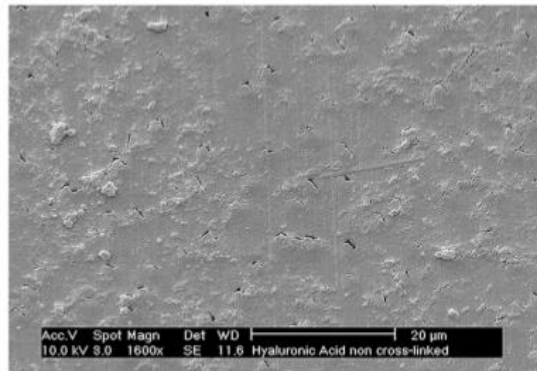
In vitro study – Effect of HYADENT on PDL cells

Results – surface morphology with SEM

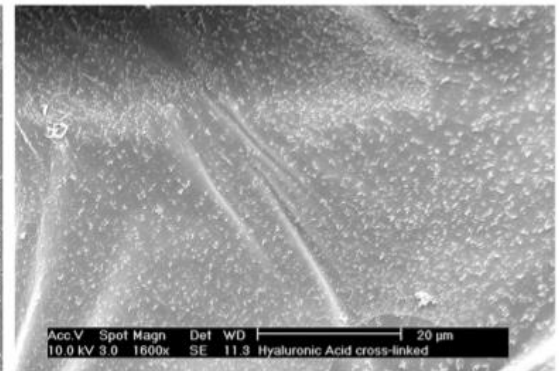
- Control dentin discs were characterized by the presence of very smooth surfaces.
- Following HYADENT coating, surface characteristics of dentin slices demonstrated a more roughened surface with the presence of a surface layer of HA on the surfaces
- HYADENT BG demonstrated surfaces with more roughened surface topography with the presence of an observable cross-linked pattern found coated on dentin surfaces



Control



HYADENT



HYADENT BG

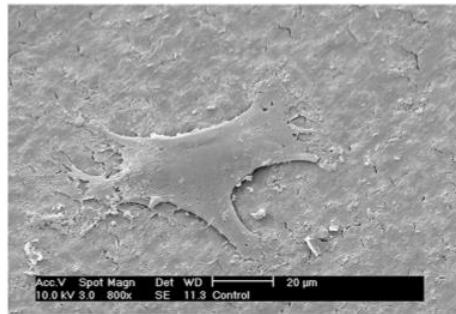
SEM images of control, HYADENT and HYADENT BG surfaces at ×1600 magnification. Control surfaces demonstrated smooth surfaces, whereas surface roughness increased on non-cross-linked HA surfaces and cross-linked HA surfaces.

HYADENT BG

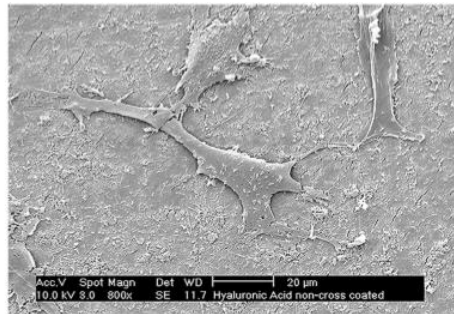
In vitro study – Effect of HYADENT on PDL cells

Results – effect on PDL cells (survival, attachment and spreading)

- Cells seeded on dentin discs demonstrated close to a 100% survival for all groups.
- The present in vitro conditions indicated that HA was an extremely biocompatible material.
- It was found that HYADENT showed significantly higher levels of PDL cells on both HA 1:10 and HA pre-coated surfaces when compared to the other groups.
- It was found that HYADENT BG surfaces demonstrated more elongated cell shapes with more spreading observed on dentin discs when compared to control and hyaDENT surfaces.



Control



HYADENT



HYADENT BG

SEM images of primary human PDL cells seeded. PDL cells seeded on HYADENT BG demonstrated qualitatively more elongated cell morphology when compared to control and HYADENT surfaces.

HYADENT BG

Laboratory study – Effect of HYADENT BG on gingival and palatal fibroblasts

Scope

- Investigate the effect of HYADENT BG on wound healing cells

Method

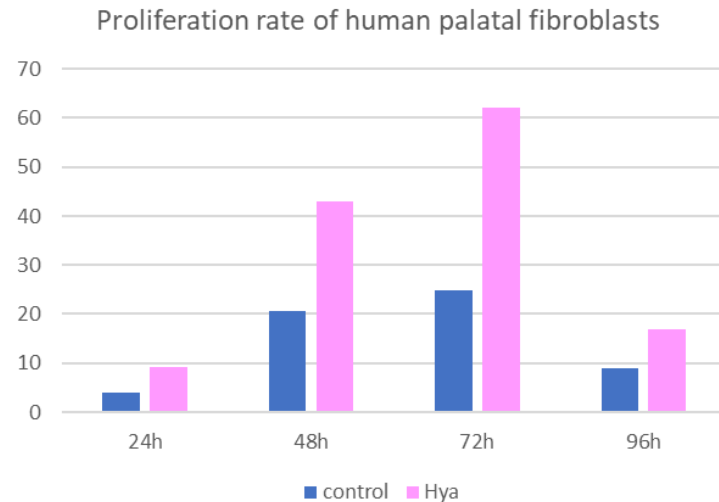
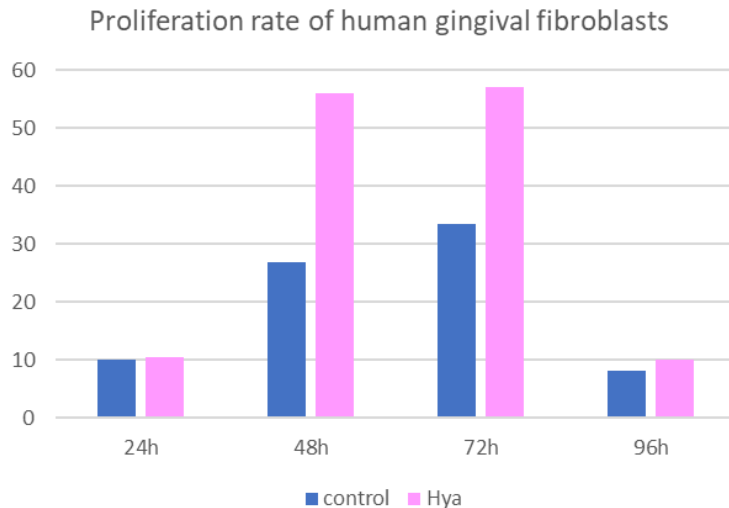
- Cells: Human gingival fibroblasts & Human palatal fibroblasts
- Control: HYADENT BG
- Test: plastic dishes
- Parameters: Cell viability, cell migration and cell proliferation at different timepoints
Quantitative RT-PCR was used for:
 - COL1A1 & COL3A1 (Collagen type I & type III)
 - TGF- β 1 & TGF- β 3 (Transforming growth factor beta 1 & 3)
 - PDGFB (platelet-derived growth factors)
 - FGF2 (fibroblast growth factor)
 - EGF (endothelial growth factors)

HYADENT BG

Laboratory study – Effect of HYADENT BG on gingival and palatal fibroblasts

Results:

- Statistical significant higher cell proliferation in the HYADENT BG group in nearly all timepoints (24h, 48h, 72h and 96h) for HGF & HPF



1) Cuttle L et al' Collagen in the scarless fetal skin wound: detection with Picrosirius-polarization.' Wound Repair Regen. 2005;13:198-204.

2) Lichtman MK, et al 'Transforming growth factor beta (TGF- β) isoforms in wound healing and fibrosis.' Wound Repair Regen. 2016;24:215-222.

HYADENT BG

Laboratory study – Effect of HYADENT BG on gingival and palatal fibroblasts

Results:

- Significant increase of COL3A and TGF- β 3 of both cell types for the HYADENT BG group **(scarless healing)** ^{1,2}
 - No effect of HYADENT BG on COL1A and TGF- β 1 **(fibrotic healing)** ^{1,2}
 - Presence of HYADENT BG led to a significant induction of the growth factors PDGFB, FGF-2 and EGF for both cell types.
-
- ➔ HYADENT BG supports a scarless wound healing process
 - ➔ HYADENT BG supports regeneration and wound healing
 - ➔ HYADENT BG induces increase on growth factors

1) Cuttle L et al' Collagen in the scarless fetal skin wound: detection with Picrosirius-polarization.' Wound Repair Regen. 2005;13:198-204.

2) Lichtman MK, et al 'Transforming growth factor beta (TGF- β) isoforms in wound healing and fibrosis.' Wound Repair Regen. 2016;24:215-222.

HYADENT BG

Clinical study – Effect HA within CAF treatment

Scope

- Effect of HA in mucogingival surgery in the coronally advanced flap (CAF) procedure in single Miller class I/recession type 1 (RT1) gingival recession treatment.

Method

- Indication: Recession Miller Class I
- Control: Without HYADENT BG (# 15)
- Test: With HYADENT BG (# 15)
- Follow up: 18 months
- Parameters: Recession (REC) & Recession Reduction (RecRed)
Clinical Attachment Level (CAL) & Attachment Level gain (CAL gain)
Pocket Depth (PPD)
Keratinized Tissue (KT)
Complete Root Coverag (CRC)
MRC (mean recession converage)
VAS for patient perception

HYADENT BG

Clinical study – Effect HA within CAF treatment

Results

- Both groups have shown a statistical significant improvement between baseline & 18 months for REC, CAL, PPD
- The test group had statistical better values after 18 months for REC, CAL, PPD
- RecRed, CAL gain, CRC and MRC was statistically significant high for the test group at 18 months compared to the control group
- Patients of the HYADENT BG group had statistical significant less discomfort and swelling

	HYADENT BG group	Control group	P-value
RecRed	2.7mm	1.9mm	0.007*
CAL gain	3.0mm	2.0mm	0.023*
CRC	80% (12/15)	33% (5/15)	0.024*
MRC	93.8%	73.1%	0.003*

HYADENT BG

Clinical study – Effect HA within CAF treatment

Results

Clin Oral Invest

Table 2 Clinical parameter changes, mean and complete root coverage at 18 months

Variables	CAF + HA baseline (n = 15); M [IQR]	CAF + HA 18 months (n = 15); M [IQR]	p value baseline versus 18 months ^c	CAF baseline (n = 15); M [IQR]	CAF 18 months (n = 15); M [IQR]	p value baseline versus CAF	p value baseline versus 18 months ^c	p value 18 months
Rec ^a	3.0 [1.0]	0.0 [0.0]	< 0.001*	3.0 [1.0]	1.0 [1.0]	0.216	0.001*	0.011*
RecRed ^a	–	2.7 [1.0]	–	–	1.9 [1.0]	–	–	0.007*
CAL ^a	4.0 [1.0]	1.0 [0.0]	< 0.001*	4.0 [1.0]	2.0 [0.0]	0.557	< 0.001*	0.011*
CAL-gain ^a	–	3.0 [1.0]	–	–	2.0 [1.0]	–	–	0.023*
PPD ^a	1.0 [0.0]	1.0 [1.0]	0.014*	1.0 [0.0]	2.0 [1.0]	0.087	0.008*	0.717
KT ^a	2.0 [1.0]	2.0 [0.0]	0.527	2.0 [1.0]	2.0 [1.0]	0.577	0.527	0.116
CRC ^b	–	80% (12/15)	–	–	33% (5/15)	–	–	0.025*
MRC ^{c, d}	–	93.8 ± 13.0%	–	–	73.1 ± 20.8%	–	–	0.003*

➔ Statistical significant higher recession reduction, attachment gain for the HA group

➔ Complete root coverage (CRC) in 80% was achieved of the cases treated with HA

HYADENT BG

Clinical study – Effect HA within CAF treatment

Results: Patient perception

Clin Oral Invest

Table 3 Patient morbidity at 7 post-surgical days (VAS)

Parameters	Test	Control	<i>p</i> value
Pain intensity	0 [1]	1 [2]	0.151
Discomfort	1 [1]	2 [2]	0.029*
Swelling	1 [1]	2 [1]	0.010*

➔ Patient of the HYADENT BG group had statistical significant less discomfort and swelling

Recession defect Miller class II

Prof. Anton Sculean

University of Berne, Switzerland



hyaDENT BG

Recession Miller class II



Initial situation



Tunnel

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

hyaDENT BG

Recession Miller class II



Mobilized Tunnel



Connective tissue graft

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

hyaDENT BG

Recession Miller class II



Application of HYADENT BG

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

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hyaDENT BG

Recession Miller class II



CTG in Tunnel



Application of
HYADENT BG on CTG

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

hyaDENT BG

Recession Miller class II



Suture

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hyaDENT BG

Recession Miller class II



Baseline



Situation after healing

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

Recession defect Miller class III

Prof. Anton Sculean

University of Berne, Switzerland



HYADENT BG

Recession Miller class III



Application of
HYADENT BG in the
tunnel



Positioning of
connective tissue
graft



Application of
HYADENT BG on
the connective
graft and the
wound

These pictures are a courtesy of Prof. Anton Sculean, University Bern (Switzerland)

HYADENT BG

Recession Miller class III



Initial situation



Outcome

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Infrabony defect

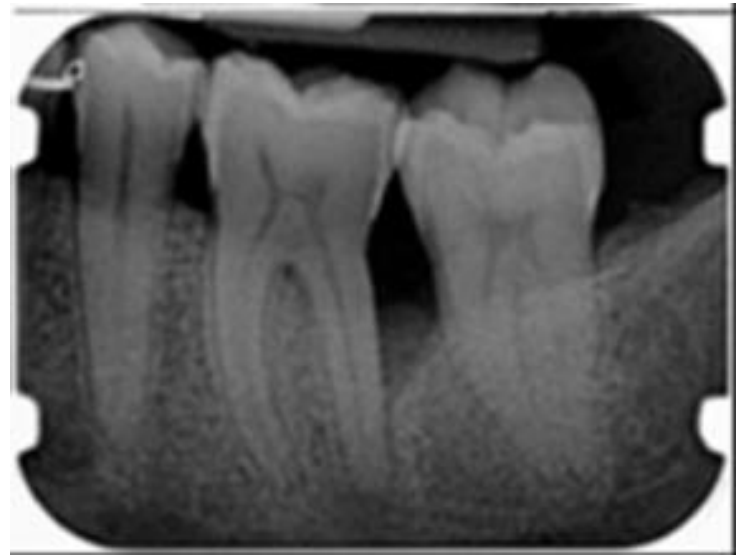
Prof. Andrea Pilloni

University La Sapienza, Rome, Italy



HYADENT BG

Infrabony defect



Deep pocket observed on probing and bone loss visualized on radiographic image

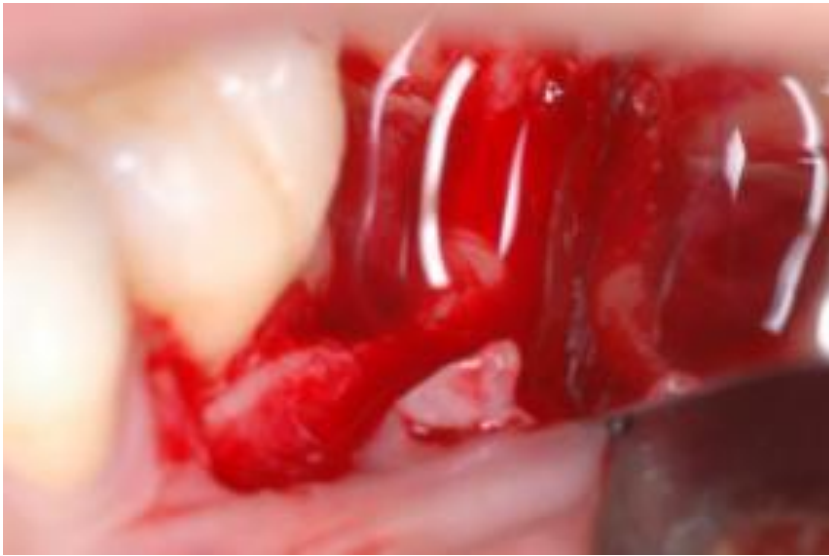
These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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HYADENT BG

Infrabony defect



Application of HYADENT BG on root surface after root surface cleaning



Application of synthetic bone graft mixed with HYADENT BG

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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HYADENT BG

Infrabony defect



Fast healing (72h)

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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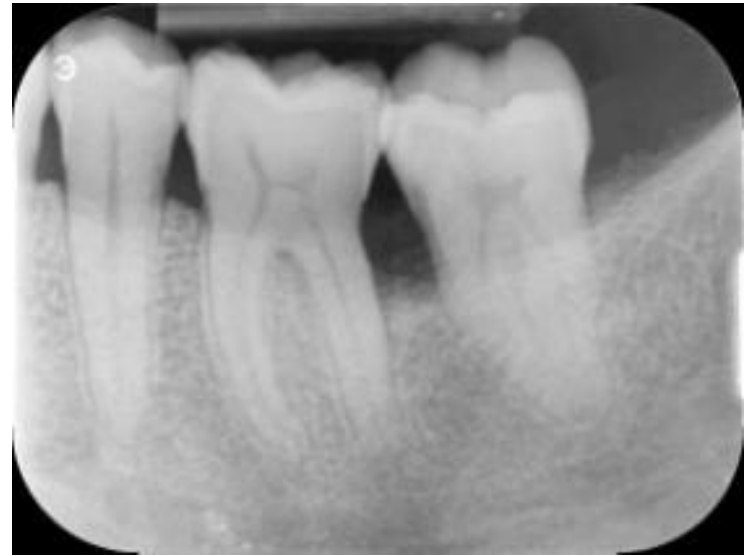
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HYADENT BG

Infrabony defect



Baseline with bony defect



Situation at 12 months showing closed defect

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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Miller class I recession defect treated with coronally advanced flap (CAF)

Prof. Andrea Pilloni

University La Sapienza, Rome, Italy

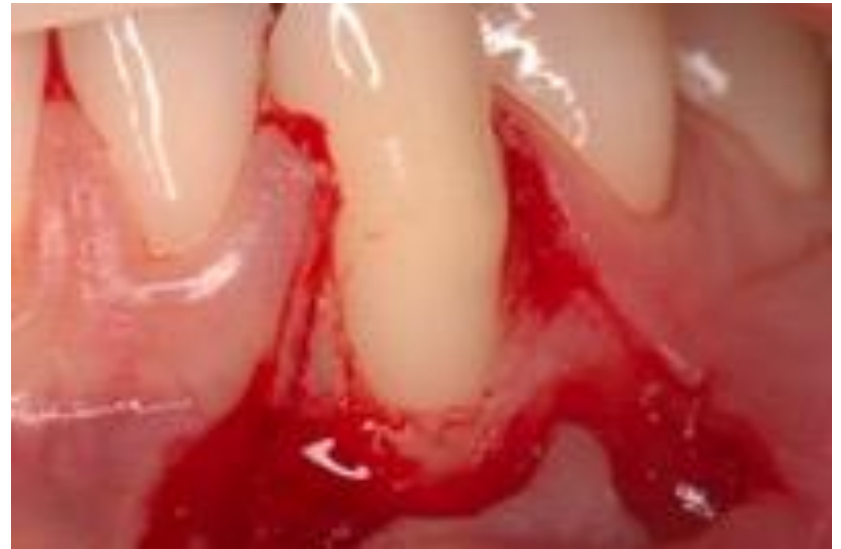


HYADENT BG

Recession Miller class I with CAF



Recssion on canine in lower jaw



Opening of the site and cleaning of the root surface

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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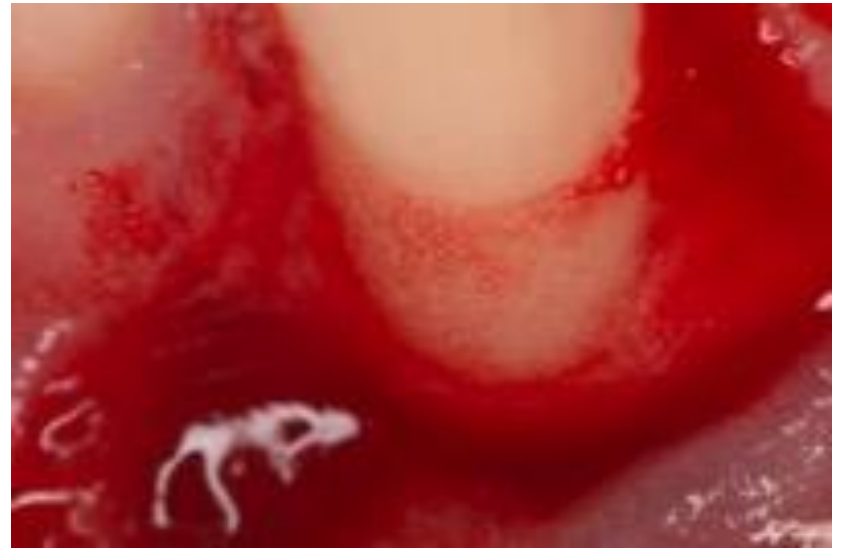
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HYADENT BG

Recession Miller class I with CAF



Application of HYADENT BG on root and incisions



Gel stays on tooth surface due to high viscosity and hydrophilicity traps blood clot keeping stable

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

HYADENT BG

Recession Miller class I with CAF



Closure of the site

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

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HYADENT BG

Recession Miller class I with CAF



Baseline



Follow up at 18 months

These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

Cemental tear-associated bony defect

Prof. Andrea Pilloni

University La Sapienza Rome, Italy

Pilloni et al 'Surgical treatment of a cemental tear-associated bony defect using hyaluronic acid and a resorbable collagen membrane. A two-year follow-up' Clinical Advances in Periodontics



SMARTBRANE – HYADENT BG

Cemental tear-associated bony defect



Pre-surgical view (frontal view). An erythematous and swollen area can be observed in the cervical and medial third of tooth #8.



Pre-surgical view (lateral view). The swollen can be observed in detail.

SMARTBRANE – HYADENT BG

Treatment of deep infrabony defect with hyaluronic acid



Initial periapical radiograph showing a radiolucent area in the medial third between the two maxillary central incisors.

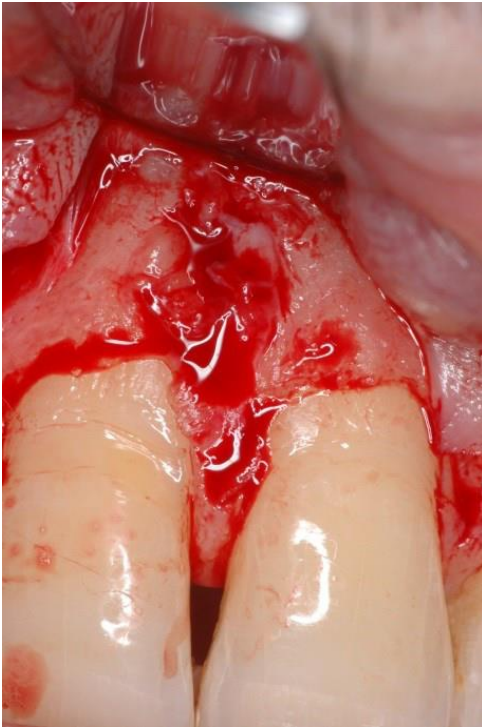
Pilloni et al 'Surgical treatment of a cemental tear-associated bony defect using hyaluronic acid and a resorbable collagen membrane. A two-year follow-up' Clinical Advances in Periodontics

Strictly confidential

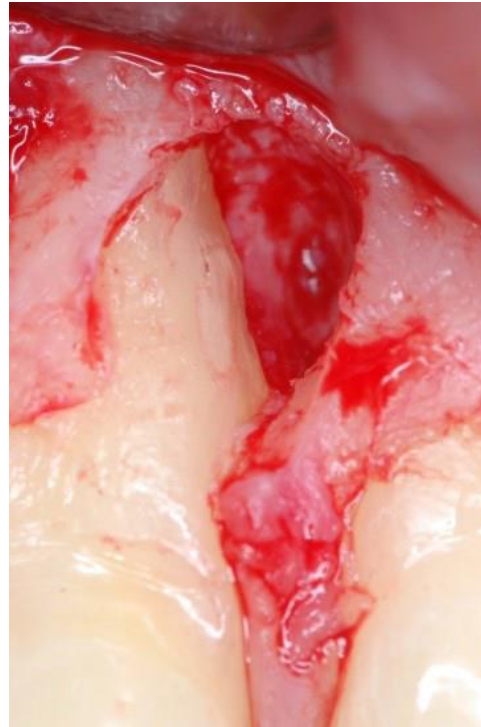
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SMARTBRANE – HYADENT BG

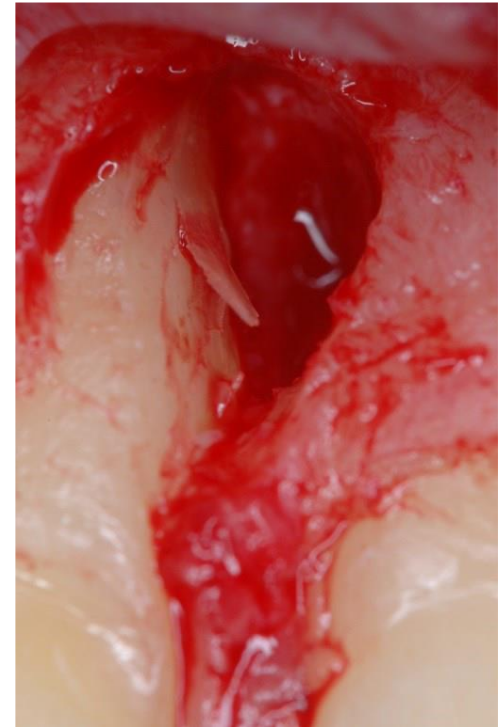
Treatment of deep infrabony defect with hyaluronic acid



A mucoperiosteal buccal flap was elevated (modified preservation papilla technique- MPPT).



A two-walls bony defect was observed on the mesial aspect of the right maxillary central incisor.



A partially detached piece of tooth structure - what appeared to be cementum (CeT)- was found..

Pilloni et al 'Surgical treatment of a cemental tear-associated bony defect using hyaluronic acid and a resorbable collagen membrane. A two-year follow-up' Clinical Advances in Periodontics

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SMARTBRANE – HYADENT BG

Treatment of deep infrabony defect with hyaluronic acid



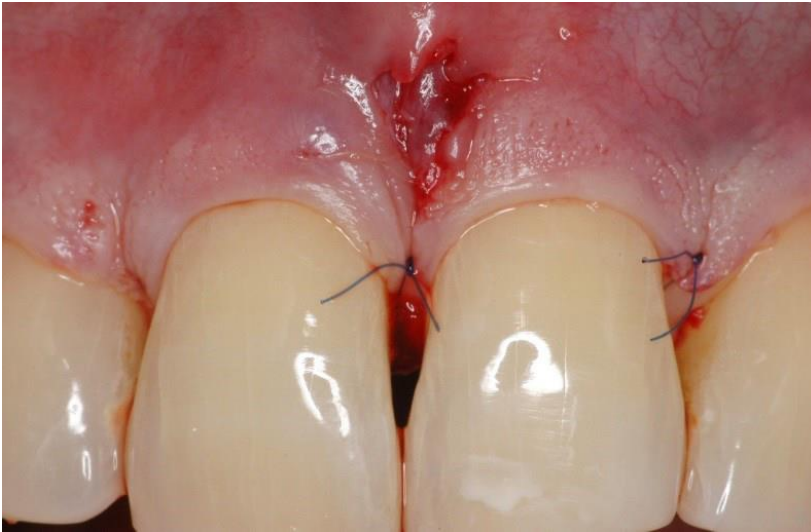
Hyaluronic acid (HYADENT BG) was applied in the bony defect.



A resorbable collagen membrane (SMARTBRANE) was placed as barrier.

SMARTBRANE – HYADENT BG

Treatment of deep infrabony defect with hyaluronic acid



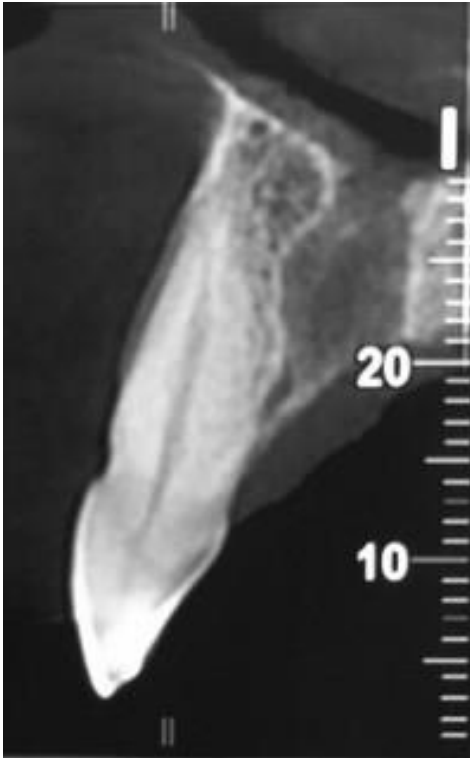
The flap was coronally displaced and sutured with sling and interrupted sutures.



Two-year follow-up showing clinically healthy soft tissue.

SMARTBRANE – HYADENT BG

Treatment of deep infrabony defect with hyaluronic acid



Two-year follow-up CBCT showing the reconstruction of the buccal bone wall.



Two-year follow-up showing clinically healthy soft tissue.

Literature of HYADENT BG

Periodontology

- Mueller A, Fujioka-Kobayashi M, Mueller HD, Lussi A, Sculean A, Schmidlin PR, Miron RJ. 'Effect of hyaluronic acid on morphological changes to dentin surfaces and subsequent effect on periodontal ligament cell survival, attachment, and spreading' Clinical Oral Investigations 2016 May .DOI 10.1007/s00784-016-1856-6
- Pilloni A, Schmidlin PR, Sahrman P, Sculean A, Rojas MA. 'Effectiveness of adjunctive hyaluronic acid application in coronally advanced flap in Miller class I single gingival recession sites: a randomized controlled clinical trial, Clinical Oral Investigations <https://doi.org/10.1007/s00784-018-2537-4>
- Eliezer M, Imber J, Radakovic S, Pirracchio L, Sculean A 'The clinical effect of Hyaluronic acid on root recession coverage: a case series, 6 months evaluation' PD172, Poster Presentation, EuroPerio 9, June 2018, Amsterdam
- Asparuhova M, Kiryak D, Eliezer M, Mihov D, Sculean A. 'Activity of two hyaluronan preparations on primary human oral fibroblasts' . J Periodontal Res 2018 Sep 27. Epub 2018 Sep 27
- Fujioka-Kobayashi M, Schaller B, Kobayashi E, Hernandez M, Zhang Y and Miron RJ 'Hyaluronic Acid Gel-Based Scaffolds as Potential Carrier for Growth Factors: An In Vitro Bioassay on Its Osteogenic Potential' J. Clin. Med. 2016, 5, 112; doi:10.3390/jcm5120112
- Fujioka-Kobayashi M, Müller H, Mueller A, Lussi A, Sculean A, Schmidlin PR, Miron RJ 'In vitro effects of hyaluronic acid on human periodontal ligament cells' BMC Oral Health (2017) 17:44 DOI 10.1186/s12903-017-0341-1
- Bayoumi A, Nadershah M, Albandar A, Alsulaimani B, Sankour I, Gadi L, Osama O, Tayeb R, Quqandi R, Dabroom W, Merdad Y 'The Effect of Cross-Linked Hyaluronic Acid in Surgical Extraction of Impacted Mandibular Third Molars' Int J Dent Oral Health 4(2): dx.doi.org/10.16966/2378-7090.254
- Peck MT, Hiss D, Stephen L, Olivier A 'The in vitro effect of leukocyte- and platelet-rich fibrin (L-PRF) and crosslinked hyaluronic acid on fibroblast viability and proliferation.' SADJ July 2018, Vol 73 no 6 p395 - p399
- Shamma MM, Ayad SS, El-dibany RM, Nagui DA 'Evaluation of the effect of hyaluronic acid mixed with biphasic calcium phosphate on bone healing around dental implants' Alexandria Dental Journal. (2017) Vol.42 Pages:104-11
- Elkarargy A. 'Alveolar Sockets Preservation Using Hydroxyapatite / Beta tricalcium Phosphate with Hyaluronic Acid (Histomorphometric study).' J Am Sci 2013; 9(1): 556-563]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>.



HYADENT BG

Clinical study – Effect of HA combined with bone substitute

Scope

- Effect of HA when mixed with bone grafting material

Method

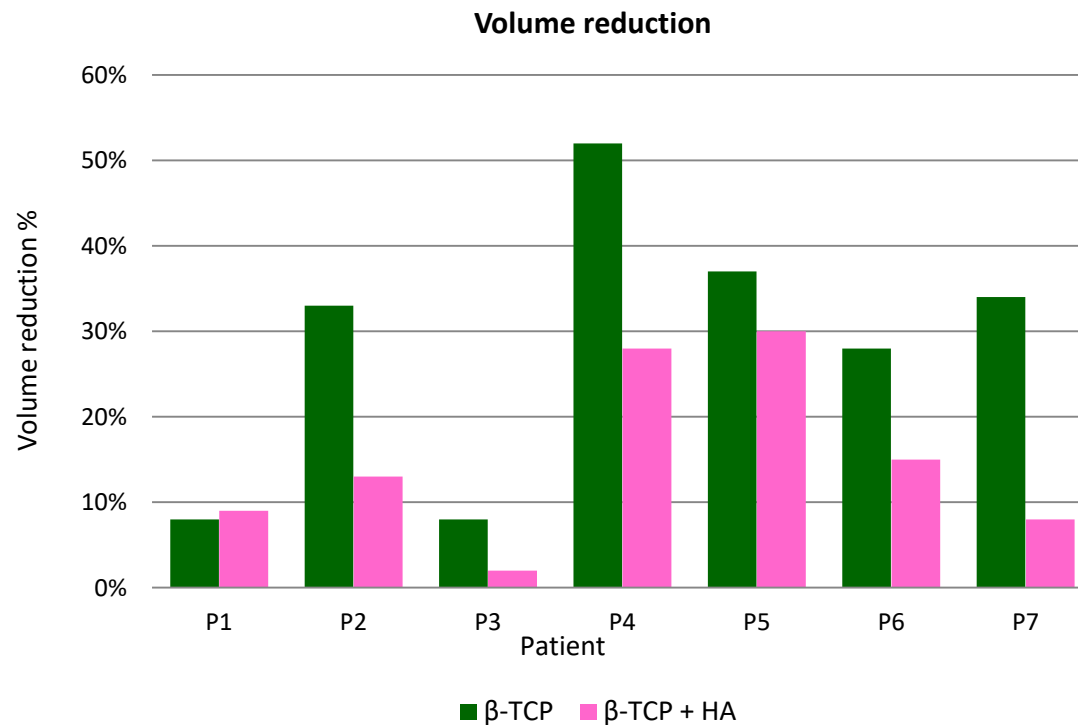
- Bilateral sinus elevation treatment in 7 patients (split mouth)
- Grafting material: β -TCP
- Test: β -TCP with HA (TCP-P)
- Control: β -TCP without HA (TCP-G)
- Follow up: 6 months
- Parameters: Volume reduction (radiologic)
Bone quality (histology)

HYADENT BG

Clinical study – Effect of HA combined with bone substitute

Radiological results:

Reduction of volume for test is lower (stat. sign.) for 6 out of 7 patients



Stiller M. et al. 'Performance of β -tricalcium phosphate granules and pitty bone grafting materials after bilateral sinus floor augmentation in humans' Biomaterials 2014

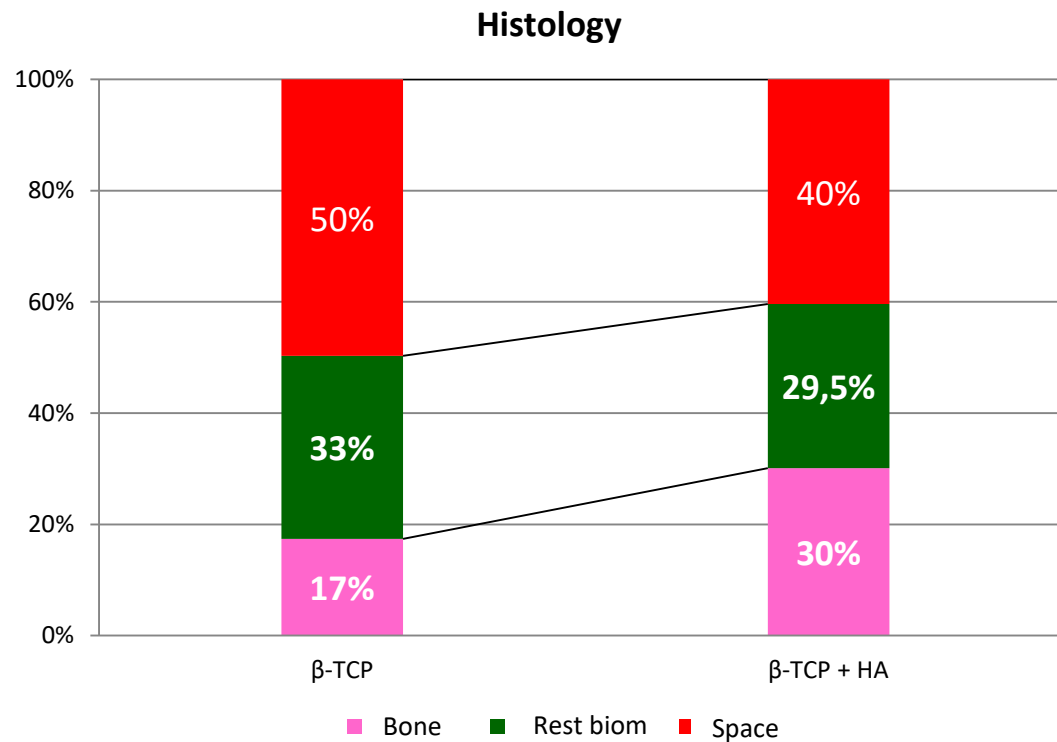
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HYADENT BG

Clinical study – Effect of HA combined with bone substitute

Results:

A statistical significant higher amount of mature bone has been found within the HA group



Stiller M. et al. 'Performance of β -tricalcium phosphate granules and pitty bone grafting materials after bilateral sinus floor augmentation in humans' Biomaterials 2014

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Bone reconstruction combining bone graft material with HYADENT BG

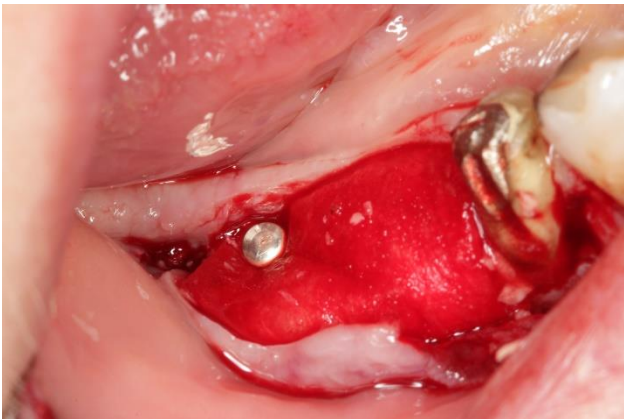
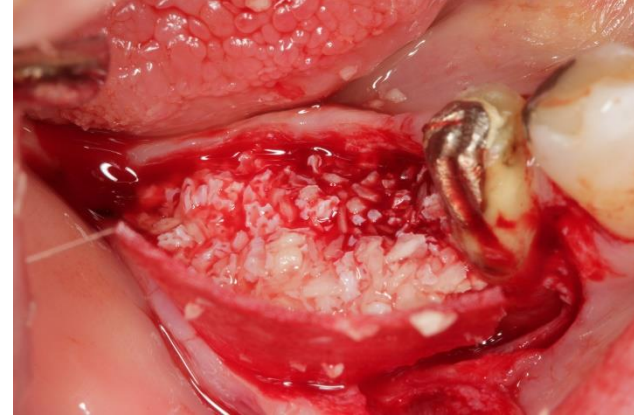
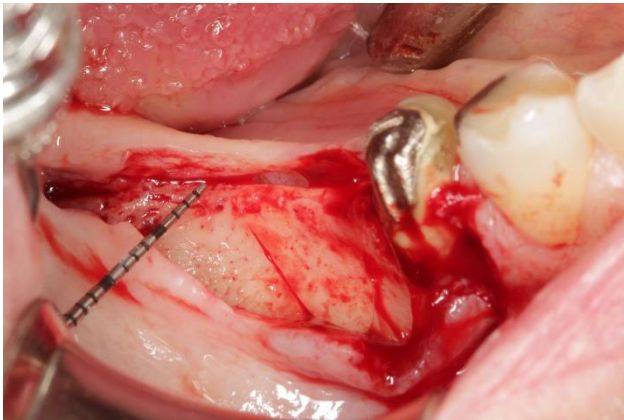
Prof. Darko Bozic

University of Zagreb, Croatia



HYADENT BG

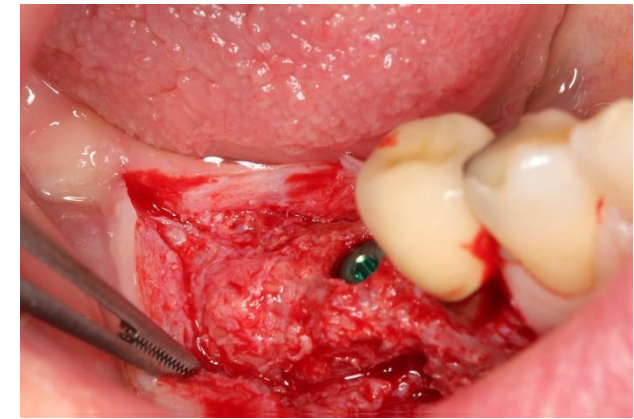
Bone augmentation with HYADENT BG and SMARTBRANE membrane



Protection with SMARTBRANE



2 weeks



Re-opening and implant placement at 6 months

These pictures are a courtesy of Prof. Darko Bozic, Coratia

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Large infrabony defect treated with HYADENT BG and bone graft

Prof. Andrea Pilloni

University of Rome, Italy



HYADENT BG

Large intrabony defect treated with HYADENT BG



These pictures are a courtesy of Prof. Andrea Pilloni , La Sapienza Roma (Italia)

WEBLINK: <https://www.youtube.com/watch?v=jCuZbQ0xjcs>

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Literature of hylauronic acid

Bone regeneration

- Stiller M. et al. 'Performance of β -tricalcium phosphate granules and pitty bone graffting materials after bilateral sinus floor augmentation in humans' Biomaterials 2014
- Muzaffer A. et al. 'The Effect of Hyaluronic Acid-supplemented Bone Graft in Bone Healing: Experimental Study in Rabbits ' J Biomater Appl 2006 20: 209
- El Karargy A. 'Alveolar Sockets Preservation Using Hydroxyapatite / Beta tricalcium Phosphate with Hyaluronic Acid (Histomorphometric study)' Journal of American Science 2013;9(1)
- Pilloni A. et al. 'Effect of hyaluronan on calcification-nodule formation from human periodontal ligament cell culture' Journal of Applied Biomaterials & Biomechanics 2003; 1: 84-90
- Pilloni A., Bernard GW 'The effect of hyaluronan on mouse intramembranous osteogenesis in vitro' Cell Tissue Res. 1998 Nov;294(2):323-33.
- Ghada Bassiouny A. 'Bioinspired Approach for Dental Implant Fuctionalization: An Experimental Study Evaluating the Effect of Hyaluronate as Bioactive Implant Coating.' J Am Sci 2013;9(11):187-192
- Schwartz Z et al. 'Clinical evaluation of demineralized bone allograft in a hyaluronic acid carrier for sinus lift augmentation in humans: a computed tomography and histomorphometric study.' Clin. Oral Impl. Res. 18, 2007; 204–211
- Sasaki T, Watanabe C, Bone. Vol. 16. No.1 January 1995:9-15

