Hospital das Clinicas

São Paulo, Brazil

Friday, April 4th 2008

Growth Factors and Bone Morphogenetic Proteins as Relevant to Spinal and Fracture Surgery

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Hughston Clinic
Columbus, Georgia

Why is Bone Grafting Important?

- Fracture Surgery

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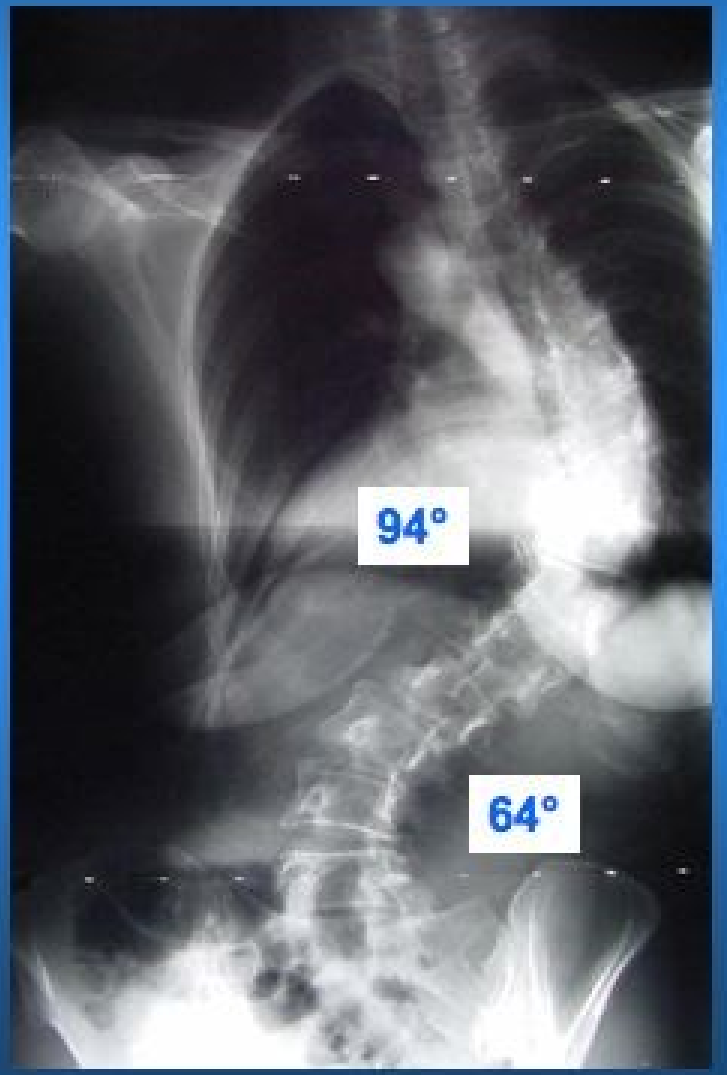
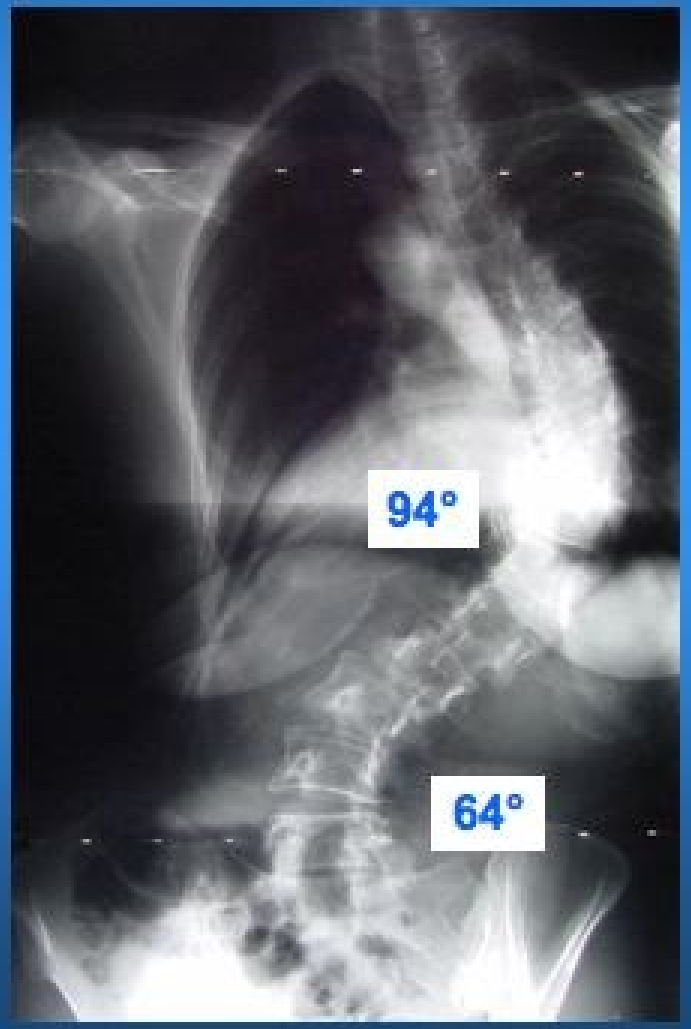
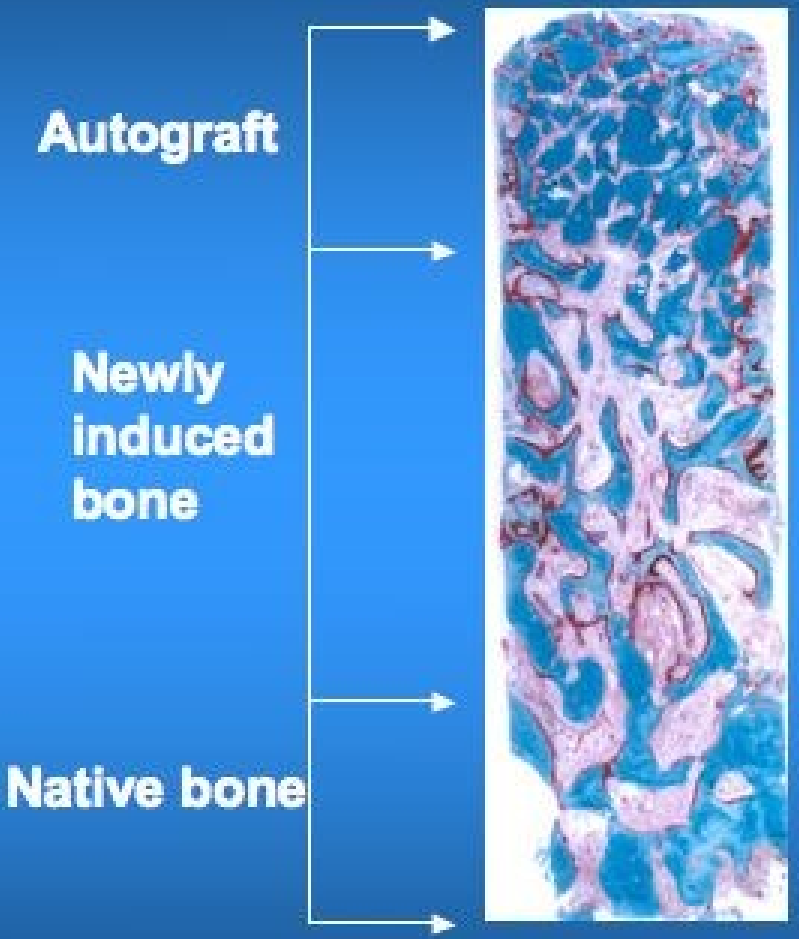


Why is Bone Grafting Important?



Benefits of Autogenous ICBG

- Objective: To harvest live viable cells capable of forming bone following transplantation
- Fresh autograft is
  - Osteoconductive
    - Scaffold for new bone formation
  - Osteogenic
    - Contains bone forming cells
  - Limited osteoinductivity
    - Contains small amounts of growth factors (BMPs) embedded in bone mineral

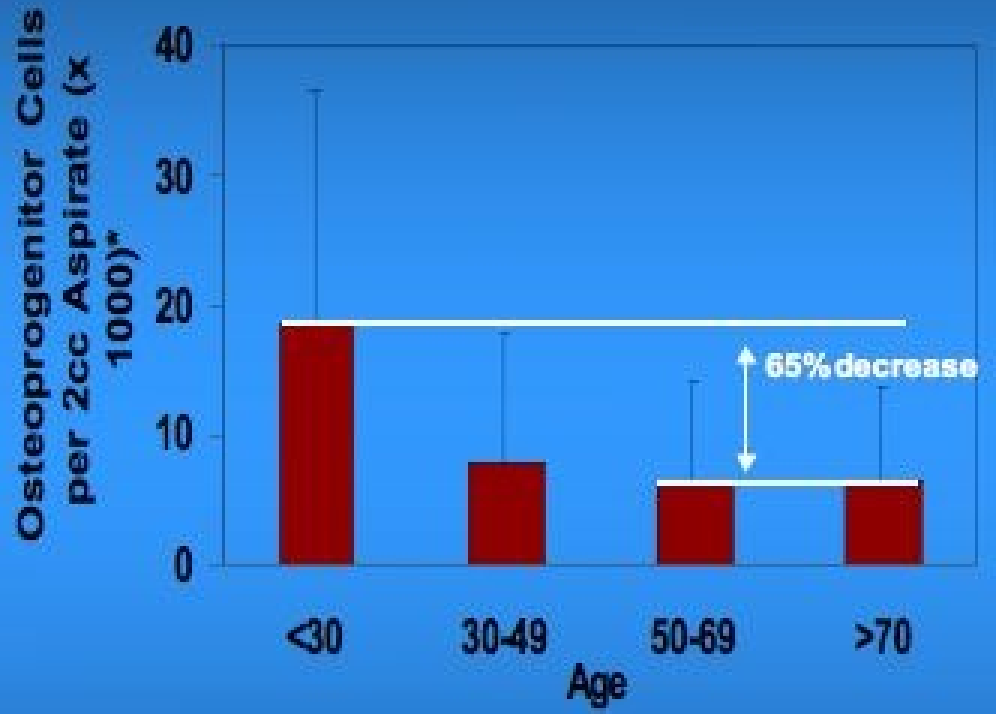


Longitudinal section of bone biopsy from human maxilla*

*Boyne et al. J Oral Max Surg 2005.

Limitations of Autogenous ICBG

- Complications
  - Pain, morbidity
- Quantity
  - Revisions, multi-levels
- Quality
  - Age
    - Stem cells decrease w/ age
  - Comorbidities
    - Diabetes, smoking, osteoporosis
  - Therapies
    - Pharmaceuticals, radiation



*Muschler, J. Orth. Res., 2001

Osteoinductivity & Bone Graft Replacements

- **Osteoinductivity is the key property for a graft replacement**
  - the ability to induce de novo bone formation at a non-bony site
- **Bone Morphogenetic Proteins are the only known differentiation factors that are osteoinductive**

Bone Morphogenic Proteins

- Family of more than 20 proteins (BMP-2, -7 and -14)
- Stimulate new bone formation
- Initiate osteoblastic differentiation of mesenchymal stem cells
- *Human bone contains* 1 part per billion *BMP-2*

Origin of rhBMP-2

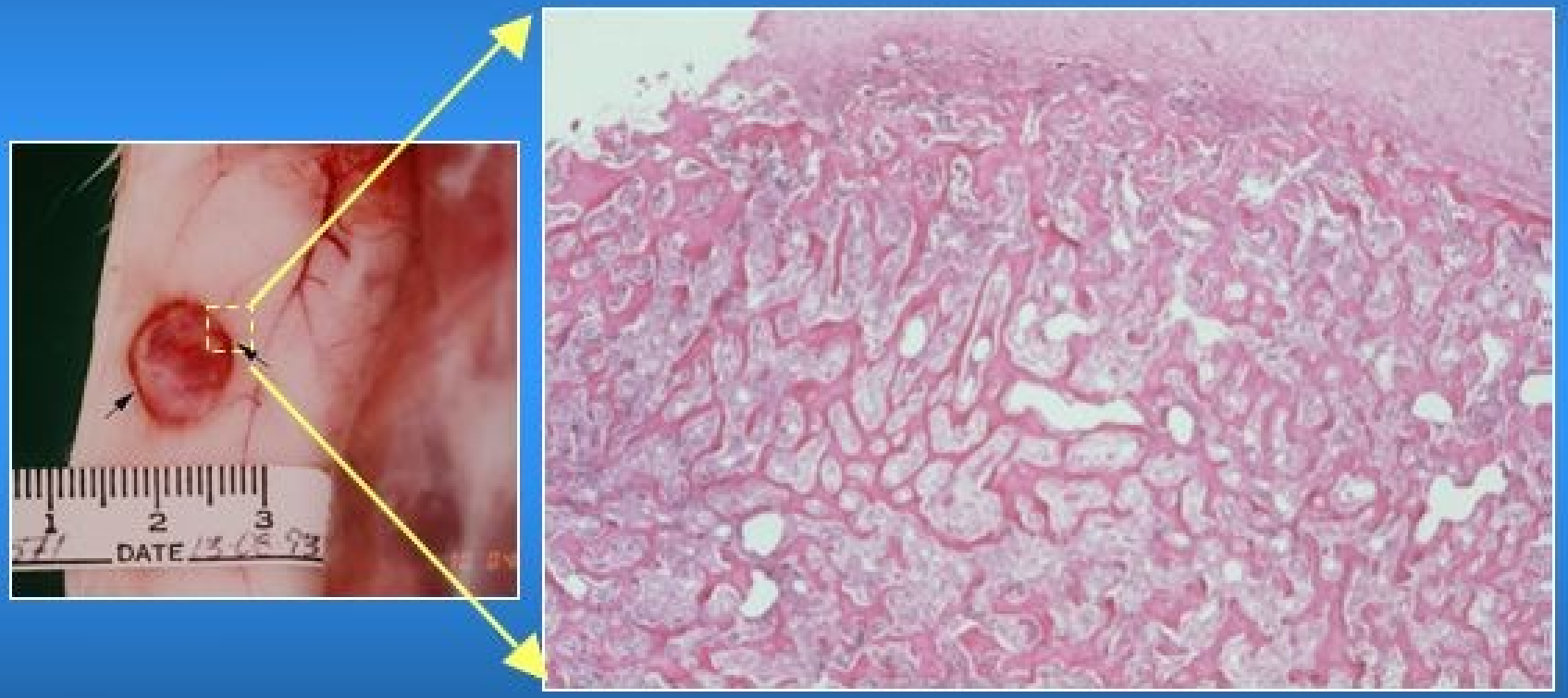
- **BMP protein was purified from bovine bone:**
- Starting material = **10 kilograms** of bovine bone

  Final yield = **20 micrograms** of all BMPs

Estimate:

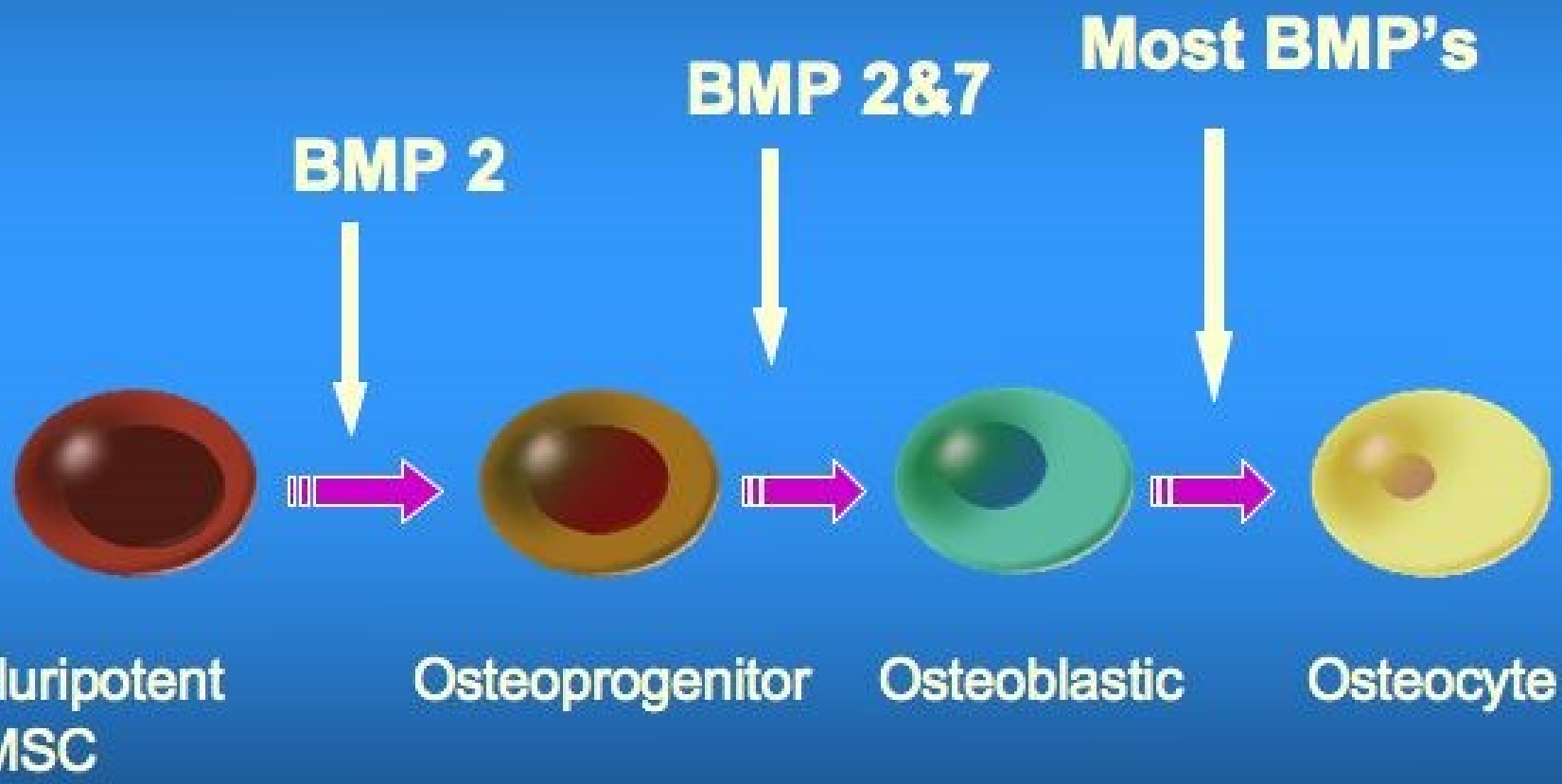
human bone contains **1 part per billion** *BMP-2*

Rat ectopic implant assay (non-bony site)



Bone formation 14 days post-implantation of rhBMP-2/ACS

Osteogenic Hierarchy of BMP's

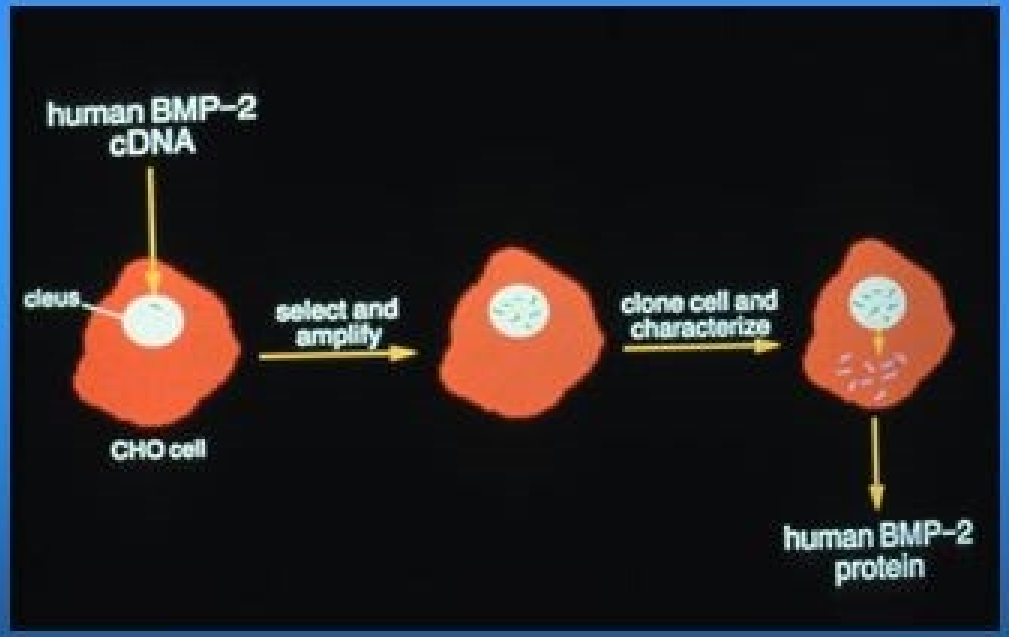


rhBMP-2 =

recombinant human
bone morphogenetic protein-2

Origin of rhBMP-2

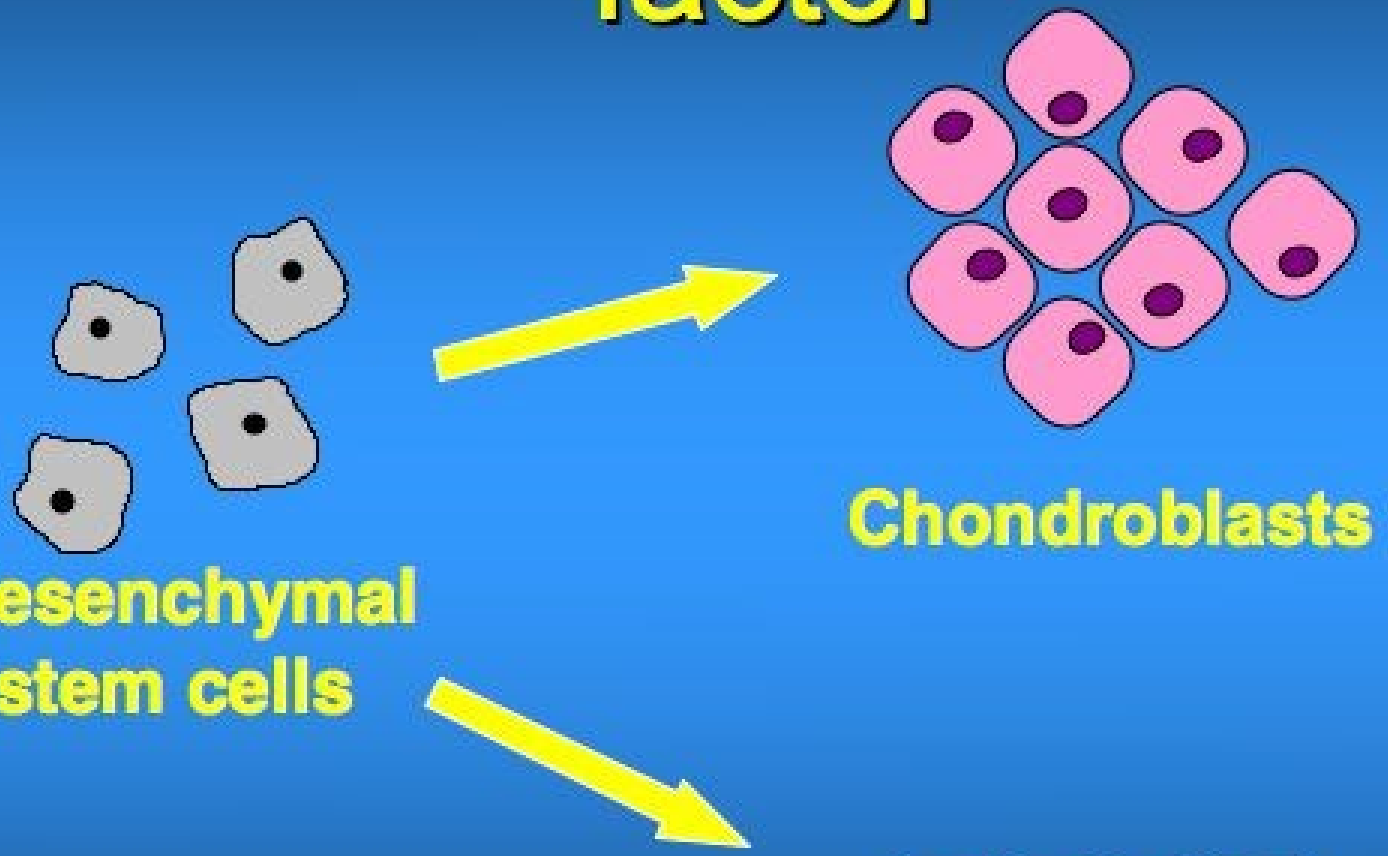
- The gene for human BMP-2 was isolated
- This gene was inserted into a chromosome of a mammalian cell
- This cell line produces a pure natural human protein



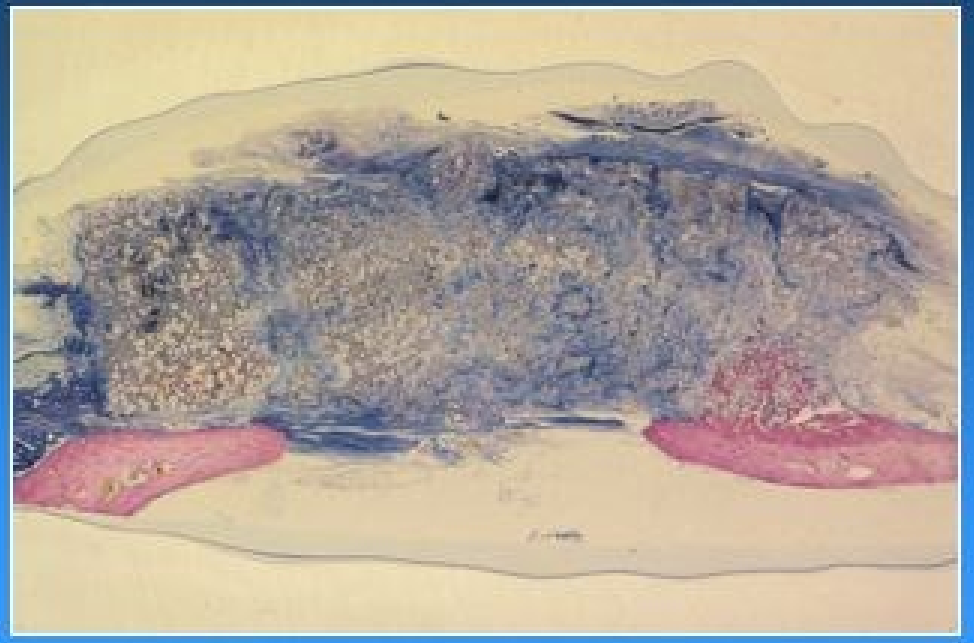
rhBMPs Manufacture

- **Process**
  - Validated
  - Consistent
  - Large scale economical production
    - delivery of therapeutic doses
- **Product**
  - High purity
  - High potency
  - Safe
    - free of pathogens

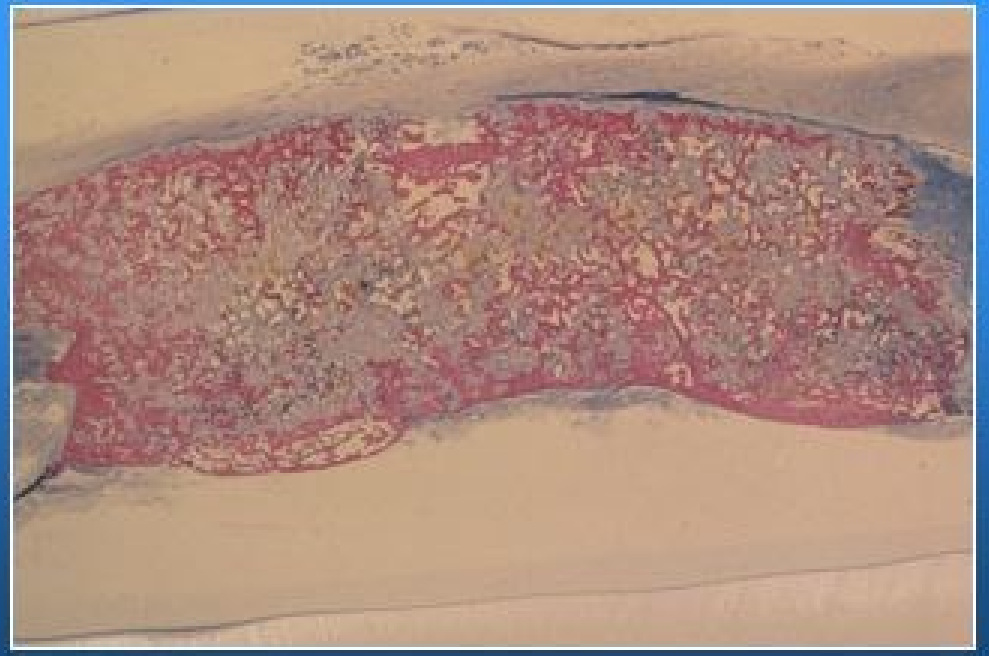
rhBMP-2 = differentiation factor



Osteoconductive Ceramic



Osteoinductive (BMP-containing) ceramic



rhBMP-2 INFUSE Carrier
Absorbable Collagen Sponge

- **Commercially available in US since 1981**
  - Approved PMA
  - Implantable hemostatic agent
  - Extensive experience of safe use
- **Bovine tendon Type I collagen**
  - Manufacturing process meets/exceeds all US and EU guidance

INFUSE Interbody Fusions

Three sequential FDA-approved IDE clinical trials involving 679 patients

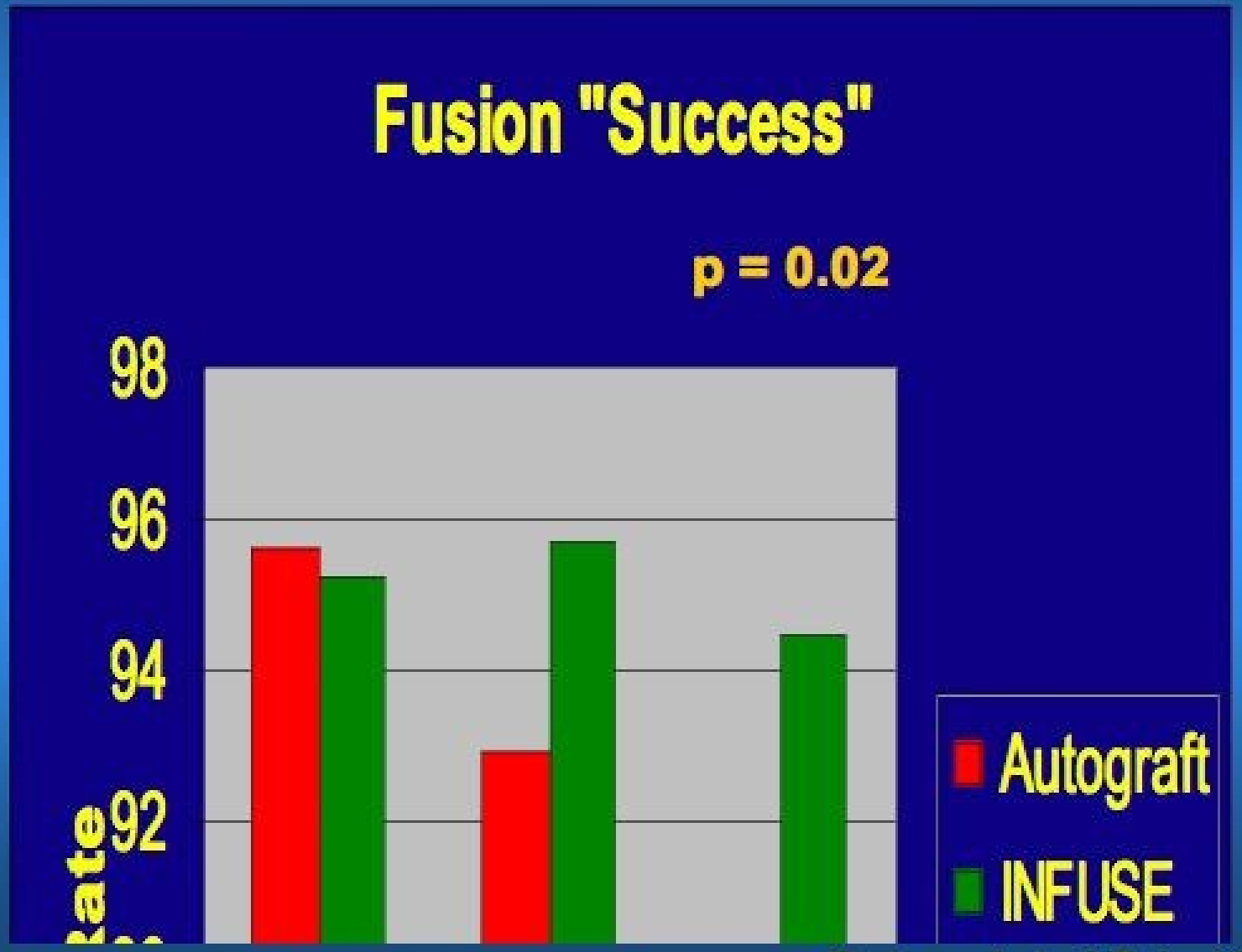
- **LT CAGE / Iliac crest bone graft**
  - **402 total patients**
    - 136 Open ALIF approach
    - 266 Laparoscopic ALIF approach

- **LT CAGE / INFUSE (rhBMP-2)**
  - **277 total patients**
    - 143 Open ALIF approach
    - 134 Laparoscopic ALIF approach

Surgical Data Summary

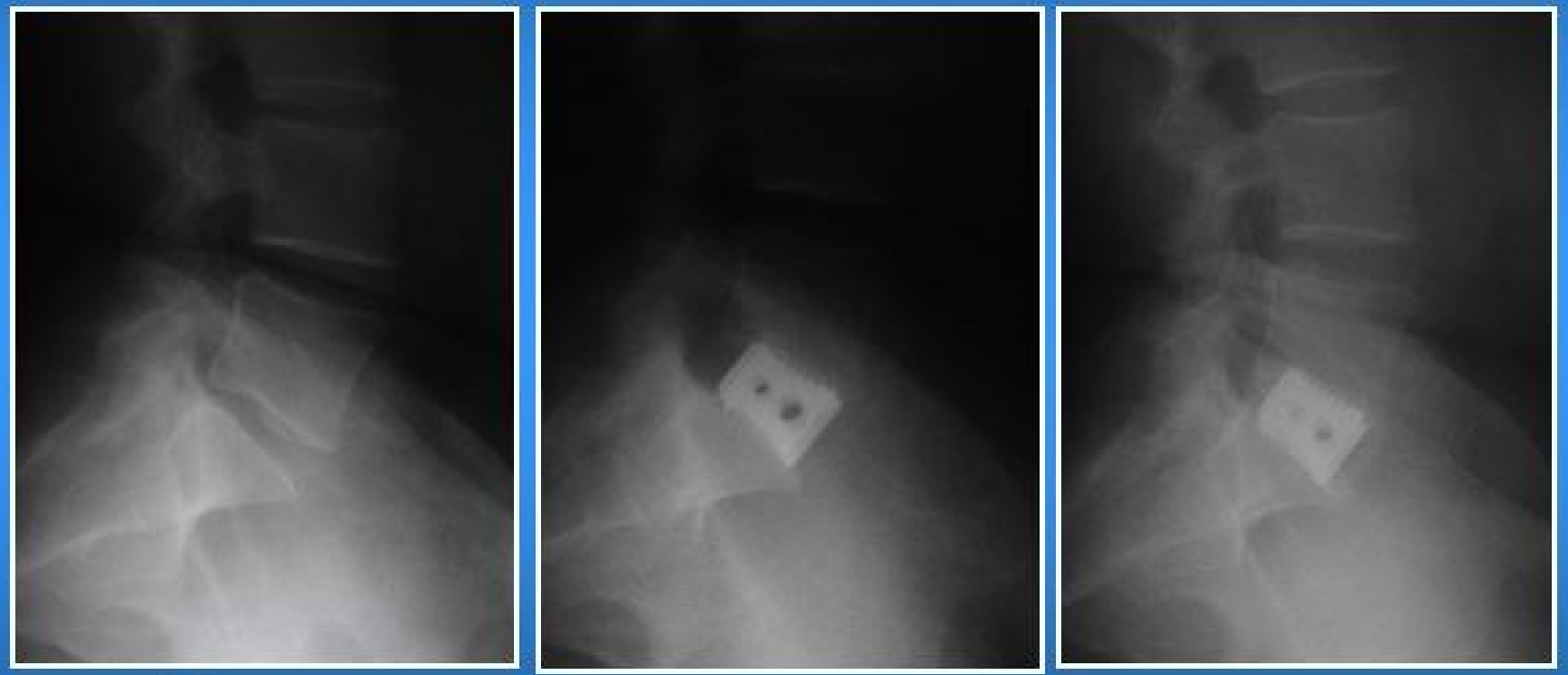
	Autograft	rhBMP-2	p
Operative time *(hours)*	2.7	1.8	<0.001
Blood loss *(ml)*	192.9	127.4	<0.024
Hospital stay *(days)*	3.1	2.2	<0.001

Fusion Success



Burkus *et al.*, J Spinal Dis, 2003

LT Cage w/ rhBMP-2

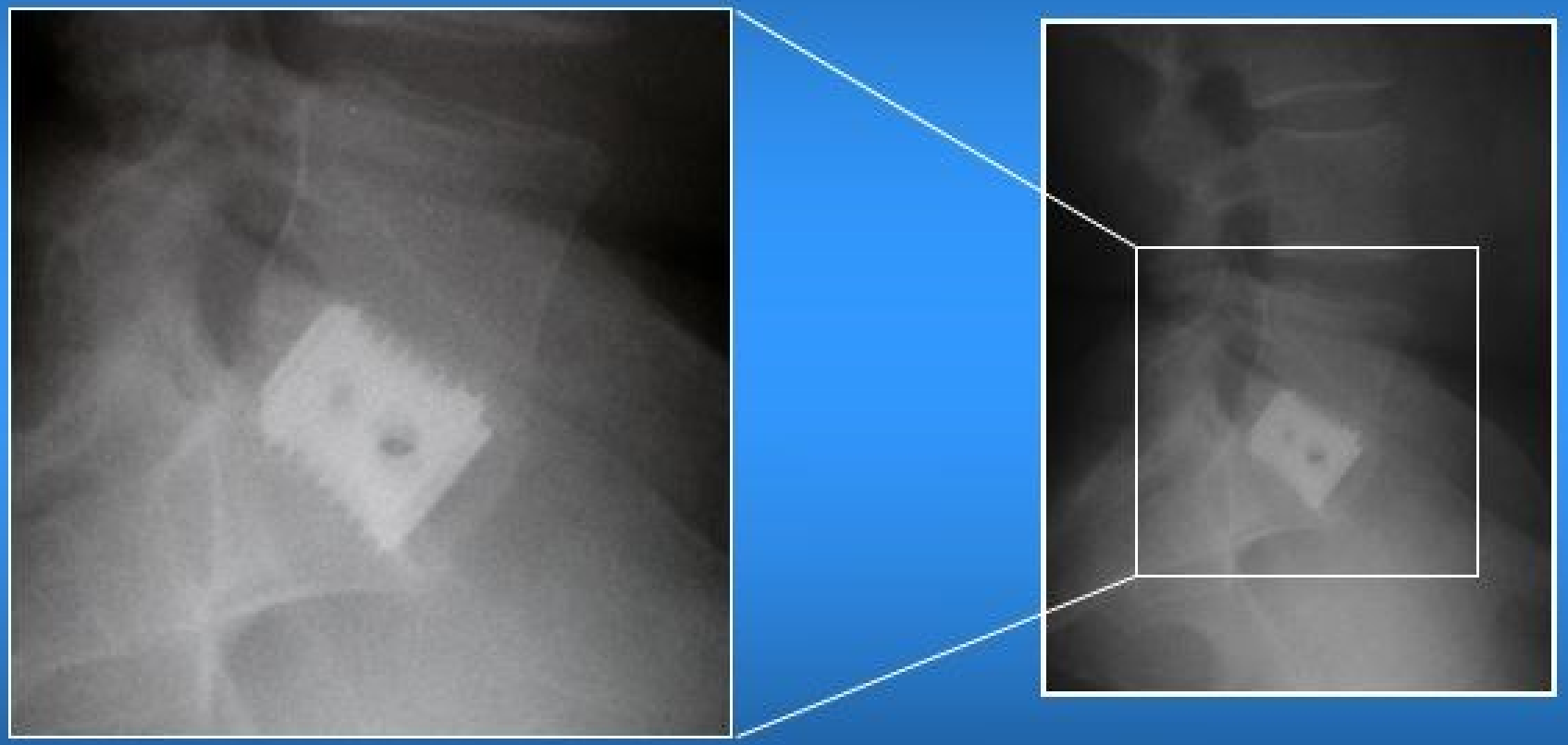


Pre-op

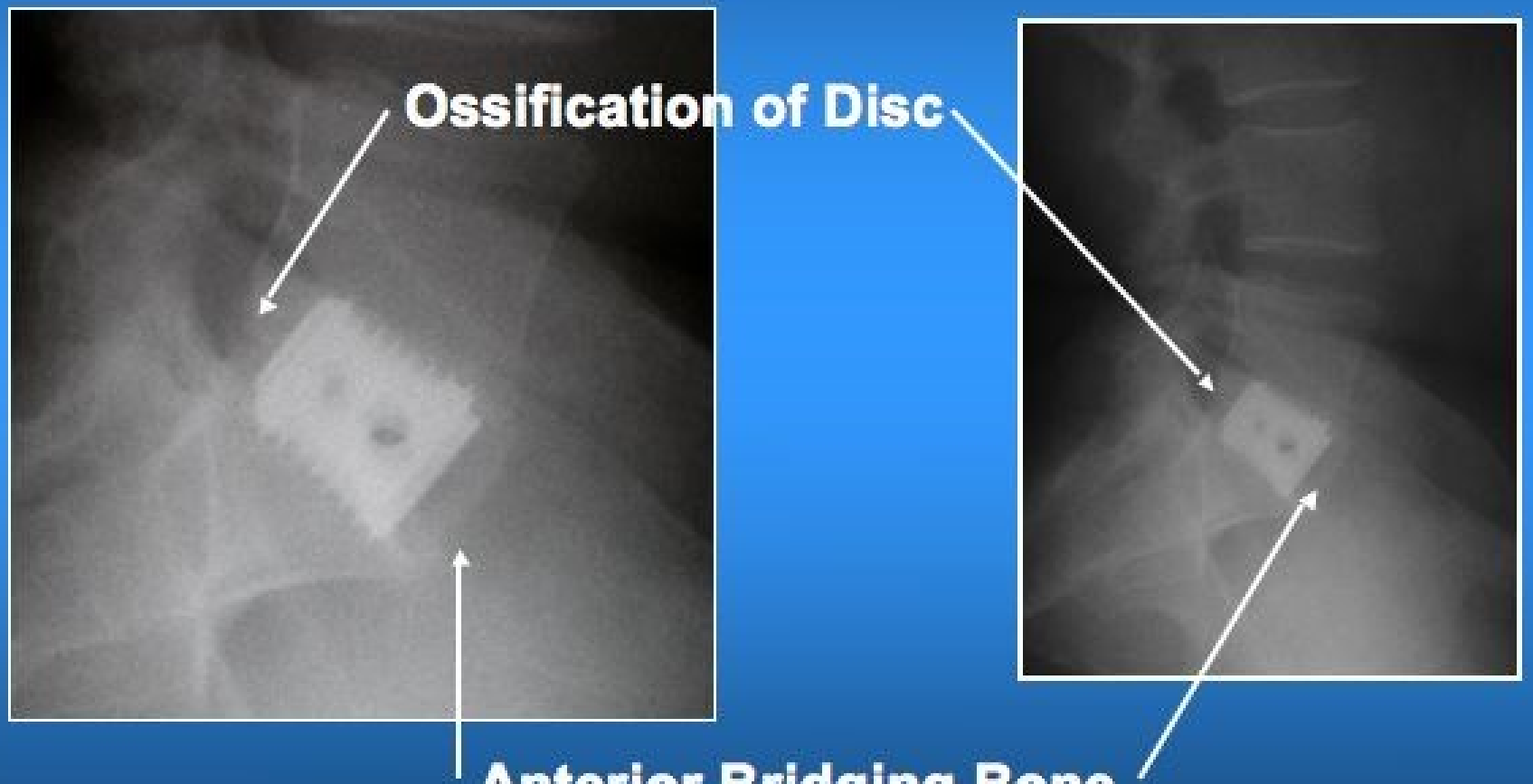
Post-op

1 yr Post-op

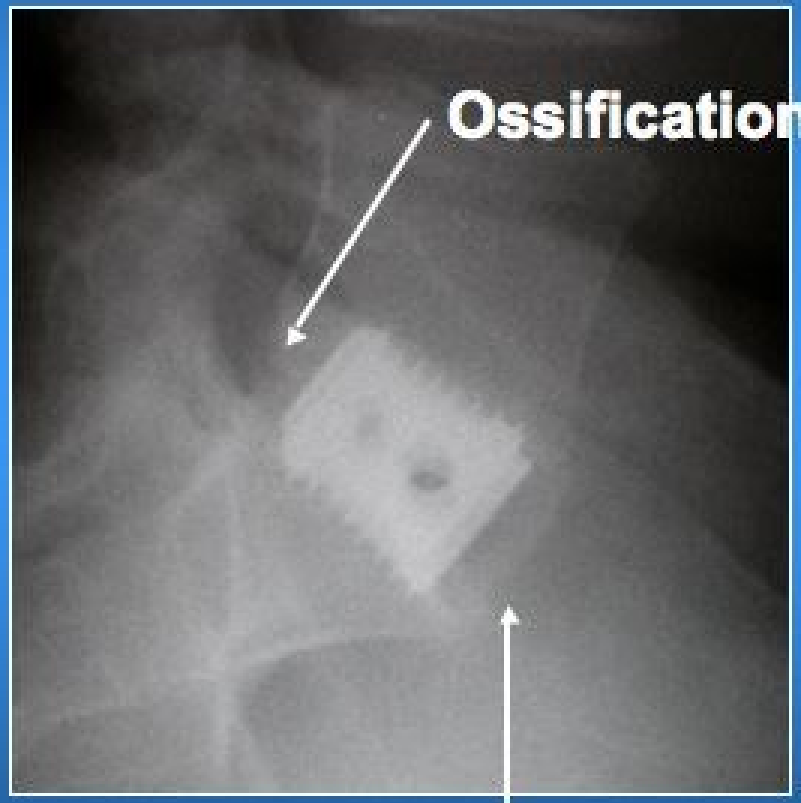
LT Cage w/ rhBMP-2

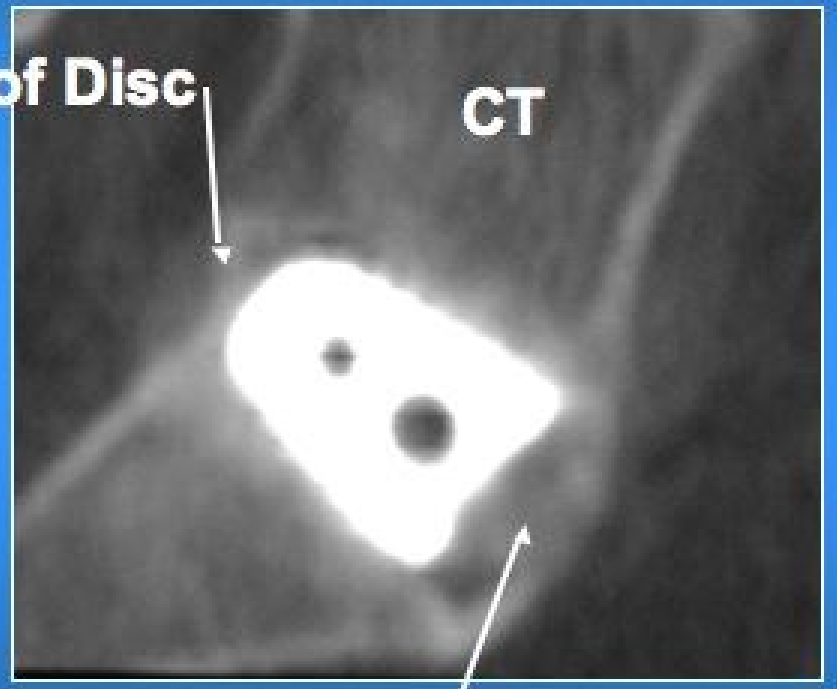


LT Cage w/ rhBMP-2



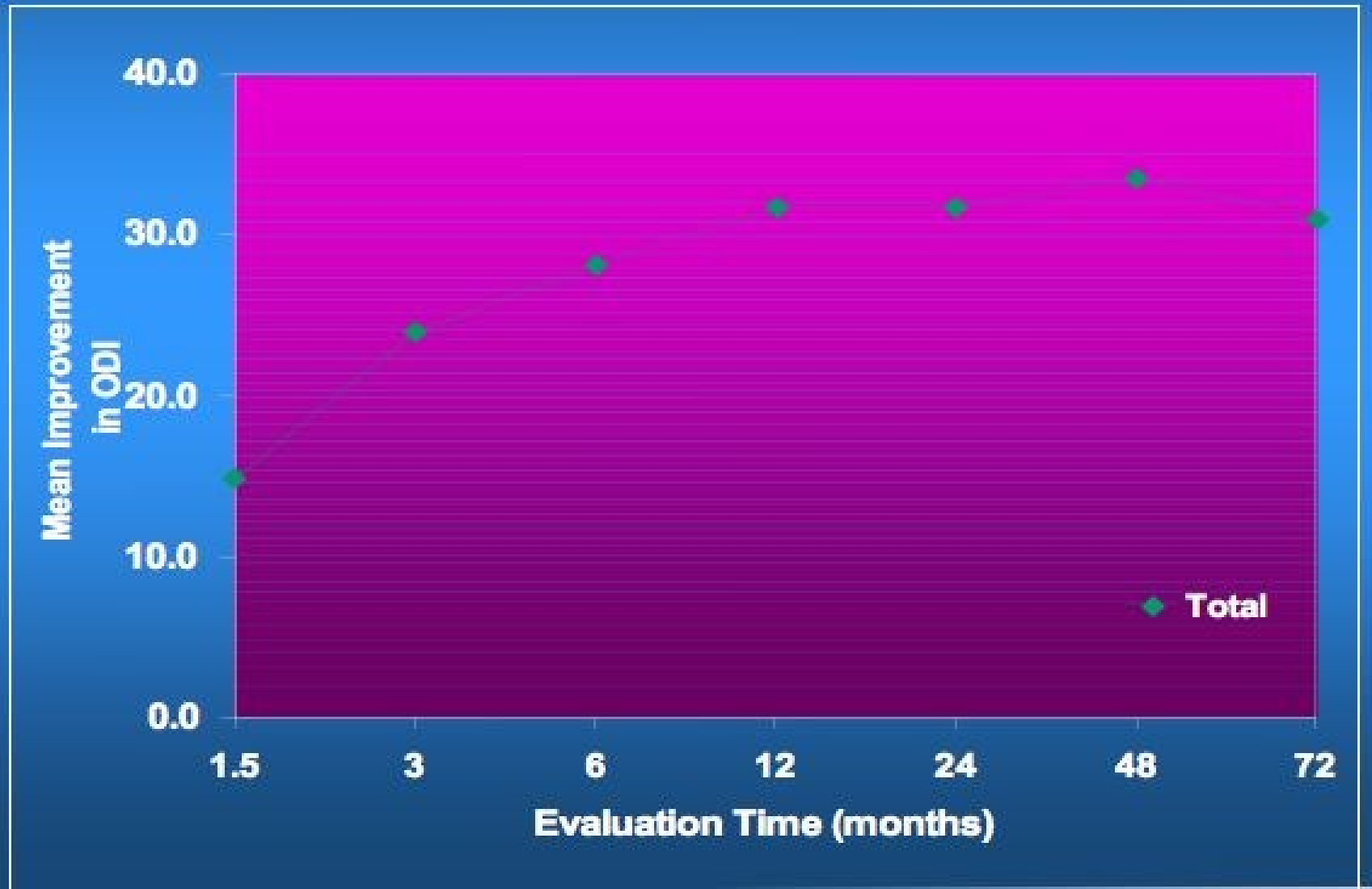
LT Cage w/ rhBMP-2





Improvement in Oswestry Scores

Low Back Pain and Disability

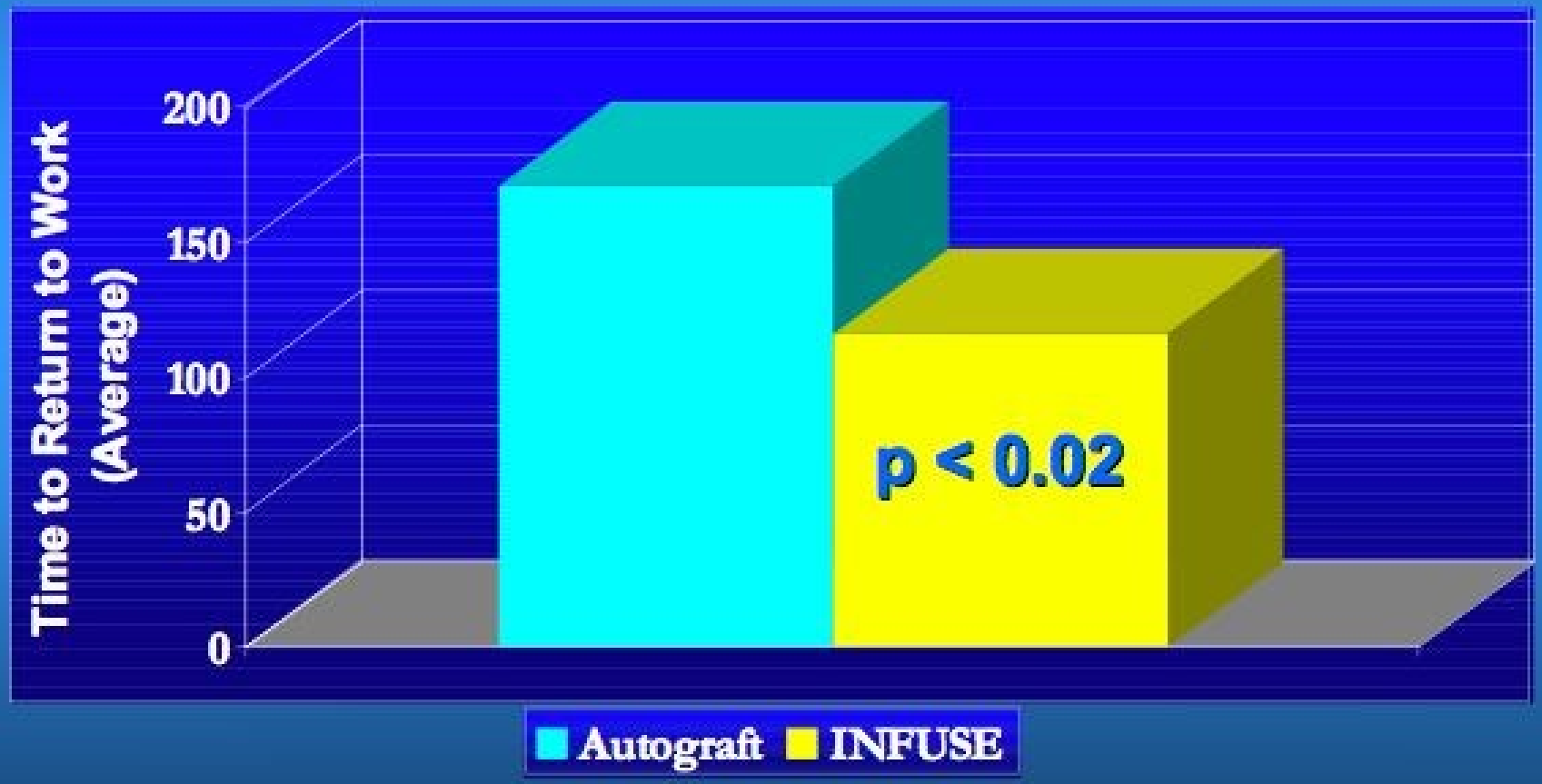


Back and Leg Pain Scores

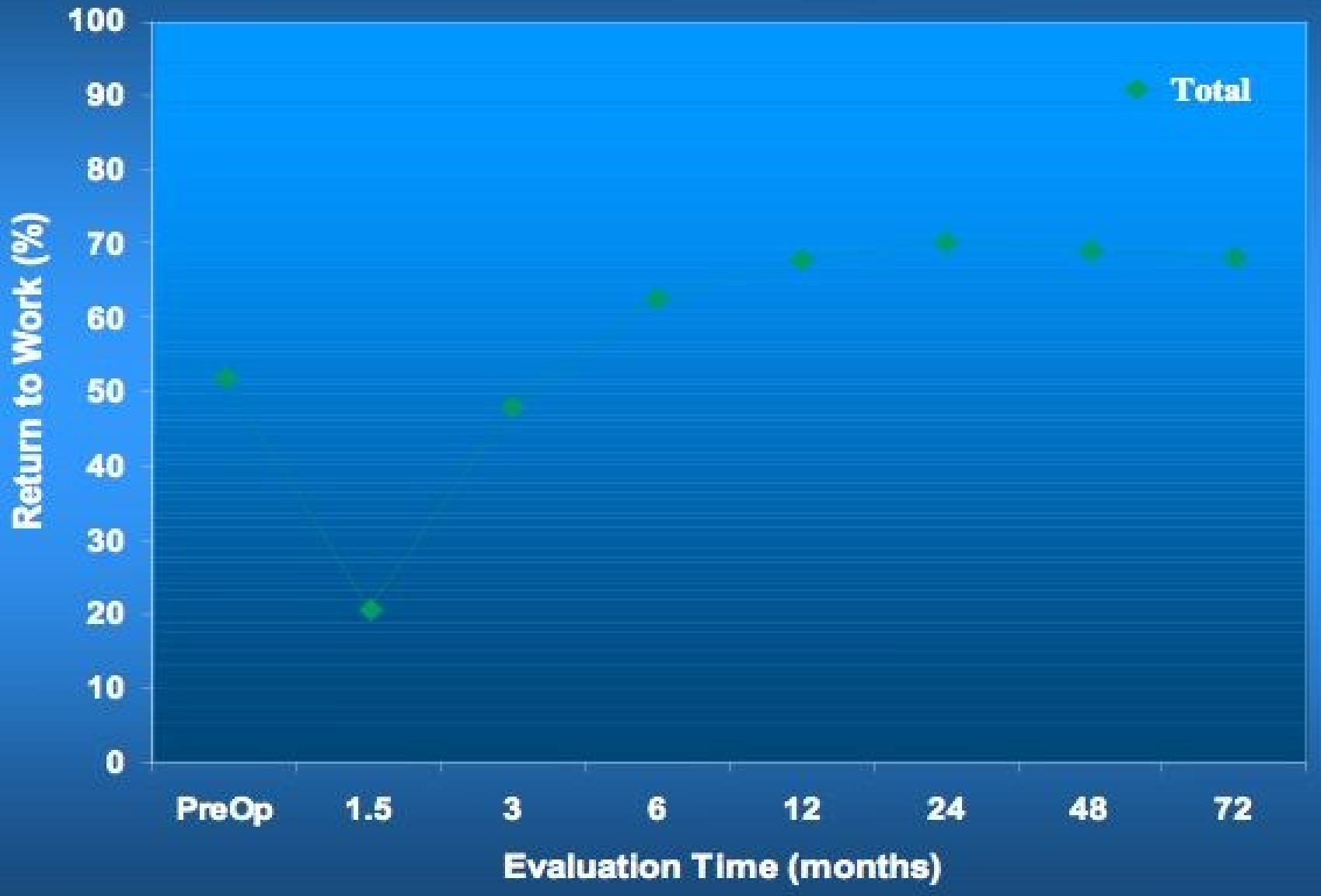
20 Point Scale: 10 pts frequency, 10 pts intensity

Return to Work

(Time-to-event analysis)



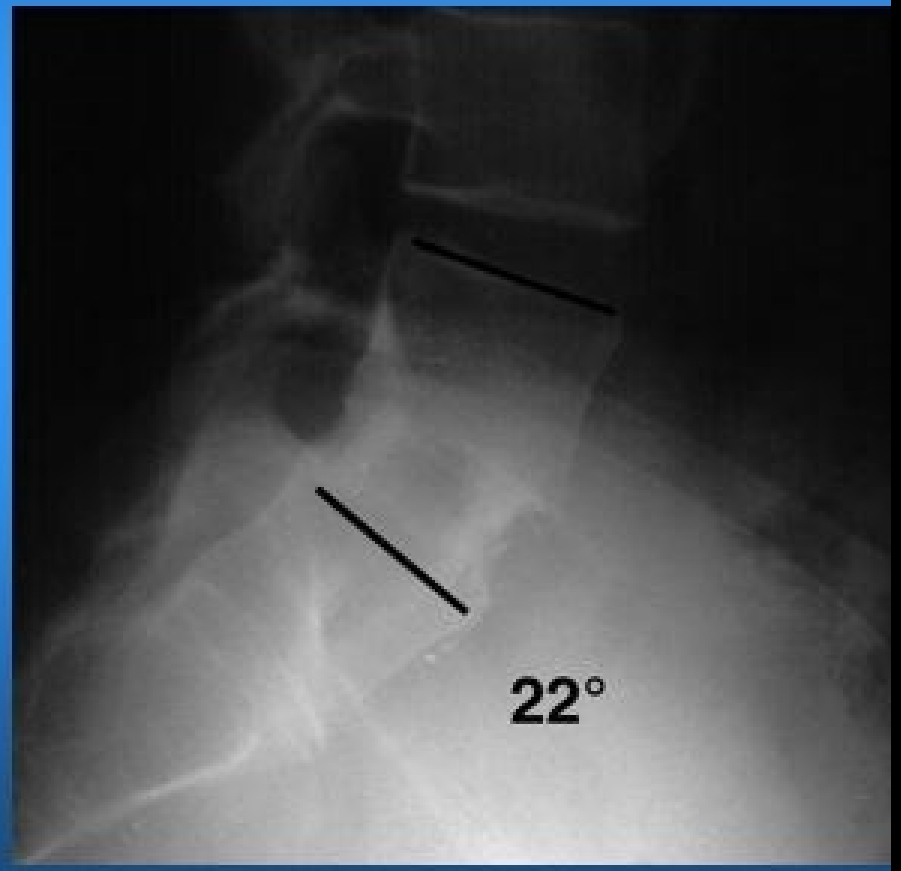
Return to Work



Use of rhBMP-2 in Combination with Structural Cortical Allografts: Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Surgery

J. Kenneth Burkus, Harvinder S. Sandhu, Matthew F. Gornet and Michael C. Longley
J Bone Joint Surg Am. 87:1205-1212, 2005. doi:10.2106/JBJS.D.02532

- Prospective
- Multi-center
  - 15 investigational sites
- Randomized 131 patients
  - 79 rhBMP-2
  - 52 Autograft control



Radiographic Fusion Success

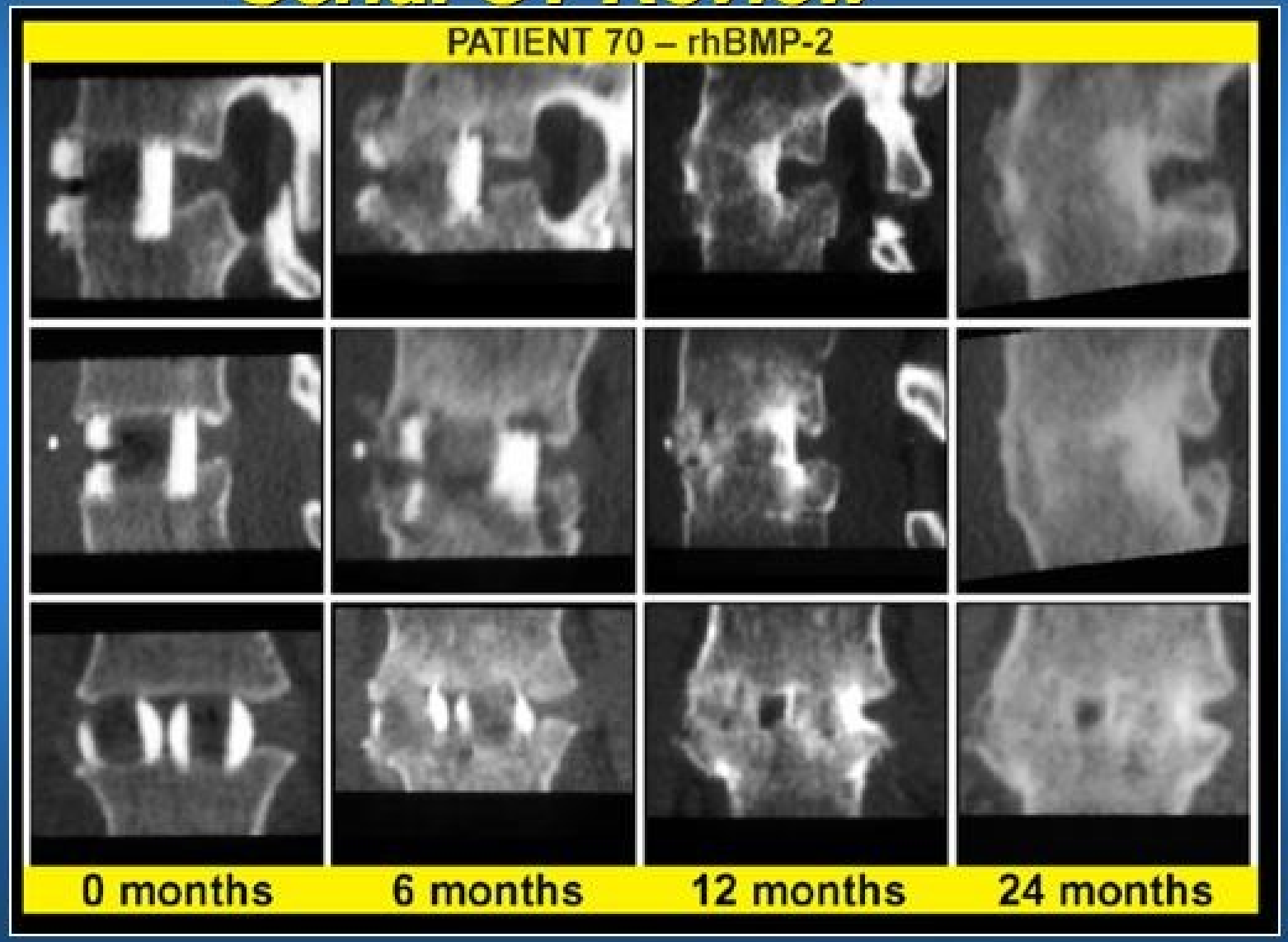
	6	12	24
Autograft	100.0	89.3	81.5
INFUSE Bone Graft	98.1	97.9	97.7

Evaluation Time (months)

Burkus et al, *JBJS*, 2005

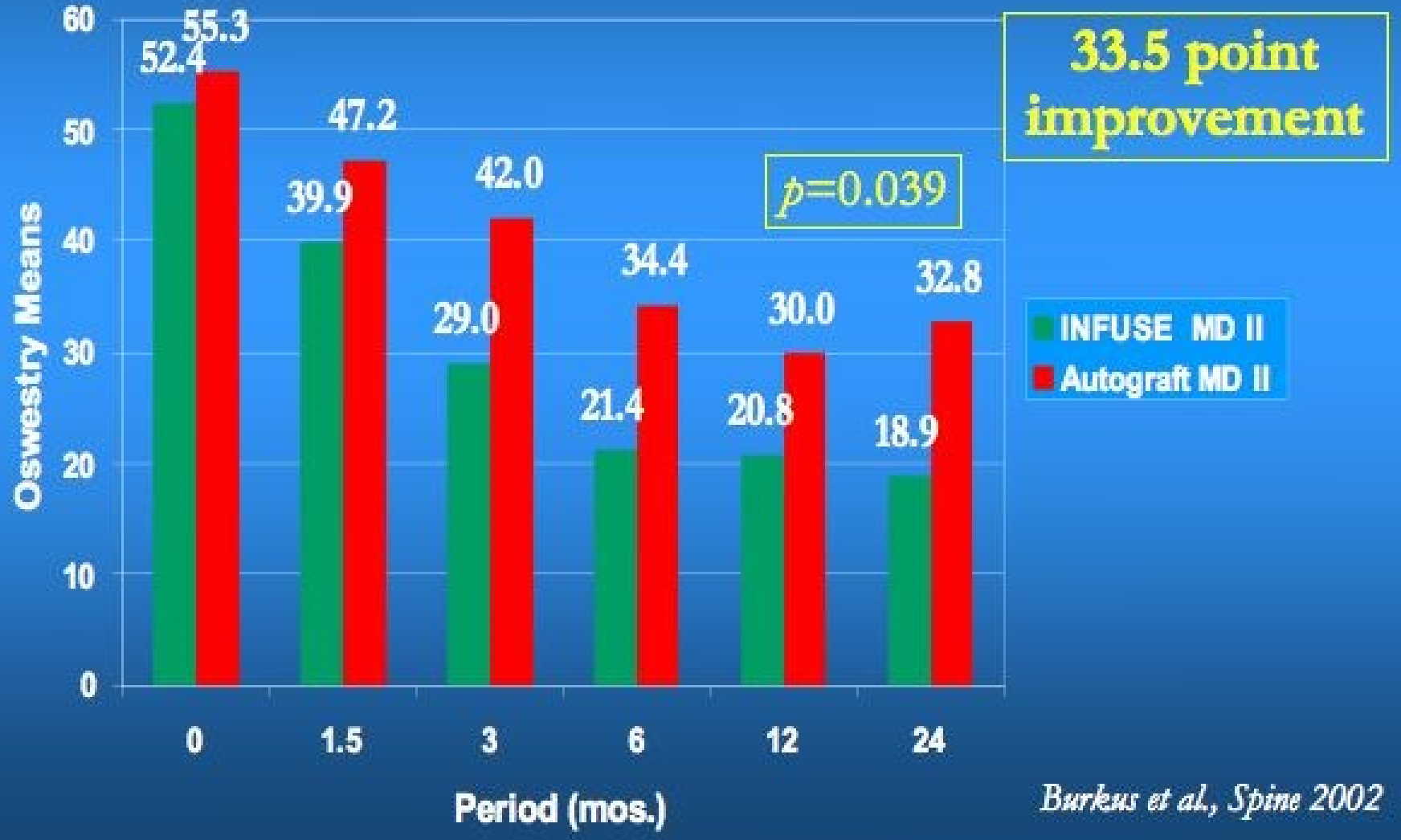
rhBMP-2 (INFUSE)

Serial CT Review



rhBMP-2 (INFUSE) vs Autograft

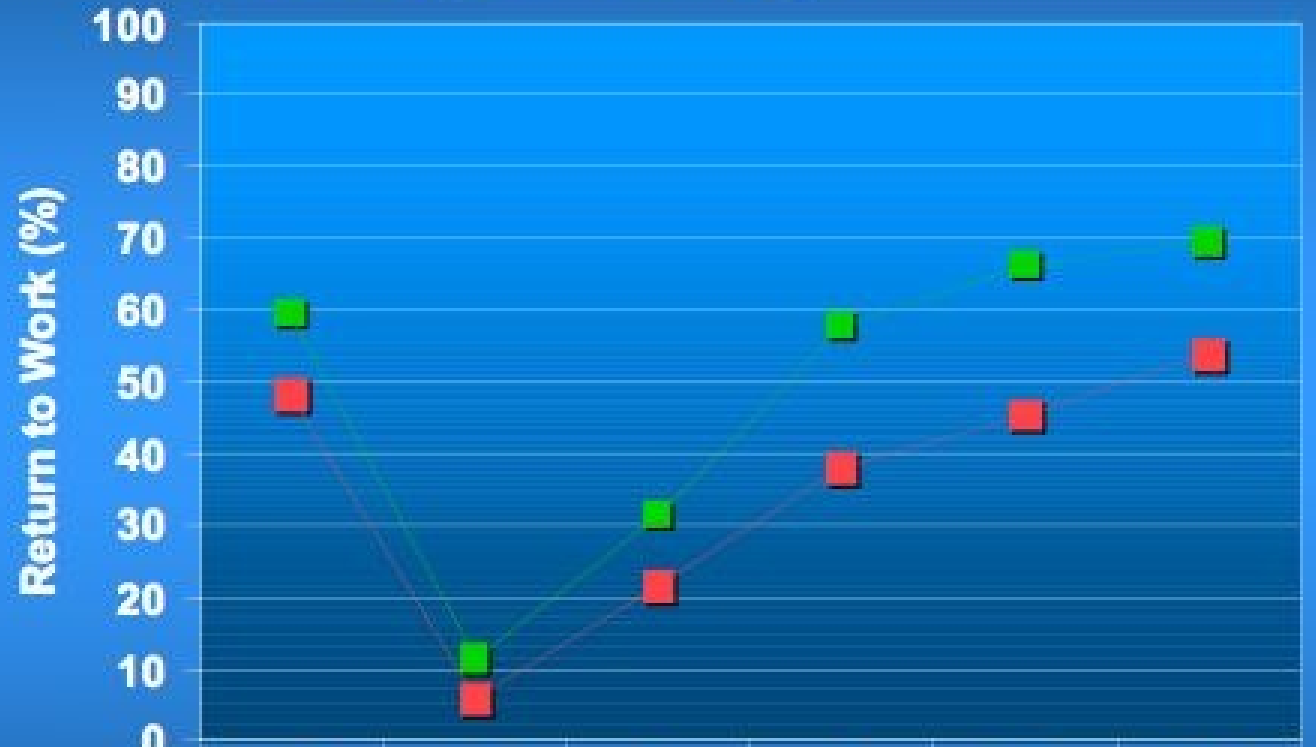
Oswestry Results



Burkus et al., Spine 2002

Work Status

(Percentage Working)



	PreOp	1.5	3	6	12	24
Autograft	48.1	5.9	21.6	38	45.5	53.8
INFUSE Bone Graft	59.5	11.5	31.6	57.7	66.2	69.4

Evaluation Time (months)

Burkus et al, *JBJS*, 2004

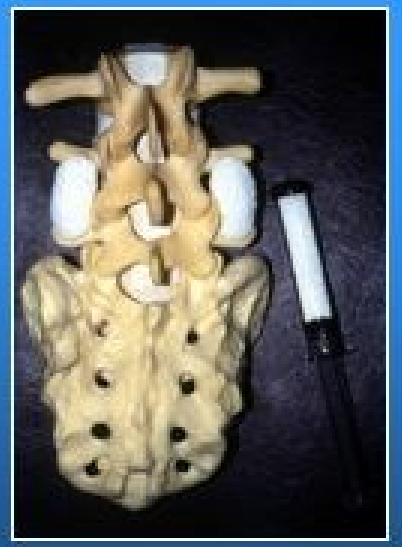
Posterolateral Fusion

Optimized Carriers and rhBMP-2 Formulations

Carrier	BCP (60 HA : 40 TCP)	CRM (Collagen + Ceramic)	INFUSE + MasterGraft
			
rhBMP-2 Concentration	2.0 mg/mL	2.0 mg/mL	1.5 mg/mL
rhBMP-2 Dose	20 mg/side	20 mg/side	6 mg/side

Canadian rhBMP-2/Ceramic BCP Posterolateral Lumbar Fusion Study

- **Prospective, randomized, multicenter study – 97 patients (Level-1 data)**
  - 1 and 2 level instrumented posterolateral fusions
    - 48 - rhBMP-2 Investigational
    - 49 – Autograft control
- Outcomes: similar in both groups
- Fusion rates:
  - 97.1% - rhBMP-2 Investigational
  - 60.6% - autograft control

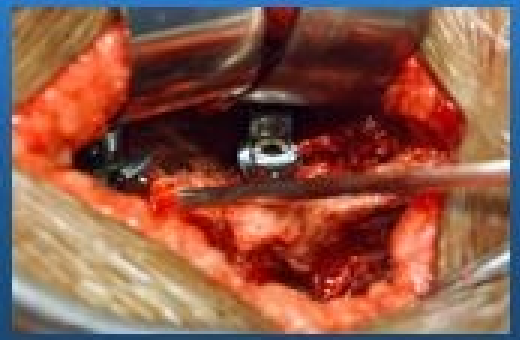


Alexander, et al AAOS 2005

Study Design

Instrumented Single-Level Posterolateral Lumbar Fusion

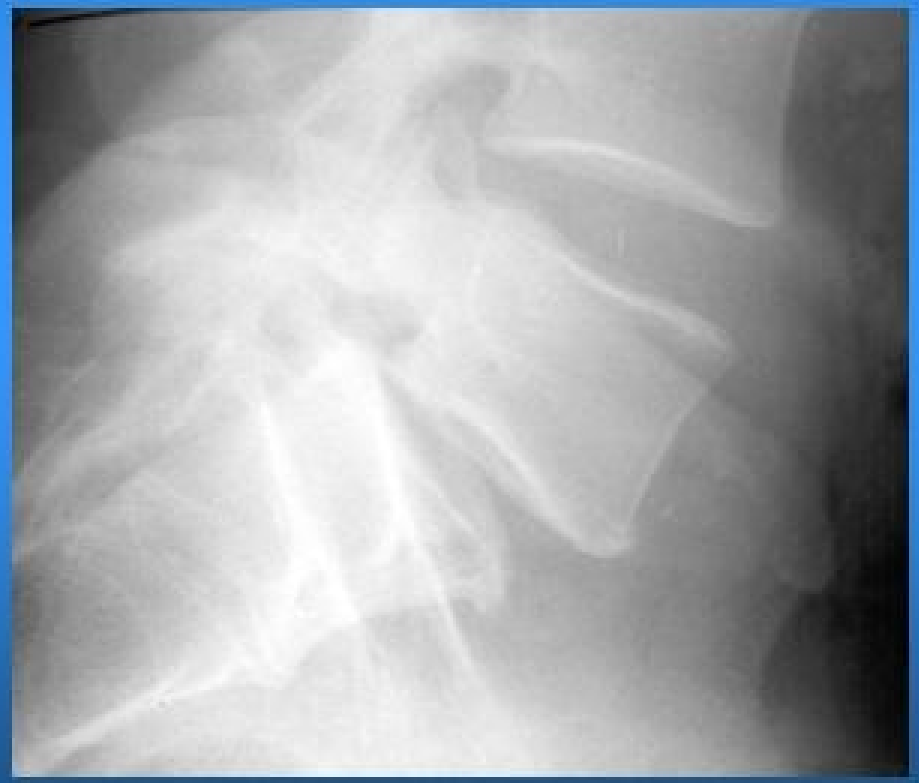
- Randomized, controlled
  - 239 patients with AMPLIFY™ rhBMP-2 Matrix (Medtronic Sofamor Danek)
    - 20 cc matrix containing 2.0 mg/cc rhBMP-2
  - 224 patients with iliac crest bone graft
  - Local bone was discarded in both groups
  - No interbody fusion was performed



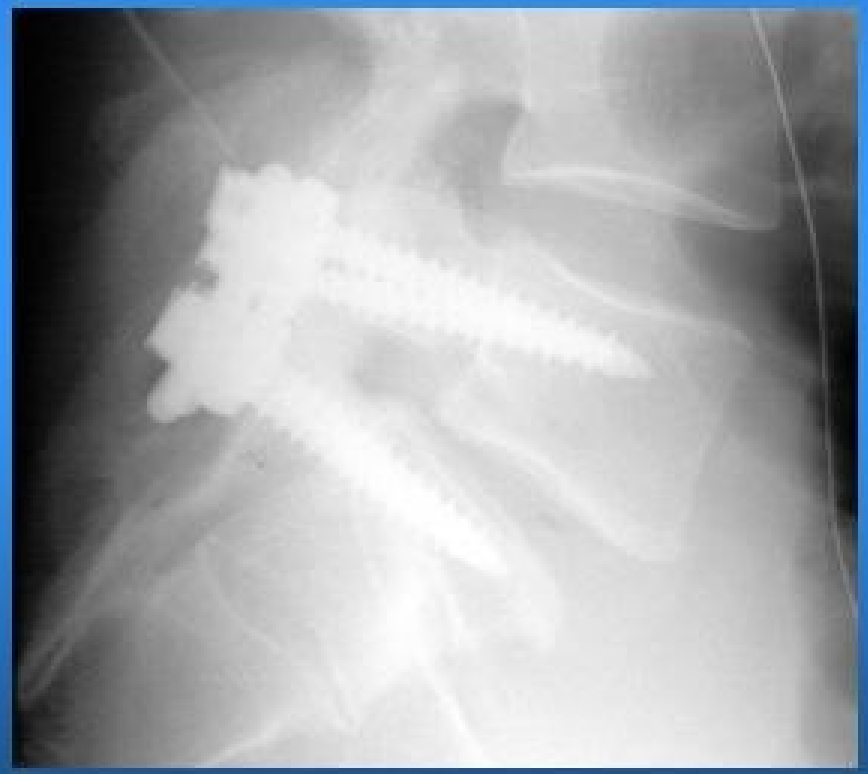
Improvement in Oswestry Disability Index

Significant improvements from pre-operative status in both groups ($p<0.001$)

Case Presentation

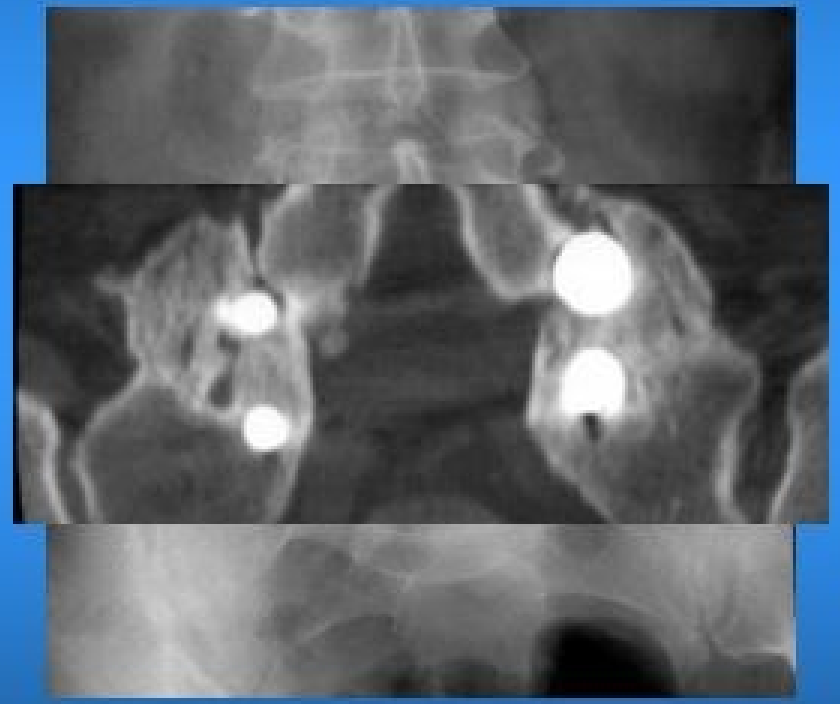


Immediate Postoperative



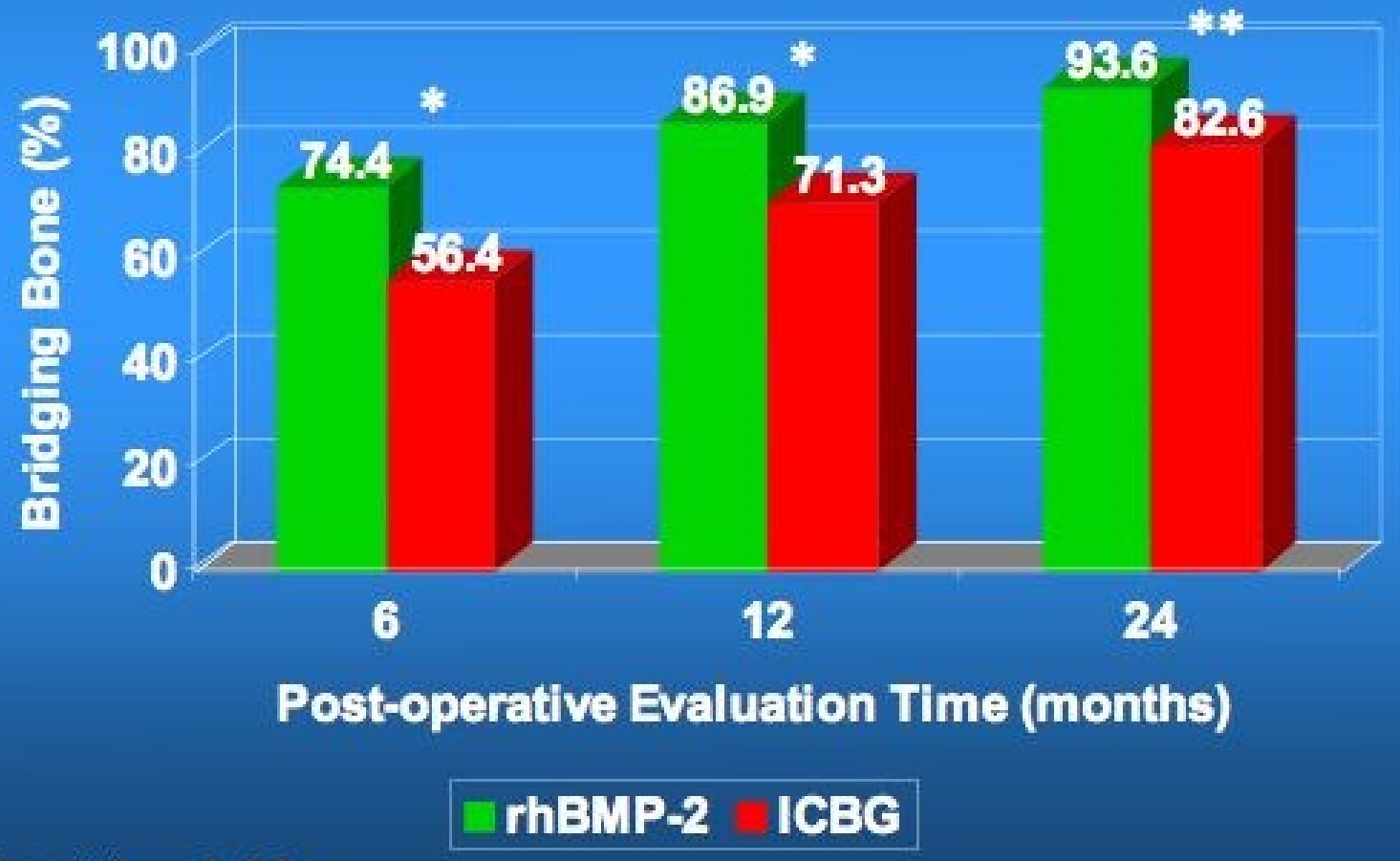
rhBMP-2/CRM Clinical Study

6-month radiographs



Incidence of Bridging Bone

CT Assessment Only

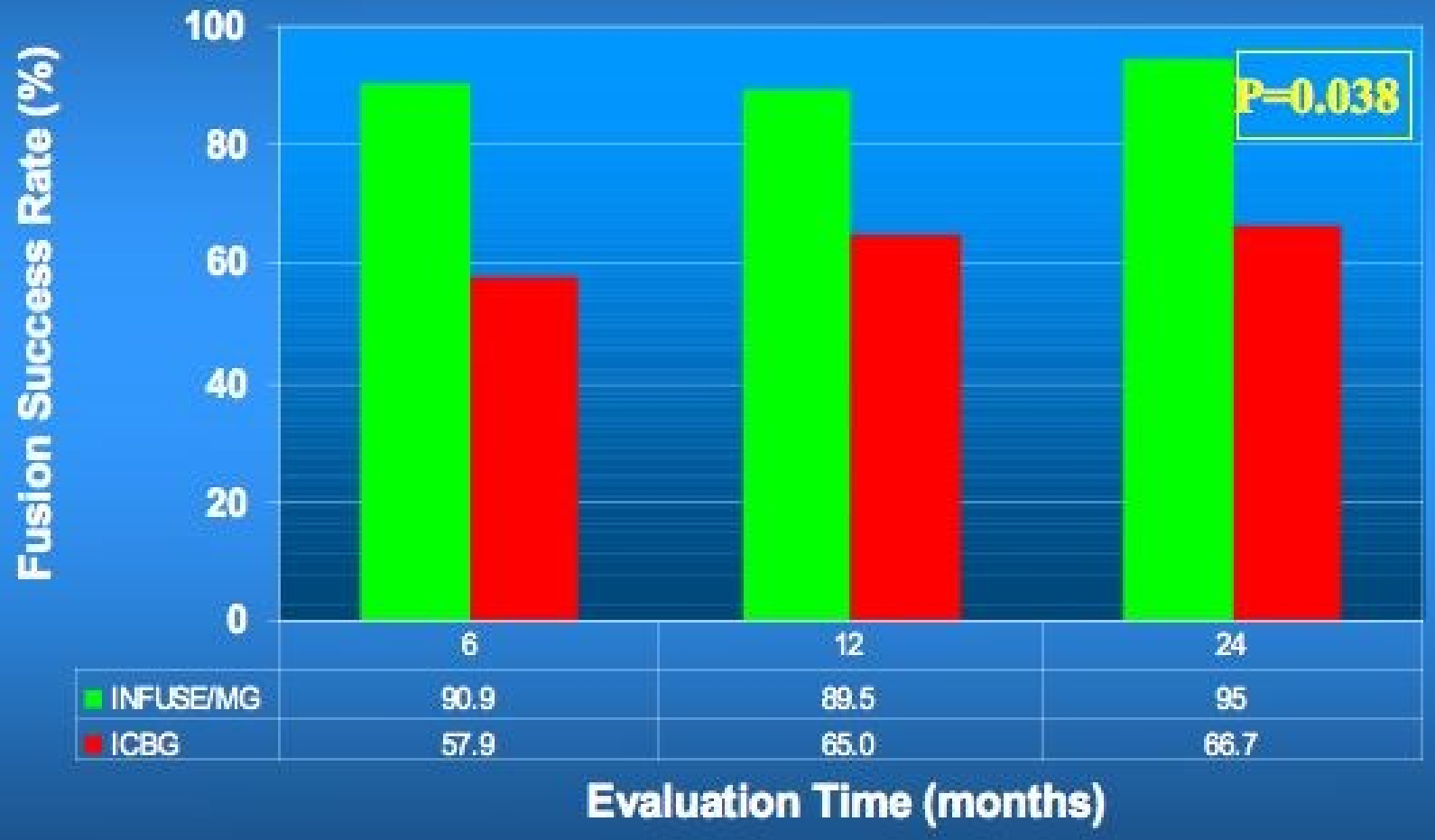


* p<0.001, **p=0.024

INFUSE Bone Graft and MasterGraft Ceramic Granules

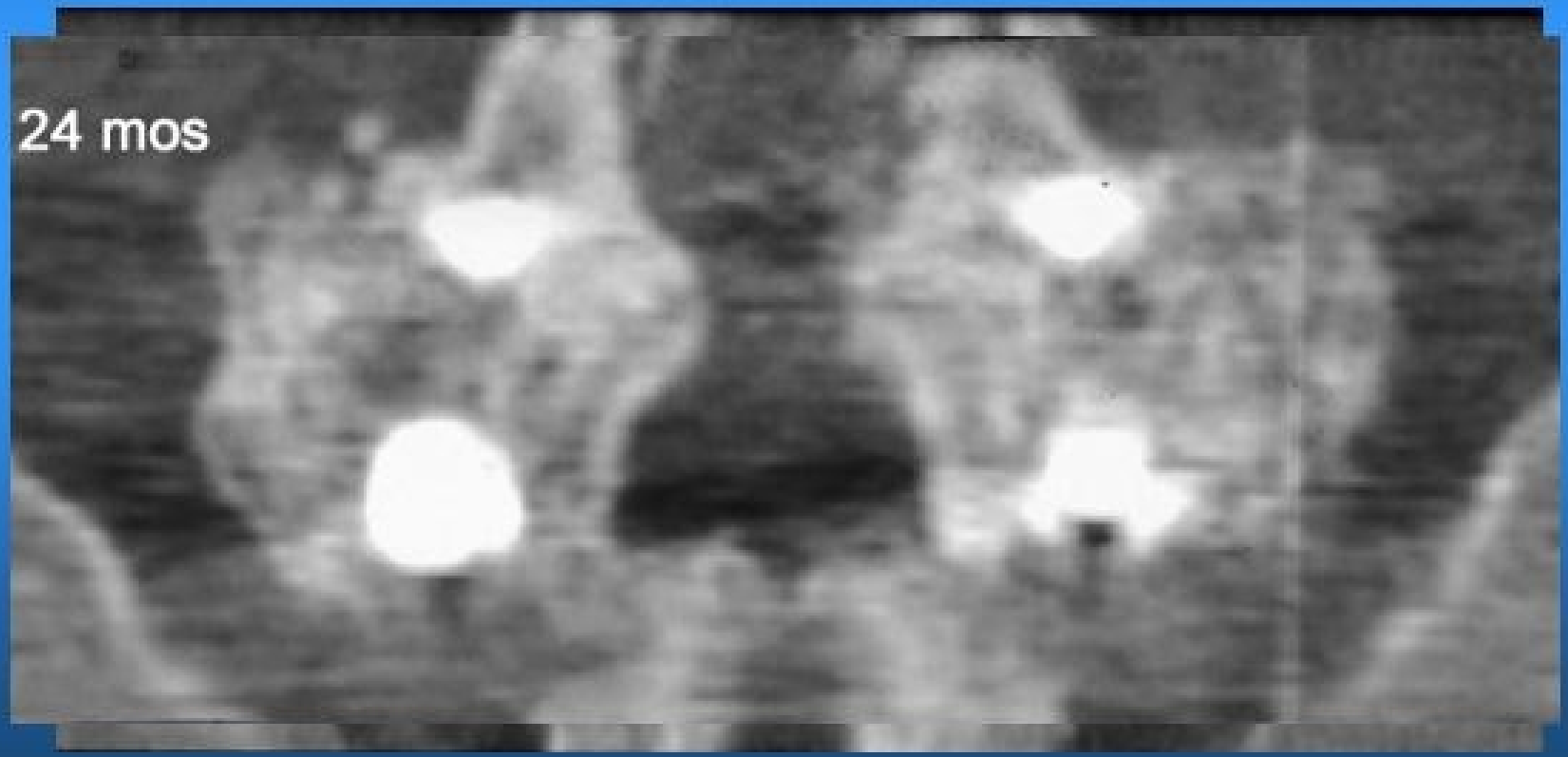
- Prospective, randomized, multicenter study
  - 1 level instrumented posterolateral fusion
  - Investigational
    - Large II kit INFUSE Bone Graft
      - 1.5 mg/cc on ACS carrier
      - 8 cc containing 12 mg rhBMP-2
    - MasterGraft Granules
      - 15% HA / 85% TCP
  - Control
    - ICBG
      - All locally harvested bone was discarded

CT Evidence of Bridging Trabecular Bone

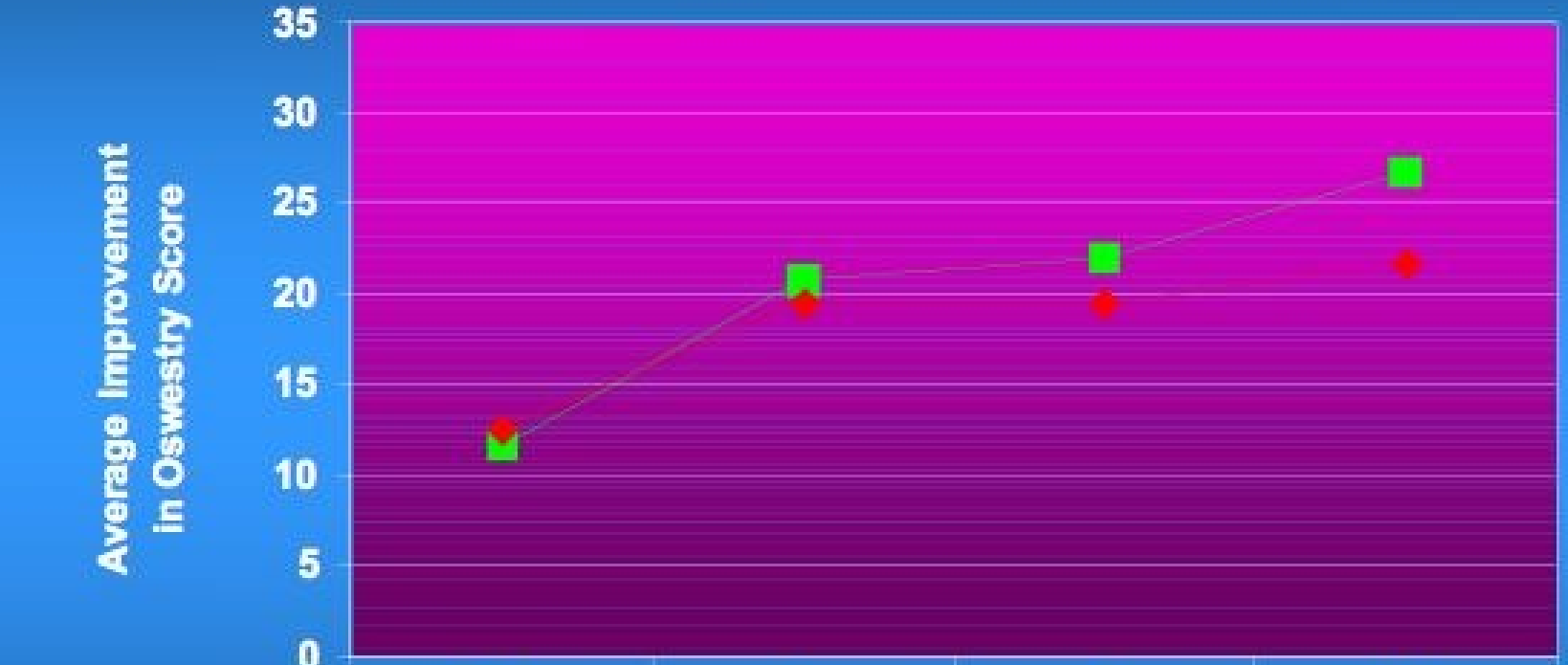


INFUSE Bone Graft and MasterGraft Ceramic Granules

- CT scan Fusion Assessment



Improvement in Low Back Pain and Disability
(Decrease in ODI)



	1.5	3	6	12
INFUSE/MG	11.7	20.8	22	26.8
ICBG	12.6	19.6	19.5	21.8

Evaluation Time (months)

ORIGINAL ARTICLE

Use of Recombinant Human Bone Morphogenetic Protein-2 as an Adjunct in Posterolateral Lumbar Spine Fusion

A Prospective CT-Scan Analysis at One and Two Years

Kern Singh, MD, Joseph D. Smucker, MD,† and Scott D. Boden, MD‡*

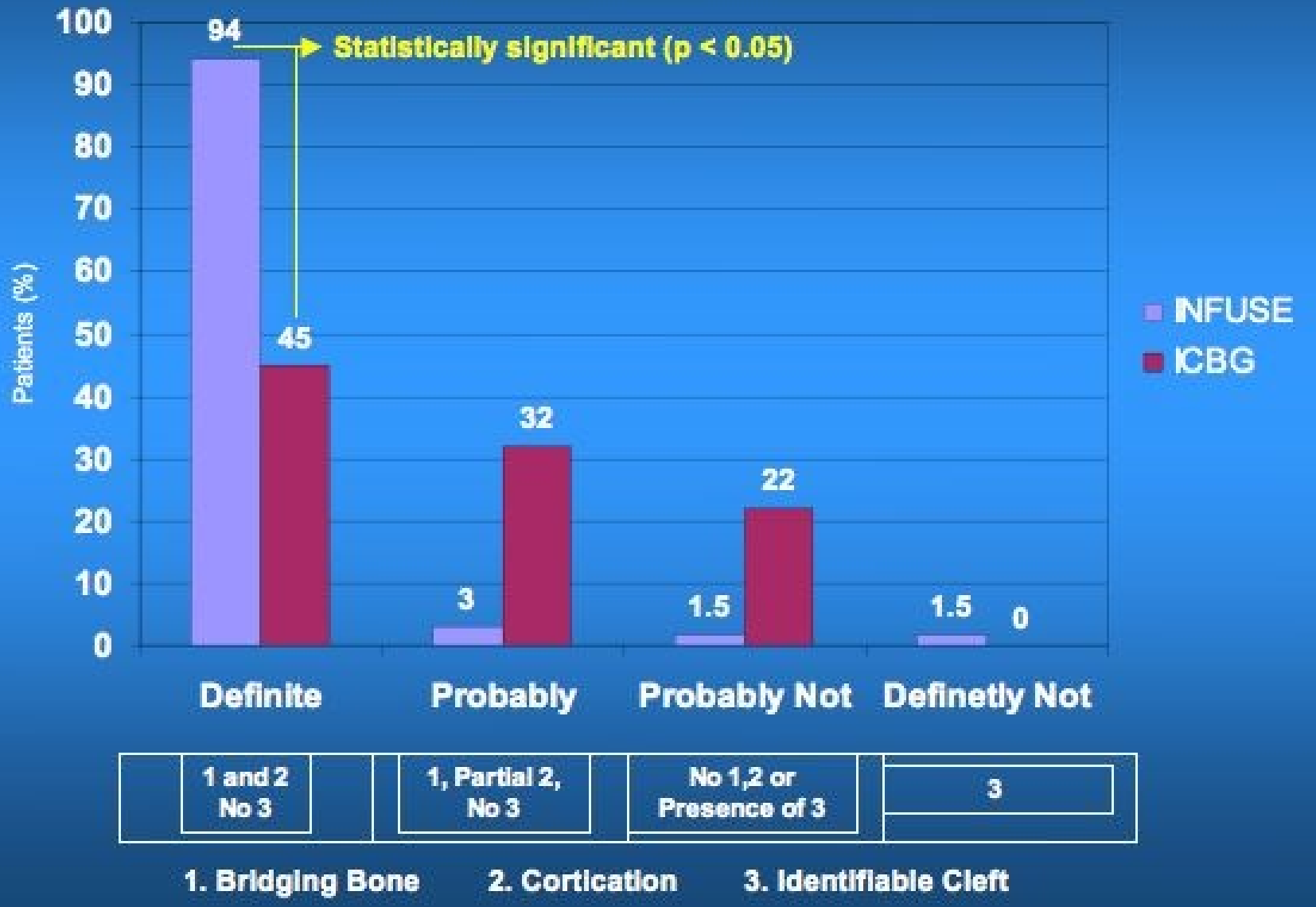
J Spinal Disord Tech • Volume 19, Number 6, August 2006

Study Design

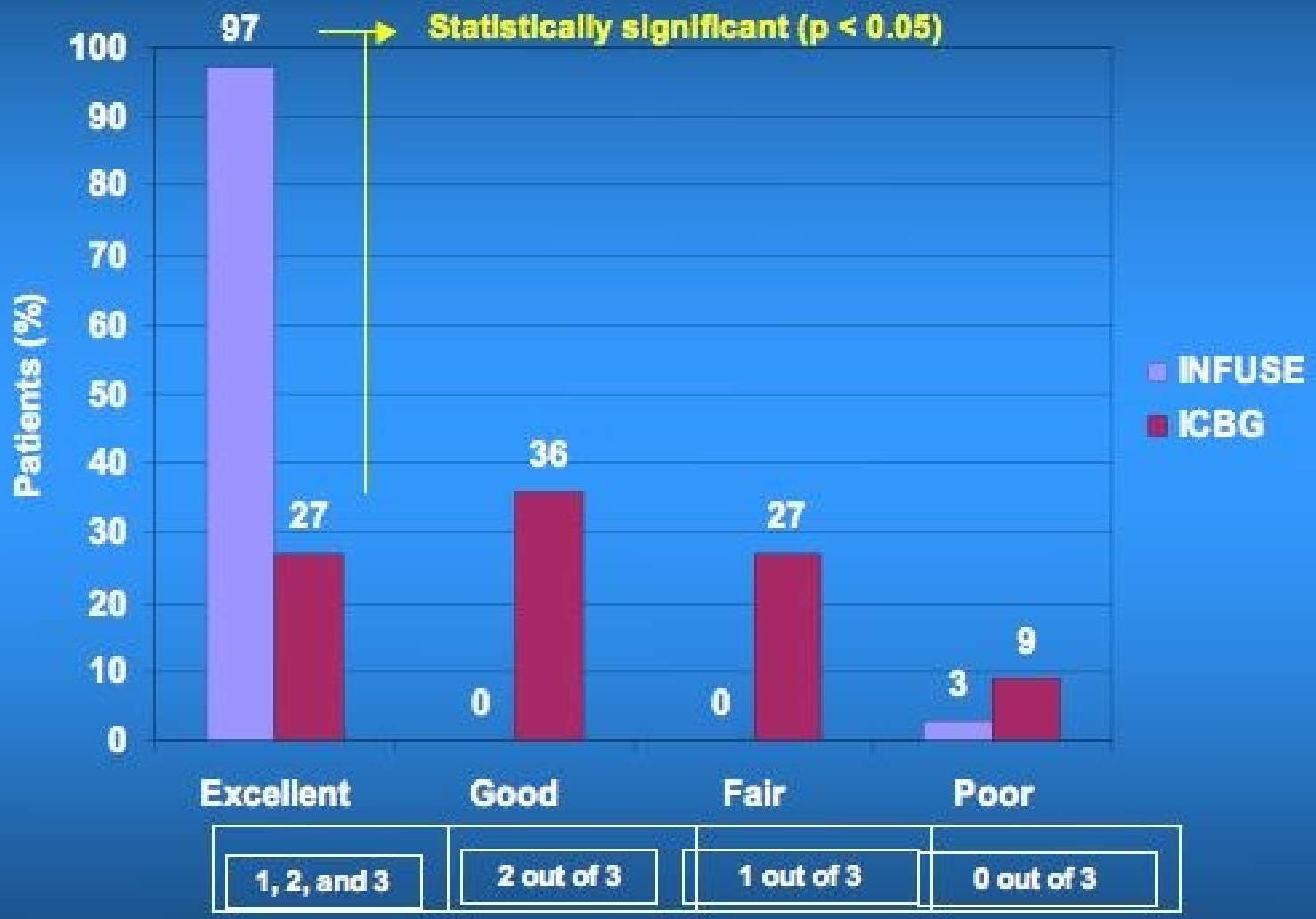
- Purpose:
  - To evaluate the presence, quality and speed of radiographic fusion induced by INFUSE® Bone Graft and a bulking agent in PL fusion procedures
- Groups:
  - INFUSE® Bone Graft + ICBG + Local Bone (n = 39 patients & 70 levels)
    - (1) Large II kit per level
  - ICBG + Local Bone (n = 11 patients & 22 levels)
  - M8 titanium or TSRH instrumentation
- Methods:
  - Single level & multi-level instrumented PL fusion
  - Range: 1- 3 levels
- Duration:
  - 24 month study
- Fusion Assessment Methodology:
  - Thin slice CTs

2 – 4 cc Laminectomy Bone

24 Month Fusion Assessment



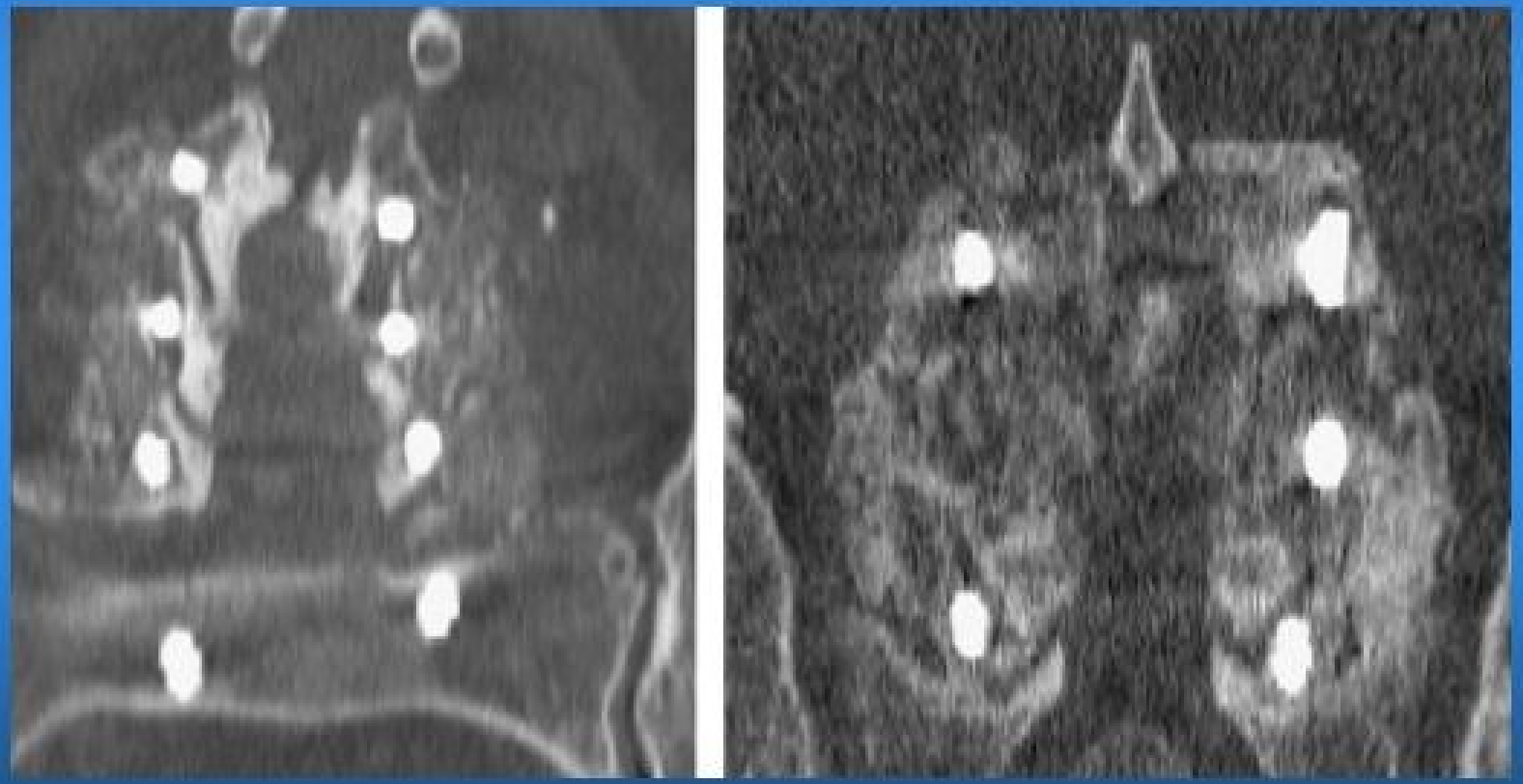
24 Month Quality of Fusion



1. Large, beyond TP's
2. Convex
3. Homogeneous

Radiographic Results

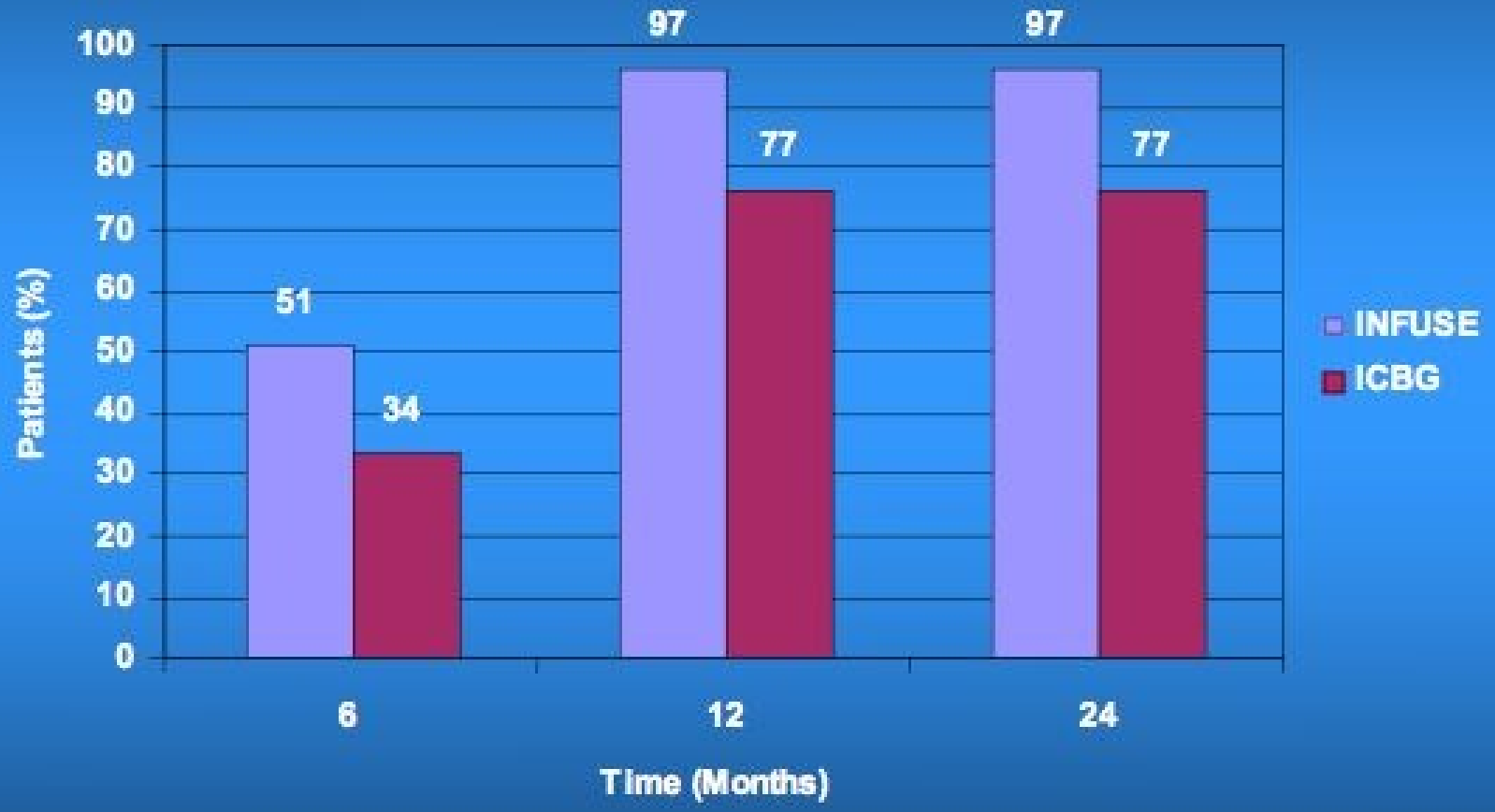
(6 month CT Scans)



ICBG

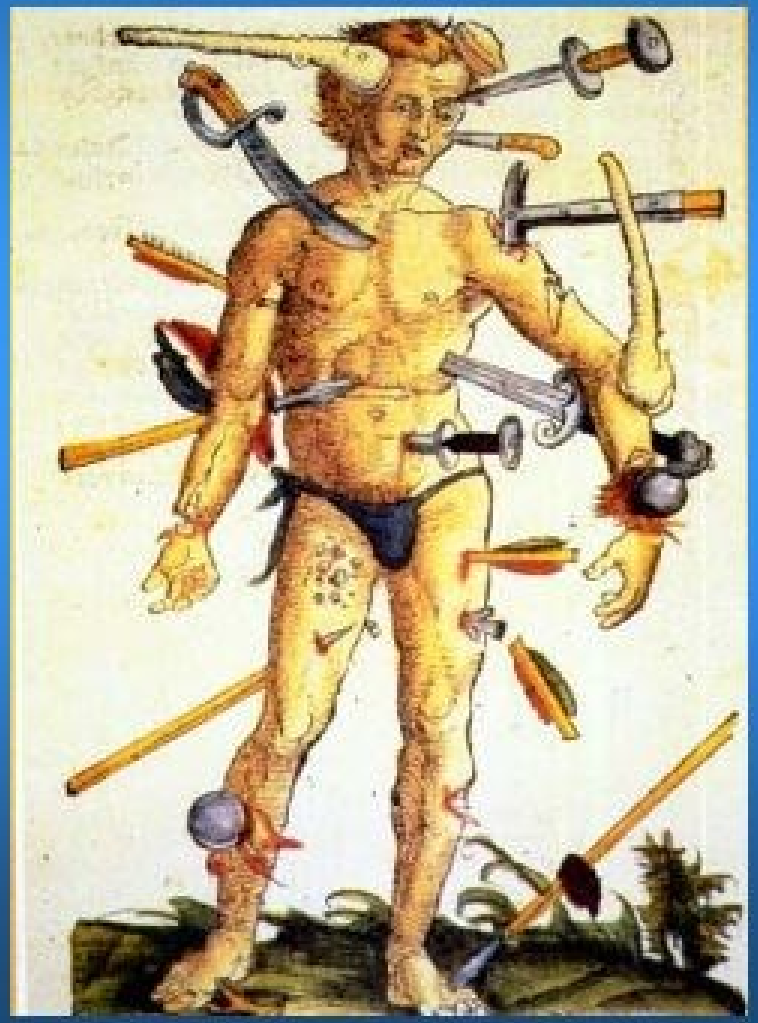
INFUSE® Bone Graft + ICBG

Speed of Fusion



% of patients graded as definitely + probably fused

INFUSE and Trauma



Acute Tibia Fractures

Govender S. et al. JBJS 2002

- 450 open tibia fractures (Grade I to IIIB)
- 44% reduction in 2nd interventions
- Patients healed 39 days faster

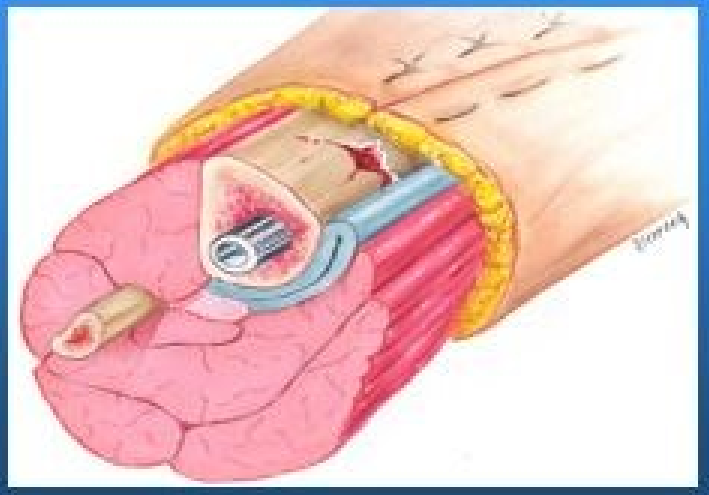
Swiontkowski M. et al. JBJS 2006

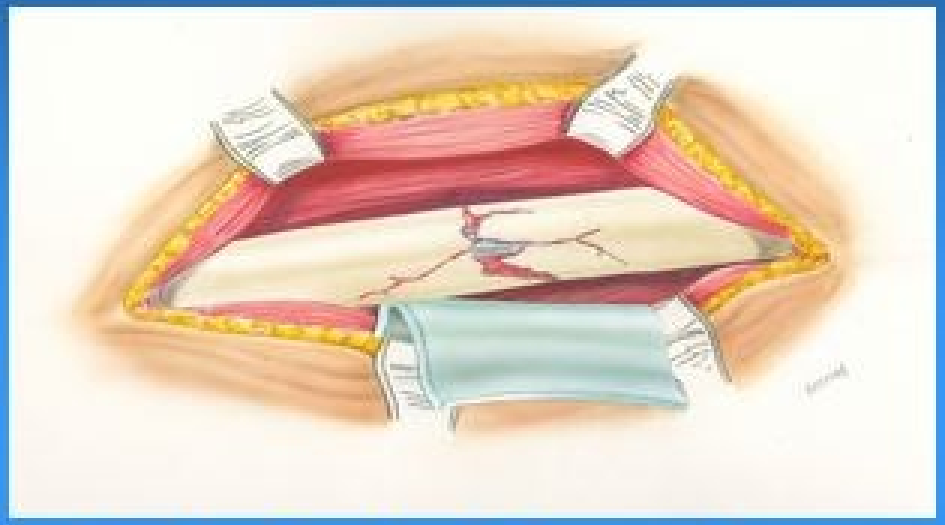
- 131 open tibia fractures (Grade IIIA &IIIB)
- 90% reduction in need for bone grafting
- 48% reduction in incidence of infection

Surgical Technique

INFUSE is implanted after IM nail placement:

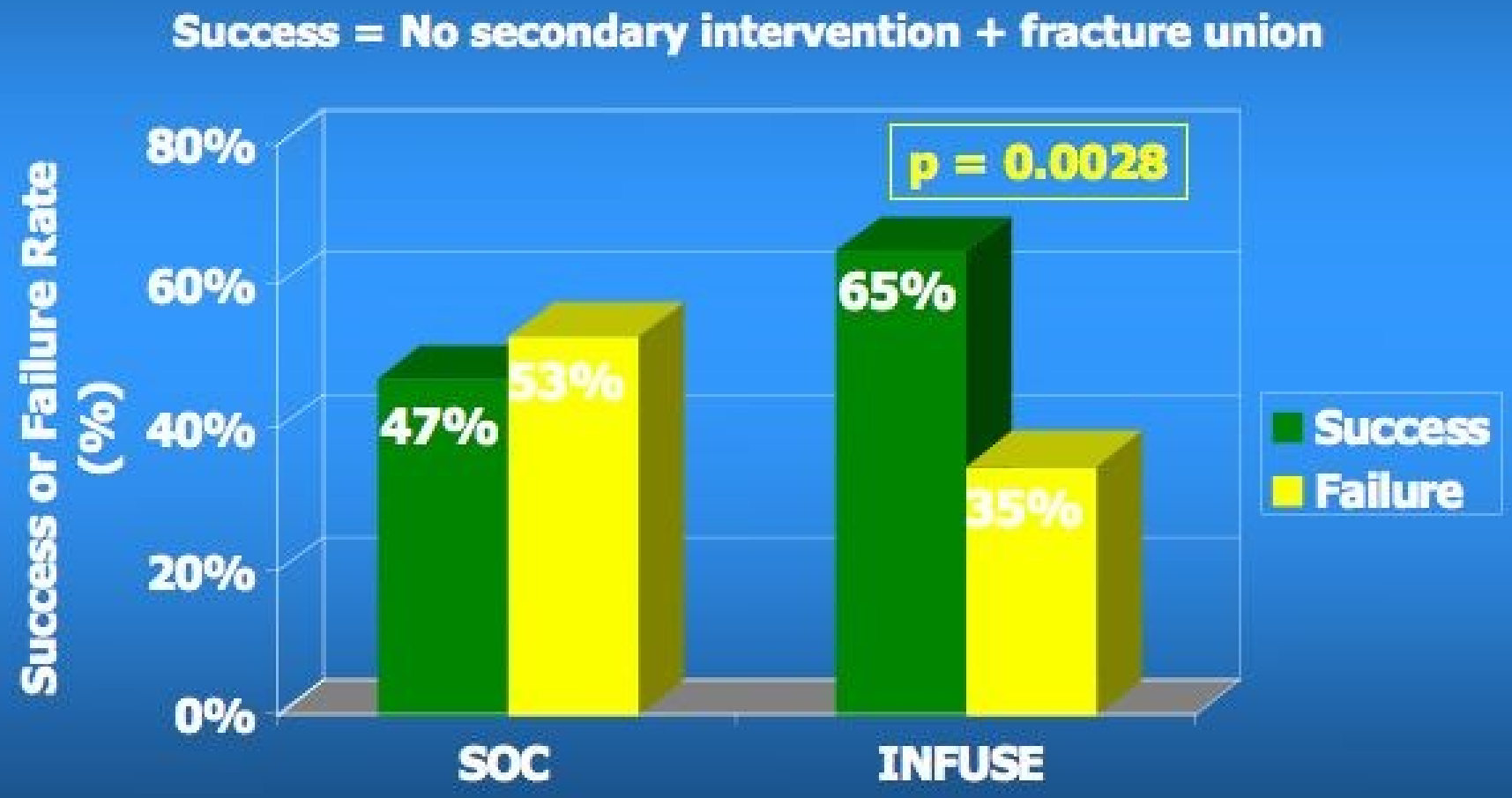
- **At definitive wound closure (may be at later surgery)**





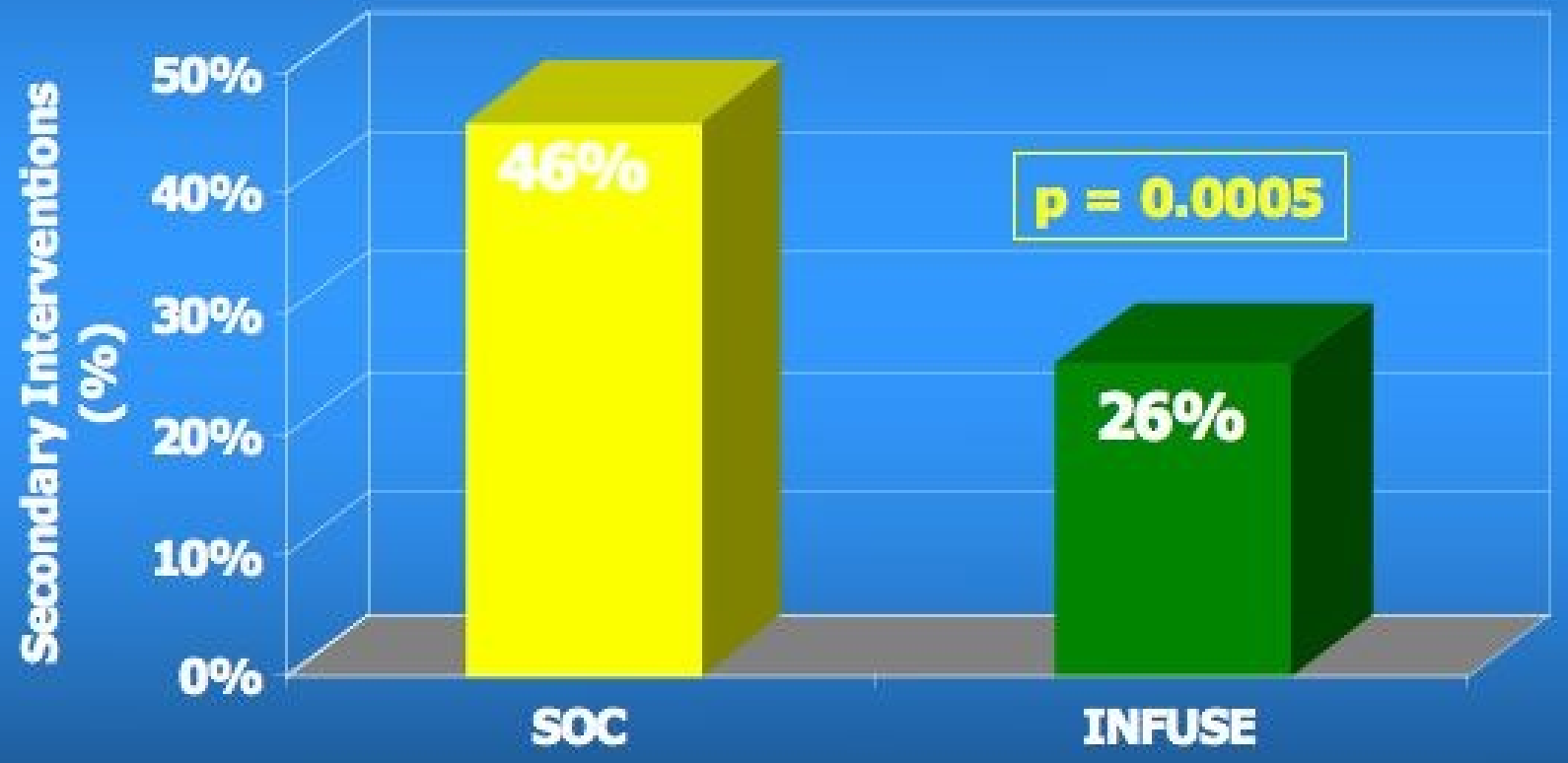
- **Bridge fracture fragments**
- **Do not strip periosteum**
- **Accessible through the wound (typically no incision),**
- **Place posteriorly near muscle tissue, if possible (may be folded)**

INFUSE Improves Rate of Overall Clinical Success by 28%



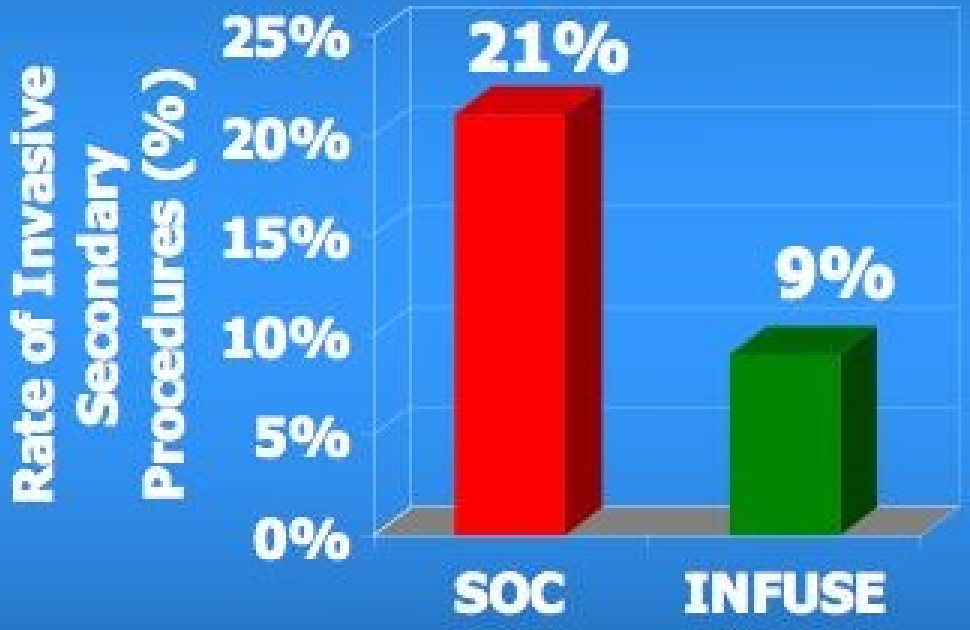
BESTT, Govender *et al. JBJS* 84A: 2123-34, 2002

INFUSE Reduces Risk of Secondary Interventions by 44%



BESTT, Govender *et al. JBJS* 84A: 2123-34, 2002

INFUSE Reduces Risk of Invasive Secondary Procedures



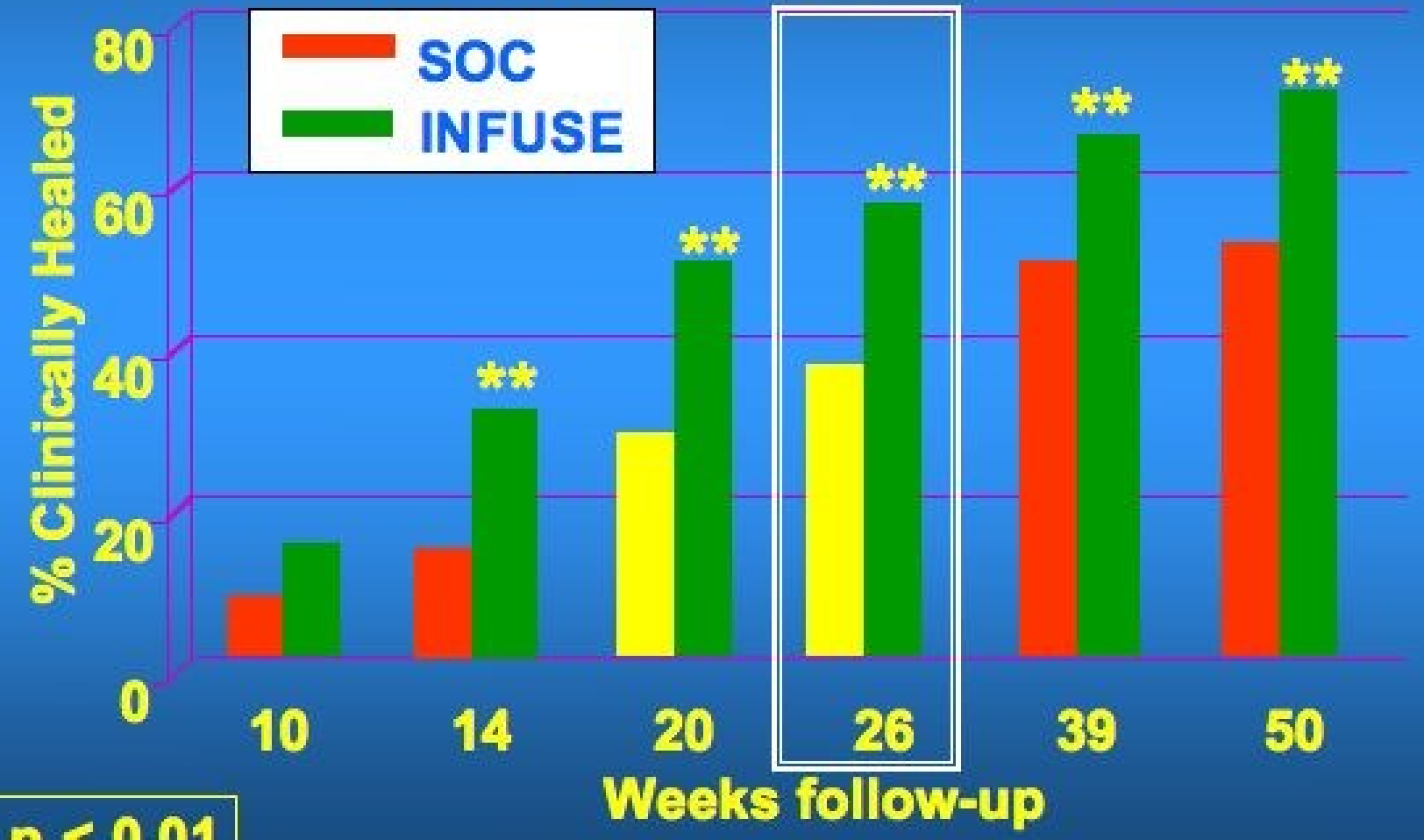
- Bone grafting
- Exchange nailing
- Plate fixation
- Fibular osteotomy
- Bone transport

p = 0.0264

BESTT, Govender *et al. JBJS* 84A: 2123-34, 2002

INFUSE Accelerates Rate of Clinical Healing

At 6 months, healing rate with INFUSE is 21% higher than SOC



(**) p < 0.01

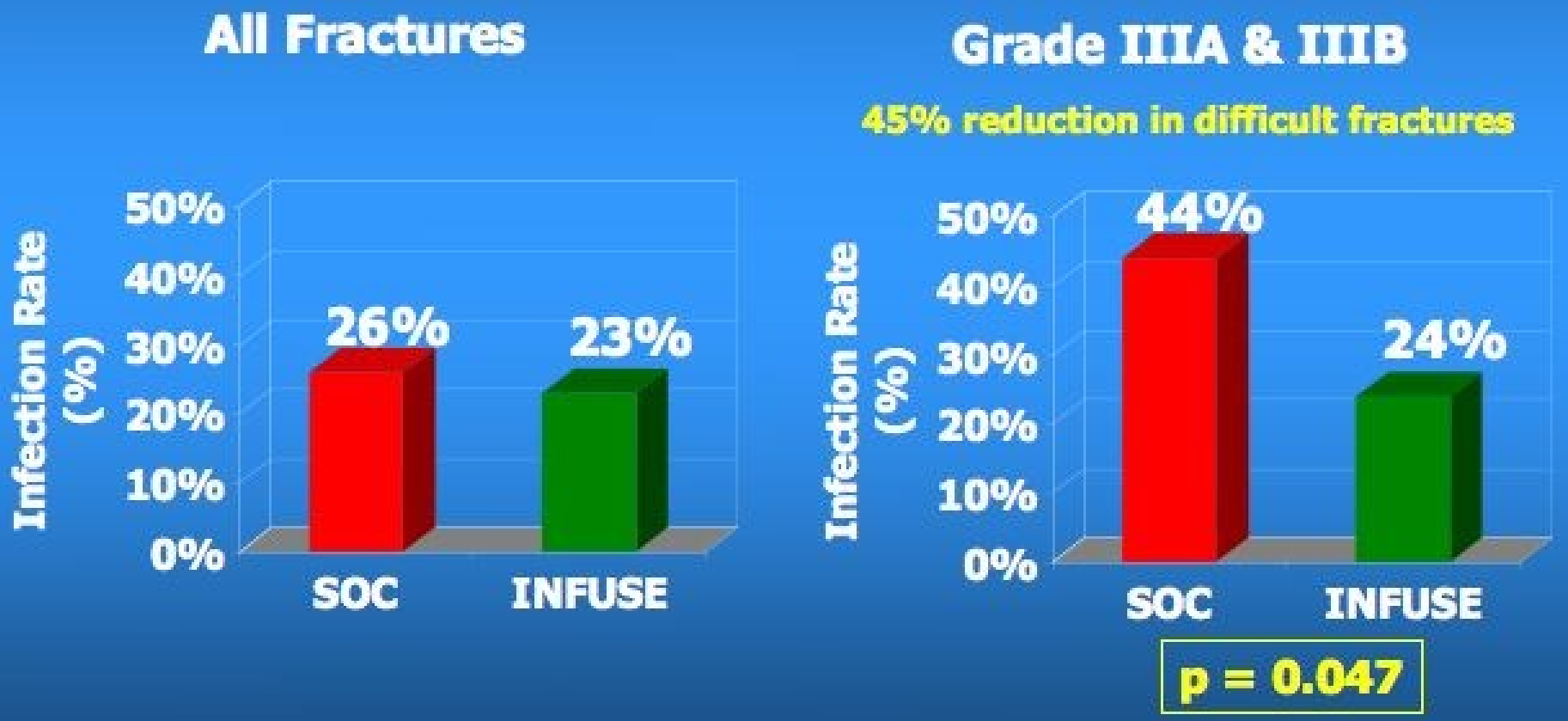
BESTT, Govender *et al. JBJS* 84A: 2123-34, 2002

Patient #32 (AP view)

wks	6	10	14	20	26	52
f/up:				Healed		

Govender S. et al. JBJS 2002

INFUSE Decreases Rate of Infection



BESTT, Govender *et al. JBJS* 84A: 2123-34, 2002

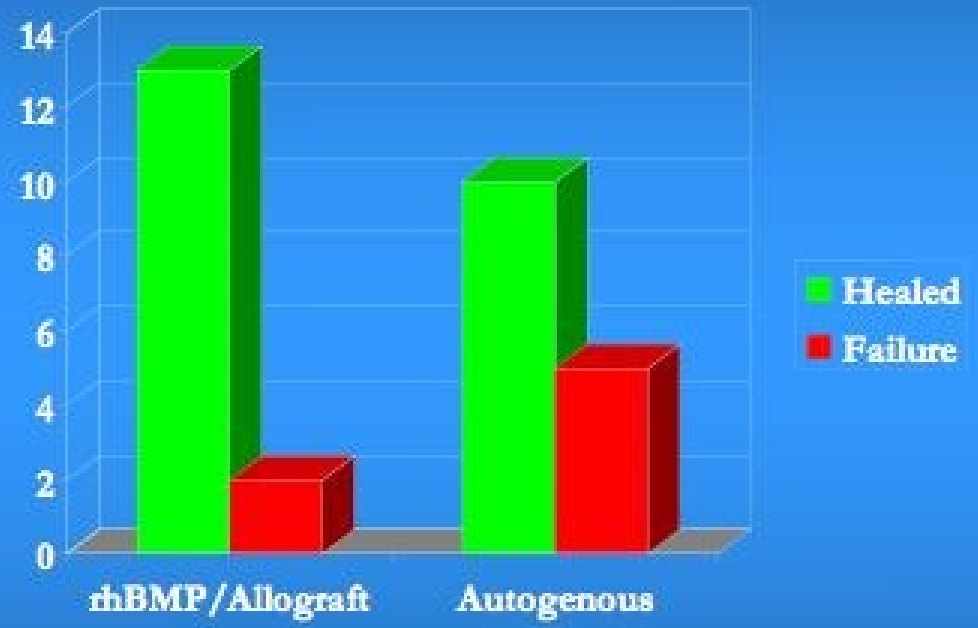
INFUSE rhBMP-2

- Reduces the risk of second surgeries by 44%
- Increases overall clinical success by 28%
- Accelerates fracture healing
  - At 6 months, rhBMP-2 improved healing rate by 21% (p=0.0008)
- Reduces infection rate
  - In Grade IIIA & IIIB, rhBMP-2 reduced the infection rate by 45% over SOC (p=0.0264)

Fractures with Bone Loss

30 Tibia Fractures

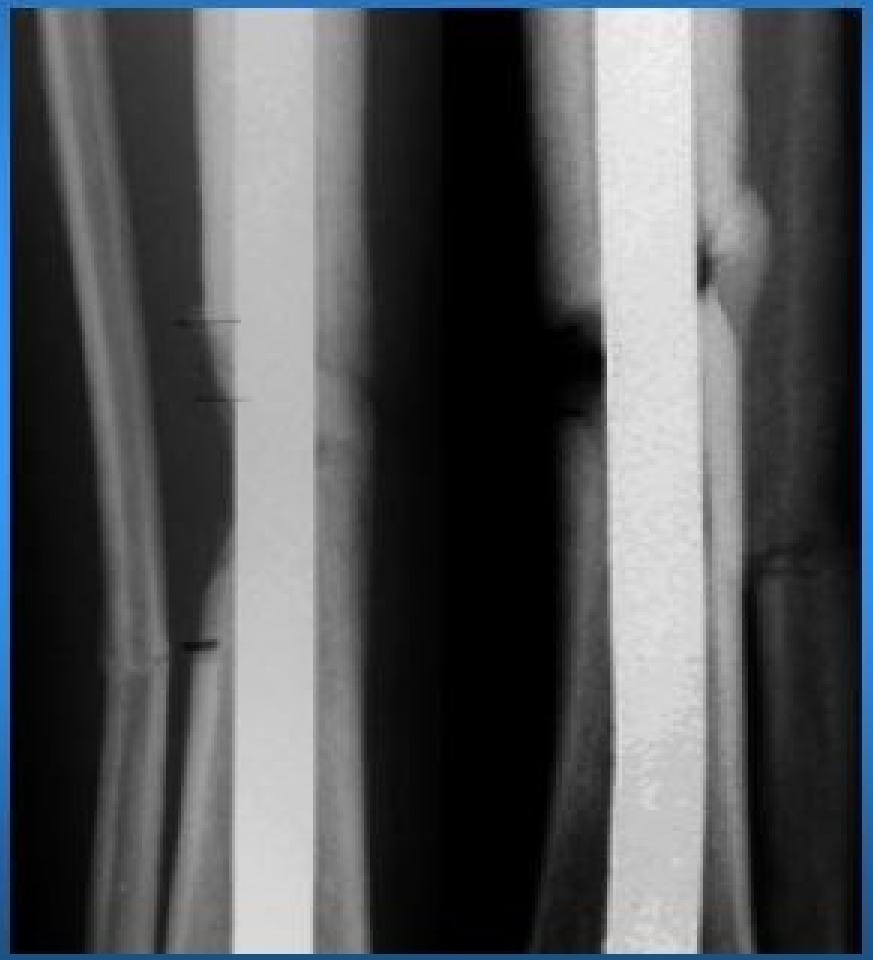
- Mean length of defect was 4 cm
  - range, 1 to 7 cm
- 15 rhBMP-2/Allograft
  - Two with 2nd interventions
- 15 Autogenous bone graft
  - Four with 2nd interventions and one nonunion



Jones AL, et al. JBJS 2006

Fractures with Bone Loss

Pre-grafting



12 months

Allograft with rhBMP-2/ACS

Jones AL, et al. JBJS 2006

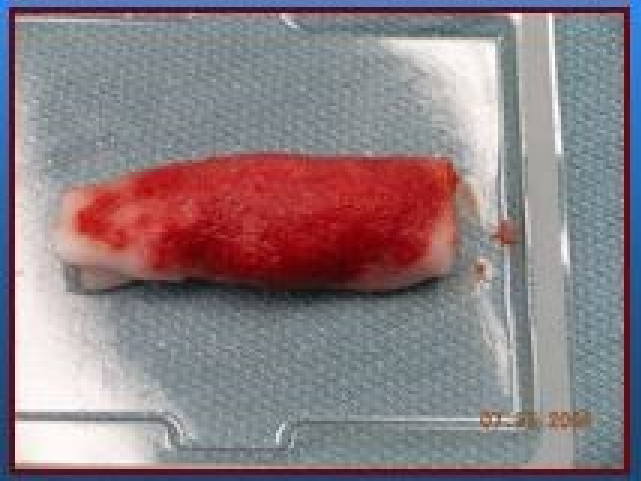
Fractures with Bone Loss

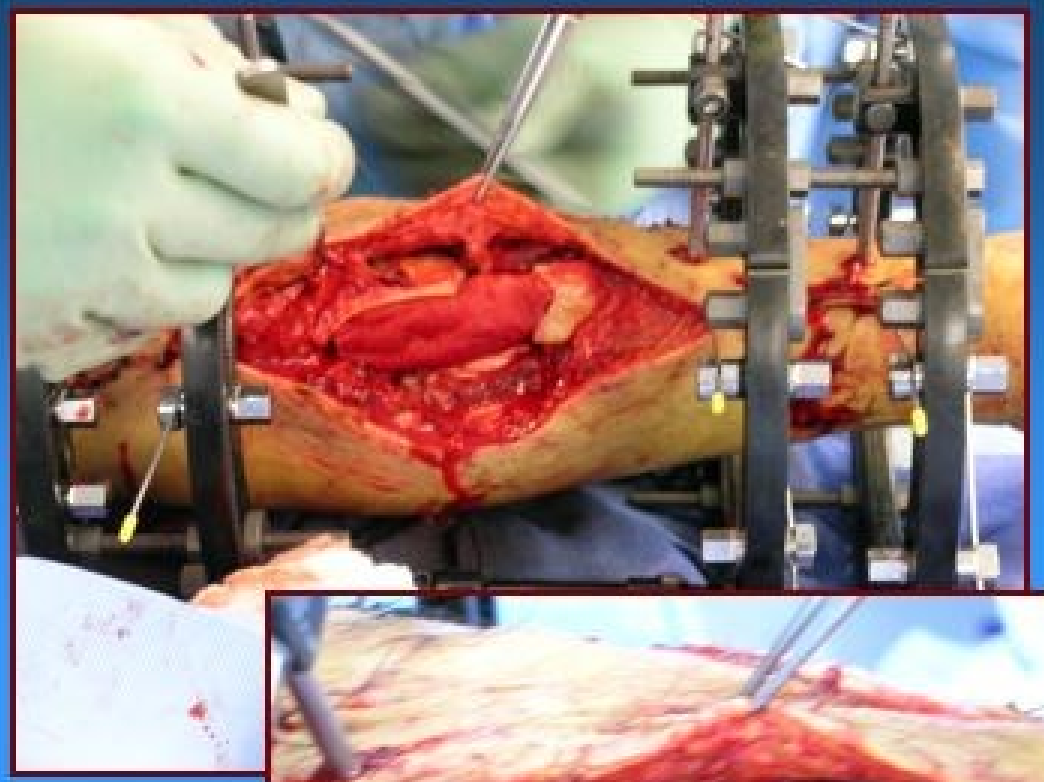
Kuklo T. et al. OTA mtg 2005

- 59 open tibia Fx with bone loss
- 2 to 10 cm defect lengths
- Allograft with rhBMP-2/ACS
- 54 of 59 patients healed (92%)

Schwartz et al. J Ortho 2006

- 19 fracture defects in 18 patients
- Various bones (defect length 1.5 to 8 cm)
- Ceramic granules with rhBMP-2/ACS
- 16 of 19 defects healed at 9 months (84%)





Kuklo T. et al. OTA mtg 2005

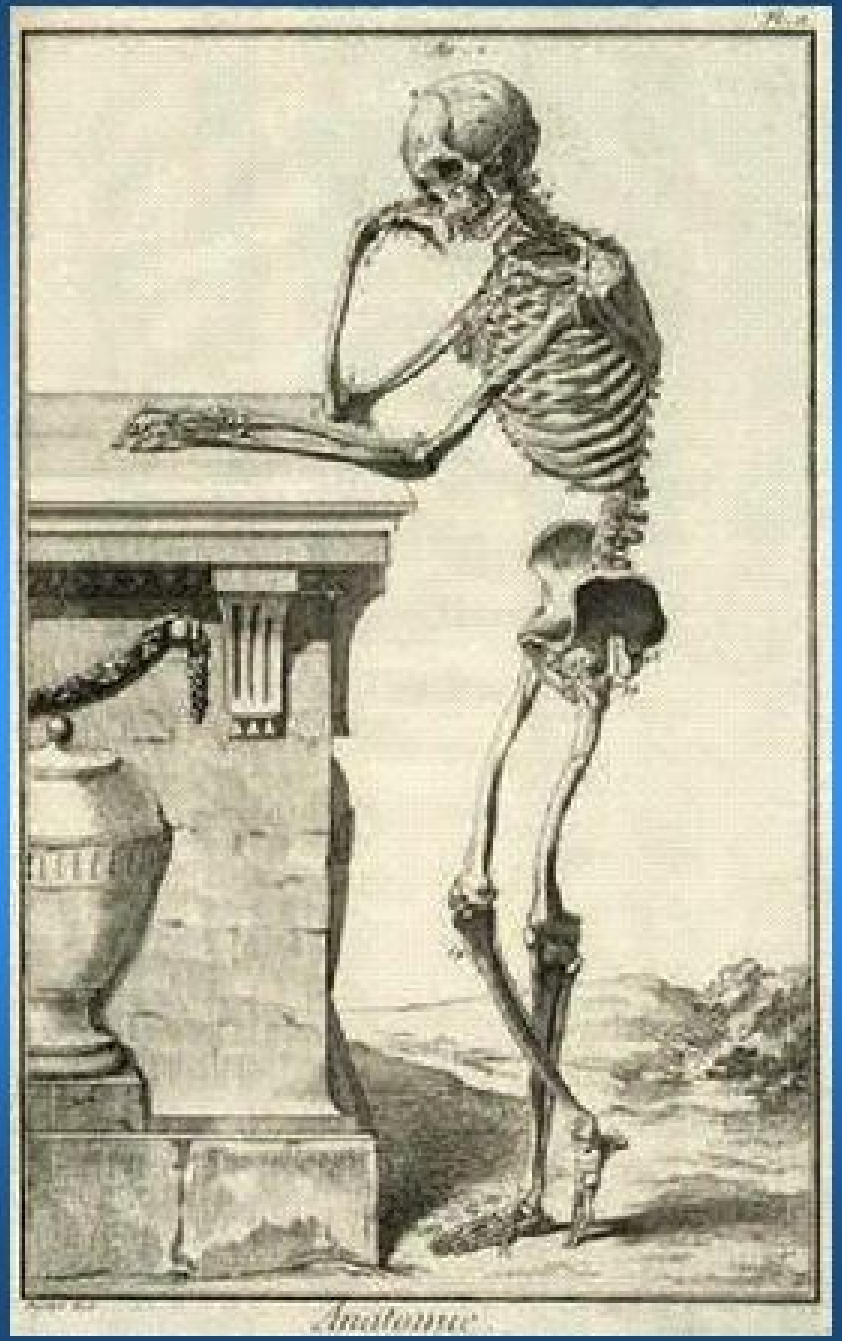
Combined Clinical Success in Long Bone Nonunion Treatment

	*Success of rhBMP-2/ACS
Hicks et al. OTA mtg 2006	44/54 (81%)
Cole et al. OTA mtg 2006	94/98 (96%)
Ringler et al. OTA mtg 2007	20/20 (100%)
Obremskey et al. OTA mtg 2006	17/22 (77%)
Hawkins BJ. Tech Foot Ankle 2007	40/40 (100%)
TOTAL	**215/234 (92%)**

* Includes various nonunions (femur, tibia, humerus, ulna/radius and ankle). The rhBMP-2/ACS was used in combination with either autograft, allograft or calcium phosphate ceramic granules.

InFUSE rhBMP-2

- Since Launch in U.S. 2002:
  - ✓>220,000 procedures
  - ✓<1% AE instance rate
- Most studied Biologic Agent
- Standard of Care for Neurosurgeons
- Documented Success Rates


Anatomie