



Antibiotic Bone cement and the Incidence of Deep Infection after Total Knee Arthroplasty

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TKA design



Cemented or cementless

- Prosthetic fixation in TKA with PMMA has consistently shown long-term durability. **Cementless fixation with bone ingrowth has been less reliable in long-term studies**
- 72% 10-year survivorship with the cementless Press-Fit Condylar design compared with 94% 10-year survivorship with similar cemented TKA
- Osteolysis** also has been reported more frequently with cementless prostheses
- Cementless designs had a **1.4 times higher rate of revision** than did cemented designs
--- Campbell's operative orthopaedics 11th ed



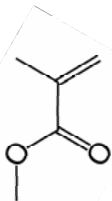
What is the bone cement ?

- PMMA (Polymethyl Methacrylate)
--- 聚甲基丙烯酸甲酯
- 1902年，德國化學家 O. Röhm 合成了 PMMA。O. Röhm 開始只是想把這種材料用於黏合劑。
- 1936年，PMMA 開始大規模生產。

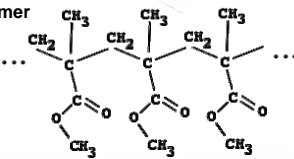


PMMA

Methyl Methacrylate
-the monomer



PMMA polymer



Acrylic glass	
Other names	poly(methyl methacrylate) (PMMA) methyl methacrylate resin
Identifiers	
CAS number	[9011-14-7]
SMILES	[show]
Properties	
Molecular formula	(C ₅ O ₂ H ₈) _n
Molar mass	varies
Density	1.19 g/cm ³
Melting point	130–140 °C (285–285 °F)
Boiling point	200.0 °C (392 °F)
Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	



PMMA

- Less than half the density of glass, and similar to that of other plastics.
- Good impact strength higher than that of glass or polystyrene, it will not shatter but instead breaks into large dull pieces.
- Softer and more easily scratched than glass.
- Excellent environmental stability compared to other plastics, material of choice for outdoors applications.
- Poor resistance to solvents, on account of its easily hydrolyzed ester groups.
- transmits up to 98% of visible light, filters ultraviolet light at wavelengths below ~300 nm.
- allows infrared light of up to 2800 nm wavelength to pass.



PMMA

- Good compatibility with human tissue
- To affix implants and to remodel lost bone
- Supplied as a powder with liquid methyl methacrylate (MMA)
- Acts like a grout and not so much like a glue in arthroplasty, primarily fills the spaces between the prosthesis and the bone preventing motion
- Young's modulus between cancellous bone and cortical bone. It is a load sharing entity in the body not causing bone resorption



PMMA

- MMA is considered to be an irritant and a possible carcinogen.
- PMMA has also been linked to cardiopulmonary events in the operating room due to hypotension
- It heats to quite a high temperature while setting and because of this it kills the bone in the surrounding area



Thermal effects of PMMA

- 30 cm-diameter cylinders of PMMA can generate temperatures in excess of 122°C
- Thermal necrosis reportedly occurs in bone tissue exposed to temperatures in excess of 50°C for more than 1 min
- Injury to sensory nerves at 45°C, for exposures longer than 30 min.

--- H. DERAMOND,* N. T. Bone Vol 25, 1999



Thermal effects in vertebroplasty

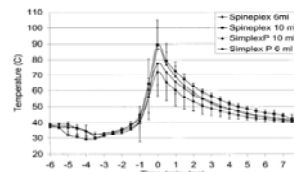


Table 1. Peak Temperatures and Dwell Times*

Cement/Volume	Peak Temperature			Time Above 50 C		
	T1	T2	T3	T1	T2	T3
Simplex P 6 mL	72.2 ± 6.5	86.0 ± 6.1	44.4 ± 2.0	2.8 ± 0.5	4.9 ± 0.7	0 ± 0.2
10 mL	86.3 ± 6.5	86.3 ± 6.7	42.0 ± 2.0	3.7 ± 0.5	5.2 ± 0.6	0.1 ± 0.2
Simplex30 6 mL	77.5 ± 6.5	71.0 ± 6.1	41.0 ± 1.8	3.6 ± 0.5	3.7 ± 0.6†	0 ± 0.2
10 mL	84.7 ± 6.5	91.8 ± 6.1	44.8 ± 1.8	4.8 ± 0.5	6.9 ± 0.6†	0.4 ± 0.2

* All values are mean ± SEM.
† Significantly different than each other.

--- Stephen M. Belfkog, SPINE Volume 28,2003



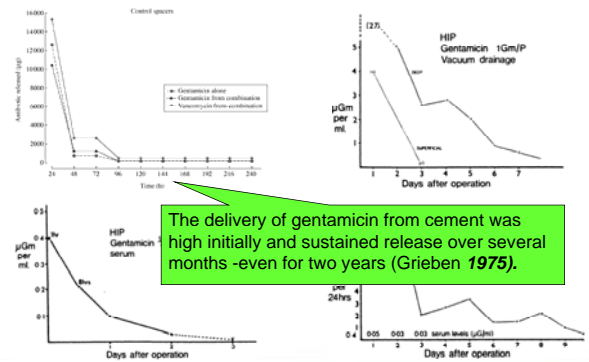
Antibiotic impregnated PMMA

- PMMA beads impregnated with heat-stable antibiotics (tobramycin, vancomycin, and gentamicin) have been used since the early 1970s
- Achieve 200 times the antibiotic concentration achieved with IV administration
- With tobramycin and vancomycin
 - Peak concentration of antibiotic delivered to local tissue occurs on the first day
 - Lasts for approximately 1 week

--- Campbell's operative orthopaedics 11th ed



Pattern of gentamicin delivery in cement





Clinical application of antibiotic-impregnated cement and beads

- Prophylaxis for total joint arthroplasty
- Treatment of total joint arthroplasty infection
- Treatment of chronic osteomyelitis
- Prophylaxis for open fractures

-- NALINI RAO, *Operative Techniques in Orthopaedics*, Vol 12, No 4, 2002



Drugs of choice for total joint

- **Gentamicin**-impregnated cement prevented infections caused by *Staphylococcus aureus*, streptococci, and gram-negative organisms in rat tibias
- prevented infection when *E.coli* was inoculated into joints up to 7 days after surgery in rabbit model
- **Erythromycin**- and **colistin**-impregnated cement prevented *S. aureus* and *E.coli* infections in rabbit femurs

--- DAVID A. WININGER, *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY*, Dec. 1996



Study Characteristics of Published Reports on Primary Prophylactic Use of Antibiotic Bone Cement in Joint Arthroplasty

Reference	Location & Years of Data Collection	Sample Size		Antibiotic Type*		Quality Score	Task Force Rating	
		Affected Joint	Antibiotic Cement	Control Cement	Control			
RANDOMIZED CONTROLLED TRIALS								
Plan & Burt ¹¹	Germany, 1972-1974	Hip	100	100	Gentamicin	None	15	Fair
Wronski & Tschopp ¹²	Germany, 1973-1976	Hip	274	202	Gentamicin	None	18	Fair
Jonsson et al ¹³	Sweden, 1976-1978	Hip	851	834	Gentamicin	Clasacillin, dicloxacillin, others	25	Fair
McQueen et al ¹⁴	United Kingdom, 1982-1985	Hip/knee	146	149	Cefuroxime	Cefuroxime	25	Fair
McQueen et al ¹⁵	United Kingdom, years not stated	Hip	190	190	Cefuroxime	Cefuroxime	25	Fair
Jonsson et al ¹⁶	Sweden, 1976-1978	Knee	14	11	Gentamicin	Clasacillin, dicloxacillin, others	24	Fair
Jonsson & Rullmer ¹⁷	Sweden, 1976-1978	Hip	853	835	Gentamicin	Clasacillin, dicloxacillin, others	25	Fair
Chiu et al ¹⁸	Taiwan, 1993-1998	Knee	41	37	Cefuroxime	Cefazolin, gentamicin	18	Fair
Chiu et al ¹⁹	Taiwan, 1994-1998	Knee	178	162	Cefuroxime	Cefazolin, gentamicin	18	Fair
Cohort Studies								
Buchholz & Engelbrecht ²⁰	Germany, 1964-1970	Hip	1115	1409	Gentamicin, penicillin, or erythromycin	None	NA	Poor
Buchholz & Garmann ²¹	Germany, 1964-1971	Hip	2928	1439	Gentamicin, penicillin, or erythromycin	None	NA	Poor
Buchholz et al ²²	Germany, 1964-1975	Hip	2716	1151	Penicillin, erythromycin, Gentamicin	None	NA	Poor
Thorer ²³	Germany, 1970-1973	Hip	331	336	Gentamicin	Ampicillin, oxacillin	NA	Fair
Buchholz et al ²⁴	Germany, 1964-1975	Hip	1655	1154	Gentamicin	None	NA	Fair
Lynch et al ²⁵	United Kingdom, 1976-1983	Hip	479	765	Gentamicin	None	NA	Good
Machuga et al ²⁶	Sweden, 1978-1980	Hip	---	---	Lentamicin	various	NA	Good
Havlin et al ²⁷	Norway, 1987-1993	Hip	2801	3788	Gentamicin, erythromycin, cloxacillin	Cephazolin, cefuroxime, others	NA	Good
Egehaug et al ²⁸	Norway, 1987-1995	Hip	6043	4862	Gentamicin, erythromycin, cloxacillin	Cephazolin, cefuroxime, others	NA	Good
Peterson et al ²⁹	Sweden, 1979-1995	Hip	7674	18,400	Gentamicin	Various	NA	Good
CASE-CONTROL STUDIES								
Egehaug et al ³⁰	Norway, 1987-1993	Hip	358	1270	Gentamicin, erythromycin, cloxacillin	Cephazolin, cefuroxime, others	NA	Good
CASE SERIES								
Rottger et al ³¹	Germany, 1973-1978	Various	7830	0	Gentamicin	NA	NA	NA
Murray ³²	United States, 1971-1980	Hip	1898	0	Erythromycin, colistin, erythromycin	NA	NA	NA

Jon E Block, Harrison A Stubbs, *Orthopaedics*, 1998



Ratio of antibiotic and cement

- 8 g of antibiotic powder with a package of 40 g of cement polymer is the highest mixture ratio with which the bone cement can be introduced into the mold and formed into a prosthesis without difficulty
- For antibiotic beads: 12 g of antibiotic : 40g of cement polymer, regardless of the strength of the cement *

--- Pang-Hsin Hsieh, *Two-Stage Revision Hip Arthroplasty for Infection*, *J Trauma*, 2004

--- Exprince from LK-CGMH



Commercial antibiotic cement

- Zimmer Palacos: 0.5 g Gentamicin
- DePuy 1 CMW: 1 g Gentamicin
- Stryker Simplex P: Tobramycin impregnated



Introduction

- Infection rates in TKA: 1%~3%
- 8% in TKA for RA

Future Clinical and Economic Impact of Revision Total Hip and Knee Arthroplasty

Steven M. Kurtz, Kriss L. Ong, Jordana Schurer, Fouad Merwet, Khaled Saleh, Eva Dylchik, Johna Kucholik, Gunnar Gavellick, Leif I. Havelin, Ole F. Fossan, Henrik Mahajan and Edmund Lau
J Bone Joint Surg Am. 2007;89:144-151. doi:10.2196/JBJS.G.00587

- The incidence of deep infection after primary TKA is rising
- Projected to reach 6.8% by 2030

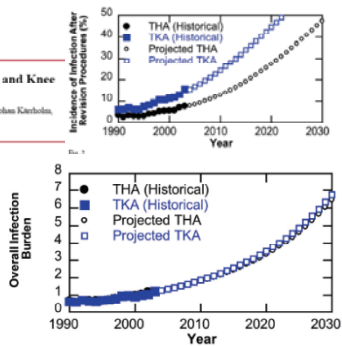


Fig. 1

Introduction

- The health care costs for treating joint sepsis after arthroplasty: \$40~80 million annually in US
- Direct costs of revision surgery for deep infection: \$55000 per case

Introduction

- Use of antibiotic laden bone cement has been introduced since 1970s by Buchholtz and Engelbrecht

This is an enhanced PDF from The Journal of Bone and Joint Surgery
The PDF of the article you requested follows this cover page.

Cefuroxime-Impregnated Cement in Primary Total Knee Arthroplasty : A Prospective, Randomized Study of Three Hundred and Forty Knees

Fang-Yao Chiu, Chuan-Mu Chen, Chien-Fu Jeff Lin and Wai-Hee Lo
J Bone Joint Surg Am. 2002;84:759-762.

- No deep infection developed in the 178 knees in antibiotic cement group, whereas a deep infection developed in five(3.1%) of the 162 knees in plain cement group ($p = 0.0238$).
- Two superficial wound infections developed in each group. (duration of follow-up: 49 months)

ANTIBIOTIC PROPHYLAXIS IN TOTAL HIP ARTHROPLASTY

REVIEW OF 10 905 PRIMARY CEMENTED TOTAL HIP REPLACEMENTS REPORTED TO THE NORWEGIAN ARTHROPLASTY REGISTER, 1987 TO 1995

- The lowest probability of revision in THRs was found among patients receiving antibiotic-containing cement in combination with systemic antibiotics
- The benefit was highest during the first and the second years after surgery
- Antibiotic-impregnated cement:
 - Gentamicin in combination with Palacos (0.5 g per 40.0 g polymethylmethacrylate)
 - Erythromycin/colistin with Simplex cement (0.5 g erythromycin and 0.24 g colistin per 40.0 g polymethylmethacrylate)

©1997 British Editorial Society of Bone and Joint Surgery
0301-620X/97/47420 \$2.00

Aim of this study

- To determine if the prophylactic use of antibiotic-laden bone cement (ALBC) decreases the deep infection rate after primary TKA at 1 year of follow-up



Materials and Methods

- Between 1998~2006, 1625 patients recruited from a single Canadian institution
- Ages 18 and older
- Primary or secondary osteoarthritis or rheumatoid arthritis
- Prior history of knee infection → excluded



Materials and Methods

- All surgeries were performed by 3 surgeons, 2 of whom routinely use ALBC
- Surgical technique was similar between the 3 surgeons, including use of tourniquet, operating room with laminar air flow, and implants type
- Pre-op: 1 dose of systemic antibiotics
Post-op: for 24h after surgery



Materials and Methods

- Simplex T (Stryker Canada, tobramycin impregnated) was used for ALBC group
- Simplex P (Stryker) was used for PBC group



Materials and Methods

- Deep infection was defined as:
 - Occurring **within 30 days of procedure or 1 year in the case of implants**
 - Related to the procedure
 - Involving deep soft tissues such as the fascia, muscles, or joints
 - Purulent drainage from the incision
 - A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms—**fever (N38 C), localized pain, or tenderness**—unless the culture is negative
 - An **abscess** or other evidence of infection involving the incision is found on direct examination or by histopathologic or radiological examination
 - A diagnosis of a deep incisional surgical site infection by a surgeon or attending physician
- plus
at least one of the following criteria:



Collection of data

- Age, sex, BMI, education
- Baseline medical health scored on the Charlson Comorbidity Illness Index (score 0,1,2,3 or above)
- Functional status and pain level: WOMAC function and pain scores pre-op and at 1 year of follow-up



Charlson Comorbidity index

Appendix 1. Revised Weighted Comorbidity Indices for Predicting Mortality or Functional Decline

Medical Conditions	Charlson's Original Index	Weights*	
		Revised Index for Predicting Mortality	Revised Index for Predicting Functional Decline
Myocardial infarction	1	1.25	
Congestive heart failure	1	0.5	1
Peripheral vascular disease	1		
Cerebrovascular disease	1		
Dementia	1		1
Chronic pulmonary disease	1		1
Connective tissue disease	1		
Peptic ulcer disease	1	1	
Mild liver disease	1		
Diabetes mellitus without complications	1		
Hemiplegia	2		
Moderate or severe renal disease	2		2
Diabetes mellitus with end organ damage	2		
Any tumor	2	0.5	1.25
Leukemia	2		
Lymphoma	2		
Moderate or severe liver disease	3		2
Metastatic solid tumor	6	1.25	
Acquired immunodeficiency syndrome	6		
Valvular disease†			2
Visual disability†		1	
Hearing disability†			2.75
Urinary problems†		0.5	1.75



WOMAC index

WOMAC index

0 : not any
 1 : a little
 2 : moderate
 3 : important
 4 : very important - extreme

P Subscale :

How much pain do you have:

- 1: walking on flat surface
- 2: going up or down stairs
- 3: at night while in bed
- 4: sitting or lying
- 5: standing upright

S Subscale :

how severe is your stiffness

- 1: After first waking in the morning
- 2: After sitting lying or resting later in the day

PF subscale:

What degree of difficulty do you have

- 1: descending stairs
- 2: ascending stairs
- 3: rising from sitting
- 4: standing
- 5: bending to floor
- 6: walking on flat
- 7: getting in / out of car
- 8: going shopping
- 9: putting on socks / stockings
- 10: rising from bed
- 11: taking off socks / stockings
- 12: lying in bed
- 13: getting in / off bath
- 14: sitting
- 15: getting on / off toilet
- 16: heavy domestic duties
- 17: light domestic duties



Statistical Analysis

- Continuous data: Age, BMI, WOMAC scores were compared between groups using t tests
- Categorical data: Sex, education, Charlson index, diagnosis and incidence of infection were compared with the X² test



Statistical Analysis

- Sample size was calculated to detect 50% difference in the deep infection rate at 1 year follow-up, assuming a 3% incidence of deep infection
- Effect size 0.5, type I error of 0.05, and 80% power
- **Required total sample size: 1534 patients**
- SPSS version 13.0, 95 % confidence intervals
- P values are 2 tailed with an α of 0.05

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}, \text{ (Rosner page 332)}$$



Results

Table 1. Unadjusted Analysis Comparing Demographic and Baseline Functional Data between Groups

	Plain Cement (n = 811)	Abx Cement (n = 814)	P
Mean Age (SD)	67.2 (10.8)	65.1 (15.4)	.13
Mean BMI (kg/m2)	30.7 (7.2)	30.5 (6.8)	.74
% Men	33.0%	35.1%	.39
% Higher education	47.1%	44.1%	.35
% Rheumatoid arthritis	17.4%	16.0%	.39
Charlson Index (%)			
0	56%	59%	.53
1	28%	25%	
2	11%	11%	
≥3	5%	5%	
Preoperative WOMAC scores			
WOMAC total	54.0 (18.7)	52.1 (16.9)	.06
WOMAC pain	11.2 (4.0)	10.8 (3.6)	.09
WOMAC function	45.3 (16.1)	43.7 (14.5)	.07



Results

Table 2. Unadjusted Analysis Comparing Outcome Data Between Groups

	Plain Cement (n = 811)	Abx Cement (n = 814)	P
1 y WOMAC scores			
WOMAC total	26.8 (17.9)	26.8 (17.8)	.92
WOMAC pain	5.5 (3.6)	5.2 (3.7)	.29
WOMAC function	22.2 (14.5)	22.4 (14.8)	.85
Deep infection (%)	25 (3.1%)	18 (2.2%)	.27

Overall infection rate: 2.6% (43/1645) at 1 year f/u **No difference !**



Results

Table 3. Linear Regression Model Predicting Deep Infection by Antibiotic Cement, Age, Sex, BMI, Charlson Index, Education, Diagnosis of Rheumatoid Arthritis and Preoperative Total WOMAC Score

	Odds Ratio (95% Confidence Interval)	P
Antibiotic cement	1.1 (0.4,3.1)	.85
Age	1.0 (0.9,1.0)	.57
Sex	0.7 (0.3,2.1)	.56
BMI	1.0 (0.9,1.1)	.50
Charlson Index	1.8 (1.0,3.2)	.05
Education	1.3 (0.4,3.6)	.67
Preoperative WOMAC	1.0 (0.9,1.0)	.94
Rheumatoid arthritis	0.5 (0.1,2.0)	.31



Discussion

- Cefuroxime impregnated bone cement was effective in preventing deep knee infection following TKA, particularly in those with DM

--- Chiu et al, JBJS-Am. 2002

- Limitations:
 - Surgeons or accessors were not blinded to the treatment allocation
 - Randomization sequence
 - Excluded patients who had previous knee surgery and peripheral vascular disease



Discussion

- Costs of PBC and ALBC:
 - US \$284 ~ \$349 greater per 40g package
- Deep infection rate need to be reduced from 1.5% to 0.3% to recover the costs associate with routine ALBC use

---Jiranek et al; JBJS-Am, 2006

→ which we did not see in this study



Discussion

- In **diabetic** patients, infection rates was reported between 3.1% and 13.5% in patients undergoing primary joint arthroplasty
- Infection rates in **rheumatoid arthritis** patients have been reported between 2% and 8% invarious studies
- Risk of deep infection was 6 times greater in revision surgery as compared to primary knee arthroplasty.
- Greater comorbidity (Charlson Index) predicted a higher incidence of infection
 - Perhaps ALBC would be beneficial in this high-risk group



Discussion:

- Considerations of the use of ALBC:
 - Toxicity
 - Allergic reactions
 - Drug-resistant organisms
 - Decreased mechanical strength of the cement



Discussion

- Potential for an increase in drug-resistant organisms with the use of prophylactic ALBC
- Use in only high-risk populations was advised

Hanssen AD. J Arthroplasty 2004 /
Jiranek WA, JBJS Am 2006;



Discussion

- There have not been any reports of toxicity or allergy attributed to the use of ALBC*
- Low-dose antibiotic impregnated bone cements have negligible reductions in fatigue strength, and implant fixation is not compromised



Acute renal failure after antibiotic-impregnated bone cement treatment

- 2 cases that had aminoglycoside-impregnated cement resulted in acute renal failure
[Curtis et al. 2005, Van Raaij et al. 2002]
- 2 cases that had combined tobramycin- plus vancomycin-impregnated cement resulted in ARF after THR
[Patrick et al. 2006]
- 1 case with history of DM and HTN, had ARF after treatment of TKA infection with gentamicin- plus vancomycin-impregnated cement
[Dovas et al.2008]



Limitation of this study

- Nonrandomized design
 - Measured potential confounders and used regression modeling techniques to adjust for their effects on the outcome



Conclusion

- ALBC did not significantly reduce the incidence of deep knee infection after primary TKA
- Further study is required to investigate the efficacy of ALBC in the above-defined high-risk groups (DM, RA, Revision TKA)
- Further cost analysis for the use ALBC in primary TKA



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