Gentamicin Release from Bone Cement: A Comparative Study between Hand Made Liquid & Powder Gentamicin beads

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Background and Purpose: *Gentamicin beads are widely used in treatment of bone and joint infections. The commercial form is expensive and may be unavailable in most hospitals in Thailand. Most orthopaedic surgeons make them from gentamicin and powdered bone cement, but this still has high costs. In this study, the author used liquid gentamicin, which was used regularly in intravenous route, to mix in bone cement and compare gentamicin release between handmade liquid and powder gentamicin beads.*

Methods: *A prospective randomized clinical trial in patients with bone and joint infections from bacterial causes in Hatyai Hospital. Patients were divided into liquid gentamicin and powder gentamicin groups. Gentamicin concentration in surgical areas were collected, compared, and analyzed.*

Results: *Thirty patients in each group who had bacterial bone and joint infections were treated with bone debridement and gentamicin beads were placed in surgical area. The liquid gentamicin group resulted in significantly higher levels than in the powder group. Both groups had gentamicin levels many times higher than the minimal inhibitory concentration (MIC) and persisted for at least 28 days. Clinical results of both groups were excellent and no renal toxicity was observed.*

Conclusions: *The liquid gentamicin group had more antibiotic released to the surgical area than the powder group, no renal toxicity detected, and appears to be cost-effective in the treatment of bacterial bone and joint infections.*

Key words: *Liquid gentamicin, Gentamicin release from bone cement, Handmade bone cement, Gentamicin-impregnated polymethymethacrylate.*

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Introduction

The use of antibiotic impregnated polymethymethacrylate (PMMA) for the treatment of bone and joint infections has been widely used since the 1970s[6,11,12,14].Various antibiotics have been mixed with bone cement including gentamicin. Gentamicin was proved to be the antibiotic of choice to add into polymethymethacrylate to create antibiotic beads because it is has a low minimal inhibitory and bactericidal concentration (MIC), a low rate of allergy, free solubility in water, and is stable in high temperatures. Commercial gentamicin beads are expensive and may be unavailable in most hospitals in Thailand. Most orthopaedic surgeons make beads and chains themselves from bone cement and powder gentamicin, but still at a rather high cost. Liquid gentamicin is the other preferred choice and is cheaper than the powder form[1,5]. The purpose of this study is to compare the releasing of gentamicin from bone cement between the liquid and powder forms.

Patients and Methods

A prospective randomized controlled trial was performed from 2011 to 2014, and included 60 patients with bacterial bone and joint infections treated at Hatyai Hospital.

Inclusion criteria for this study were as follows: (a) Chronic osteomyelitis of a long bone, defined by one or more foci in the bone contained purulent material, infected granulation tissue, and sinus tract from bone or sequestrum, (b) Infected fracture of long bone, defined by purulent discharge from the surgical wound after bone debridement and / or fixation in the acute or subacute period within 6 weeks, (c) Hip or knee joint infections, defined by bacterial infective arthritis of hip or knee joints that need surgical debridement, and (d) Infection after spinal surgery, defined by purulent discharge from the surgical wound after thoracolumbar spine surgery, either disease or trauma, within 6 weeks.

Exclusion criteria were as follows: (a) Infection other than bacterial causes, (b) Infection in sarcoma, (c) Wound that were unable to be closed into closed space, and (d) Cases with insufficient space to insert chains of 6 beads of gentamicin beads. A pilot study was performed after permission from the ethics committee of Hatyai hospital was granted. The pilot study had 5 patients in each group and calculated for sample size. The process of this study is divided into 4 steps:

1. Preoperative period: Every patient was informed by the surgeon, and they gave their consent and agreed to be included in this study. Ward nurses randomly picked a number from 4 envelopes. If the number was 1 or 2 that patient was put in the liquid gentamicin group, and if the number was 3 or 4 they were put into the powder group. Essential preoperative laboratory tests including creatinine were done in every case.
2. Procedure in operating room: Prophylactic antibiotics (1 gram of cefazolin) were administered 30 minutes before bone debridement. In cases of allergy to cefazolin, ciprofloxacin (500 milligrams) was used instead. No post-operative antibiotics were used. Liquid Gentamicin beads were made case by case using 480 mg of liquid gentamicin (NIDA pharma incorporation company limited, 80 milligrams /ampule, 2 ml/ ampule) and 40 grams of bone cement (Zimmer ^{R}). Liquid gentamicin was mixed with the liquid monomer first, then cement powder was added. The mix was put into a 50 mL syringe and injected to a polyethylene mold with a core wire (Fig. 1). For powder gentamicin bead preparation, 40 grams of antibiotic cement (Zimmer ^{R}) which contained 500 milligrams of powder gentamicin, was put into the liquid monomer and beads and chain created in the same manner as the liquid gentamicin beads. Six chains of 30 beads per chain were made from 40 grams of cement. After performing bone debridement, bacterial cultures were collected and placement of gentamicin beads in the surgical area was done. The wound was then closed. Suction drainage was placed and clamped. Postoperative film was examined after placement gentamicin beads present (Fig. 2).
3. Process after gentamicin beads placement: After 24 hours, 5 ml of fluids was taken from drain tube for gentamicin level assessment and then clamped again. Specimens were collected daily for 7 days and sent to the laboratory department to measure for gentamicin concentrations by the VITROS 4600 Enzymatic instrument multiple-point Immuno-rate Test (Johnson & Johnson Thailand. LTD.).
4. Removal of gentamicin beads were performed at the twenty eighth day after bead placement. Fluid was taken again for gentamicin concentration measurements. Gentamicin concentrations were analyzed between the 2 groups using Independent Sample *t*-tests.

Results

There were 60 patients in the present study, 30 per group, with an average age of about 30 years in both groups. Sex, creatinine levels, diagnosis, and pathogens are shown in Table 1.

The results of gentamicin release in the surgical areas in the two groups showed the highest level on the first day after surgery and decreased with time. The liquid form had a higher level than the powder form. According to the experiments performed, it gave an average gentamicin level in the liquid form of 41.556 mg/L, while the powder form was at 38.093 mg/L, collected on the first day. On day seven, the level of the liquid form dropped to 3.266 mg/L and1.936 mg/L in the powder form. Gentamicin levels at the time of bead removal average 25.973 mg/L in the liquid group and 22.90 mg/L in the powder group (Fig. 3). Analysis of gentamicin levels with Independent Sample T-test showed normal distribution of data in both groups, and that the liquid gentamicin group was significantly different from the powder group (Table 2).

Regarding clinical results, all patients were followed for one year after the gentamicin beads placement and there were no cases of recurrent of purulent discharge, sinus tract, or the need for redebridement in any patient in both groups. The results of the blood tests for inflammation, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) had returned to normal levels.

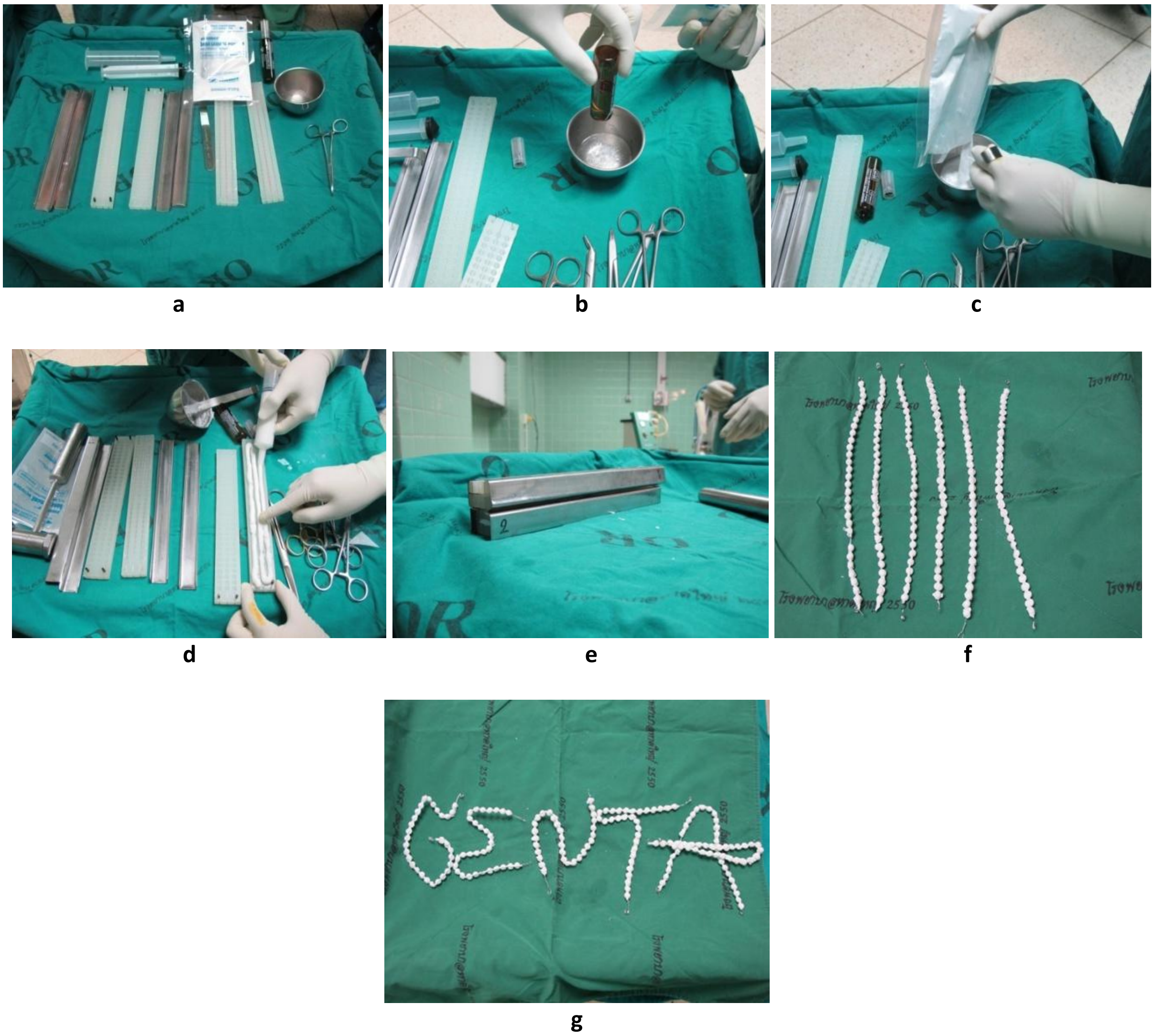

Fig. 1 Handmade Gentamicin Beads

(a) Mold made from polyethylene and cement
(b) Liquid monomer was mixed with liquid gentamicin
(c) Cement powder was added and mixed
(d) Cement was put into syringe and injected to polyethylene mold
(e) Compression of cement with mold compressor
(f) & (g) Beads and chains were made

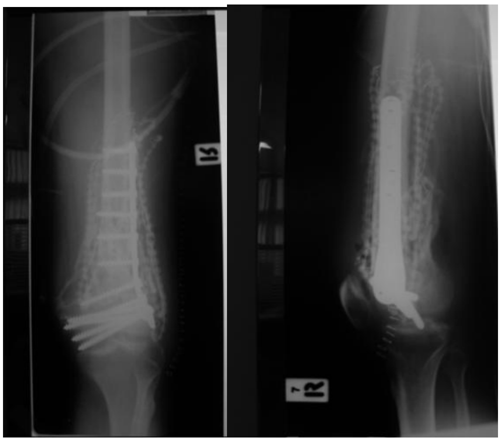

Fig. 2 Postoperative film after placement gentamicin beads

Table 1 Characteristics of patients with bacterial bone and joint infections

Characteristics	Liquid gentamicin group (N = 30)	Powder gentamicin Group (N = 30)
Age (years)	30.06 (16 - 54)	30.03 (17 – 52)
Sex Male / female	21/9	18/12
Creatinine level at preoperative period Creatinine level at date of removal of gentamicin beads	1.1 (0.8-1.3) 1.0 (0.8-1.2)	1.0 (0.8-1.2) 1.0 (0.9-1.2)
Diagnosis		
- Chronic osteomyelitis of proximal femur	3	5
- Chronic osteomyelitis of femoral shaft	4	6
- Chronic osteomyelitis of distal femur	13	10
- Septic arthritis of the hip	1	0
- Infected fracture of proximal femur	2	1
- Infected fracture of femoral shaft	2	3
- Infected fracture of distal femur	3	4
- Infected fracture of tibia	2	0
- Spinal infection after surgery	0	1
Pathogens		
- Methicillin Resistance Staphylococcus aureus (MRSA)	3	2
- Methicillin Sensitive Staphylococcus aureus	8	5
- *Streptococcus spp.*	6	9
- *Escherichia coli*	3	2
- *Klebsiella pneumonia*	1	0
- Mixed Organisms	9	12

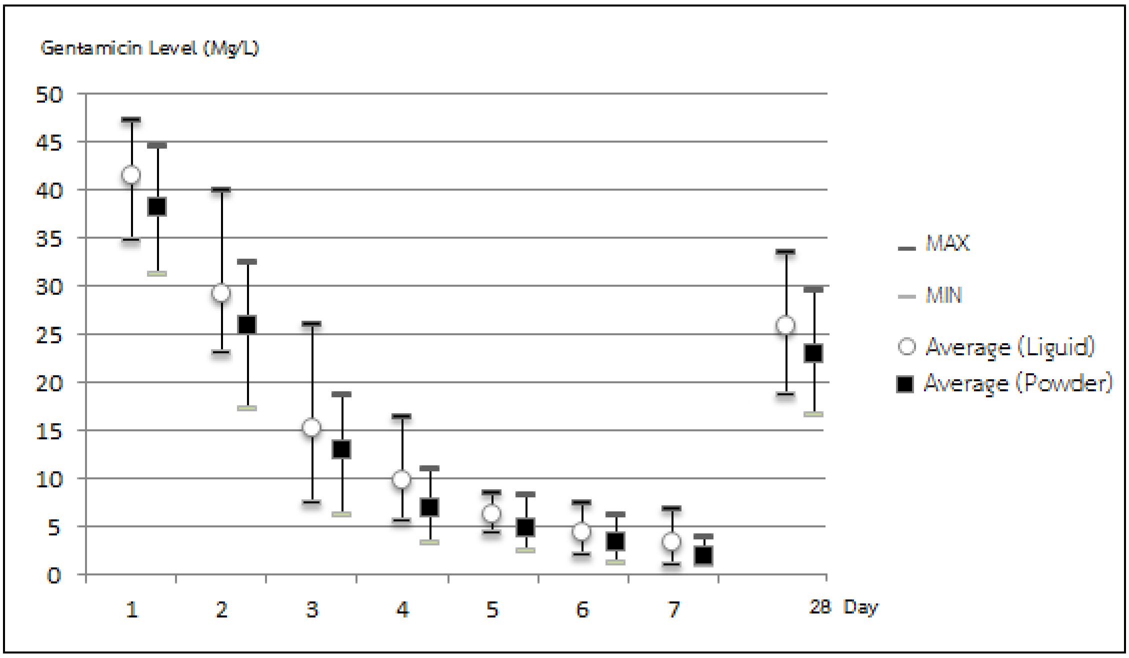

Fig. 3 Comparison of gentamicin levels between liquid and powder groups

Table 2 Analysis of gentamicin levels

Day	Mean Gentamicin Level		Mean Difference	P Value	95% Confident Interval	
	Liquid Group	Powder Group			Lower	Upper
1	41.556	38.093	3.462	0.000	1.7092	5.2155
2	29.243	25.802	3.441	0.001	1.4256	5.4571
3	15.338	12.972	2.365	0.036	1.6323	4.5672
4	9.774	6.871	2.903	0.000	1.6607	4.1453
5	6.310	4.756	1.554	0.000	0.9193	2.1880
6	4.494	3.319	1.174	0.010	0.5130	1.8357
7	3.266	1.936	1.330	0.000	0.7959	1.8641
28	25.973	22.900	3.073	0.020	1.1616	4.9838

Discussion

Gentamicin is a common antibiotic used in the treatment of infections. It is effective against organisms with a low minimal inhibitory and bactericidal concentration (MIC). This antibiotic also has a low rate of allergy, free solubility in water, and is stable at high temperatures(1,6,14). It has a therapeutic drug level between 0.6- 0.8 mg/L, higher doses or prolonged treatment may lead to renal toxicity. This limitation is one of the problems in treating with gentamicin. Local administration of gentamicin with PMMA is the prefer choice of treatment for bone and joint infections. Gentamicin beads can be used with doses many times higher than standard doses without renal toxicity(1,3). In this study, antibiotic levels in the liquid gentamicin group were significantly higher than the powder group from the first day after the operation until the seventh day. Antibiotic levels were highest on the first day after operation; the liquid gentamicin group had levels 51.9 times higher than the MIC and 47.6 times higher in the powder group before levels gradually reduced. By the seventh day after operation, the liquid gentamicin group had levels 4 times higher than the MIC and the powder group had levels 2.4 times higher than MIC. By the twenty eighth day, when we removed the gentamicin beads, we collected fluid in the surgical areas for antibiotic level measurements and found that gentamicin levels in the liquid gentamicin group were 32.46 times higher than the MIC and levels were 28.62 times higher in the powder group. Therefore, both forms of gentamicin beads had high antibiotic levels in the surgical area and which lasted at least 28 days. The gentamicin levels at twenty eighth day were higher than at days 3-7 in the first week (Figure 3). This could be explained by gentamicin infiltration into local tissue around surgical areas. Higher elution of liquid gentamicin from the bone cement results from more porosity in the liquid beads type[1,4]. Liquid gentamicin 480 milligrams (12 ml) were mixed properly with 40 grams of bone cement[2]. However, more fluid was unable to be incorporated with powder cement. 500 milligrams of liquid gentamicin were not used when compared with 500 milligrams gentamicin powder because it may lead to errors in dosages during preparation. There are some limitations of this study such as differences in the size of surgical area which may affect the gentamicin concentration, limit the gentamicin volume to mix with cement, hinder the application in cases with small space to insert the antibiotic beads. Additionally, this study had a short duration of follow up for recurrent infection. Many studies report that gentamicin beads with high antibiotic levels were able to get rid of infections despite the presence of gentamicin resistant organisms identified by laboratory tests [7,11,12]. Gentamicin beads can treat MRSA, as shown in 5 cases of this study, due to the locally high dose of antibiotic bathing the surgical area. Even mixed organisms could be treated with gentamicin beads effectively.

Liquid gentamicin may lead to weakening of the bone cement due to the higher porosity than powder forms [4,8], but this did not affect the treatment of infection, except in cement spacers for infected total joint arthroplasty. With regards to safety, none of the patients had renal toxicity in this study. This was because of the local action with no systemic effect[1,3]. Handmade liquid gentamicin beads are cheaper than handmade powder gentamicin beads by about 55 percent, and four times cheaper than the commercial form.

Conclusions

Liquid gentamicin in bone cement has significantly higher antibiotic levels than powder gentamicin form. They are safe and cost-effective for the treatment of bacterial bone and joint infections.

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การปลดปล่อยยาเจนตาไมซินจากซีเมนต์กระดูก: การศึกษาเปรียบเทียบระหว่างเจนตาไมซินแบบน้ำและแบบผง

สุรสิทธิ์ ปานมณี, พบ.

หลักการและวัตถุประสงค์ : *การใช้เม็ดยา gentamicin (เจนตาไมซิน) รักษาการติดเชื้อของกระดูกและข้อได้ผลดี แต่ยาแบบสำเร็จรูปมีราคาแพงและหาซื้อได้ยากไม่สอดคล้องกับการใช้งานจริง ศัลยแพทย์ออร์โธปิดิกส์มักจำเป็นต้องทำขึ้นใช้เองจาก bone cement (ซีเมนต์กระดูก) ที่มียาเจนตาไมซินแบบผง ผสมอยู่ แต่ก็ยังมีต้นทุนการผลิตสูงระดับหนึ่ง ผู้วิจัยจึงศึกษาการใช้ยาเจนตาไมซินแบบน้ำที่ใช้ฉีดในโรงพยาบาล มีราคาถูกกว่ามาใช้ทดแทน การศึกษานี้จะทำการเปรียบเทียบการปลดปล่อยยาเจนตาไมซินจากซีเมนต์กระดูกระหว่างยาแบบน้ำและแบบผง*

วิธีการศึกษา : *เป็นการศึกษาทดลองเปรียบเทียบแบบสุ่ม โดยศึกษาในผู้ป่วยติดเชื้อแบคทีเรียในกระดูกและข้อจำนวน 60 รายที่มารักษาที่โรงพยาบาลหาดใหญ่ จับฉลากแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มที่ 1 ใช้ยาเจนตาไมซินแบบน้ำ กลุ่มที่ 2 ใช้ยาเจนตาไมซินแบบผง ผสมในซีเมนต์กระดูกวัดระดับยาที่ถูกปลดปล่อยออกมาในบริเวณที่ฝังยานำมาเปรียบเทียบกัน*

ผลการศึกษา: *การศึกษานี้ทำในผู้ป่วยติดเชื้อในกระดูกและข้อกลุ่มละ 30 ราย พบว่าการผสมยาเจนตาไมซินแบบน้ำมีระดับยาในบริเวณฝังยาสูงกว่าแบบผงอย่างมีนัยสำคัญ ระดับยาทั้ง 2 กลุ่มสูงกว่าระดับยาขั้นต่ำที่สามารถฆ่าเชื้อโรคได้หลายเท่าและคงอยู่จนถึง 28 วันเป็นอย่างน้อย ให้ผลการรักษาทางคลินิกดีเท่าเทียมกันทั้ง 2 กลุ่มและปลอดภัยต่อการทำงานของไต*

สรุป: *การผสมยาเจนตาไมซินแบบน้ำในซีเมนต์กระดูกสามารถปลดปล่อยยาออกฤทธิ์เฉพาะที่ได้สูงกว่าแบบผง มีความปลอดภัย ไม่เป็นพิษต่อไต ให้ผลการรักษาทางคลินิกที่ดี และมีต้นทุนที่ถูกกว่า ทำให้สามารถประหยัดค่าใช้จ่ายในการรักษาผู้ป่วยกลุ่มนี้ได้*