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Antibiotics Elution Depth in Bone Cement: Impact of Surface Area and Volume

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Abstract: Antibiotic-loaded bone cement (ALBC) plays a pivotal role in infection prevention and treatment related to musculoskeletal surgery. The release efficacy of antibiotics from ALBC is closely tied to its surface area, yet little is known about the effective release depth. To investigate the relationship between surface area, volume, and antibiotic elution, spheric ALBC specimens with consistent outer diameters but different internal metal sphere diameters were prepared. Two vancomycin doses were utilized in ALBC specimens with an outer diameter of 35 mm: high (4 g) and low (1 g). Each dosage group included five specimens containing embedded metal spheres with diameters of 15, 25, 29, 32, or 33 mm. The resulting shell-like ALBC specimens had thicknesses of 10 mm, 5 mm, 3 mm, 1.5 mm, or 1 mm, respectively. The specimens were immersed in sterile phosphate buffer solution, and antibiotic elution was measured at designated sampling times (1, 3, 6, 10, 24, 48, 72, and 168 hours). Methylene blue was employed to visualize penetration depth. Vancomycin elution did not display statistically significant differences between high- and low-dose groups. In both groups, specimens with 1 mm thickness exhibited a higher vancomycin release efficiency (high-dose group: 18560±5474 μg, 6.7%; low-dose group: 2017±419 μg, 2.6%), decreasing sharply in thicker ALBC specimens. Methylene blue penetration depth showed no apparent difference between high-dose and low-dose groups. ALBC thickness does not significantly impact antibiotic elution, while surface area and antibiotic dose exert notable effects. These in vitro findings offer potential applications in clinical treatments for musculoskeletal infections.

Keywords: antibiotics-loaded bone cement; musculoskeletal infections; vancomycin elution; surface area; volume

1. Introduction

Deep infections in orthopedic surgery, such as osteomyelitis and periprosthetic joint infection (PJI), constitute a formidable complication, often resulting in recurrent surgical debridement, bone loss, and a diminished quality of life [1]. Treatment approaches may involve comprehensive debridement, effective drainage, dead space obliteration, and prolonged antibiotic therapy [2]. However, systemic antibiotic administration carries the risk of kidney or liver toxicity, necessitating regular monitoring of serum antibiotic levels. Furthermore, the efficacy of systemic antibiotic administration can be hindered by compromised blood supply around infected skeletal tissue [3].

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Antibiotic-loaded bone cement (ALBC) addresses these challenges by allowing for localized control of the antibiotic concentration [4,5]. ALBC serves as a drug delivery system, ensuring a high antibiotic concentration at the surgical site that cannot be achieved by systemic administration, while minimizing systemic toxicity [6,7]. Additionally, ALBC can offer sufficient mechanical strength for prosthetic fixation or be crafted into a spacer to maintain joint range of motion during two-stage revision surgery [8]. This innovation enhances the therapeutic arsenal against deep infections while minimizing systemic antibiotic-related concerns [9].

The efficiency of antibiotic release from ALBC is determined by factors such as cement brand, cement body geometry, cured cement porosity, and the specific antibiotic combination [10–13]. The quantity of antibiotics embedded in the cement is a crucial determinant of elution efficacy [14]. Numerous studies have shown a direct correlation between in vitro antibiotic elution from acrylic cement and the exposed cement surface area in a liquid medium [7,15,16]. The elution efficacy of ALBC can be optimized by modifying the surface area and antibiotic dosage [17,18]. Concerns persist regarding the mechanical strength of ALBCs, both pre- and post-elution, especially when they are utilized for the mechanical fixation of prostheses or implants [19].

However, the "effective depth" from which ALBC releases antibiotics remains unknown. To our knowledge, no reports addressing the elution characteristics of an in vitro model of ALBC specimens with identical surface areas but varying volumes have been published [20]. This knowledge gap highlights the need for further investigation into the nuanced factors affecting antibiotic release in ALBC to enhance our understanding of its therapeutic capabilities.

The primary objective of the current study was to determine the effective depth of ALBC, representing the region from which the majority of antibiotic release occurs. A secondary goal was to analyze and compare the effective elution depth between high-dose and low-dose ALBC. The clinical relevance of this research lies in optimizing antibiotic elution from bone cement to enhance therapeutic efficacy without compromising the mechanical strength of ALBC.

2. Methods

2.1. Preparation of ALBC Specimens

One gram (low-dose group) or 4 g (high-dose group) vancomycin hydrochloride (Gental Pharmaceutical Co., Yulin, Taiwan) was mixed with 40 g of bone cement polymer (Simplex P, Stryker Orthopaedics, Limerick, Ireland) before adding 20 ml of the monomer. The antibiotic–cement mixture was mixed in a ceramic container for 2 minutes to achieve a doughy texture, and then manually pressed into a spherical plastic mold with a diameter of 35 mm. The center of the molds contained a single metal sphere of varying diameter. The ALBC was then cured at room temperature for 1 hour.

Specimen preparation of ALBC with various surface area-to-volume ratios

One group of ALBC specimens did not contain a metal sphere, while the remaining five groups contained a single metal sphere at the center with different diameters: 15, 25, 29, 32, and 33 mm. The preparation resulted in shell-like ALBC specimens with thicknesses of 10, 5, 3, 1.5, and 1 mm, respectively. Using this method, ALBC specimens with identical surface areas but varying amounts of impregnated antibiotic could be prepared. The surface area-to-volume ratio could be calculated as follows:

Surface area of ALBC (A) = $4 \cdot \pi \cdot R^2$

Volume of outer sphere (V_o) = $(4/3) \cdot \pi \cdot R^3$

Volume of inner sphere (V_i) = $(4/3) \cdot \pi \cdot r^3$

Volume of ALBC (V) = $V_o - V_i = (4/3) \cdot \pi \cdot R^3 - (4/3) \cdot \pi \cdot r^3 = (4/3) \cdot \pi \cdot (R^3 - r^3)$

Ratio of surface area-to-volume (A/V) = $[4 \cdot \pi \cdot R^2] / [(4/3) \cdot \pi \cdot (R^3 - r^3)]$

$= 3 \cdot R^2 / (R^3 - r^3)$

where “R” denotes the outer radius of the specimen and “r” denotes the radius of the metal sphere.

Three specimens were made for each metal sphere diameter. The six groups of ALBC specimens with the same outer diameter of 35 mm, but different thicknesses, are illustrated in Figure 1. The

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specifications of the various metal sphere diameters, cement thicknesses, and surface area-to-volume ratios are listed in Table 1.

Figure 1. Photograph illustrating six spherical ALBC specimens with a consistent outer diameter of 35 mm but varying cement thickness. (a) Six spherical ALBC specimens showcasing an identical outer diameter of 35 mm, (b) metal spheres utilized for embedding in the specimens, (c) X-ray image displaying six spherical ALBCs with an identical outer diameter of 35 mm, highlighting the variations in cement thickness.

Table 1. The specifications of the various metal sphere diameters, cement thicknesses, and surface area-to-volume ratios.

No.	Metal sphere diameter (mm)	Cement thickness (mm)	Surface area-to-volume ratio (1/mm)
1	None (control)	17.5	0.17
2	15	10	0.19
3	25	5	0.27
4	29	3	0.40
5	32	1.5	0.73
6	33	1	0.99

2.2. Antibiotic Elution Test

Each ALBC sphere was immersed in a glass tube containing 30 ml of sterile phosphate buffer solution (PBS) and kept at 37°C until designated sampling time points (1, 3, 6, 10, 24, 48, 72, and 168 hours) when the specimens were removed from the test tubes. The eluate in each test tube was frozen at –20°C prior to antibiotic concentration analysis. The ALBC sphere was then washed in 10 ml of PBS and re-immersed in another test tube containing 30 ml of fresh PBS. The vancomycin concentration was determined via a fluorescence polarization immunoassay on an Abbot Laboratories TDx Analyzer (Abbot Laboratories, Abbot Park, IL). The lower limit of detection was 1.0 μg/ml for vancomycin.

2.3. Vancomycin Release Efficiency

The vancomycin release efficiency was calculated as the amount of vancomycin released divided by total vancomycin contained in the ALBC. To calculate the total vancomycin contained in each ALBC group, we obtained the standard density of low- and high-dose ALBCs (0.069 and 0.018 g/cm^3, respectively) by measuring the volume and weight of a cylindrical ALBC specimen. The volume of vancomycin was calculated by multiplying the density and the volume of the ALBC specimen.

2.4. Methylene Blue Visualization Test

The amount of antibiotic elution is thought to be related to the penetration depth of the solution into the ALBC specimen. We used methylene blue to visualize this penetration depth. ALBC specimens without antibiotics (control), those with high-dose vancomycin, and those with low-dose vancomycin were immersed in 50 ml of saline solution and 2 ml of methylene blue. The specimens were incubated for certain time points (1, 3, 6, 10, 24, 48, 72, 168 hours) at 37°C and then re-immersed in fresh solution until the next time point. After 168 hours, the cross-sectional area of each specimen was examined after being cut with a power saw.

2.5. Statistical Analysis

The results were presented as means ± standard error of the means. A 2-tailed Student t-test was employed to compare the antibiotic concentration between samples with high-dose and low-dose vancomycin at each time point. To assess statistical differences in the accumulated antibiotic release and release efficacy among the groups, a 1-way analysis of variance was utilized. A significance level

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of 0.05 was applied, and all statistical analyses were performed using IBM SPSS Statistics 25 (IBM; Armonk, New York, USA).

3. Results

3.1. Vancomycin Elution – Low-Dose Group

For all groups of specimens, a burst release of vancomycin was observed in the first 10 hours, followed by a much slower release. In the low-dose group, the total weight of vancomycin released in the 1, 1.5, 3, 5, 10, and 17.5 mm specimens were 2017 ± 419, 2177 ± 219, 2163 ± 249, 2166 ± 58, 2175 ± 51, and 2353 ± 43 μg (Figure 2a), respectively. These amounts did not show statistically significant differences ($p > 0.05$). The highest vancomycin release efficiency was observed in the 1 mm specimen and the release efficiency decreased sharply with increasing ALBC thickness (Figure 3a).

Figure 2. (a) Accumulated low-dose vancomycin release in the 1, 1.5, 3, 5, 10, and 17.5 mm specimens over 168 hours. (b) Accumulated high-dose vancomycin release in the 1, 1.5, 3, 5, 10, and 17.5 mm specimens over 168 hours.

Figure 3. (a) Relationship between different surface area-to-volume ratios and the efficiency of low-dose vancomycin release. (b) Relationship between different surface area-to-volume ratios and the efficiency of high-dose vancomycin release.

3.2. Vancomycin Elution – High-Dose Group

In the high-dose group, vancomycin eluted in the 1, 1.5, 3, 5, 10, and 17.5 mm specimens amounted to 18560 ± 5474, 21407 ± 948, 21090 ± 2806, 21368 ± 1435, 21208 ± 16686, and 23873 ± 1894 μg, respectively (Figure 2b). There were no statistically significant differences among the groups ($p > 0.05$). The vancomycin release efficiency was largest in the 1 mm specimen and decreased with increasing ALBC thickness ($p < 0.05$) (Figure 3b).

The accumulated of vancomycin release was markedly higher in the high-dose group compared to the low-dose group ($p < 0.05$) (Table 2). Additionally, the efficiency of vancomycin release was significantly greater in the high-dose group than in the low-dose group ($p < 0.05$) (Table 3).

Table 2. Accumulated vancomycin release in each group.

No.	Cement thickness (mm)	Surface area-to-volume ratio (1/mm)	Accumulated vancomycin release (μg) (low-dose group)	Accumulated vancomycin release (μg) (high-dose group)	*p*- value
1	17.5	0.17	2353 ± 43	23873 ± 1894	**< 0.05**
2	10	0.19	2175 ± 51	21208 ± 16686	**< 0.05**
3	5	0.27	2166 ± 58	21368 ± 1435	**< 0.05**
4	3	0.40	2163 ± 249	21090 ± 2806	**< 0.05**
5	1.5	0.73	2177 ± 219	21407 ± 948	**< 0.05**
6	1	0.99	2017 ± 419	18560 ± 5474	**< 0.05**

Values are expressed as mean ± standard error. Boldface indicates statistical significance.

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Table 3. The vancomycin release efficiency in each group.

No.	Cement thickness (mm)	Surface area-to-volume ratio (1/mm)	Vancomycin release efficiency (%) (low-dose group)	Vancomycin release efficiency (%) (high-dose group)	*p*-value
1	17.5	0.17	0.00063 ± 0.00000012	0.00160 ± 0.000001	**< 0.05**
2	10	0.19	0.00312 ± 0.00000073	0.00760 ± 0.000006	**< 0.05**
3	5	0.27	0.02484 ± 0.00000664	0.06125 ± 0.000041	**< 0.05**
4	3	0.40	0.11483 ± 0.00013201	0.27986 ± 0.000372	**< 0.05**
5	1.5	0.73	0.92427 ± 0.00093040	2.27247 ± 0.001007	**< 0.05**
6	1	0.99	2.89013 ± 0.00600473	6.64968 ± 0.019612	**< 0.05**

Values are expressed as mean ± standard error. Boldface indicates statistical significance.

3.3. Methylene Blue Visualization Test

In methylene blue visualization test, more obvious surface methylene blue pigmentation was observed in the high-dose group than that in the control group and low-dose group. However, there were no apparent differences in methylene blue penetration depth among the three groups (Figure 4).

Figure 4. Comparison of adsorbed methylene blue among three groups of bone cement spheres. (a) Bone cement sphere without added antibiotics. (b) Bone cement sphere with low-dose antibiotics. (c) Bone cement sphere with high-dose antibiotics.

4. Discussion

The current study yielded several significant and non-significant findings. First, there was no significant difference in the amount of eluted vancomycin regardless of ALBC thickness for both low- and high-dose groups. This indicates that vancomycin elution was similar for bone cement with the same surface area and was unrelated to the thickness of the cement. Research on ALBC has long recognized this surface phenomenon where the majority of antibiotics are released from the surface and therefore the amount of release is determined by the surface area, not the volume [21,22]. Earlier studies, such as the in vitro study by Masri et al [15], explored the antibiotic elution characteristics of ALBC prostheses with different surface patterns (smooth, four rows, and eight rows) and varying surface area-to-volume ratios in three sets of bone cement blocks. Their results showed that antibiotic elution was solely associated with the surface area-to-volume ratio, regardless of the surface pattern. This conclusion aligns with the findings of our current study, as we meticulously controlled the surface area, and our observations revealed that varying cement volume did not significantly impact the amount of antibiotic elution.

Second, we observed significantly higher degrees of vancomycin elution in the high-dose groups compared to those in the low-dose groups. Across all specimen groups, there was a high rate of vancomycin released from ALBC within the first 10 hours, followed by a gradual decrease in the rate of release, which is consistent with previous studies. While we anticipated that the high-dose group would release four times more antibiotics than the low-dose group, the results revealed a nearly tenfold difference. Notably, when comparing the low-dose group with the thickest ALBC to the high-dose group with the thinnest ALBC, it became evident that the former released a smaller total quantity of antibiotics than the latter. These phenomena may be understood by considering the combined effect of surface area and the porosity of the bone cement [23]. The high-dose specimens exhibited a porous and rough texture, while the low-dose specimens had a smooth and dense appearance [24]. A higher degree of porosity and roughness may facilitate antibiotic release, allowing fluid penetration into the cement layers and subsequent antibiotic release [8].

Additionally, methylene blue visualization revealed no obvious difference in penetration depth between different thicknesses of ABLC in the control, high-dose, and low-dose groups. Only surface

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methylene blue penetration was observed in all groups, indicating that fluid penetration, whether in PBS or synovial fluid, is limited to the superficial layer [23]. Antibiotics will solely elute when dissolved in the fluid. Although the current study did not quantify the penetration depth of methylene blue, gross observations and observations of cross sections did not reveal significant differences in penetration depth.

Clinical studies addressing hip ALBC spacer treatment for PJI often notes complications, such as spacer fractures [9,25]. One contributing factor is the design of the spacer, where a more robust endoskeleton augments strength and helps prevent spacer fractures [26]. Cacciola et al [27] demonstrated that a modular articulating spacer with a robust endoskeleton yields satisfactory functional outcomes while minimizing the risk of mechanical complications. However, these studies fail to address whether ALBC spacers with enhanced endoskeletons provide sufficient antibiotic release and local concentration. Our study, utilizing metal spheres of varying sizes enveloped in cement of different thicknesses to form experimentally equivalent shells, addresses this question. For the same dose and surface area, varying thicknesses yielded no statistically significant differences in antibiotic elution, indicating that the majority of antibiotic elution is confined to the surface area of the bone cement.

The elution of antibiotics is limited to a thin surface layer of the ALBC [4,15,16,28]. This characteristic raises concerns about utilizing expensive antibiotics within ALBC, as the majority of it may be unused. Moreover, an excess of antibiotics within ALBC poses a dual challenge—lacking substantial antibacterial effects, while potentially compromising the mechanical strength of the construct [7]. A potential solution to optimize antibiotic usage could involve employing a low-dose ALBC or a more robust metal construct, such as an endoskeleton, complemented by an external coating of high-dose ALBC. This strategic combination aims to balance cost-effectiveness, antibacterial efficacy, and mechanical integrity in the context of ALBC application [7,18].

Our study is subject to certain limitations. First, being an in vitro investigation conducted on specimens in a controlled laboratory environment, the findings may not precisely mirror real-world clinical conditions. Variables such as bodily fluid quantity, limb mobility, host response, and in vivo antibiotic dynamics were not taken into account. Second, our study only utilized a single type of bone cement, one specific antibiotic, and a particular preparation method. Third, we did not subject our ALBC specimens to mechanical tests, and as a result, we lack numerical data to quantify the strength of metal spheres of different sizes and ALBC coatings. Nevertheless, prior studies assessed the mechanical strength of ALBC with different antibiotic doses, suggesting potential structural weakening at higher doses [29]. Clinical evidence also indicates increased mechanical failures at high antibiotic doses [30]. Moreover, the released antibiotics were not subjected to anti-bacterial activity testing in this study, leaving uncertainty regarding their bactericidal effectiveness. However, anti-bacterial activity of vancomycin eluted from ALBC has been proven effective against *Staphylococcus aureus* [31]. Additionally, the depth of methylene blue penetration could not be quantified in this study. While these limitations may restrict the generalizability of our results to specific clinical scenarios, the uniform preparation and testing of specimens in our study contribute valuable and consistent insights.

5. Conclusions

The thickness of ALBC does not significantly impact antibiotic elution, while surface area and antibiotic dose exert notable effects on antibiotic elution. These in vitro findings hold potential applications in clinical treatments for musculoskeletal infections.

Author Contributions: Yu-Yi Huang wrote the final manuscript. Sheng-Hsun Lee, Ching-Lung Tai and Pang-Hsin Hsieh contributed to the study design. Ching-Lung Tai and Wei-Lin Hsiao were responsible for project administration. Yu-Yi Huang and Sheng-Hsun Lee conducted the statistical analyses. Yu-Chih Lin, Chih-Hsiang Chang, and Pan-Hsin Hsieh were involved in designing the article, analysis and interpretation of data. Sheng-Hsun Lee assisted in assembling the manuscript draft and revising it critically. All authors reviewed and approved the final manuscript.

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