

Original Article

Development of New Bone Cement utilizing Low Toxicity Monomers

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Acrylic bone cement is self-curing cement comprising of liquid and powder component of methyl methacrylate (MMA). It has been used extensively in orthopedics; however, adverse effects were associated with its use. Hence we investigated in this paper the possibility of new cement utilizing methacrylates with lower toxicity than MMA. LD50s of candidate monomers were determined with administration to the medullary cavity of the rat's femur. 2-Ethylhexyl methacrylate (EHMA) and trimethylolpropane trimethacrylate (TMP) demonstrated greater LD50 values of 187 mg/kg and 380 mg/kg, respectively, than MMA (108 mg/kg); they were selected as the liquid components of the new cement. The copolymer of EHMA and cyclohexyl methacrylate was then selected as the powder component. With this combination, we developed the new cement (EHMA cement). Temperature rise during polymerization of EHMA cement was 9°C–13°C, which was significantly lower than that of conventional cement. The compression strength of the polymerized EHMA cement was 57 MPa without TMP, and 67 MPa with TMP (15 wt%). Thus we concluded that new EHMA cement was slightly inferior in the compression strength than the conventional cement. However, it was characterized by the low toxicity of utilized monomers and the low temperature rise during polymerization.

Key words: bone cement, monomer toxicity, methyl methacrylate, 2-Ethylhexyl methacrylate, cyclohexyl methacrylate

Introduction

Acrylic bone cement is a self-curing two-component cement comprising of a powder component, PMMA beads, and a liquid component, MMA.¹ It has been used for many years in orthopedic procedures such as hip and knee arthroplasty,² and today its applications have been further extended to include percutaneous vertebroplasty.³ The bone cement has a number of unique advantages, which have extended its clinical applications.

However, the cement is also known to be associated with several adverse effects. An exothermic reaction during cement polymerization causes temperature rise and tissue necrosis in an adjacent bone, and thereby increases the risk of prosthetic loosening.⁴ Another serious complication is "bone cement implantation syndrome (BCIS)," which is characterized by hypotension, hypoxemia, cardiac arrhythmias, cardiac arrest, or a combination of these.^{5,6} This is typically experienced during hip arthroplasty just after the injection of cement to the medullary canal. Although this complication is rare, 37 lethal cases of BCIS have been reported in Japan during the period from April 2001 to March 2005.⁷ Furthermore, there is concern regarding risks faced by operators accompanying the manipulation of cement.^{8,9}

In order to diminish the risks relating to the use of the cement, many investigations have been performed. For example, the addition of n-butyl methacrylate (nBMA)

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to the liquid components,¹⁰ changes in the chemical composition of two-solution acrylic bone cement,¹¹ and the addition of bioactive fillers to the powder component¹² have been investigated. Nonetheless, the use of methacrylates other than MMA as the major part of the liquid component has not yet been fully explored. Despite its strong odor, MMA is known to have relatively low toxicity among methacrylate monomers; this fact could be possibly associated with the extensive and successful utilization of the MMA bone cement. Accordingly, the most important factor in the search of alternative monomers for the new cement is considered to be their toxicity.

Hence, in this paper, we investigated the toxicity of several methacrylate monomers and searched for monomers having lower toxicity than MMA. After the selection of the candidate monomer, we determined a suitable copolymer that was soluble in the monomer. Based on these combinations, we developed the new bone cement (designated as EHMA cement) utilizing 2-ethylhexyl methacrylate (EHMA) as the major liquid component and poly(CHMA/EHMA) beads as the powder component. Subsequently, the temperature rise during polymerization and the compressive strength and elastic modulus were measured, and the efficacy of EHMA cement was examined.

Materials and Methods

Materials

Several methacrylate monomers were used in this experiment for the development of a new bone cement; they were MMA, ethyl methacrylate (EMA), nBMA, cyclohexyl methacrylate (CHMA), and EHMA. The other chemicals used were trimethylolpropane trimethacrylate (TMP) (Kyoei Chemicals, Tokyo, Japan) as the crosslinking agent, benzoyl peroxide (BPO) (Nacalai Tesque, Kyoto, Japan) as the polymerization initiator, N,N-dimethyl-p-toluidine (DMPT) as the polymerization accelerator, sodium n-dodecyl sulfate (SDS) as the surfactant, and Supertite (Nippon Chemical Industrial, Tokyo, Japan) as the dispersant. Chemicals without any specified manufacturers were of reagent grade and purchased from Kanto Chemicals, Tokyo, Japan. Furthermore, commercial bone cement (No. 1102-12; Zimmer, Warsaw, IN, USA) was used as the control.

Acute toxicity test of candidate monomers

Acute toxicity tests were performed for MMA, EMA, nBMA, EHMA, CHMA, and TMP. By following the up-

and-down procedure described in the OECD testing guideline,¹³ the amount of monomers administered to experimental animals was increased or decreased and the LD50 was determined. Eight-week old female Sprague Dawley rats were utilized in the experiment. The animal was anesthetized by the inhalation of isoflurane (Isoflu; Dainippon Sumitomo Pharma., Osaka, Japan). Then the prescribed amount of monomers was injected to the medullary cavity of the femur through the intercondylar area with a glass microsyringe (LF-100; Kusano Science, Tokyo, Japan). The number of animals in each group was more than 5. The experiment was conducted in compliance with the protocol that had been approved by the Institutional Animal Care and Use Committee of Tokyo Medical and Dental University, and in compliance with the Committee's guidelines.

Synthesis of copolymers by suspension polymerization method

Homopolymers and copolymers of MMA, EMA, nBMA, CHMA, and EHMA were synthesized by using the suspension polymerization method. First, we passed the respective monomers through an alumina column in order to remove polymerization inhibitors. 50 g of monomer was poured to 150 ml of water in a flask. Then 0.01 g of SDS as a surfactant, 10 g of Supertite as a dispersant, and 0.5 g of BPO as a polymerization initiator were added. The flask was then placed in a water bath stirred at 800 rpm under a gentle nitrogen stream, and maintained 75°C for 90 min and then at 90°C for another 30 min for polymerization. After cooling to room temperature, 2.5 g of nitric acid was added to the flask and the dispersant was dissolved. Consequently, polymer beads were separated by suction filtration; they were then washed with demineralized water, dried under vacuum for 12 h. In this manner, we obtained the final products. The yields were approximately 97–99%. Subsequently, these copolymers, for example, 90 wt% of CHMA and 10 wt% of EHMA, were represented as 90/10 poly (CHMA/EHMA). The molecular structures of CHMA, EHMA, and poly (CHMA/EHMA) are presented in Fig. 1.

Solubility test of candidate polymers

In order to develop the experimental bone cement comprising a liquid component of EHMA, we tested the solubility of several candidate polymers that might be utilized as the powder component. By using the suspension polymerization method, we prepared homopolymer beads from MMA, EMA, nBMA, EHMA, and

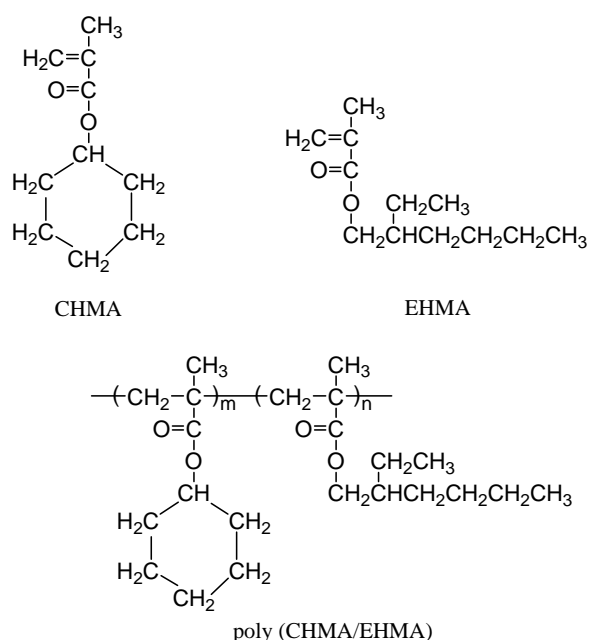


Fig. 1. Molecular structure of EHMA, CHMA, and poly (CHMA/EHMA).

CHMA. 3 mg of each type of homopolymer beads were mixed with 2 ml of EHMA in a glass test tube, and then the tube was sealed and kept at room temperature. After 24 h, we observed the presence or absence of the remaining polymer powders and determined the solubility.

Mechanical test of specimens prepared by the bulk polymerization method

Before experimenting with the EHMA cement, we synthesized several kinds of copolymers of CHMA and EHMA by using bulk polymerization method and studied the way in which their compositions affect their mechanical properties. 11 mixtures of CHMA and EHMA were prepared with the weight ratio of CHMA/EHMA ranging from 100:0 to 0:100 with intervals of 10. After the addition of 1 wt% of BPO, the mixture was poured into a glass test tube, sealed, and placed in a hot water bath at 75°C for 4.5 h. After cooling to room temperature, the polymerized materials were removed from the test tubes. Then they were machined to prepare cylindrical testpieces with a height of 12 mm and diameter of 6.4 mm. We performed the compression test according to ISO 5833,¹⁴ with a universal testing machine (Model 1185; Instron, Canton, MA, USA). The cross-head speed was 20 mm/min, and the number of specimens was 5.

Measurement of temperature rise during polymerization of powder/liquid cement

We measured the temperature rise during the polymerization of EHMA cement for several powder compositions. Polymer beads of PCHMA, 90/10 poly (CHMA/EHMA), 80/20 poly (CHMA/EHMA), and 70/30 poly (CHMA/EHMA) were synthesized by using the suspension polymerization method. A powder component of the EHMA cement was prepared using these beads and 2 wt% of BPO as a polymerization initiator. A liquid component was prepared with EHMA and 1 wt% of DMPT as a polymerization accelerator supplemented with or without 15 wt% of a crosslinking agent TMP. We measured the temperature rise according to ISO 5833.¹⁴ By setting the powder/liquid ratio to be 3.5:1, the powder and liquid were mixed and poured into a Teflon mold. The temperature was measured with a sheath-type thermoelectric couple (TK1.6×50; AsOne, Osaka, Japan) and a data logger (TDS-302; Tokyo Sokki Kenkyujo, Tokyo, Japan). The room temperature was set to be 20°C, and the number of specimens was 3.

Mechanical properties of specimens prepared from powder/liquid cement

We measured the compressive mechanical properties of EHMA cement; the compositions were identical to that used in the temperature rise measurement. The test was performed according to ISO 5833.¹⁴ By setting the powder/liquid ratio to 3.5:1, the powder and liquid were mixed and polymerized in a Teflon mold, and cylindrical test pieces having a height of 12 mm and diameter of 6.0 mm were prepared. The compression test was performed with the universal testing machine. The crosshead speed was 20 mm/min and the number of specimens was 5.

Statistical analysis

A statistical analysis of the compressive strength and modulus of the copolymer specimens prepared by the bulk polymerization method was performed using one-way analysis of variance (ANOVA) for the factor of the CHMA/EHMA ratio. A statistical analysis of the temperature rise and mechanical properties of the experimental cement was performed using two-way ANOVA for the factors of presence or absence of the supplemented TMP and CHMA/EHMA ratio of the powder component. Scheffe's multiple comparisons were performed as a post hoc analysis. A statistical analysis of the temperature rise and mechanical properties of the experimental cements and the control cement was

Table 1. LD50 (mg/kg) of methacrylate monomers. Intramedullary LD50s of rat are the values obtained in this report, whereas the others are compiled from the data from the toxicological database (TOXNET - Available at: <http://toxnet.nlm.nih.gov/>). EHMA and TMP were found to have greater intramedullary LD50 than MMA.

organism	route	monomer					
		MMA	EMA	nBMA	EHMA	CHMA	TMP
mouse	oral	3,625	7,836	12,900	-	-	-
mouse	intraperitoneal	945	1,369	1,490	2,614	-	2,889
rat	oral	7,872	14,800	16,000	>2,000	11,000	5,830
rat	intraperitoneal	1,328	1,223	2,304	-	-	3,100
rat	intramedullary	108	84	<81	187	<81	380

performed using Welch's *t*-test between the combined experimental group and the control group. Statistical significance was assumed for $p < 0.05$. The statistical analyses were performed with the use of an open software R (Available at <http://www.r-project.org/>).

Results

Acute toxicity of the monomers

The values of LD50 obtained from the acute toxicity tests are presented in Table 1. MMA was found to have relatively low toxicity among methacrylates if tested using the intramedullary injection method. Only methacrylates EHMA and TMP were found to have lower toxicity than MMA in this investigation.

Solubility of the homopolymers

The result of the solubility test is presented in Table 2. In the table, the homopolymers that dissolved in EHMA have been shown using "+" whereas those that do not fully dissolve are shown as "-." The candidate powder components of the experimental bone cement were determined to be PEHMA, PCHMA, or copolymers of EHMA and CHMA.

Mechanical properties of copolymer specimens prepared by the bulk polymerization method

The results of the compression tests of copolymer specimens prepared by the bulk polymerization method are presented in Fig. 2. One-way ANOVA with the factor of the CHMA/EHMA ratio demonstrated that the ratio had a significant effect on the compressive strength and modulus. Both the strength and modulus of poly (CHMA/EHMA) with low CHMA-composition ratios were small, and they increased with the CHMA-composition ratio whereas those of 90/10 poly (CHMA/EHMA) and PCHMA did not demonstrated a significant difference. 60/40 poly (CHMA/EHMA) had a strength

Table 2. Solubility of methacrylate homopolymers in EHMA. Poly(*n*-butyl methacrylate) (PnBMA), poly(cyclohexyl methacrylate) (PCHMA), and poly (2-ethylhexyl methacrylate) (PEHMA) were soluble in EHMA, whereas poly (methyl methacrylate) (PMMA) and poly (ethyl methacrylate) (PEMA) were not.

homopolymer	PMMA	PEMA	PnBMA	PEHMA	PCHMA
solubility in EHMA	-	-	+	+	+

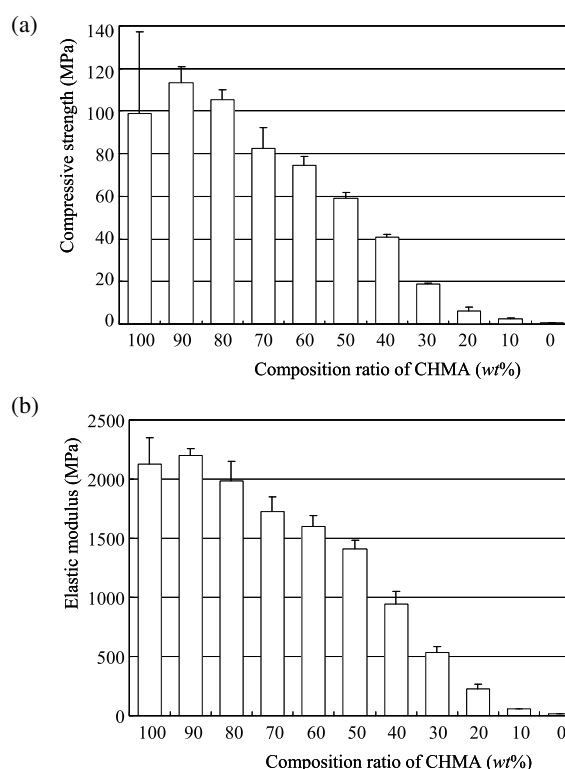


Fig. 2. Mechanical properties of specimens prepared by the bulk polymerization method. Data are presented as mean + 95% confidential interval.

(a) Compressive strength. ANOVA demonstrated that the composition ratio of CHMA had a significant effect on the compressive strength ($p < 0.01$).

(b) Compressive elastic modulus. ANOVA demonstrated that the composition ratio of CHMA had a significant effect on the elastic modulus ($p < 0.01$).

of 74.3 ± 4.4 MPa (mean \pm 95% confidence interval), and the copolymers with a higher composition ratio of CHMA had greater strength. Since the ISO 5833 standard requires bone cement to have a compressive strength of more than 70 MPa, we determined that the composition ratio of CHMA would preferably be greater than 60 wt% in the case of the experimental bone cement.

Temperature rise during polymerization of powder/liquid cement

The maximum temperature rises observed in the polymerization of the experimental cement are shown in Fig. 3. Two-way ANOVA demonstrated a significant effect of the addition of TMP ($p < 0.01$), whereas it showed non-significant effects of the CHMA/EHMA composition ratio ($p > 0.05$) and the interaction of two factors ($p > 0.05$). Welch's t test demonstrated that the experimental bone cement had a significantly lower temperature rise than the control cement ($p < 0.01$). Actually, experimental bone cement without TMP demonstrated a temperature rise of approximately 9°C, while that with TMP showed a rise of 13°C. On the other hand, the control bone cement demonstrated a temperature rise of approximately 41°C.

Mechanical properties of specimens prepared from powder/liquid cement

Specimens without the addition of TMP did not exhibit clear yielding at mechanical test, whereas

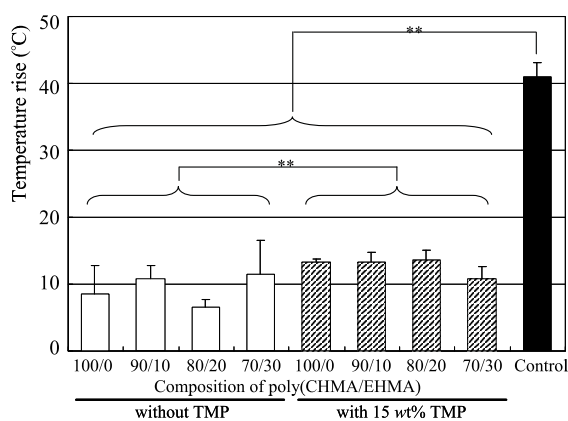


Fig. 3. Temperature rise during the polymerization of cement. Data are presented as mean + SD. 2-way ANOVA demonstrated significant effect of the addition of TMP ($p < 0.01$) and a non-significant effect of the composition ratio of CHMA ($p > 0.05$). Welch's t test demonstrated that the temperature rise by EHMA cements was significantly lower than that by the control cement ($p < 0.01$). **Significant difference ($p < 0.01$).

those with TMP demonstrated yielding. In the cases no yielding was observed, the 2% offset strength was adopted as the compressive strength according to ISO 5833.¹⁴ The compressive strength and modulus of the experimental cement are presented in Fig. 4. Two-way ANOVA for the factors of the presence or absence of the TMP and the CHMA/EHMA composition ratio of the powder component demonstrated that the addition of TMP significantly increased both the strength and

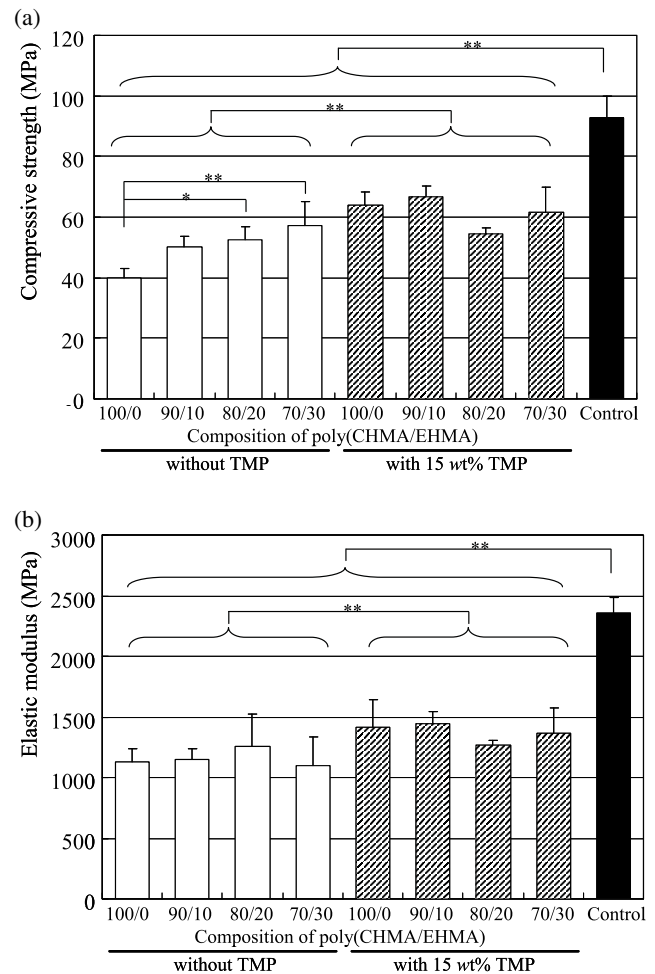


Fig. 4. Mechanical properties of specimens prepared from powder/liquid cement. Data are presented as mean + SD. **Significant difference ($p < 0.01$), and *significant difference ($p < 0.05$).

(a) Compressive strength. 2-way ANOVA demonstrated significant effect of the addition of TMP ($p < 0.01$) and the composition ratio of CHMA ($p < 0.01$). Welch's t test demonstrated significant differences between the EHMA cement and control cement ($p < 0.01$).

(b) Compressive elastic modulus. 2-way ANOVA demonstrated significant effect of TMP ($p < 0.01$) and non-significant effect of composition ratio of CHMA ($p > 0.05$). Welch's t test demonstrated significant difference between the EHMA cement and control ($p < 0.01$).

modulus ($p < 0.01$), whereas the CHMA/EHMA composition ratio significantly affected the strength ($p < 0.01$) but not the modulus ($p > 0.05$). The interaction of two factors also affected the strength ($p < 0.01$) but not the modulus ($p > 0.05$). The maximum strength, 66.6 ± 3.8 MPa, was achieved in the case of the powder of 90/10 poly (CHMA/EHMA) and the addition of TMP, although multiple comparisons of Scheffe did not demonstrate statistical differences between the cements with the powder of PCHMA, 90/10 poly (CHMA/EHMA), 80/20 poly (CHMA/EHMA), or 70/30 poly (CHMA/EHMA).

Discussion

The pathogenic mechanism of BCIS has not yet been elucidated completely. Embolization of the hearts and lungs as a consequence of the entry of marrow contents into the venous system during cementation is confirmed as one of the major cause of BCIS.^{15,16} However, we considered that the potential toxicological risk of the cement itself was not negligible noticing cases of transient hypotension in which small quantities of cement was used during percutaneous vertebroplasty.¹⁷ Considering the many reports concerning the adverse effects of MMA including the toxicity,¹⁸ the allergic reaction,¹⁹ the direct vasodilating effects,²⁰ and the vasodilating effects via endogenous mediators²¹ as well as the operator's risk such as the inhalation exposure to MMA vapors⁸ and skin hypersensitivity,⁹ in this study, we investigated the possibility of a new bone cement utilizing monomers with lower toxicity than MMA.

Noticing the advantages of a self-curing two-component powder liquid cement, we started the investigation by searching for methacrylate monomers with lower toxicity than MMA. In general, the acute toxicity test of chemicals is performed by their oral or intraperitoneal administration. In the applications of the bone cement, however, hypotension was experienced when the cement was injected into the medullary cavity.¹⁵ Hence, we determined the LD50 of candidate methacrylates with their intramedullary administration; in this case, the chemicals might rapidly enter the circulatory system after their injection into a medullary cavity. The procedure to determine the LD50 was based on the up-down method described in the OECD guideline.¹³

EMA, nBMA, and EHMA have a greater oral or intraperitoneal LD50 value than MMA;¹⁴ however, only EHMA and TMP had greater intramedullary LD50 value than MMA, as shown in Table 1. This result

was consistent with the report of Mir et al.,¹⁸ in which the toxicological effects of methacrylate monomers on cardiac functions were investigated. For example, they found that MMA and EMA produced an irreversible effect on an isolated rabbit heart when the concentration is 1:100,000 in the medium, while nBMA had the same effect with a concentration of 1:1,000. In contrast, EHMA produced only a reversible effect at the concentration 1:1,000.¹⁸

With respect to the hypotensive effect of monomers, Mir et al.²² also found that an intravenous injection of methacrylates monomers to dogs caused an abrupt fall in the blood pressure. The percent changes in blood pressure by MMA, EMA, and nBMA were -78.99% (0.0599 ml/kg), -58.66% (0.0684 ml/kg), and -38.95% (0.0830 ml/kg), respectively, where the dose per body weight was given in parentheses. On the other hand, that by EHMA was -19.56% (0.0652 ml/kg), which was significantly smaller than those by other methacrylates.

According to the results of the toxicity test and the literatures, we decided to create a new bone cement utilizing EHMA and TMP as the liquid components. To the authors' knowledge, such a cement has not been investigated yet. By using this new cement designated as EHMA cement, we believe that the risk of BCIS will decrease. Furthermore, the vapor pressure and water solubility of EHMA at 25°C were 0.076 mm Hg and 5.920 mg/L, respectively, and those of TMP were 1.37×10^{-4} mm Hg and 13 mg/L (TOXNET - Available at: <http://toxnet.nlm.nih.gov/>). Since they were considerably smaller than the respective values of 38.5 mm Hg and 1.50×10^4 mg/L of MMA,¹⁴ we considered that the EHMA cement would diminish the potential risk to an operator caused by contact or inhalation exposure to MMA.

Subsequently, the solubility of several methacrylate homopolymers in EHMA was examined in order to find candidate powder component of the cement. By observing that PEHMA and PCHMA were soluble in EHMA as shown in Table 2, we determined the powder component of the new bone cement to consist of poly (CHMA/EHMA).

In order to determine the composition ratio of CHMA and EHMA in EHMA cement, we next synthesized poly (CHMA/EHMA) of various compositions by using the bulk polymerization method and investigated the relation between the composition and mechanical properties of copolymers. The results demonstrated that a greater amount of CHMA in the composition of poly (CHMA/EHMA) resulted in greater compressive

strength, as illustrated in Fig. 2 (a). We noticed that if the amount of CHMA was greater than 60 wt%, the compressive strength was greater than 70 MPa. Since the ISO 5833 standard on bone cement¹⁴ requires a compressive strength of more than 70 MPa, we concluded the ratio of CHMA in the composition of EHMA cement was preferably greater than 60 wt%. Noticing that CHMA was contained only in the powder component, we further determined the powder liquid ratio of the cement to be as large as 3.5:1 in order to obtain a greater composition of CHMA in the cement without serious difficulty in mixing the powder and liquid components.

The beads of poly (CHMA/EHMA) were synthesized by using the suspension polymerization method, and they were utilized as the powder component of EHMA cement. The size of beads was not specified in this study, since the size was considered to have some effect on the solution rate but not on the strength significantly. For the polymerization of the cement, BPO that generates radicals and starts the radical copolymerization was added. The cement thus prepared was tested for their exothermic properties. Temperature rises during the polymerization of the control cement was approximately 41°C, which was consistent with the reported values.³ On the other hand, the temperature rises during the polymerization of EHMA cements were demonstrated to be very low; they were approximately 9°C and 13°C without and with the addition of TMP, respectively; in both cases, the temperature rises were significantly lower than that of the control bone cement. Thus we concluded that the EHMA cement has a less adverse effect of high temperature rise than MMA cements.

Mechanical tests revealed that the mechanical properties of the control cement were consistent with the reported values,¹ whereas the maximum compressive strength of the specimens prepared from powder/liquid cement without TMP was 57 MPa in the case of the cement using 70/30 poly (CHMA/EHMA) powder. This value was somewhat smaller than the expected value of 61 MPa, which was calculated by interpolating the strength data of specimens prepared by the bulk-polymerization method in the case of the same composition. The nonuniformity of specimens, the contamination of small air bubbles, and/or the lower polymerization conversion accompanying the curing of the powder/liquid cement might be the cause of such smaller strength.

Since the acrylic bone cement was required to have the compressive strength greater than 70 MPa

according to the standard,¹⁴ we then investigated the strengthening of the cement by the introduction of a crosslink using the crosslinking agent TMP that has three polymerizable double bonds in its molecule. The mechanical test demonstrated that the addition of TMP significantly increased the strength, as shown in Fig. 4 (a). This result is consistent with the report of Puska et al.²³ in which the increased strength accompanying the addition of a crosslinking agent EGDMA to the liquid component of cement was demonstrated. The addition of TMP increased the maximum strength to 67 MPa in the case of the cement with a powder component of 90/10 poly (CHMA/EHMA). Nevertheless, the achieved strength was slightly smaller than 70 MPa specified in the standard. However, we considered that a further increase in the strength of EHMA cement was possible since we noticed that the bulk polymerization method had provided us specimens with strength exceeding 70 MPa, and various technologies^{24,25} have been developed for strengthening bone cement.

With respect to the elastic modulus of EHMA cement, they were significantly lower than those of the control cement, as shown in Fig. 4 (b). The composition ratio of CHMA did not have a significant effect on the magnitudes of the modulus. Furthermore, although the addition of TMP increased the modulus with statistical significance, the increase was relatively small in comparison with that of the control cement. Similar to the compressive strength, the modulus was smaller than those of the specimens prepared by using the bulk-polymerization method; the difference can be attributed to a similar reason. On the other hand, a lower elastic modulus would be beneficial for realizing uniform distribution of stress.²⁶ Although such advantages have not yet been fully verified, the EHMA cement can be favorably utilized when its low modulus had advantages.

Another important issue to be discussed is radiopacifiers. In this paper, we tested the material without the addition of commonly utilized radiopacifiers such as BaSO₄ particles. The addition of these particles upto the typical amount of 10%¹ did not significantly affect the mechanical properties of MMA cement.²⁷ However, it was reported that the addition of siranated BaTiO₃ pacifiers considerably increased the strength and modulus.²⁷ Particle reinforcement of EHMA cement might be possible by the use of such radiopacifiers.

In conclusion, we developed an EHMA cement, which is a self-curing two-component powder/liquid cement comprising a powder component consisting of poly (CHMA/EHMA) beads and liquid component of EHMA with or without the addition of TMP. It has been

demonstrated that EHMA and TMP in the liquid component have lower toxicity than MMA. The temperature rise during the polymerization of EHMA cement was significantly lower than that of the conventional bone cement. On the other hand, the compressive strength of the polymerized EHMA cement was 57 MPa without TMP and 67 MPa with TMP; hence, EHMA cement was slightly inferior than the conventional bone cement with respect to the compressive strength. Hence, the EHMA cement might be utilized for non-load-bearing purposes. Further improvements including the strengthening of the cement are necessary for clinical applications.

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