



OPEN Impact of saline irrigation on the early mechanical characteristics and microstructure of bone cement

Seyed Morteza Kazemi¹, Alireza Mirahmadi¹, Pooya Hosseini-Monfared¹,
Hamid Reza Moghimi³, Arash Mahboubi³, Marzieh Gandomkarzadeh³,
Amirhossein Salmannezhad¹ & Mehrdad Farrokhi²✉

Very high heat is generated during the polymerization of poly (methyl methacrylate) (PMMA) bone cement, which is used for implant fixation in orthopedic surgery. As such, it has been suggested that irrigating the bone cement layer in the surgical site with a saline solution is a way of cooling the layer. In this study, we aimed to determine the influence of irrigation with a saline solution on the flexural strength and the microstructure of the test specimens of two PMMA bone cement brands: Simplex P and FIX 1. Specimens were assigned to three groups: (1) irrigation with normal saline solution at 25 °C (RS group), (2) irrigation with cold saline at 4 °C (CS group), and (3) no irrigation (control group). For each of the groups, the specimens were tested after various times of aging in phosphate-buffered saline solution (PBS) at 37 °C for 1 h, 24 h, and 7 days. Flexural strength was measured following ISO 5833 protocol, and the surface microstructure was determined using scanning electron microscopy (SEM). The flexural strength results showed that for each of the cement brands, the difference between the groups was not significant, except for Simplex P specimens aged for 24 h, for which flexural strength of the RS and CS group specimens was lower than in the control group. The microstructural features of the surface of the specimens were similar across groups. These findings suggest that in a cemented arthroplasty, irrigation of the bone cement for the purpose of cooling it must only be used after very careful consideration.

Keywords Arthroplasty, Bone cement, Flexural Strength, Scanning Electron Microscopy, Temperature, Aseptic loosening

Polymethyl methacrylate (PMMA) bone cement is widely used in orthopedic procedures such as total hip and knee arthroplasties to fix prostheses¹. The primary function of PMMA bone cement is to transfer the loads in the contact areas of bone and implants and secure prostheses in the adjacent bone^{2,3}. Proper cementing technique prevents implant micromotion and subsequent aseptic loosening and improves long-term implant survival^{4,5}.

Primary concerns with the use of PMMA bone cement are its extended setting time and the heat produced during the polymerization process, which increases the risk of thermal injury to the surrounding tissues^{6–9}. Previous studies demonstrated that contact with temperatures about 47–50 °C for 1 min can impair bone regeneration¹⁰. Time-temperature-dependent mechanisms have been shown for thermal injury to the bone and related tissues. For instance, a temperature of 70 °C kills the cells immediately, but to have the same effect, a temperature of 50 °C needs to be maintained for 30 s and a temperature of 45 °C for 5 h¹¹. Furthermore, reducing the setting time in cemented arthroplasty can shorten surgery duration, helping to mitigate adverse effects associated with prolonged surgery duration, such as increased risk of periprosthetic joint infection (PJI) and septic loosening^{12–14}.

To reduce the polymerization temperature of PMMA bone cement and, hence, reduce the potential for thermal necrosis of the periprosthetic tissues, techniques such as combining nanoparticle additives and alternative monomers have been suggested¹⁵. Also, composite PMMA bone cements have been studied to reduce the polymerization temperature of PMMA bone cement^{16–19}. However, these methods tend to result in longer setting times, lower compressive strength, and lower bulk modulus compared to commercial PMMA bone

¹Bone, Joint and Related Tissues Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Student Research Committee, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ³Department of Pharmaceutics and Nanotechnology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ✉email: dr.mehrdad.farrokhi@gmail.com

cement^{16–18}. Other thermal reduction techniques, such as pre-cooling the environment and implant, reducing cement thickness to less than 5 to 7 mm, or using fluid cooling after implant insertion, have been suggested^{20–22}. Fluid cooling has been demonstrated to effectively reduce the peak temperature of polymerization of bone cement^{23,24}. One of the concerns regarding fluid cooling is the risk of cement shrinkage and the formation of minimal cracks that disturb the integrity of the bone cement. To the best of our knowledge, no previous study has investigated whether fluid cooling with low temperatures during bone cement polymerization affects the surface integrity of the bone cement and if this leads to any surface cracks. Since bone cement is usually used in contact with fluids such as saline and blood during the final stages of the cementing procedure, we aimed to investigate whether the fluid cooling of acrylic bone cement via normal saline (NS) solution irrigation with different temperatures affects its bending strength and surface microstructure. We hypothesized that the use of NS would result in a reduction in flexural strength compared to the control group and that colder NS would further decrease flexural strength compared to room-temperature NS.

Materials and methods
Cement brands and specimen preparation

In this study, we utilized two commercially available bone cement brands: Stryker Simplex P (Stryker, Mahwah, NJ, USA) and FIX 1 (Groupe Lepine, Genay, France). The compositions of the brands are presented in Table 1. The cement was prepared using three steps. First, the powder (polymer) and liquid (monomer) were mixed according to the manufacturer’s instructions in a plastic bowl using a spatula to become homogenous at room temperature ($24 \pm 1\text{ }^{\circ}\text{C}$) for 1 min. Second, we waited once the mixture reached a high adherence nature for 90 s. Third, after the mixture reached the dough stage, we injected the cement into a stainless-steel mold.

Groups
Both types of cement have medium viscosity. Specimens from each cement were prepared for the three study groups. The cement in the first group (RS group) was irrigated with 200 cc of normal saline solution at a temperature of 25°C (room temperature). The second group (CS group) was irrigated with 200 cc of cold saline at 4°C . The cement specimens of the first two groups were irrigated with saline for 2–3 min. In the third group (Control group), the bone cement was placed in a sterile place in room air without any saline lavage. The bone cement specimens were immersed in phosphate-buffered saline solution (PBS) at 37°C to simulate post-surgery contact with fluid in-situ for 1 h, 24 h, and 7 days after the preparation of bone cement specimens.

Bending strength evaluation
The flexural strength, defined as the ability to withstand bending stresses, was tested using the H25KS Universal Testing Machine (Hounsfield Co., USA). We prepared rectangular-shaped specimens measuring $75\text{ mm} \times 10\text{ mm} \times 3.3\text{ mm}$, and the four-point bending test was conducted with a crosshead speed of 5 mm/min , and the bending strength was calculated according to ISO 5833:2002²⁵. Five specimens were tested for each study group.

Surface microstructure
Also, specimens with a diameter of $< 1\text{ cm}$ were collected and sprayed with a metal layer, and the surface cracks were assessed using scanning electron microscope (SEM) imaging (Hitachi Scanning Electron Microscope SU3500, Tokyo, Japan) at 2 and 24 h after the preparation of bone cement.

Statistical analysis
Statistical analysis was performed using SPSS software ver. 26.0 (IBM, Armonk, NY, USA). The normal distribution of data was assessed using the Kolmogorov-Smirnov Z-test. Parametric or non-parametric tests are used depending on the result of normal distribution. One-way ANOVA and Kruskal-Wallis tests were used to compare quantitative variables between the three groups. Continuous variables were reported as mean \pm standard deviation. A p-value < 0.05 was considered statistically significant.

Simplex P		Fix1	
Component	wt%	Component	wt%
Powder (40 g)		Powder (40 g)	
Poly methylacrylate-styrene	73.5	Polymethyl-methacrylate	87.6
Poly methylmethacrylate (PMMA)	15	Benzoyl peroxide	2.4
Benzoyl peroxide	1.5	Barium sulphate	10
Barium sulphate	10		
Liquid (20 mL)		Liquid (14.4 g)	
Methyl methacrylate (MMA) (monomer)	97.45	Methyl methacrylate (MMA) (monomer)	85.3
N, N-Dimethyl-p-toluidene	2.55	Butylmethacrylate	13.2
Hydroquinone	80 ppm	N, N-Dimethyl-p-toluidene	1.5
		Hydroquinone	20 ppm

Table 1. Compositions of Simplex P and FIX 1 bone cements.

Results

The results show that those bone cement specimens that were exposed to a normal saline solution had lower flexural strength compared to the control group at the same time (Fig. 1). The flexural strengths in RS and CS groups of Simplex P bone cement were significantly lower than the control group 24 h after preparation

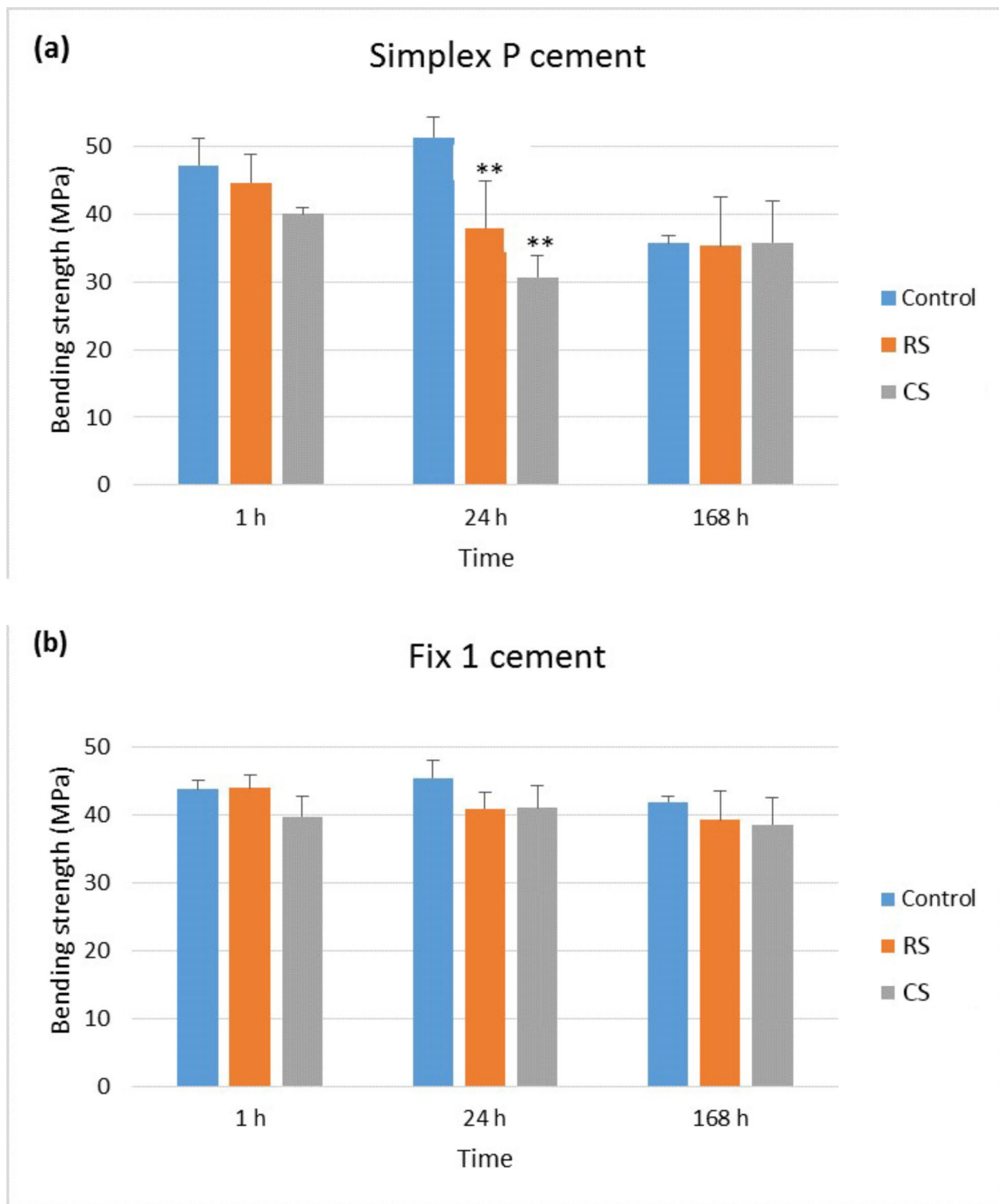


Fig. 1. Comparison of flexural strength values of bone cement specimens at different stages (a) Simplex P and (b) FIX 1: 1 h after preparation, after 24 h and 7 days (168 h) storage in PBS and temperature 37 °C, in three different groups: control, normal saline solution (NS) and cold normal saline solution (Cold NS) at the time of cement preparation. Asterisks indicate significance compared to the control group (**: $p < 0.01$) (Mean \pm SD).

Cement	Group	Aging time		
		1 h	24 h	1 w
Simplex P	Control	47.16 ± 4.01	51.30 ± 2.89	35.63 ± 1.23
	NS	44.56 ± 4.20	37.93 ± 6.32**	35.26 ± 7.22
	Cold NS	40.31 ± 1.23	30.67 ± 3.10**	35.73 ± 6.16
FIX 1	Control	43.76 ± 1.21	45.45 ± 2.51	41.89 ± 0.74
	NS	43.91 ± 1.86	40.91 ± 2.39	39.23 ± 4.27
	Cold NS	39.70 ± 3.10	40.95 ± 3.29	38.51 ± 4.08

NS: Normal saline solution at room temperature
Cold NS: Cold normal saline solution (4 °C)
**: $P < 0.01$, ANOVA, LSD Test, In comparison to the control group

Table 2. Flexural strength (MPa) after aging of bone cement specimens in PBS at 37 °C.

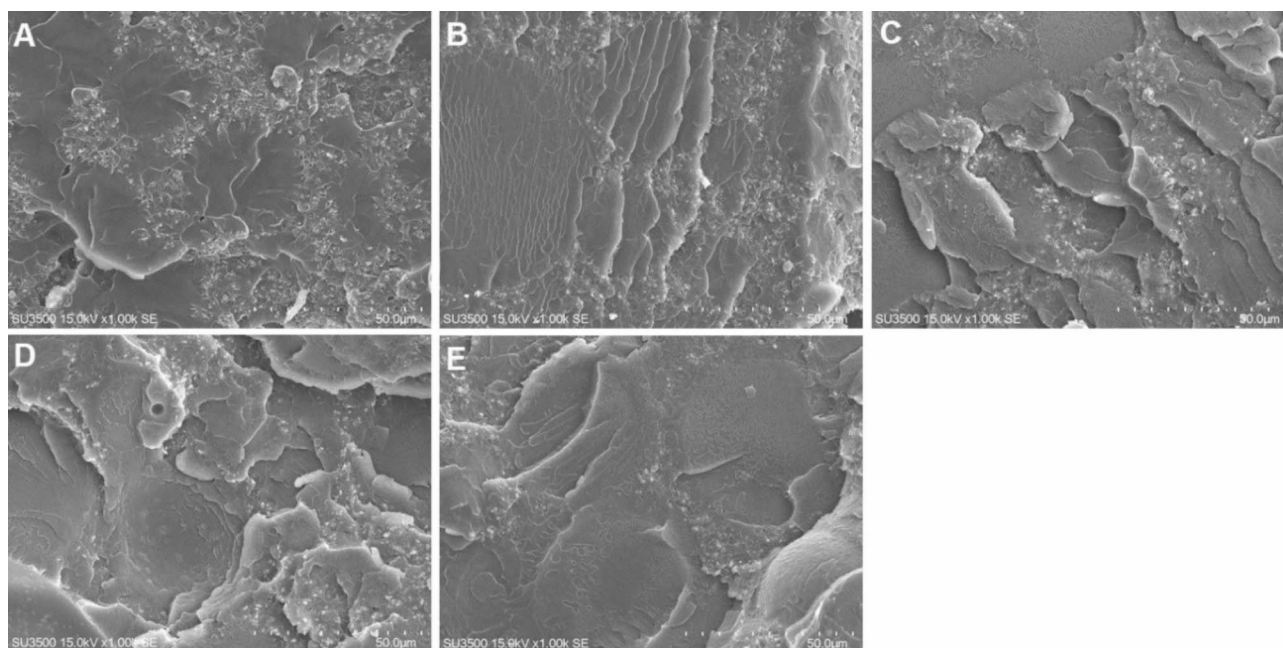


Fig. 2. The microstructures of the fractured surfaces of dry bone cement after 2 h of storage, (A) Simplex P control cement, (B) Simplex P cement exposed to NS (ambient temperature), (C) FIX 1 control cement, (D) FIX-1 cement exposed to NS (ambient temperature), and (E) FIX 1 cement exposed to cold NS.

($P < 0.01$). However, there were no significant differences between the three groups at 1 h and 1 week after production of Simplex P bone cement concerning the flexural strength ($P > 0.05$). The findings also show that exposure to cold normal saline solution causes a further reduction in the flexural strength of cement compared to the normal saline solution group at room temperature for 1 h and 24 h after the cement preparation.

For the FIX 1 bone cement specimens, no significant difference was found between the three groups at 1 and 24 h and 1 week after preparation with respect to the flexural strength, as demonstrated in Table 2 ($P > 0.05$).

The strength of Simplex P cement specimens irrigated with cold normal saline solution was lower compared to the RS group 1 and 24 h after the cement preparation. Similarly, the flexural strength of FIX 1 cement in the CS group was lower compared to the normal saline solution group 1 h after the cement preparation, but these differences were not statistically significant (Table 2).

Evaluation of the surface microstructure of the bone cement specimens using SEM images demonstrated that no surface cracks were visible in any of the three groups (Figs. 2 and 3).

Discussion

Our findings demonstrated that the bending strengths of PMMA bone cement specimens of RS and CS groups were lower than those of the control group for samples aged 24 h in PBS after production. This trend can be attributed to the effect of saline irrigation on the cement's polymerization process. Also, irrigation with cold normal saline solution reduced the bending strength more than the NS with 25 °C. The accelerated polymerization due to cold saline exposure likely leads to less organized polymer chains and increased microstructural inconsistencies, such as porosity, which are not visually detectable as cracks but could affect the long-term mechanical integrity^{26,27}.

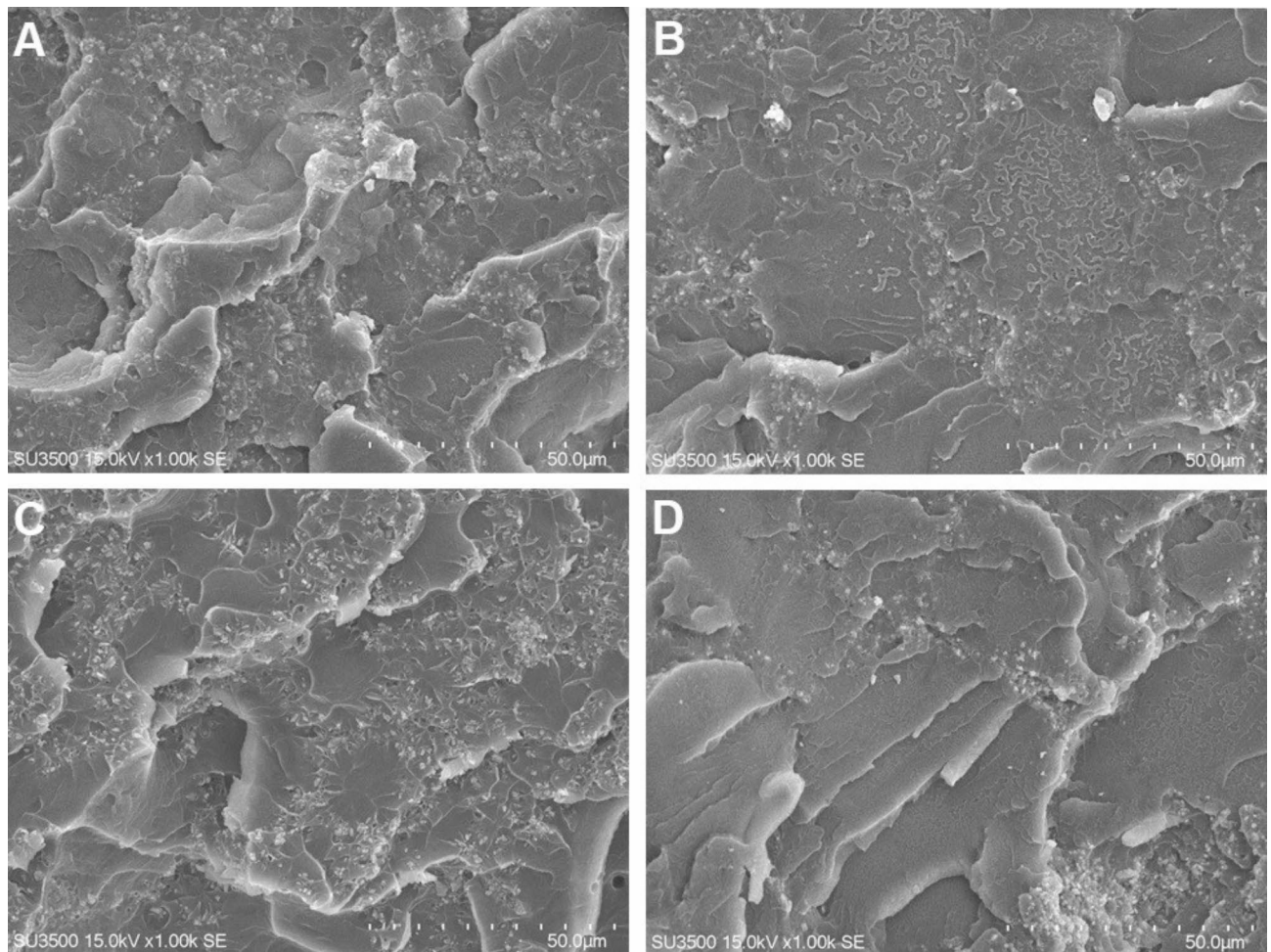


Fig. 3. The microstructures of the fractured surfaces of bone cement after 24 h of storage, (A) Simplex P control cement, (B) Simplex P cement exposed to NS (ambient temperature), (C) Simplex P cement exposed to cold NS, and (D) FIX 1 cement exposure to cold NS.

The trend of decreased strength of the CS group compared to the RS group (at ambient temperature) suggests a temperature-dependent effect on the curing kinetics of the cement. However, bending strength was not significantly different between the three groups one week after bone cement polymerization.

The bending strength of the control group reached its highest peak 24 h after the cement preparation, and the strength of both cements decreased after 24 h. This finding aligns with recommendations of international standards, including ISO 5833, which declares that the appropriate time to assess the strength of cement is 24 h after its preparation^{25,28}. Studies have shown that mixing techniques, temperature, cement viscosity, and cement porosity can affect the fracture toughness of acrylic bone cement specimens^{29–31}.

Previous studies have reported that exposure of cement to fluids in physiological conditions (at 37 °C) reduces the bending strength of cement compared to the dry specimens³². In our study, we put all the specimens, including the control group, in PBS at 37°. The strength of control cement specimens decreased 10 to 35% after one week of storage under physiological conditions. In the RS and CS groups, which were exposed to the normal saline solution at different temperatures, the cement specimens' bending strength after one week of storage in PBS solution showed approximately the same values. Our findings showed that exposure of bone cement to normal saline at room temperature or cold normal saline solution causes a significant decrease in bending strength 24 h after formation. Based on previous studies, no significant difference was recorded regarding complications such as aseptic loosening between immediate unrestricted weight-bearing compared with partial weight-bearing in patients undergoing uncemented hip arthroplasty³³. As shown, using a normal saline solution reduced the bending strength of cement 24 h after surgery compared to the control group. Evaluating the possibility of increased aseptic loosening at 24 h after arthroplasty between NS-cemented, non-NS cemented, and cementless groups is recommended.

Using the water-cooling method could lead to slower cement polymerization^{34,35}, which may increase the working and setting times and finally increase the operation time. An increase in operation time could escalate the rate of periprosthetic joint infection (PJI)³⁶. Also, it should be noted that the irrigation of the surgical site and the bone cement with saline carries the risk of dissolution of antibiotics from the outer surface of the cement

mantle, which may increase the rate of PJI³⁷. Therefore, evaluating the effect of saline irrigation with PJI after arthroplasty is recommended for future clinical studies.

We assessed the microstructure of the bone cement specimens by SEM findings and found no significant differences between groups at 2 h and 24 h after the storage. In a previous study, the porosity of bone cement tended to decrease with increasing the prosthesis's temperature, as shown in their SEM results³⁸. Our results show that decreased bending strength due to lavage by normal saline solution may not necessarily be associated with surface microfractures.

We designed a three-group study and evaluated the effect of bone cement exposure to normal saline solution and cold normal saline solution compared to the control group at three intervals, including 1 h, 24 h, and 7 days. This study benefited from integrating biomechanical analyses and imaging evaluations as we illustrated flexural strength and SEM findings. Our findings highlight the critical impact of cooling methods on the early-stage flexural strength of PMMA bone cement. A reduction in flexural strength, as observed with cold saline, could potentially increase the risk of micromovement and subsequent aseptic loosening. Therefore, our study highlights the need for careful consideration of cooling techniques during cemented arthroplasties. Surgeons should be aware that while cooling with saline might mitigate thermal damage to surrounding tissues, the use of cold saline can adversely affect the mechanical properties of the cement. By understanding these effects, surgeons can make more informed decisions about the cooling methods they employ, balancing the need to manage heat generation with the imperative to maintain the structural integrity of the cement. This knowledge can ultimately improve patient outcomes by reducing the incidence of implant failures (such as aseptic loosening) associated with compromised cement strength.

Despite these strengths, our study also has several limitations. First, our study focused on the in-vitro assessment of the bending strength and microstructure of the specimens and the peak temperature for each group was not assessed. Although in-vitro studies do not replicate the exact biological environment, they provide essential preliminary data that is fundamental for understanding the basic properties of materials. The lack of peak temperature assessment does not invalidate our findings on bending strength and microstructure, as these were measured consistently across all specimens. Our study was specifically designed to assess the bending strength and microstructure of the specimens. Other properties, such as fatigue resistance, wear characteristics, or biocompatibility, are important but were considered beyond the scope of the current research. Our conclusions are valid within this specific context and provide a strong foundation for future studies to explore additional characteristics. We evaluated bone cement specimens from the two most common brands in our region. The two cement specimens used in this study had medium viscosity, and evaluation of the effect of viscosity on the exothermic temperature is recommended for future studies. Another limitation of our study was that we prepared the specimens using manual mixing, and the effect of vacuum mixing was not available due to limited resources.

Conclusion

Our findings demonstrated that saline irrigation, particularly cold saline, adversely affects the early bending strength of PMMA bone cement by disrupting the polymerization process. Although the mechanical properties of all groups equalized after one week in PBS, the early-phase reduction in strength highlights the need to balance thermal management with maintaining cement integrity during cemented arthroplasties.

Data availability

The data used and analyzed during the current study are available from the corresponding author upon reasonable request.

Received: 12 June 2024; Accepted: 9 December 2024

Published online: 28 December 2024

References

- Wall, V., Nguyen, T. H., Nguyen, N. & Tran, P. A. Controlling Antibiotic Release from Polymethylmethacrylate Bone Cement. *Biomedicine* **9** (1), 26 (2021).
- Aganostakos, K. Therapeutic use of antibiotic-loaded bone cement in the treatment of hip and knee joint infections. *J. bone Joint Infect.* **2** (1), 29–37 (2017).
- Webb, J. & Spencer, R. The role of polymethylmethacrylate bone cement in modern orthopaedic surgery. *J. Bone Joint Surg. Br. Volume.* **89** (7), 851–857 (2007).
- Refsum, A. M. et al. Cementing technique for primary knee arthroplasty: a scoping review. *Acta Orthop.* **90** (6), 582–589 (2019).
- Schonhoff, M. et al. Is TKA femoral implant stability improved by pressure applied cement? A comparison of 2 cementing techniques. *BMC Musculoskelet. Disord.* **24** (1), 51 (2023).
- Dunne, N. J. & Orr, J. F. Curing characteristics of acrylic bone cement. *J. Mater. Science: Mater. Med.* **13** (1), 17–22 (2002).
- Stańczyk, M. & Van Rietbergen, B. Thermal analysis of bone cement polymerisation at the cement–bone interface. *J. Biomech.* **37** (12), 1803–1810 (2004).
- Mazzullot, S., Paolini, M. & Verdi, C. Numerical simulation of thermal bone necrosis during cementation of femoral prostheses. *J. Math. Biol.* **29**, 475–494 (1991).
- Li, C. et al. Finite element thermal analysis of bone cement for joint replacements. *J. Biomech. Eng.* **125** (3), 315–322 (2003).
- Eriksson, R. & Albrektsson, T. The effect of heat on bone regeneration: an experimental study in the rabbit using the bone growth chamber. *J. Oral Maxillofac. Surg.* **42** (11), 705–711 (1984).
- Swenson, L. W., Schurman, D. J. & Piziali, R. L. Finite element temperature analysis of a total hip replacement and measurement of PMMA curing temperatures. *J. Biomed. Mater. Res.* **15** (1), 83–96 (1981).
- LawrieCM, Schwabe, M., Pierce, A., Nunley, R. M. & Barrack, R. L. The cost of implanting a cemented versus cementless total knee arthroplasty. *Bone Joint J.* **101-b** (7_Supple_C), 61–63 (2019).
- Puri, S. et al. Cementless Versus cemented total knee arthroplasty of the same design: shorter operative Times and minimal differences in early outcomes. *HSS Journal* **20**, 15563316231179220 (2023).

14. Wang, Q. et al. Longer Operative Time results in a higher rate of subsequent periprosthetic joint infection in patients undergoing primary joint arthroplasty. *J. Arthroplasty*. **34** (5), 947–953 (2019).
15. Khandaker, M. & Meng, Z. The effect of nanoparticles and alternative monomer on the exothermic temperature of PMMA bone cement. *Procedia Eng.* **105**, 946–952 (2015).
16. McKee, R., Harris Anthony, M., Hadley, J., Zhang, J. & Lewis, G. Comparative influence of two compositional modifications on Maximum Exotherm temperature and other Properties of an antibiotic-loaded PMMA bone cement. *Curr. Appl. Polym. Sci.* **2** (2), 76–88 (2018).
17. Lv, Y. et al. A Novel Composite PMMA-based bone cement with reduced potential for thermal necrosis. *ACS Appl. Mater. Interfaces*. **7** (21), 11280–11285 (2015).
18. Xia, X. et al. Development of a phase change microcapsule to reduce the setting temperature of PMMA bone cement. *J. Appl. Biomater. Funct. Mater.* **18**, 2280800020940279 (2020).
19. Tavakoli, M. et al. Graphene oxide-encapsulated baghdadite nanocomposite improved physical, mechanical, and biological properties of a Vancomycin-loaded PMMA bone cement. *J. Biomater. Sci. Polym. Ed.* **35** (6), 823–850 (2024).
20. DiPisa, J. A., Sih, G. S. & Berman, A. T. The temperature problem at the bone-acrylic cement interface of the total hip replacement. *Clin. Orthop. Relat. Research*, **121**, 95–98 (1976).
21. Li, C., Kotha, S. & Mason, J. Evaluation of the effects of implant materials and designs on thermal necrosis of bone in cemented hip arthroplasty. *Biomed. Mater. Eng.* **13** (4), 419–428 (2003).
22. Gergely, R. C., Toohey, K. S., Jones, M. E., Small, S. R. & Berend, M. E. Towards the optimization of the preparation procedures of PMMA bone cement. *J. Orthop. Res.* **34** (6), 915–923 (2016).
23. Wykman, A. G. Acetabular cement temperature in arthroplasty: effect of water cooling in 19 cases. *Acta Orthop. Scand.* **63** (5), 543–544 (1992).
24. Rothstock, S. et al. Influence of cooling on curing temperature distribution during cementing of modular cobalt-chromium and monoblock polyethylene acetabular cups. *Surg. Innov.* **20** (6), 607–613 (2013).
25. ISO. 5833 *Implants for surgery—acrylic Resin Cements* (International Testing Organization, 2002).
26. Ramanathan, S. et al. Poly (methyl methacrylate) in orthopedics: strategies, challenges, and prospects in bone tissue Engineering. *Polymers* **16** (3), 367 (2024).
27. Jiang, H.-J. et al. Mechanical properties and cytocompatibility improvement of vertebroplasty PMMA bone cements by incorporating mineralized collagen. *Materials* **8** (5), 2616–2634 (2015).
28. Nottrott, M., Mølster, A. O., Moldestad, I. O., Walsh, W. R. & Gjerdet, N. R. Performance of bone cements: are current preclinical specifications adequate? *Acta Orthop.* **79** (6), 826–831 (2008).
29. Kumar, A. & Ghosh, R. Fracture toughness of acrylic PMMA bone cement: a mini-review. *Indian J. Orthop.* **55** (5), 1208–1214 (2021).
30. Kumar, A., Mondal, S. & Ghosh, R. Biomechanical performance of the cemented acetabular cup with combined effects of bone quality, implant material combinations and bodyweight. *Proc. Institution Mech. Eng. Part. H: J. Eng. Med.* **236** (9), 1309–1327 (2022).
31. Kumar, A., Mondal, S. & Ghosh, R. Influence of obesity on load-transfer mechanism, contact mechanics, and longevity of cemented acetabular cup. *J. Orthop.* **55**, 118–123 (2024).
32. Bargar, W. et al. In vivo versus in vitro polymerization of acrylic bone cement: effect on material properties. *J. Orthop. Res.* **4** (1), 86–89 (1986).
33. Huang, L. et al. Early unrestricted vs. partial weight bearing after uncemented total hip arthroplasty: a systematic review and meta-analysis. *Front. Surg.* **10**, 1225649 (2023).
34. Sullivan, S. J. & Topoleski, L. D. Influence of initial component temperature on the apparent viscosity and handling characteristics of acrylic (PMMA) bone cement. *J. Biomed. Mater. Res. B Appl. Biomater.* **81** (1), 224–230 (2007).
35. Koh, B. T., Tan, J. H., Ramruttan, A. K. & Wang, W. Effect of storage temperature and equilibration time on polymethyl methacrylate (PMMA) bone cement polymerization in joint replacement surgery. *J. Orthop. Surg. Res.* **10**, 178 (2015).
36. Wang, Q. et al. Longer operative time results in a higher rate of subsequent periprosthetic joint infection in patients undergoing primary joint arthroplasty. *J. Arthroplast.* **34** (5), 947–953 (2019).
37. Kühn, K.-D. *PMMA Cements* 1 edn 291 (Springer Berlin, Heidelberg, 2014).
38. Chen, W. & Zhang, H. An experimental study on the impact of prosthesis temperature on the biomechanical properties of bone cement fixation. *BMC Surg.* **23** (1), 191 (2023).

Author contributions

All authors contributed to the study's conception and design. HRM, AM, and MG performed material preparation and data collection. MF did the data analysis. AM, PHM, and AHS wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

The author(s) received no financial or material support for the research, authorship, and/or publication of this article.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M.F.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2024