Systematic Review and Meta-Analysis

Medicine

OPEN

Induced membrane technique for large bone defects

A systematic review and individual participant data meta-analysis

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Abstract

Aims: The aim of this study was to evaluate the efficacy of induced membrane technique (IMT), and to analyze the relationships between patient factors and surgical parameters as well as their impacts on achieving bone union and complication rates.

Materials and methods: A comprehensive, computerized search of PubMed, Embase, and The Cochrane Library was conducted, and articles published from January 1, 1978 to February 1, 2021 were included. Clinical trials matching the following inclusion criteria were included:

1. published as a case series, case-controlled studies, or cohort study;
2. IMT was performed for more than 10 cases within the study.

Univariate and multivariate logistic regression were performed with random intercepts to determine the association of specific predictor variables with nonunion rate, postoperative infection, the need for additional procedures, and time to union.

Results: Seventy eight trials were included in the study with a total of 3840 patients managed with IMT. Mean age was 38.6 (0.8–88) years, mean size of bone defects was 6.4 (0–25) cm primarily distributed in the tibia (n = 1814, 60.9%), and overall union rate was 87.6%. Multivariate analysis showed the odds of nonunion were significantly increased in patients with an interval between two stages from 8 to 12 weeks and ≥12 weeks. Patients with preoperative infection and addition of antibiotic to bone cement during IMT had significantly decreased odds of longer union time, but preoperative infection caused increased odds of additional surgery. External fixation throughout 2 stages had significantly increased odds of postoperative infection and additional surgery.

Conclusions: We recommend that the timing of the second stage should be delayed until 6 to 8 weeks after the first stage. Bone cement with antibiotics can control the infection rate and shorten the healing time. Furthermore, there is no need to avoid using internal fixation due to possible concerns about causing postoperative infection.

Abbreviations: BMP-2 = bone morphogenetic protein-2, CI = confidence interval, ICBG = iliac crest bone graft, IMT = induced membrane technique, NOS = Newcastle-Ottawa Scale, PMMA = polymethylmethacrylate, RIA = irrigator aspirator.

Keywords: bone defect, induced membrane technique, Masquelet technique, meta-analysis, systematic review

1. Introduction

Managing large bone defects remains a difficult clinical challenge. Alain-Charles Masquelet developed the induced membrane technique (IMT) more than 30 years ago to treat large bone defect.[1,2] It has become a popular modality and is now widely implemented all over the world. IMT can be divided

The authors have no funding and conflicts of interests to disclose.

All data relevant to the study are included in the article or uploaded as supporting information.

Supplemental Digital Content is available for this article.

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How to cite this article: Sun SH, Tsai WW, Shiu SI, Chen CH. Induced membrane technique for large bone defects: a systematic review and individual participant data meta-analysis. Medicine 2022;101:25(e29292).

Received: 31 October 2021 / Received in final form: 28 March 2022 / Accepted: 27 April 2022

http://dx.doi.org/10.1097/MD.0000000000029292

into 2 stages. The first stage consists of meticulous debridement at the lesion site, maintaining the stability of fracture ends, and implanting polymethylmethacrylate (PMMA) cement spacer into the created bone defect. During the second stage, cement spacer is removed, and autologous bone graft is inserted. An interval between the 2 stages of 6 to 8 weeks is recommended.[3,4]

Though Masquelet has already described how to perform IMT in detail,[4,5] the guidelines for application in clinical practice remain limited and there is still no consensus on the optimal approach for IMT. Numerous clinical trials and systematic reviews have been performed in an attempt to propose a guideline for implementation.[6–10] Currently, several issues remain controversial. For example, there is no consensus on the following: initial stabilization with internal or external fixation, the use of PMMA cement spacer with or without antibiotic, and the duration of the interval between the two stages. Most situations depend on the surgeon's clinical experience.

The aim of this systematic review and meta-analysis was to evaluate the efficacy of the IMT and to conduct an analysis of the relationships between patient factors and surgical variants, as well as their impacts on achieving bone union and complication rates.

2. Methods

The study protocol is registered in the international prospective register of systematic reviews (PROSPERO), number CRD42021260968.

2.1. Search strategy and selection criteria

This systematic review was organized according to prior established statements of PRISMA[11] and MOOSE[12]. Additionally, we followed the guidelines for reporting systematic reviews and meta-analyses, as well as those for observational studies, and a PRISMA 2020 Checklist was available, documenting the completeness of reporting (Supplemental Digital Content Table S1, http://links.lww.com/MD2/B36). Comprehensive, computerized searches of PubMed (National Library of Medicine, Bethesda, MD), Embase, and the Cochrane Central Register of Controlled Trials published from January 1, 1978 to August 1, 2021 were conducted. A detailed description of the search strategies is provided in Supplemental Digital Content Table S2, http://links.lww.com/MD2/B37. In the searches, there were no language limitations, and we performed a manual literature search of references in retrieved articles and reviews for eligible publications. Both the titles and abstracts were reviewed initially, and primary screening was undertaken by two independent reviewers (S-SH and T-WW) after removal of any duplicated articles. Potentially relevant articles were obtained in full text and reviewed independently in accordance with the pre-defined criteria. We also contacted the authors if necessary, and any disagreements were settled by a third reviewer (C-CH).

Clinical trials were included in the systematic review if they matched the following inclusion criteria:

1. published as a case series, case-controlled studies, or cohort study;
2. IMT was performed for more than 10 cases within the study.

The studies which met the additional inclusion criteria involving individual participant data related to IMT were enrolled into the meta-analysis. The exclusion criteria were unrelated topics, animal studies, review articles, conference abstracts, or research articles reporting only preliminary results.

2.2. Data extraction and quality assessment

The following variables were extracted independently by 2 investigators (S-SH and T-WW): the first author, year of publication, country of study, study design, sample size, participants' characteristics, surgical location, mean length of these defects, etiology of bone defect, details of the IMT, mean follow-up period, mean interval between two stages, and proportion of union, nonunion, postoperative infection, and additional procedure. We defined a patient as having achieved union when union was confirmed by a physician according to radiological images regardless of whether an additional procedure was performed or not. We also classified superficial and deep operative site infection after surgery as surgery-related infections.

Two authors (S-SH and T-WW) evaluated the risk of bias in all studies independently, based upon the Newcastle-Ottawa Scale (NOS) assessment tool.[13] Any disagreement was resolved by consensus with the third review author (C-CH).

2.3. Data synthesis and statistical analysis

The results were analyzed using Comprehensive Meta-analysis 2.0 software (Biostat, Englewood, NJ) and IBM SPSS version 22.0 (International Business Machines Corp., New York, USA). We performed a subgroup analysis for the union rate of IMT according to different intervals between 2 stages, as well as important etiological and technical factors. Furthermore, univariate analysis logistic regression was performed using individual patient data with random intercepts to examine the unadjusted relationships between patient-related and technique-related factors and outcomes of interest, including nonunion rate, postoperative infection, the need for additional procedures, and time to union. If statistical significance was reached in the univariate analysis, multivariate logistic regression models with random intercepts were used to examine the association of specific predictor variables and these outcomes. A two-sided $P < .05$ was considered statistically significant and 95% confidence intervals were also reported.

2.4. Ethics and dissemination

No ethical approval will be required as this study will retrieve and synthesize data from already published studies.

3. Results

3.1. Literature search and eligible studies

A detailed PRISMA flowchart is outlined in Fig. 1. Initially, we identified 1252 abstracts and reviewed 121 articles with full-text articles independently after the exclusion of 1131 studies which were not relevant to our topic. This resulted in 78 enrolled trials for the systematic review (Supplemental Digital Content Table S3, http://links.lww.com/MD2/B38), with 31 of the trials included in the individual participant data meta-analysis. Only 2 studies were case-controlled studies while the others were single-arm case series, which used IMT as the crucial intervention.

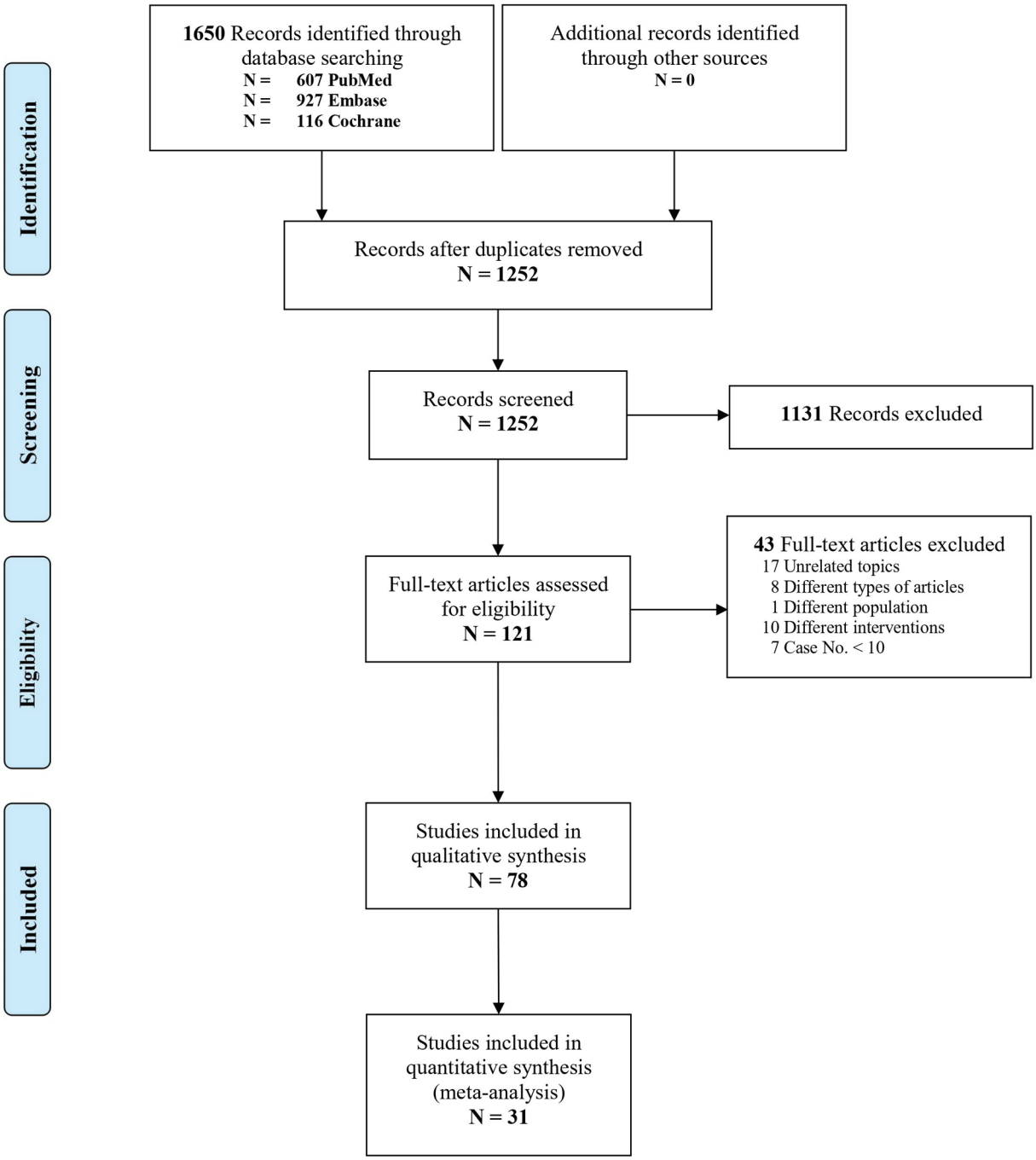

Figure 1. PRISMA Flow Diagram.

3.2. Characteristics and clinical parameters of included studies

The characteristics of IMT extracted from the enrolled trials are shown in Supplemental Digital Content Table S4, http://links.lww.com/MD2/B39. A total of 3903 bone defects presenting in 3840 patients were managed with IMT with a mean follow-up of period 27.5 (6.5–180) months. The mean age of these participants was 38.6 (0.8–88) years with male predominance (73.3%), while the mean size of bone defects was 6.4 (0–25) cm, primarily distributed in the tibia (n = 1814, 60.9%), followed by the femur (n = 809, 27.1%), radius/ulna (n = 97, 3.2%), humerus (n = 89, 2.9%), and fibula (n = 65, 2.1%). The main etiology for bone defect was categorized into 2 categories: infectious (including osteomyelitis and septic nonunions) and noninfectious (including trauma, tumor, and aseptic non-unions). In summary, the infectious group (n = 2163, 55.2%) accounted for a larger proportion of patients than the noninfection group (n = 1754, 44.8%). Due to different locations and etiology of bone defect, heterogeneity among study results was high.

The majority of studies combined antibiotics into the PMMA spacer (n = 2618, 67.1%), including single antibiotic (n = 1051, 40.2%) and dual antibiotics (n = 1567, 59.8%). After the first

stage of debridement, spacer was inserted and the interval before the second stage was 11.7 weeks on average. Internal fixation (n = 1776, 67.8%) and external fixation (n = 458, 17.5%) were defined as the same fixation type throughout 2 stages. The main source of autologous bone graft was the iliac crest bone graft (ICBG) in 60.2% of our cases (n = 1583). In 1.5% of the cases (n = 40) ICBG was combined with the reamer irrigator aspirator (RIA) system, and the RIA system was used alone in 20.5% of the cases (n = 539). Other autologous bone grafts (n = 466, 17.7%) were collected from femur or tibia, and ICBG with addition of osteoinductive agents, including bone morphogenetic protein-2 (BMP-2), BMP-7, platelet-rich plasma, and other unspecified biological adjuncts.

Supplemental Digital Content Table S5, http://links.lww.com/MD2/B40 presents the pooled data on the proportions of union, postoperative infection, and the need for additional surgeries in patients receiving IMT. The results revealed that the overall union rate was 87.6%, ranging from 41.6 to 100%. In the subgroup analysis, the union rates of IMT in the interval between the 2 stages for intervals lasting 6 to 8 weeks, 8 to 12 weeks, and ≥12 weeks were 93.1% (95% confidence interval [CI], 86.7%–96.6%; $I^2 = 45.1\%$), 86.7% (95% CI, 79.4%–91.6%; $I^2 = 60.9\%$), and 86.4% (95% CI, 77.4%–92.2%; $I^2 = 74.6\%$), respectively (Supplemental Digital Content Figures S1–S3, http://links.lww.com/MD2/B35). Regarding the etiological and technical factors, the pooled union rates were 94.7% (95% CI, 91.6%–96.6%; $I^2 = 30.5\%$) in the infectious nonunion group and 85.3% (95% CI, 79.2%–89.9%; $I^2 = 58.7\%$) in the noninfectious nonunion group; 80.1% (95% CI, 65.4%–89.5%; $I^2 = 83.5\%$) in the RIA use group, and 89.9% (95% CI, 87.2%–92.1%; $I^2 = 58.7\%$) in the non-RIA use autologous bone graft group; 89.7% (95% CI, 83.3%–93.8%; $I^2 = 77.9\%$) in the internal fixation group and 92.7% (95% CI, 88.2%–95.6%; $I^2 = 0\%$) in the external fixation group.

Complications were reported in 40% of the cases in our analysis, most of which had more than 1 episode of complications. The majority of complications were infection (n = 811, 21.1%), nonunion (n = 430, 11.2%), or amputation refractory to both medical and surgical treatments (n = 153, 3.9%). Moreover, in 15.6% (n = 457) of the cases, detailed information about additional procedures, such as re-implantation of new PMMA spacer or removal of implants, was not available.

We evaluated 78 trials and conducted a meta-analysis using the NOS assessment tool to detect any risk of bias in the enrolled studies (Supplemental Digital Content Table S6, http://links.lww.com/MD2/B41). The scores in the majority of the trials were less than 7 points, which suggests a low quality. In the assessment of the comparability domain, only 3 trials had adequate study control for any important factors. Regarding outcome assessment outcome, only 19 out of 78 studies had well-controlled quality using independent blinding, an adequate follow-up period, and acceptable follow-up rates.

3.3. Univariate and multivariate analysis of individual patient data

A univariate analysis was performed based on individual patient data to clarify any possible predictive factors associated with patient outcomes. A total of 31 studies reported patient-specific data with pooled analysis to form a cohort of 526 patients. Multivariate analysis was performed only in parameters that achieved statistical significance in the univariate analysis. The results from the univariate and multivariate analysis are presented in Tables 1 and 2. Factors significantly associated with increased odds of nonunion rate included interval between 2 stages from 8 to 12 weeks (OR = 4.17, 95% CI, 1.28–13.56; $P = .02$), interval ≥12 weeks (OR = 3.81, 95% CI, 1.69–8.58; $P = .001$), but with decreased odds of nonunion rate in bone cement with antibiotic (OR = 0.31, 95% CI, 0.16–0.61; $P = .001$) in the univariate analysis, and involved interval between 2 stages from 8 to 12 weeks (OR = 7.67, 95% CI, 1.55–37.85; $P = .01$), and interval ≥12 weeks (OR = 6.44, 95% CI, 2.32–17.88; $P < .001$) in the multivariate analyses. Preoperative infection (OR = 0.41, 95% CI, 0.24–0.70; $P = .001$) and bone cement with antibiotic (OR = 0.14, 95% CI, 0.04–0.47; $P = .002$) decreased the harm of longer union time in the univariate analysis and multivariate analysis with OR of 0.43 (95% CI, 0.24–0.76; $P = .004$) and 0.15 (95% CI, 0.04–0.50; $P = .002$), respectively.

Bone defect in femur (OR = 0.35, 95% CI, 0.15–0.81; $P = .01$) and bone cement with antibiotics (OR = 0.17, 95% CI, 0.07–0.38; $P < .001$) were associated with lower risk of postoperative infection, while preoperative infection (OR = 2.16, 95% CI, 1.15–4.09; $P = .02$) and external fixation at the second stage conferred increased risk for postoperative infection in the univariate analysis and multivariate analysis with OR of 3.93 (95% CI, 2.02–7.66; $P < .001$) and 8.16 (95% CI, 2.36–28.21; $P = .001$), respectively. Younger age (OR = 0.97, 95% CI, 0.96–0.98; $P < .001$), bone defect in femur (OR = 0.53, 95% CI, 0.31–0.90; $P = .02$), and bone cement with antibiotics (OR = 0.18, 95% CI, 0.10–0.34; $P < .001$) were protective factors against the need for additional surgery, while larger defect size (OR = 1.13, 95% CI, 1.07–1.19; $P < .001$), preoperative infection (OR = 1.57, 95% CI, 1.01–2.45; $P = .045$), and external fixation (OR = 6.71, 95% CI, 4.05–11.11; $P < .001$) were factors strongly associated with risk of additional surgery in the univariate analysis. In the multivariate analysis, preoperative infection (OR = 3.73, 95% CI, 1.46–9.51; $P = .006$) as well as using external fixation (OR = 3.73, 95% CI, 1.46–9.51; $P = .006$) were correlated with increased risk of additional surgery.

4. Discussion

In this study, we clearly demonstrated that an interval of 6 to 8 weeks between the two stages was superior to an interval of longer than 8 weeks. The strategy of adding bone cement with antibiotics could lower the postoperative infection rate effectively and the use of external fixation at the second stage was associated with elevated risk of postoperative infection rate when compared with internal fixation.

Though Assal et al reported successful completion of healing at 8 years after the first stage,[3] numerous authors, based on their clinical experience and the results of basic science research, have reported that fracture repair or bone anabolism peak occurs within 2 to 8 weeks, indicating that an interval between the first and second stage of IMT lasting less than 8 weeks might be more appropriate than an interval ≥8 weeks.[5,14–16] Expression of STRO-1, vascular endothelial growth factor, BMP-2, and thickening of the induced membrane were found to be significantly greater in the femur of rats at 2 to 6 weeks after occurrence of osteogenesis and angiogenesis, and hence Henrich et al recommended that the second stage of IMT be performed within 4 weeks.[16] Moreover, autologous bone graft could

Table 1

Univariate and multivariate analysis of nonunion rate and time to union more than 9 months.

Variable	Nonunion				Time to union (>9months)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.00 (0.99–1.02)	.85			1.00 (0.98–1.01)	.71		
Gender								
F	Reference				Reference			
M	1.22 (0.64–2.35)	.55			1.46 (0.77–2.76)	.25		
Interval between two stages, weeks								
≤ 8	Reference		Reference		Reference			
8–12	4.17 (1.28–13.56)	.02*	7.67 (1.55–37.85)	.01*	1.31 (0.37–4.60)	.68		
≥ 12	3.81 (1.69–8.58)	.001**	6.44 (2.32–17.88)	<.001**	0.98 (0.44–2.18)	.96		
Defect size, cm	1.03 (0.97–1.09)	.36			1.04 (0.98–1.11)	.19		
Defect site								
Tibia	Reference				Reference			
Femur	0.96 (0.51–1.79)	.90			1.17 (0.69–1.98)	.56		
Etiology								
Non-infection	Reference				Reference		Reference	
Preoperative infection	1.02 (0.60–1.75)	.93			0.41 (0.24–0.70)	.001**	0.43 (0.24–0.76)	.004**
Antibiotic use								
Without antibiotics	Reference		Reference		Reference		Reference	
Bone cement with antibiotics	0.31 (0.16–0.61)	.001**	1.18 (0.45–3.05)	.74	0.14 (0.04–0.47)	.002**	0.15 (0.04–0.50)	.002**
Bone graft								
Non-RIA use	Reference				Reference			
RIA use	1.52 (0.70–3.33)	0.29			0.96 (0.47–1.96)	.92		
Fixation type								
Internal fixation	Reference				Reference			
External fixation	0.87 (0.48–1.57)	.64			1.50 (0.82–2.72)	.19		

CI = confidence interval, F = female, M = male, OR = odds ratio, RIA = reaming irrigation aspirator.
* $P < .05$.
** $P < .01$.

integrate with induced membrane with the aid of specific cell surface marker and the abovementioned proteins. In our study, an interval of 6 to 8 weeks between the two stages was significantly superior to an interval of longer than 8 weeks in the multivariate analysis, which could be a useful guideline for clinical physicians. However, whether the interval between the 2 stages could be shorter than 6 weeks requires further study.

Traditionally, the risk of postoperative infection is considered to have a potential association with infectious nonunion before surgery. Nonetheless, according to our study findings, infectious nonunion before surgery does not increase the postoperative infection rate and could have a benefit in terms of shortening the healing time, although it can lead to requiring an additional procedure after surgery. This is consistent with the previous literature showing no difference in outcomes of infected patients at any particular stage.[17] In an effort to treat and prevent infection during IMT, most studies reported adding antibiotics to the cement spacer. However, whether antibiotics affect the biological activity of induced membrane remains controversial. Masquelet et al stated that bone cement with antibiotics may increase the biological resistance of bacteria and cause adverse effects on the characteristics of the induced membrane.[18] An in vivo animal study confirmed that antibiotic could prevent the osteoinductive effects of BMP-2 by interfering with its mode of action,[19] which may negatively impact the formation of induced membrane. However, another in vivo study conducted using an infected rat femoral defect model demonstrated that antibiotic was effective in mitigating surgical site infection and restoring inflammatory cytokines and growth factor expression, such as BMP-5, interleukin-1β, IL-6, IL-10, and tumor necrosis factor-α to the induced membrane, which indicates antibiotics might play a role in bone regeneration and antimicrobial ability.[20] Our results indicate that PMMA cement with antibiotic does not actually increase the risk of nonunion rate, but shortens the healing time. If there is still a concern that antibiotic may cause adverse effects in induced membrane, Masquelet et al noted the importance of eradicating infection bone defect by thorough debridement of the membrane and surrounding soft tissues and re-initiating the technique if needed.[5]

Initial stabilization with external fixation was safe due to adequate mechanical stability and allowing daily inspection of the healing soft tissue.[21] Most surgeons use external fixation due to concerns that immediate internal fixation might incur a risk of postoperative infection, especially in patients with infectious nonunion before surgery. However, a retrospective cohort study reported that use of internal fixation did not seem to aggravate severe infectious complications when compared with external fixation.[22] Furthermore, use of external fixation increased the incidence of delayed stress fracture when compared with use of internal fixation.[14] Our results indicate that the use of external fixation through 2 stages leads to an increased risk of postoperative infection (OR = 8.16, $P = .001$) and additional surgery (OR = 14.00, $P < .001$). This means internal fixation may be a preferable method through two stages, although a detailed elucidation of membrane formation in the first stage of IMT[23] and the bio-mechanical environment for each fixation method[24] have yet to be provided.

Table 2

Univariate and multivariate analysis of postoperative infection and additional surgery.

Variable	Infection				Additional surgery			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95%CI)	*P* value
Age	1.01 (1.00–1.03)	.13			0.97 (0.96–0.98)	<.001**	1.00 (0.97–1.03)	.946
Gender								
F	Reference				Reference			
M	1.68 (0.72–3.92)	.23			1.05 (0.60–1.81)	.87		
Interval between two stages, weeks								
≤8	Reference				Reference			
8–12					1.94 (0.64–5.93)	.24		
≥12	3.12 (0.88–11.04)	.08			1.19 (0.57–2.49)	.64		
Defect size, cm	1.07 (0.99–1.16)	.08			1.13 (1.07–1.19)	<.001**	1.05 (0.96–1.15)	.26
Defect site								
Tibia	Reference		Reference		Reference		Reference	
Femur	0.35 (0.15–0.81)	.01*	1.81 (0.49–6.72)	.37	0.53 (0.31–0.90)	.02*	1.24 (0.51–3.00)	.64
Etiology								
Noninfection	Reference		Reference		Reference		Reference	
Preoperative infection	2.16 (1.15–4.09)	.02*	2.52 (0.73–8.67)	.14	1.57 (1.01–2.45)	.045*	3.73 (1.46–9.51)	.006**
Antibiotic use								
Without antibiotics	Reference		Reference		Reference		Reference	
Bone cement with antibiotics	0.17 (0.07–0.38)	<.001**	0.31 (0.07–1.36)	.12	0.18 (0.10–0.34)	<.001**	1.69 (0.50–5.76)	.40
Bone graft								
NonRIA use	Reference				Reference			
RIA use	1.06 (0.42–2.64)	.91			1.04 (0.59–1.83)	.91		
Fixation type								
Internal fixation	Reference		Reference		Reference		Reference	
External fixation	3.93 (2.02–7.66)	<.001**	8.16 (2.36–28.21)	.001**	6.71 (4.05–11.11)	<.001**	14.00 (5.12–38.25)	<.001**

CI = confidence interval, F = female, M = male, OR = odds ratio, RIA = reaming irrigation aspirator.
* $P < .05$.
** $P < .01$.

There were several limitations in our study. First of all, all included studies were non-randomized, observational case series. Thus, bias in the statistical analysis might have existed. To decrease this probability, we employed the NOS assessment tool to evaluate the risk of bias and only included studies with more than 10 cases. Secondly, some studies did not report individual patients' data. Without detailed data on bone healing time, follow-up time, and complications, it is difficult to perform univariate and multivariate analysis. Thirdly, there was no standard definition of union or infection among the included studies. This may have caused potential bias in the estimation of union and infection rate.

In conclusion, we recommend that the timing of the second stage should be delayed 6 to 8 weeks after the first stage. Bone cement with antibiotics could control the infection rate well and shorten the healing time. In addition, there is no need to avoid using internal fixation due to concerns about possibly causing postoperative infection.

Supplementary References, http://links.lww.com/MD2/B42

Acknowledgments

The authors acknowledge the contribution of the Evidence-based Practice and Policymaking Committee, Taichung Veterans General Hospital, Taichung, Taiwan.

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