Comparative Study

PROPHYLACTIC USE OF ANTIBIOTIC-LOADED BONE CEMENT IN PRIMARY HIP REPLACEMENT: A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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ABSTRACT

Periprosthetic joint infection (PJI) is a challenging complication following joint replacement and represents a significant health expense. Literature comparing antibiotic-loaded bone cement (ALBC) and plain bone cement (PBC) for total hip replacement is lacking and inconclusive. This research aims to meta-analyze the available literature in order to state if ALBC is superior to PBC for the prevention of PJI and, therefore, justify its widespread use in primary hip replacement. A systematic review of the literature was carried out about survival, in terms of septic revision, of cemented primary hip replacement, comparing ALBC and PBC following PRISMA guidelines. Articles published before 2005 have been excluded because cementing techniques have significantly improved over the last few years. The indication for surgery was both for hip osteoarthritis and for femoral neck fracture. National registry studies, cohort studies, and case series were included in this systematic review. Five articles were eligible for the meta-analysis, with 502.702 hip replacements. The forest plot comparing ALBC and PBC, with a CI of 99%, was in favor of the usage of antibiotics [χ^2=5.88, Risk Ratio=1.55 (1.29, 1.85)]. The sub-group analysis of the effect of ALBC when compared to PBC was not possible, based on total and partial replacement, nor the surgical indication. This meta-analysis, critically analyzing the available literature, proved the superiority and rationality of ALBC usage vs PBC. The present article proved a statistically significant reduction in PJI rate in primary hip replacements cementing with ALBC compared to PBC, but strong recommendations cannot be made. Further prospective randomized trials are requested to confirm the efficacy of ALBC in preventing PJI.

KEYWORDS: *antibiotic bone cement, hip, infection, revision, prosthesis*

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INTRODUCTION

Periprosthetic joint infection (PJI) is a challenging complication following joint replacement and represents a significant health expense. Incidence of revision for PJI accounts for 5 to 20% of total revisions, and it has been estimated that less than 1% of total hip replacements will undergo revision surgery for an infection in the ten years after surgery (1-3).

Cemented hip arthroplasty is indicated in displaced intra-capsular femoral neck fracture or primary osteoarthritis (OA) in patients with poor bone quality, age 70 or greater, and diagnosis of osteoporosis or osteopenia (4). Bone cement during hip replacement can be loaded with antibiotics: since its introduction in the '70, antibiotic-loaded bone cement (ALBC) is routinely used and globally accepted for septic revision surgery, but there are still doubts and inhomogeneity about its use in primary hip replacement with different treatment trends depending on the country (5).

The cost-efficacy of ALBC in preventing periprosthetic infection is still debated, and scientific evidence is lacking and contradictory. Only a few articles systematically compare the use of ALBC and plain bone cement (PBC) for primary hip replacement with contrasting findings.

The aim of this study is to analyze the effects of ALBC in primary hip replacement, both performed for femoral neck fracture or osteoarthritis, in terms of implant failure. The primary endpoint was to evaluate the number of cemented hip prostheses revised for infection by comparing ALBC and PBC. The secondary endpoint was to assess and compare the number of revisions for any cause.

METHODS

Systematic research has been performed in Google Scholar, Cochrane Library e PubMed, about the efficacy of ALBC in comparison to PBC implants, in terms of primary hip implant survival. The study was conducted in conformity with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (6). The primary outcome was the comparison of revision rate due to PJI between cemented primary hip replacements with plain PBC and ALBC.

As a temporal cutoff, we included only articles published from 2005 on, since the cementing techniques significantly improved in recent past years (7). The keywords inserted in the research engines, properly matched using the Boolean operators AND or OR, were: "antibiotic-loaded bone cement", "primary hip prosthesis", "laden cement", "plain bone cement", "total hip arthroplasty", "periprosthetic", "infection", "cost analysis", "septic", and "revision". The research was screened for randomized controlled trials (RCT), retrospective analyses, national registry studies and retrospective case series.

The final inclusion criteria were the following:

1) RCT, systematic revisions, observational cohort studies, national prosthesis registries, retrospective case series;
2) articles dealing with primary total or partial cemented hip replacement, both performed for fracture or osteoarthritis;
3) articles comparing the usage of ALBC vs PBC in hip replacement;
4) date of publication later than 2005.

The exclusion criteria were the following:

1) studies published before 2005;
2) hip resurfacing;
3) revision surgery, not primary implants.

Whenever more than one article with data obtained from a different year but the same national prosthesis registries were available, the latest paper was included. The search results were independently assessed, filtered and selected by two authors (BG, PG) for eligibility. Every disagreement was resolved by a consensus meeting with a third author (MAM). The risk of bias was classified using the Methodological Index for Non-Randomized Studies (MINORS) (8). Each item of the MINORS was scored 0 when absent, 1 when present but inadequate, and 2 when present and adequate. The ideal score for comparative studies was 24, and 16 for non-controlled studies.

Comparative studies were classified as at high risk of bias if the overall score was ≤ 20, and at low risk of bias when > 20. Non-controlled studies were considered at high risk of bias when the overall score was ≤ 12 and at low risk of bias when > 12.

RESULTS

The research identified 1042 articles; deleting duplicates and non-inherent studies based on title and abstract, 714 papers remained, of whom only 97 were available for full-text assessment. Those have been screened in full-text: only 5 papers respected the inclusion criteria and two among them were retrospective analyses of the national United Kingdom prosthesis register. Only the newest published articles were included (Fig. 1).

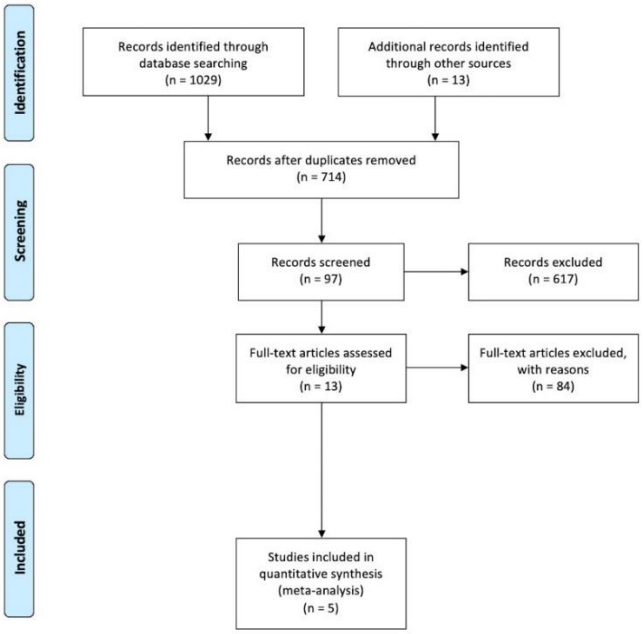

Fig. 1. *PRISMA flow diagram.*

Five papers have been included (9-13); all five were retrospective descriptive studies based on national prosthesis registries or case series; the publication date was between 2009 and 2020 (Table I, II).

Table I. *MINORS.*

	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoint appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to the study aim	<5% lost to follow-up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of	Adequate statistical analyses	total	Adequate number of patients	Risk of bias
HOSKINS	2	1	1	2	0	1	2	1	2	2	2	1	17/24	1	high
AEDO-MARTIN	2	1	1	2	0	2	0	1	2	2	2	2	17/24	1	high
SANZ-RUIZ	2	2	1	2	1	2	2	1	2	1	2	2	20/24	1	high
LEONG	2	1	1	2	0	2	0	1	1	2	0	2	14/24	2	low
DALE	2	1	1	2	0	2	0	1	1	2	0	2	14/24	2	low

Data have been analyzed with RevMan V.5.0.18.33, to create a forest plot. Possible publication bias has been assessed using a funnel plot.

Table II. *List of the studies included in the meta-analyses and their characteristics.*

	Year of publication	Study design	Nation	Study period	Diagnosis and implant type	PBC
Hoskins (9)	2020	retrospective case series	USA	2016-2018	total and partial hip replacement	50
Aedo-Martín (11)	2019	retrospective descriptive	Spain	2011-2017	partial hip replacement for fracture	147
Sanz-Ruiz (12)	2017	retrospective	Spain	2009-2012	total and partial hip replacement	262
Leong (10)	2020	retrospective from national prosthesis registry	UK	2005-2017	THA for OA	20961
Dale (13)	2009	retrospective from national prosthesis registry	Norway	1987-2007	THA	17991

The total THA collected was 502.702, 39.411 in the PBC group, and 463.291 in the ALBC group. Two studies included a population of elective total hip replacements (10, 13), one study (11) included hip replacements performed for femoral neck fracture, and other studies (9, 12) had a mixed population of elective and trauma cases.

It was impossible to provide the proportion of male and female patients because one of the studies (9) included hip and knee surgeries, not specifying the relative percentages for the two sub-groups of replacement.

Table III itemizes the number of cases of hip replacement for each article included, giving information about the type of cement used and the respective number of periprosthetic deep infections detected during the follow-up.

The primary outcome was to evaluate the number of events of "deep infection" encountered in the two categories, PBC vs ALBC.

Table III. *Cases of hip replacement for each article.*

	PBC	ALBC	PJI PBC	PJI ALBC	p-value	
Hoskins (9)	50	39	0	0	1.000	
Aedo-Martín (11)	147	94	28	8	**0.027**	*
Sanz-Ruiz (12)	262	257	22	6	**0.003**	*
Leong (10)	20961	397896	92	1288	**0.005**	*
Dale (13)	17991	65005	157	360	**<0.001**	*

***ALBC** = antibiotic-loaded bone cement, **PBC** = plain bone cement, **PJI** = periprosthetic joint infection. Asterisks highlight significant p-values (Fisher's exact test).*

Gathering the cases presented by these articles, a Forest plot assessed the odds ratio (CI 95%) of developing the event. Analyses demonstrated a significant prophylactic effect in preventing PJI with the usage of ALBC ($p<0.001$), $\chi^2=6.52$, $I^2=54\%$, OR 1.65 (1.27 to 2.14) (Fig. 2).

Precisely, the prevalence of PJI in patients who underwent THA with PCB was 0.8% versus 0.4% of patients treated with ALBC ($p<0.001$).

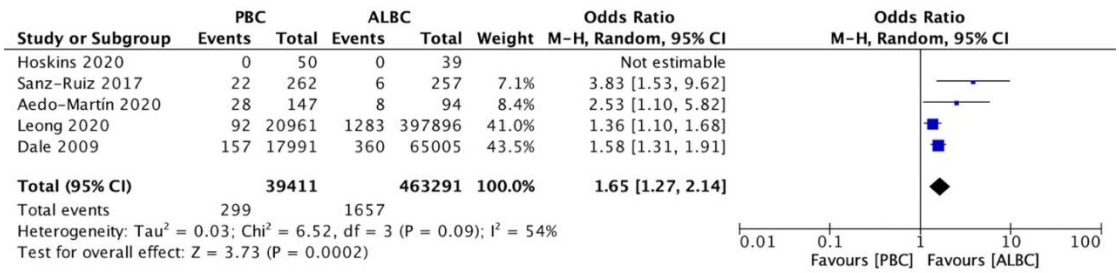

Fig. 2. *Forest plot.*

The Funnel plot (Fig. 3) referred to the included studies reveals a low data dispersion; a low risk of publication bias is expected.

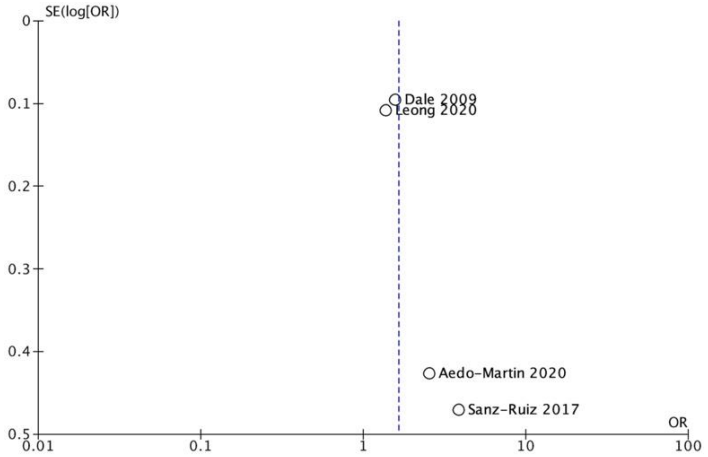

Fig. 3. *Funnel plot of the primary outcome.*

Compared to the analysis of Farhan-Alaine (3), this systematic review and meta-analysis provided updated data, replacing the article of Trela-Larsen (17) with the more recent analysis from the UK national register report performed by Leong et al. (10). However, further prospective randomized studies are necessary to provide a precise and high-level meta-analyze.

DISCUSSION

The main finding of this research is a statistically significant decrease in PJI rate in primary hip replacements when cementing with ALBC compared to PBC. However, considerable heterogeneity of reported data in the study leads to a careful interpretation of reported results.

The effectiveness of ALBC in PJI treatment is globally accepted. Its usage during septic revision received Federal Drug Administration (FDA) approval in 2003; on the other hand, its employment for primary joint arthroplasties is still debated (18). Literature about the benefit of ALBC usage in primary hip replacement is scarce and inconclusive, and no available guidelines provide strict recommendations.

Although there are only a few published studies in the literature with low quality, the number is even lower if only recent articles are selected. The difficulty in the design of a prospective study lies in the prolonged follow-up phase, the possibility of choosing different hip approaches, different cement brands, and other factors (i.e., operating room environment, operative field preparation method, and specific surgeon-related factors).

Regarding primary knee replacement, a meta-analysis published in 2022 (19) found no significant evidence to declare a decrease in peri-prosthetic infection rate using ALBC and authors recommended the routine use of PBC, to reduce surgeries cost.

On the contrary, other recent studies (20, 21) found a significant benefit from routine ALBC usage in total joint replacement, reducing the incidence of deep infection. This research concluded that the addition of antibiotics to cement is a safe and effective method for PJI prevention in primary total knee arthroplasties (TKA), although it is not effective in preventing superficial wound infections. The findings of this study can be justified by the difficulty encountered by the antibiotic mixed in the cement matrix to reach the superficial wound at a therapeutic concentration (20).

Similar conclusions in TKA and THA are given by Zhang et al. (21) as systemic administration of antibiotics had a role in preventing superficial surgical site infections, whereas the utility of ALBC is represented by the efficacy to prevent deep infections.

Data published in the literature support the findings of the present article: a previous meta-analysis by Parvizi (22), evaluated the use of ALBC in the prevention of PJI, however, the included articles have been published between 1987 and 1997 and several improvements in cement proprieties (6, 23) have been achieved over the years. Furthermore, this research showed a reduction in all causes of revision using antibiotic-soaked PMMA. These results potentially supported those who promote the routine use of ABLC, even in primary implants.

A systematic review and meta-analyses of RCT by Wang et al. (24) evaluated the prophylactic role of ALBC in primary THA and its effectiveness in preventing peri-prosthetic infection. The authors demonstrated a significant reduction of PJI without differences in superficial surgical site infections.

The present research study included a population of proximal femoral fractures and elective hip replacement that allowed to select only five studies. Furthermore, this systematic review and meta-analysis provided updated national United Kingdom registry data (10).

The rationale for the routine use of ALBC during primary hip replacement is still unconfirmed due to a lack of high-quality studies. Further prospective randomized trials are necessary to support the reduction of the incidence of PJI, decreasing the risk of re-intervention, with an advantage in terms of money-saving and patients' health.

Leong (10) found a protective role, in terms of revision for aseptic loosening, by using ALBC during THR and TKA. This result could highlight that some aseptic revisions may ultimately be caused by low-grade infections. Furthermore, these data supported that the mechanical properties of cement are not compromised by antibiotic addition at recommended doses (23).

The results found in the study by Farhan-Alaine et al. (3) showed a lower, but not significant, revision rate for any cause, in the group treated with ALBC.

To our knowledge, the present study is the most recent meta-analysis to compare the efficacy of ABLC and PBC for preventing PJI in primary hip replacement. Nevertheless, this study presents several limitations: the main limitation is the design of selected articles including only observational studies. Furthermore, due lack of high-level studies reporting comparative outcomes there is high heterogeneity in follow-up duration, type of cement used, type of antibiotic and implant design. Finally, the assessment of outcome "revision" could underestimate those patients with PJI treated with debridement, antibiotics and implant retention (DAIR), whenever not specified.

CONCLUSIONS

This meta-analysis critically analyzed the available literature and proved the superiority and rationality of ALBC usage vs PBC in primary THA.

The present article proves a statistically significant reduction in PJI rate in primary hip replacements cementing with ALBC compared to PBC, but strong recommendations cannot be made. Further prospective randomized trials are requested to confirm the efficacy of ALBC in preventing PJI.

Conflicts of interest statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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