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To cite this article: Øystein Birkeland, Birgitte Espehaug, Leif I Havelin & Ove Furnes (2017) Bone cement product and failure in total knee arthroplasty, *Acta Orthopaedica*, 88:1, 75-81, DOI: [10.1080/17453674.2016.1256937](https://doi.org/10.1080/17453674.2016.1256937)

To link to this article: <https://doi.org/10.1080/17453674.2016.1256937>



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Published online: 14 Nov 2016.



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Bone cement product and failure in total knee arthroplasty

A follow-up study of 26,147 knee replacements between 1997 and 2013 in Norway

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Submitted 2016-01-27. Accepted 2016-08-04

Background and purpose — The bone cement market for total knee arthroplasty (TKA) in Norway has been dominated by a few products and distributors. Palacos with gentamicin had a market share exceeding 90% before 2005, but it was then withdrawn from the market and replaced by new slightly altered products. We have compared the survival of TKAs fixated with Palacos with gentamicin with the survival of TKAs fixated with the bone cements that took over the market.

Patients and methods — Using data from the Norwegian Arthroplasty Register for the period 1997–2013, we included 26,147 primary TKAs in the study. The inclusion criteria were TKAs fixated with the 5 most used bone cements and the 5 most common total knee prostheses for that time period. 6-year Kaplan-Meier survival probabilities were established for each cement product. The Cox proportional hazards regression model was used to assess the association between bone cement product and revision risk. Separate analyses were performed with revision for any reason and revision due to deep infection within 1 year postoperatively as endpoints. Adjustments were made for age, sex, diagnosis, and prosthesis brand.

Results — Survival was similar for the prostheses in the follow-up period, between the 5 bone cements included: Palacos with gentamicin, Refobacin Palacos R, Refobacin Bone Cement R (Refobacin BCR), Optipac Refobacin Bone Cement R (Optipac Refobacin BCR), and Palacos R+G.

Interpretation — According to our findings, the use of the new bone cements led to a survival rate that was as good as with the old bone cement (Palacos with gentamicin).

(Robertsson et al. 2010). Aseptic loosening of the primary TKA is the most common reason for revision (Carr et al. 2012, Furnes et al. 2014).

The acrylic bone cements are regulated by 2 international standards (Nottrott 2010), with current versions ISO-5833-2002 and ASTM F451-08. Complying with the requirements of the standards, which are based on preclinical testing, does not seem to guarantee clinical success. In the past, there have been examples of poor clinical performance of some of the approved bone cements (Espehaug et al. 2002). The bone cement Boneloc is perhaps the most prominent case. This product was introduced in the early 1990s, but was withdrawn from the market already in 1995. Short-term studies had revealed poor clinical performance compared to conventional acrylic bone cements (Havelin et al. 1995, Suominen 1995, Thanner et al. 1995, Furnes et al. 1997, Markel et al. 2001). Generally speaking, the regulatory framework worldwide for medical devices including implants and bone cements has been much less rigorous than that for new drugs (Riehmman 2005, Carr et al. 2012, Labek et al. 2015).

Approximately 20 bone cement products used for TKAs have been reported in the Norwegian Arthroplasty Register (NAR). Even so, only 5 different high-viscosity polymethylmethacrylate (PMMA) bone cement products with antibiotics have been used in over 90% of all the reported TKAs (Furnes et al. 2014).

Before 2004, Palacos with gentamicin (Schering-Plough) had a market share of approximately 90% in Norway. This product was the result of a collaboration between Heraeus Kulzer, who produced the cement components, and Schering-Plough, who supplied and added the antibiotic gentamicin. The distributor of the end-product in Scandinavia was Schering-Plough. This bone cement product was seen by many orthopedic surgeons to be the gold standard in this area. In other parts

Fixation methods for total knee arthroplasty (TKA) implants are cemented, cementless, or a combination (hybrid). The majority of TKAs performed in Scandinavia are cemented

of Europe, Heraeus Kulzer had a collaboration with Merck, and the end-product was distributed by Merck under the name Refobacin Palacos R (Kühn 2000). In 1998, Biomet entered a joint venture with Merck, and in 2004 they purchased Merck's interest, and founded the Biomet Europe Group. Then, in 2005, Heraeus Kulzer decided to self-distribute the bone cement end-product to all territories, and the well-known products Palacos with gentamicin and Refobacin Palacos R were removed from the market (Bridgens et al. 2008, Neut et al. 2010). Heraeus Kulzer and Biomet then introduced the new products Palacos R+G and Refobacin BCR, respectively.

Both of the companies, Biomet and Heraeus Kulzer, have claimed in the past that their new products are equivalent to their predecessor (Neut et al. 2010, KOFA 2011). On the other hand, it has been shown that even small differences in processing and source of substances may influence the end-product, for example the release of gentamicin (Kühn 2000). A number of *in vitro* studies also brought to light various minor differences between the old and new products in the years that followed (Dall et al. 2007a and b, Bridgens et al. 2008, Kock et al. 2008, Neut et al. 2010).

With this background, and using data from the NAR, we compared the survival of TKAs fixated with the old Palacos with gentamicin and that of TKAs fixated with the most used bone cement products that took over the market. We also studied deep infection up to 1 year postoperatively, which would include both early postoperative infections and most of the late chronic infections (Tsukayama et al. 1996).

Patients and methods

The data were taken from the Norwegian Arthroplasty Register (NAR), a national registry covering Norway's approximately 5 million inhabitants, which was founded in 1987 as a hip registry (Havelin et al. 2000). In 1994, knee arthroplasty was included in the registry (Furnes et al. 2002), and by the end of 2013 approximately 50,000 TKAs had been registered. For the period 1999–2002, 99% of all TKAs and 97% of all TKA revision operations in Norway were reported to the register (Espeshaug et al. 2006). For the period 2008–2012, an external analysis found a completeness of more than 95% for primary TKA operations and of 89% for TKA revision operations (Furnes et al. 2014). The information from each operation is reported using a standardized form filled out by the surgeon on a voluntary basis, and sent by post to the registry. The information collected in the registry includes the date of the operation, the civil registration number of the patient, indication for the procedure, bone cement product (as identified by catalogue numbers from stickers in the cement wrapping), hospital, and prosthesis brand at the catalogue number level. The NAR publishes annual reports with descriptive statistics (<http://nrlweb.ihelse.net>).

Study sample

47,503 TKAs were reported to the NAR in the period from January 1, 1997 to December 31, 2013. We excluded TKAs with patellar component ($n = 3,205$), with unknown diagnosis ($n = 103$), those uncemented/fixated without antibiotic-loaded bone cement ($n = 2,605$), and those with unequal proximal and distal bone cement (including hybrid prostheses) ($n = 6,018$). Figure 1 shows a breakdown of the bone cements used in the remaining TKAs.

In addition, we excluded bone cements used for less than 3 years and in less than 1,000 knees in total ($n = 2,846$). The remaining bone cements were: Palacos with gentamicin (Schering-Plough), Palacos Refobacin R (Merck), Palacos R+G (Heraeus Kulzer/Heraeus Medical), Refobacin BCR (Biomet), and Optipac Refobacin BCR (Biomet).

TKAs with unequal prosthesis type in the proximal and distal part, or with missing information, were excluded ($n = 508$). Furthermore, only TKAs with prosthesis brands used over the whole study period (1997–2013) and in over 2,000 knees were included. These criteria left Profix (Smith and Nephew), LCS/LCS Complete (DePuy), AGC (Biomet), and NexGen (Zimmer), and led to exclusion of 6,057 TKAs. For each of the bone cements, a specific time interval for inclusion was defined, leading to exclusion of 14 other TKAs.

These exclusion/inclusion criteria were used to make the study population as homogeneous as possible regarding the influence of the bone cement product. Maximum possible follow-up was 9 years for the different bone cements, except for Optipac Refobacin BCR, which had only been in use for 6 years (since 2008).

We identified 26,147 TKAs in the total study population for comparison of survival rate according to the bone cement products (Table 1 and Figure 2).

In this study, some patients received 2 TKAs and the study population consisted of 20,979 individuals.

Outcome

The outcome variable was prosthesis survival, defined as time from implantation to revision. Revision was defined as exchange, or addition or removal of the implant or part of the implant. Observation times were censored at time of death, emigration, or end of study. Information on death and emigration was obtained from the National Population Registry (TaxAdmin 2014) using the civil registration numbers of Norwegian residents.

Predictor

Bone cement product (Palacos with gentamicin, Refobacin Palacos R, Refobacin BCR, Optipac Refobacin BCR, and Palacos R+G) was evaluated as a predictor of prosthesis survival.

Other variables

Adjustment was performed for possible confounding by age (< 60 , $60–69$, $70–79$, > 79), sex, diagnosis (arthrosis, other),

Table 1. Inclusion criteria for bone cements and prostheses with product information

Inclusion criteria	Products included	Distributor	Comments
Cements			
Used > 3 years. Used in over 1,000 knees. Equal bone cement in proximal and distal part of prosthesis	Palacos with gentamicin	Schering-Plough ^a	The cement components (poly/monomers) was produced by Heraeus Kulzer and antibiotics were added by Schering-Plough. The single most used cement before 2005, and considered as the gold standard for many years. Mostly used in Scandinavia. Also referred to as Palacos R with gentamicin or Palacos R40G in some papers. Withdrawn from the market in 2005.
	Palacos Refobacin R	Merck	Identical cement components (poly/monomers) as in Palacos with gentamicin. Antibiotics added under license from Merckby Heraeus Kulzer, and end product distributed by Merck ^b . Withdrawn from the market in 2005.
	Palacos R+G	Heraeus Kulzer ^c	The cement components (poly/monomers) are identical to those in Palacos with gentamicin. New vendor for gentamicin. Minor differences in production method for the addition of the gentamicin.
	Refobacin BCR	Biomet ^d	Copy product of the old "Palacos" cement. New vendor of cement monomers/polymers. Antibiotics added with the same procedure as in Palacos Refobacin R.
	Optipac Refobacin BCR	Biomet ^d	Identical components as Refobacin BCR, but all ingredients come pre-packaged in a mixing system, which remains closed until the cement is appl
Prostheses			
Used in the whole study period (1997–2013). Used in over 2,000 knees. Equal prosthesis proximally and distally.	Profix	Smith and Nephew	Cruciate retaining.
	LCS	DePuy	Mobile bearing. LCS was used until 2006.
	LCS Complete	DePuy	Mobile bearing. Assessed as same prosthesis as LCS in this paper, due to the similarities. Used from 2003.
	AGC	Biomet	Cruciate retaining.
	NexGen	Zimmer	Cruciate retaining.

^a Merged with Merck & Co. in 2009
^b Later Biomet-Merck
^c Heraeus Medical from year 2009 (company re-organization)
^d Zimmer Biomet from year 2015

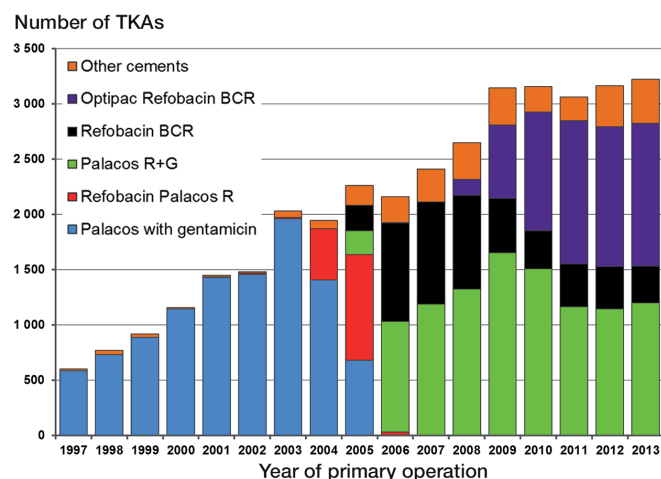


Figure 1. Bone cements used for TKAs in Norway in the period 1997–2013. TKAs with patellar component, unknown diagnosis, fixation without antibiotic-loaded bone cement, and hybrid fixation (or unequal bone cement in distal and proximal part) are not included.

and prosthesis brand (LCS/LCS Complete, AGC, NexGen, Profix).

Statistics

6-year survival probabilities with 95% confidence intervals

(CIs) were established for each bone cement product using the Kaplan-Meier method. Any p-values < 0.05 were considered statistically significant. We used the Cox proportional hazards regression model to assess the association between cement product and revision risk. Unadjusted and adjusted relative revision risk (RR) estimates were established for each bone cement relative to the Palacos R+G, and are presented with CIs and p-values. We also calculated p-values for tests of the overall impact on survival of the cement product. Survival curves were constructed based on the adjusted estimates, and stratified for the different bone cements to illustrate possible differences in the distribution of time from insertion of the prosthesis to revision. Separate analyses were performed with revision for any reason and revision due to deep infection within 1 year postoperatively, as endpoints. The proportional hazards assumption of the Cox model was investigated visually and tested based on scaled Schoenfeld residuals (Ranstam et al. 2011), and found to be valid for cements in the analyses with revision for any reason as endpoint (all $p > 0.3$). With revision due to deep infection within 1 year as endpoint, the assumption was violated for 2 cement products: Palacos with gentamicin ($p < 0.001$) and Optipac Refobacin BCR ($p = 0.03$). The residual plot (not shown) and the reported survival curves indicated that analyses performed for different follow-up periods were unlikely to change our conclusions.

Table 2. Patient and procedure characteristics for the different bone cement products

Variables	Palacos with gentamicin	Refobacin Palacos R	Palacos R+G	Refobacin BCR	Optipac Refobacin BCR	Total
TKAs	7,650	1,206	8,278	4,505	4,508	26,147
Proportion of total, %	29	5	32	17	17	100
Males, %	29	31	35	35	37	33
Age in years, %						
< 60	15	15	17	18	18	16
60–69	27	29	34	34	36	32
70–79	43	41	36	35	36	38
> 79	15	15	14	13	10	14
Prosthesis, %						
AGC	22	20	6	28	9	15
NexGen	2	9	15	8	11	9
Profix	40	39	52	16	7	34
LCS/LCS complete	36	33	27	48	73	42
Diagnosis, %						
Osteoarthritis	85	89	88	88	91	88
Other	15	11	12	12	9	12
No. of hospitals	65	33	52	40	29	75

est period of time in use (3 years). The distribution of age was homogenous for the different cements, with most patients between 60 and 80 years of age. The least used prosthesis/cement combination was the NexGen prosthesis in combination with the cement Palacos with gentamicin (138 knees). The most frequent combination was Optipac Refobacin BCR with LCS Complete (3,304 knees). Over 85% of all the TKAs were done because of osteoarthritis. 75 different hospitals had performed TKAs, and 61 of them had used more than 1 cement product (Table 2 and Figure 2).

Survival

All the bone cements had almost identical results ($p = 0.9$) with an unadjusted survival percentage of approximately 95% at 6 years. Similar findings were obtained with adjustment for differences in age, sex, diagnosis, and prosthesis brand ($p = 0.4$) (Table 3 and Figure 3).

Infection

Within one year postoperatively, 147 revisions were done due to deep infection. Compared to Palacos R+G, Palacos with gentamicin had a statistically significantly lower risk of revision due to infection (RR = 0.5, CI: 0.3–0.8; $p = 0.01$). There were no statistically significant differences between the 3 bone cements that are currently on the market ($p = 0.7$) (Table 4 and Figure 4).

Discussion

Summary

We found no statistically significant differences in TKA survival for the bone cements Palacos with gentamicin, Refobacin Palacos R, Palacos R+G, Refobacin BCR, and Optipac Refobacin BCR. Palacos with gentamicin had a significantly lower risk of infections than Palacos R+G. The bone cements currently on the market had practically the same risk of infection 1 year postoperatively.

Other relevant studies

Olerud et al. (2014) performed a consecutive radiostereometric study comparing Refobacin BCR cement with Palacos with gentamicin, which were used in total hip arthroplasty (THA)

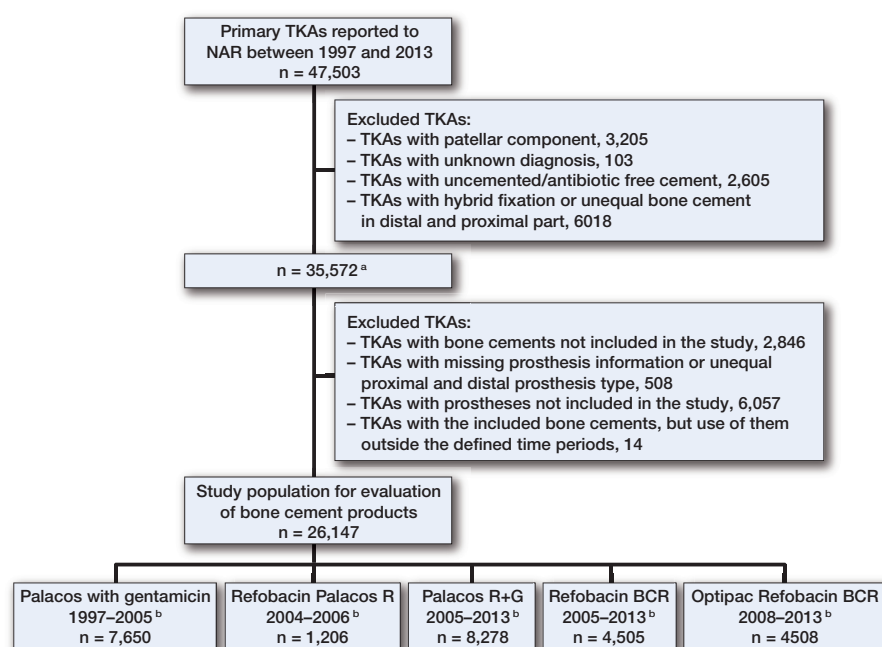


Figure 2. The selection procedure from the data registered in the NAR. n = number of knees with TKA. ^a Illustrated in Figure 1. ^b The time period of use included in study.

Statistical analyses were performed using the software SPSS Statistics version 22.

Results

None of the bone cements had been used over the entire study period. Palacos R+G was the most frequently used bone cement (used in 8,278 knees). Refobacin Palacos R was used in 1,206 knees and was the least used; it also had the short-

Table 3. Cox relative revision risk (RR) estimates with revision for any reason as endpoint. Unadjusted and adjusted for age, sex, diagnosis, and prosthesis brand

Bone cement	Median follow-up, years	Maximum follow-up, years	No. revised	No. at risk, 6 years	Kaplan-Meier survival at 6 years (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	p-value
Palacos R+G	3.9	8.4	299	2,034	95.2 (94.6–95.7)	1 (ref)	1 (ref)	–
Palacos with gentamicin	2.9	9.0	259	821	94.9 (94.2–95.6)	1.00 (0.85–1.18)	0.98 (0.83–1.17)	0.9
Refobacin BCR	5.2	8.3	183	1,771	95.2 (94.5–95.9)	0.98 (0.82–1.18)	0.88 (0.73–1.06)	0.2
Optipac Refobacin BCR	2.2	6.0	120	a	b	0.96 (0.78–1.19)	0.84 (0.67–1.05)	0.1
Refobacin Palacos R	7.7	9.0	53	1,020	95.5 (94.3–96.7)	0.88 (0.66–1.18)	0.86 (0.64–1.16)	0.3

^a Last revision at 4.5 years; at risk: 339.
^b Last revision at 4.5 years; survival (95% CI): 95.3% (94.2–96.5).

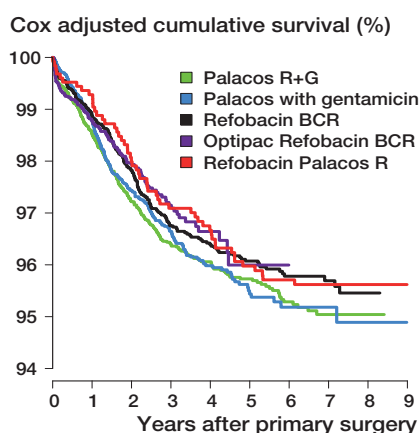


Figure 3. Cox survival curves with cement product as stratification variable for all TKAs with revision for any reason as endpoint. The curves were estimated with adjustment for age, sex, diagnosis, and prosthesis brand.

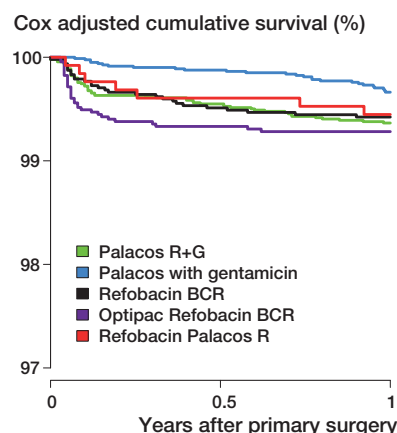


Figure 4. Cox survival curves with cement product as stratification variable for TKAs with revision due to deep infection within one year postoperatively as endpoint. The curves were estimated with adjustment for age, sex, diagnosis, and prosthesis brand.

Table 4. Cox relative revision risk (RR) estimates with revision due to deep infection within 1 year postoperatively as endpoint. Adjusted for age, sex, diagnosis, and prosthesis brand

Bone cement	At risk, 1 year	No. revised	Adjusted RR (95% CI)	p-value
Palacos R+G	7,027	55	1 (ref)	–
Palacos with gentamicin	6,812	26	0.52 (0.32–0.84)	0.01
Refobacin BCR	4,220	27	0.92 (0.56–1.50)	0.7
Optipac Refobacin BCR	3,975	32	1.18 (0.73–1.91)	0.5
Refobacin Palacos R	1,190	7	0.87 (0.39–1.92)	0.7

for 2 patient groups. They studied 51 patients, observing them for 2 years. They found no clinical or statistically significant difference between the 2 cements, and concluded that Refobacin BCR should be safe for clinical use in THAs. However, they also stressed the need for longer follow-up and for results from national registries. Limitations of their study included the short follow-up time (2 years), the lack of randomization, and the length of time between the 2 study groups (due to use

of the bone cements in different time periods). Their results may not be transferrable to TKAs.

Kock et al. (2008) conducted in vitro tests of different properties between the “Palacos” cements Refobacin Palacos R and Palacos R+G and the bone cements SmartSet GHV and Refobacin BCR. Their study included handling properties, chemical analysis, and testing according to the ISO standard for acrylic bone cements. Their findings clearly indicated that the copolymers used in the cements SmartSet GHV and Refobacin BCR were different from those used in the 2 “Palacos” cements. They also found differences in viscosity and waiting/hardening times. Since the cement products clearly appeared to be dissimilar, they concluded that clinical data from long-term use of the Palacos cements cannot be extrapolated to Refobacin BCR (and SmartSet GHV).

Neut et al. (2010) compared in vitro gentamicin release from Refobacin Palacos R, Refobacin BCR, Palacos R+G, and SmartSet GHV. All the 3 newer cements showed higher sustained release of gentamicin compared to that from Refobacin Palacos R. They therefore concluded that the gentamicin release characteristics of the old and new cements were different.

Dall et al. (2007a) performed an *in vitro* comparison of mechanical and handling properties between Refobacin Palacos R and the newer Palacos R+G and Refobacin BCR. All 3 cements were found to have comparable mechanical properties, and to release similar amounts of gentamicin. On the other hand, they found different handling/viscosity curves for the different products, and concluded that these bone cements may perform differently in the operating theater from a surgeon's point of view.

Dall et al. (2007b) also conducted a study assessing the inter-batch and intra-batch variability in the handling characteristics and viscosity for the cements Refobacin BCR, Palacos R+G, Simplex P Tobramycin, and SmartSet GHV. Refobacin BCR was found to have a different viscosity from Palacos R+G. Their results also suggested that extrinsic factors, such as preparation conditions, may be of more importance than intrinsic variability.

Bridgens et al. (2008) performed an *in vitro* study comparing Palacos with gentamicin with the cements Palacos R+G and SmartSet GHV. All cements performed well, with minor differences. Regarding the difference between the old and new Palacos cements, they wrote: "We have also shown that the properties of Heraeus Palacos (meaning: Palacos R+G) compared with Schering-Plough Palacos (meaning: Palacos with gentamicin) are different, with superior elution of antibiotics and mechanical characteristics shown by Heraeus Palacos".

Explanations and interpretation

All these studies indicated some minor differences between the old and new bone cements. The new bone cements are almost identical to the old ones, but the small differences may be due to new suppliers of monomers, copolymers, and gentamicin—and/or slightly changed production procedures. Such minor changes in the chemical properties of the ingredients could affect the end-product (Kühn 2000, Milner 2004, Dall et al. 2007a and b). This explanation was also suggested by an official statement from Heraeus Kulzer, given in Bridgens et al. (2008). Furthermore, a legal dispute between Heraeus Medical Nordic and Biomet at the Norwegian Complaints Board for Public Procurement regarding the procurement of cement has indicated that the suppliers of antibiotics and monomers, and also production methods, do actually vary to some extent between the old and new products (KOFA 2011).

Our study has shown that these minor changes did not influence the clinical performance using survival of the TKAs as the outcome measure, but may have influenced other parameters. For example, several of the studies referred to suggest a possibly higher gentamicin release from the bone cements that are currently on the market (Bridgens et al. 2008, Neut et al. 2010). One hypothesis would be that these properties may lead to fewer deep infections and therefore less septic loosening/revision (Espøhaug et al. 1997). The present study does not indicate that there may be any clinical effect of a possibly higher gentamicin release. In fact, the old Palacos with gentamicin cement

had a statistically significantly lower deep infection rate than the new cements within 1 year postoperatively. We believe that this is a time-dependent effect, and a result of comparison of results from different time periods—as Palacos with gentamicin was stopped in 2005. Other registry-based studies have found an increased risk of revision due to deep infection from around year 2000, and especially after 2005, for THAs (Dale et al. 2009, 2012). Possible explanations include change in reporting awareness, revision policy, selection of patients, more resistant bacteria, and more modular prostheses. The AGC prosthesis is non-modular, and was used more frequently in the "Palacos with gentamicin" era before 2005. All deep infections of the AGC knee may not have been captured due to the inclusion criteria for revision. The cements currently on the market had practically the same risk of infection 1 year postoperatively.

Another parameter that may be altered is the preparation and the different phases during use (Kühn 2000). These properties are of importance to the operator. To our knowledge, almost all cements for TKAs in Norway are prepared with vacuum mixing systems in the operating theaters. The NAR does not have information on the mixing systems used, except for the pre-packaged systems. In our study, we included Optipac Refobacin BCR. This is the same bone cement as Refobacin BCR, but it comes pre-packaged with a closed-vacuum mixing system. Such products may have some advantages—in, for example, reducing the risk of wrong preparation. In the present study, we found no statistically significant differences between these 2 products.

Strengths and limitations

High-powered randomized clinical trials are seldom performed for comparison of rare incidences, such as loosening of cemented TKAs. Large observational studies from arthroplasty registries may therefore provide a good alternative for the study of such events.

The large number of TKAs assessed (26,147), and the fact that potential confounders had been adjusted for in the statistical models, is a strength of the study. Yet, survival of TKAs may also be confounded by other factors such as surgeon experience, patient comorbidities, temperature of the bone cement or of the operating theater, and the use of dissimilar vacuum mixing systems.

A limitation of the study was the short follow-up time. For the Boneloc cement, the chemical properties were dissimilar to those of the standard PMMA bone cements, and revisions started to appear after a short time (Suominen 1995, Havelin et al. 1995, Furnes et al. 1997, Markel et al. 2001). With only minor differences between the bone cements investigated in this study, any differences might therefore become apparent after a longer follow-up time.

One flaw might be that the change in the bone cement market in 2005 may have caused confusion for the reporting surgeons as well. All of sudden, the cements had a different name but had packaging of the same color. The registry may therefore

contain some minor errors from this period—if the surgeons reported the cement product in writing, instead of using the usual stickers delivered from the company as normally.

Further research

Our study consisted of TKAs only. Whether our result can be extrapolated to—for example—THA remains to be investigated. A longer follow-up period would also be desirable.

Conclusion

We found no difference in prosthesis survival between the bone cement Palacos with gentamicin and the new products introduced after 2005, with this relatively short follow-up time. All the new bone cements included in this study appear to be as good as their predecessor.

ØB performed the analyses and wrote the manuscript. BE supervised the analyses and helped write the manuscript. OF planned the study and helped write the manuscript. LH helped write the manuscript. All the authors contributed to editing of the manuscript, to interpretation of the analyses, and to revision of the manuscript.

No funding was received.

No competing interests declared.

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