No difference in risk of revision due to infection between clindamycin and cephalosporins as antibiotic prophylaxis in cemented primary total knee replacements: a report from the Norwegian Arthroplasty Register 2005–2020

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Background and purpose — Systemic antibiotic prophylaxis with clindamycin, which is often used in penicillin- or cephalosporin-allergic patients', has been associated with a higher risk of surgical revision for deep prosthetic joint infection (PJI) than cloxacillin in primary total knee replacement (TKR). We aimed to investigate whether clindamycin increases the risk of surgical revisions due to PJI compared with cephalosporins in primary cemented TKR.

Patients and methods — Data from 59,081 TKRs in the Norwegian Arthroplasty Register (NAR) 2005–2020 was included. 2,655 (5%) received clindamycin and 56,426 (95%) received cephalosporins. Cox regression analyses were performed with adjustment for sex, age groups, diagnosis, and ASA score. Survival times were calculated using Kaplan–Meier estimates and compared using Cox regression with revision for PJI as endpoint. The cephalosporins cefalotin and cefazolin were also compared.

Results — Of the TKRs included, 1.3% (n = 743) were revised for PJI. 96% (n = 713) had received cephalosporins and 4% (n = 30) clindamycin for perioperative prophylaxis. Comparing cephalosporins (reference) and clindamycin, at 3-month follow-up the adjusted hazard ratio rate (HRR) for PJI was 0.7 (95% confidence interval [CI] 0.4–1.4), at 1 year 0.9 (CI 0.6–1.5), and at 5 years 0.9 (CI 0.6–1.4). Analysis using propensity score matching showed similar results. Furthermore, comparing cefalotin (reference) and cefazolin, HRR was 1.0 (CI 0.8–1.4) at 3 months and 1.0 (CI 0.7–1.3) at 1-year follow-up.

Conclusion — We found no difference in risk of revision for PJI when using clindamycin compared with cephalosporins in primary cemented TKRs. It appears safe to continue the use of clindamycin in penicillin- or cephalosporin-allergic patients.

Revisions for prosthetic joint infection (PJI) are on the rise [1]. This is not only a health issue with significant patient morbidity and mortality, but also has a substantial financial impact for society. The mean cost of a revision for PJI is between €11,000 and €15,000 in Europe [2].

Prophylactic systemic antibiotics are effective in reducing PJI, however, antibiotics selection remains controversial [3]. Recommendations differ from country to country, with Norway currently recommending cephalosporins (and in the case of penicillin allergy, clindamycin) whereas Sweden recommends cloxacillin preoperatively followed by 3 postoperative doses (and in the case of penicillin allergy, clindamycin) [4,5].

Robertsson et al. [5] found that systemic clindamycin as a prophylactic antibiotic was associated with a higher risk of total knee replacement (TKR) revision for PJI than cloxacillin.

We aimed to investigate whether clindamycin was associated with a higher risk of revision for PJI compared with 1st-generation cephalosporins. Additionally, 2 of the cephalosporins, cefalotin and cefazolin, were compared, to investigate their risk of revision for PJI.

Patients and methods

We identified 83,045 primary TKRs between 2005 and 2020 in the Norwegian Arthroplasty Register (NAR). Fully constrained TKRs (n = 300), unicondylar (n = 9,371), patello-femoral (n = 532), and bi-compartmental knee replacements (n = 2) as well as unspecified TKRs (n = 7) were excluded. Cases with missing information on ASA (n = 1,404) were also excluded. Cases receiving any antibiotic other than cefazolin, cefalotin, or clindamycin, or with missing data were excluded (n = 5,453). Further, uncemented TKRs were excluded (n =
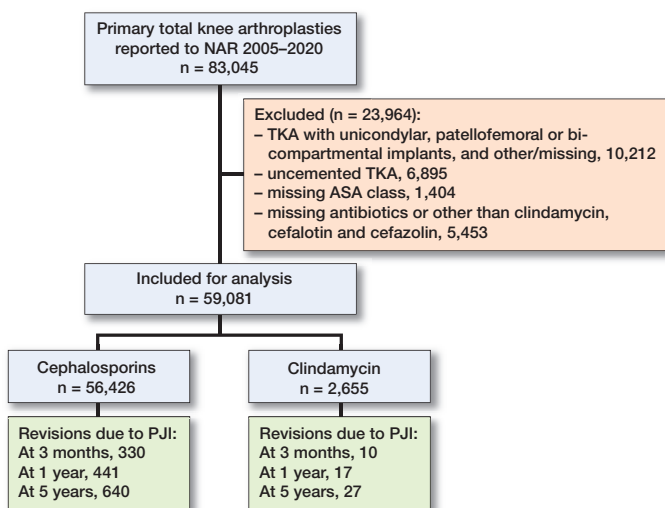
Figure 1. Demographic flowchart.

6,895). This left 59,081 knees eligible for analyses (Figure 1). These were further split up into Period 1 from 2005 to 2012 (n = 22,357) and Period 2 from 2013 to 2020 (n = 36,724), as revisions due to PJI had become more frequent in later years.

59,081 TKRs, in 48,569 patients (82% unilateral, 18% bilateral), reported to the NAR between 2005 and 2020, were included for analyses. Of these, 95% (n = 56,426) received cephalosporins (47,612 received cefalotin, 10,148 received cefazolin) and 5% (n = 2,655) received clindamycin as antibiotic prophylaxis. The majority of clindamycin patients either received 3 doses (41.5%) or 4 doses (45.3%). In the cephalosporin group 86.9% of patients received 4 doses.

The NAR has continuously monitored the quality of knee replacement surgery in Norway since 1994. Both primary and revision operations are reported by the orthopedic surgeons, who fill in a form directly after surgery [6]. Therefore, it is the surgeon who makes the diagnosis of PJI based on the clinical appearance and available evidence at the time of surgery, and the diagnosis is not always based on microbiological results. The results of perioperative cultures taken during the revision were not known at the time of diagnosis. The surgeons are educated to use the definition of PJI as described by the European Bone & Joint Infection Society [7].

The unique personal identification number of each Norwegian resident links information from any subsequent revisions to the primary operation, thus making it possible to trace them [6]. In the NAR's most recent report, it was estimated that 97.7% of all primary TKRs and 93.2% of all revisions taking place in Norway were reported in the years 2017–2018 [6], and this rate had been equally high over the previous years [8].

Statistics

IBM SPSS 25 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. Means, medians, and total numbers of TKRs were analyzed by descriptive statistics. Unadjusted time to event analysis (Kaplan–Meier) was used to calculate survival probabilities with revision due to PJI as endpoint. Comparison of revision risks (expressed as hazard rate ratios, HRR) was calculated using Cox regression, with systemic antibiotic drug as the main exposure. Sex, age groups (< 45, 45–54, 55–74, ≥ 75), diagnosis (osteoarthritis/other), and ASA class (1, 2 and ≥ 3) were used as adjustment factors, as these are known risk factors for infection [9]. BMI was not included as the registration of BMI in the NAR started as late as 2021. We reported the HRR for the clindamycin group compared with the control group (cephalosporin). HRRs and survival probabilities were presented with 95% confidence intervals (CI).

To account for the higher rate of revisions early postoperatively, 3-month, 1-year, and 5-years revision rates were analyzed. The outcome was revision due to PJI. Revision was defined as the exchange, removal, or addition of part of an implant or the whole implant. Sensitivity analysis did not show a change in statistical significance when excluding bilateral TKRs, which were therefore included in the interest of maximum numbers.

To reduce selection bias and correct for known confounding factors, propensity score matching was used for the comparison between clindamycin and cephalosporins. Age, sex, diagnosis, ASA class, and year of operation were used as predictors for calculation of the propensity of receiving treatment with clindamycin. The propensities were based on logistic regressions with the predictors as categorical variables. Cases that received clindamycin (n = 2,655) were matched 1:3, using a tolerance of 0.00001, with the cephalosporin TKRs (Table 1). Unadjusted Cox regression analyses were performed based on the propensity score matched data.

Ethics, funding, and conflicts of interest

Results

Mean age was 68.9 years. 61.4% were female. Osteoarthritis was the most common reason for TKR (89.8%) (Table 1). Median follow-up was 6 years for the cephalosporin group and 5 years for the clindamycin group (Table 1).

73 hospitals had performed primary TKRs and 58 revision TKRs due to infection between 2005 and 2020. Some units have since stopped performing such procedures, whereas

Table 1. Demographic data for cases receiving cephalosporins or clindamycin during primary cemented TKR with non-resurfaced patella in Norway 2005–2020. Values are count (%) unless otherwise specified

Factor	Group 1 (cephalosporin)	Group 2 (clindamycin)	Group 1 [a] (PSM 1:3)
Procedures	56,426 (95)	2,655 (5)	7,896
Revisions	2,641 (4.7)	126 (4.7)	369 (4.7)
due to PJI	713 (1.3)	30 (1.1)	70 (0.9)
Deaths	9,254 (16)	301 (11)	1,167 (15)
Median FU b (CI)	6.4 (6.3–6.4)	5.6 (5.4–5.8)	7.0 (6.9–7.2)
Bilateral TKR	10,200 (18)	521 (19)	1,399 (18)
Male sex	22,321 (39)	664 (24)	1,917 (24)
Age, mean (SD)	69 (9.6)	68 (9.7)	68 (9.6)
Age group			
< 45	623 (1.2)	41 (1.5)	135 (1.7)
45–54	3,397 (6.3)	191 (7.2)	693 (8.5)
55–74	33,523 (63)	1,643 (62)	5,238 (66)
≥ 75	15,990 (30)	626 (24)	1,854 (24)
Missing	2,893 (5.1)	154 (5.8)	
Diagnosis			
Osteoarthritis	51,897 (90)	2,394 (90)	7,116 (90)
Other	5,863 (10)	261 (9.8)	780 (10)
ASA class			
1	7,020 (12)	191 (7.2)	567 (7.0)
2	37,532 (67)	1,777 (67)	5,274 (67)
≥ 3	11,874 (21)	687 (26)	2,055 (26)
Mean operation time, minutes	91	91	91

[a] PSM: propensity score matching, 69 excluded due to missing values.
[b] Median FU: calculated by inverse Kaplan–Meier in years.

Table 2. Kaplan–Meier survival probabilities (KM) and Cox-adjusted relative risk of revision due to PJI expressed as hazard rate ratio (HRR) for patients receiving clindamycin or cephalosporins at primary TKR in Norway 2005–2020

Time	Clindamycin	Cephalosporins
3 months		
Revised due to PJI, n	10	330
KM survival, % (CI)	99.8 (99.6–100)	99.6 (99.6-99.6)
Numbers at risk	2,635	55,876
Cox-adjusted HRR [a] (CI)	0.7 (0.4–1.4)	1
1 year		
Revised due to PJI, n	17	441
KM survival, % (CI)	99.4 (99.2–99.6)	99.2 (99.2–99.2)
Numbers at risk	2,609	55,225
Cox-adjusted HRR [a] (CI)	0.9 (0.6–1.5)	1
5 years		
Revised due to PJI, n	27	640
KM survival, % (CI)	98.9 (98.5–99.3)	98.8 (98.8–98.8)
Numbers at risk	1,468	34,705
Cox-adjusted HRR [a] (CI)	0.9 (0.6–1.4)	1

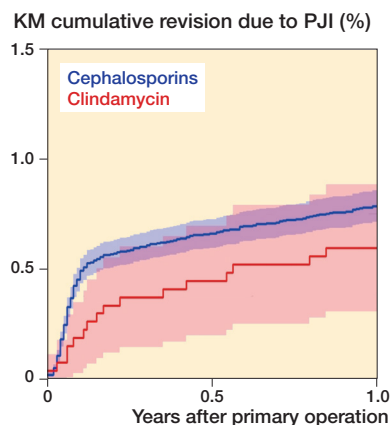[a] HRR: hazard ratio, clindamycin vs. cephalosporins (reference), adjusted for age, sex, diagnosis, ASA class.

Figure 2. Kaplan–Meier cumulative revision due to PJI.

others have started. At any given year, 53–58 units were active. The completeness of the primary TKRs reported to the Norwegian register is high (> 96%).

Incidence of infection was 1.2% in unilateral TKRs (605/48,569) and 1.3% in bilateral TKRs (138/10,512) (not shown in table).

Revision rate cephalosporins vs. clindamycin

1.3% (n = 743) had a revision due to PJI; 96% (n = 713) of these had received cephalosporins and 4% (n = 30) clindamycin for perioperative antibiotic prophylaxis. 5-year mortality was 5.4% for all patients, 4.4% in the clindamycin group, 5.5% in the cephalosporin group. By the end of follow-up, 16.2% of all patients had died (Table 1).

46% of the revisions due to infection were performed within the first 3 months of follow-up and 62% within 1 year of follow-up.

At 3 months, 0.6% (n = 340) were revised due to PJI, 97% (n = 330) had received cephalosporins and 3% (n = 10) clindamycin. The unadjusted Kaplan–Meier survival probabilities free from revision due to PJI were for clindamycin 99.8% (CI 99.6–100) and for cephalosporin 99.6% (CI 99.6–99.6) (Table 2). The adjusted Cox regression analyses confirmed no statistically significant difference with cephalosporins used as the reference category (HRR 0.7, CI 0.4–1.4) (Table 2). At 3 months, there was no statistically significant difference in

Period 1 (HRR 0.6, CI 0.1–2.3) or in Period 2 (HRR 0.6, CI 0.3–1.2).

At 1 year, 0.8% (n = 458) were revised due to PJI; 96% (n = 441) had received cephalosporins and 4% (n = 17) clindamycin during primary operation (Table 2 and Figure 2). Log rank testing with unadjusted Kaplan–Meier analysis showed similar survival probabilities for clindamycin 99.4% (CI 99.2–99.6) and cephalosporin 99.2% (CI 99.2–99.2) (Table 2). Adjusted Cox regression also showed no significant difference (HRR 0.9, CI 0.6–1.5) (Table 2). At 1 year there was no significant difference in Period 1 or in Period 2 (HRR 0.9, CI 0.4–2.3 vs HRR 1.1, CI 0.6–2.0, respectively).

After 5 years, 1.1% (n = 667) were revised for PJI; 96% (n = 640) had received cephalosporins and 4% (n = 27) clindamycin at their primary operation (Table 2). Differences in revision rates were not statistically significant in log-rank testing in unadjusted Kaplan–Meier analysis (clindamycin 98.9%, CI

Table 3. Comparison using propensity score matching dataset (1:3): risk of revision due to PJI for patients receiving clindamycin or cephalosporins at primary TKR in Norway 2005–2020

Time	Clindamycin	Cephalosporins
3 months		
Revised due to PJI, n	10	35
Cox-unadjusted HRR [a] (CI)	0.9 (0.4–1.7)	1
1 year		
Revised due to PJI, n	17	46
Cox-unadjusted HRR [a] (CI)	1.0 (0.6–1.8)	1
5 years		
Revision due to infection, n	27	71
Cox-unadjusted HRR [a] (CI)	1.1 (0.7–1.8)	1

[a] See Table 2

Table 4. Cements used during the primary TKR in Norway 2005–2020

Cement used	Cephalo-sporin	Clinda-mycin	Total
Palacos with gentamicin	840	11	851
Simplex	1	0	1
CMW I with gentamicin	1	0	1
Refobacin-Palacos	847	14	861
Simplex with tobramycin	504	2	506
Copal with gentamicin+clindamycin	2	0	2
Cemex with gentamycin	1936	51	1,987
Palacos R+G	20,779	1,057	21,836
Refobacin Bone Cement R	5,674	206	5,880
SmartSet GHV	15	2	17
Cemex System Genta FAST	211	0	211
Optipac Refobacin Bonecement R	13,307	636	13,943
Refobacin Revision	12	1	13
Optipac Refobacin Revision	9	0	9
SmartSet GHV Genta. Smartmix	2,168	71	2,239
Copal G+ V	30	8	38
Copal spacem	1	0	1
Palacos R+G pro	9,375	571	9,946
Palacos fast R+G	1	0	1
Cemex system genta ID green	3	0	3
Optipac Refobacin Bonecement R-3	585	20	605
Refobacin Revision-3	4	1	5
Refobacin Bone Cement R-3	12	0	12
Missing	109	4	113
Total	56,426	2,655	59,081

Table 5. Types of revision for PJI. Values are count (%)

Type of revision	Cephalo-sporin n = 713	Clinda-mycin n = 30	Total n = 743
Change of femur, tibia or whole prosthesis	63 (9)	5 (17)	68 (9)
DAIR [a]	466 (65)	19 (63)	485 (65)
Addition of patellar component	5 (0.7)	1 (3)	6 (0.8)
Arthrodesis or amputation	6 (0.8)	0	6 (0.8)
Removal of 1 or more parts	190 (27)	8 (27)	198 (27)
Missing information	2 (0.3)	0	2 (0.3)

Surgeons can mark for more than 1 type of revision; hence total numbers and percentages will not add up to the numbers of revision due to PJI.
[a] Debridement, antibiotics and implant retention with change of tibia polyethylene component only.

years (HRR 1.1, CI 0.7–1.8) postoperatively, similar results were found with cephalosporins used as the reference category (Table 3).

Our sensitivity analysis with exclusion of non-Palacos type of cements showed the same results as in the main analysis. A breakdown of types of cement used can be found in Table 4. We have previously investigated the Palacos and Palacos-like cements and have found the same results in these cement types [10].

Cefalotin vs. cefazolin

As cefazolin was introduced in 2017, only revision rates at 3 months and 1 year follow-up could be compared. Cefazolin was used in 20.8% (n = 9,905), of which 1.0% (n = 96) had a revision due to PJI and cefalotin was used in 79.2% (n = 46,521), of which 1.3% (n = 617) had a revision due to PJI. No differences in revision rate for PJI between cefazolin and cefalotin (reference) were found either at 3 months (HRR 1.0, CI 0.8–1.4) or at 1 year (HRR 1.0, CI 0.7–1.3).

Types of revisions for PJI

In the cephalosporin group (n = 713), 65% of the knees had debridement, antibiotics, and implant retention (DAIR) as a surgical procedure, 27% removal of 1 or more parts, 0.8% arthrodesis or amputation, and 0.3% did not have the type of procedure listed. In the clindamycin group (n = 30), 63% of the knees had had a DAIR, 27% removal of 1 or more parts (Table 5).

98.5–99.3 vs. cephalosporin 98.8%, CI 98.8–98.8) or adjusted Cox regression (HRR 0.9, CI 0.6–1.4) (Table 2). There was no significant difference in Period 1 or in Period 2.

Overall, male sex (HRR 2.1, CI 1.8–2.5) compared with females, ASA ≥ 3 (HRR 1.8, CI 1.8–2.5) compared with ASA 1, older age (HRR 1, CI 1–1), and osteoarthritis (HRR 0.7, CI 0.5–0.8) compared with other diagnoses were factors associated with the risk of revision due to PJI.

When comparing the risk of revision due to PJI in propensity score matched knees, the previously defined time points were analyzed with unadjusted Cox regression. At 3 months (HRR 0.9, CI 0.4–1.7), 1 year (HRR 1.0, CI 0.6–1.8), and 5

Discussion

We found no difference in risk of revision due to PJI with the use of clindamycin or 1st-generation cephalosporins as perioperative antibiotic prophylaxis at TKR. This finding diverges from the current view that clindamycin is inferior to cepha-

losporins, a notion that has only been investigated in a small number of observational studies.

Robertsson et al. [5] found an increased risk of revision in TKRs that had received clindamycin compared with cloxacillin. 79% of their revisions were done before 1 year postoperatively, compared with 62% in our study. No demographic table was provided in the paper by Robertsson et al. Hence, we were not able to determine demographic differences between their cases and ours. Prevalence of clindamycin administration was 7.2% in the Swedish study, compared with 5% in our study. The completeness of reporting of revision due to infection is lower than for other revisions in both Norway and Sweden, but there is no reason to believe that the completeness of reporting is different for the clindamycin and cephalosporin knees [9]. The power in our study was somewhat lower than in the Swedish study, but there was a trend towards a lower risk for the clindamycin group.

Dosage of clindamycin did not differ between Sweden and Norway, with the Swedish study reporting the use of 600 mg x 3 in the majority (79%) of their patient group receiving clindamycin, the same dose as in Norway [4,5].

A study from Mayo Clinic, United States, investigated the rate of PJI for both TKRs and total hip replacements (THRs) and compared cefazolin with all other antibiotics that were used at the primary operation [11]. They found that administration of cefazolin at the primary operation reduced the risk of PJI by 32% compared with the "other" group. However, it must be noted that only 28.7% of the cefazolin group and 30.9% of the "other antibiotics" group received antibiotic-loaded bone cement, an option that is standard in most of Europe and less so in the United States. The effectiveness of antibiotic-loaded bone cement in TKRs is disputed, and this matter is currently being studied by the NAR in a register-based nationwide randomized control trial [12]. All TKRs in our study received antibiotic-loaded cement.

The overall number of knees strengthens this study. A total of 58,091 knee operations provides a better evaluation of the general population undergoing TKRs in various settings than randomized control trials, which usually have too few participants and a more strictly controlled environment. Moreover, propensity score matching was used, reducing bias in estimating treatment effects. The propensity score is the probability that a patient would receive the treatment based on the chosen covariates. We split our data into 2 groups, treated with clindamycin or not, and matched individuals with identical propensity scores.

There were, however, limitations that come with any register-based study. Registry data quality can vary depending on the collection method and reporting rates. The NAR has attempted to optimize this by using standardized forms and having a high reporting rate. Dale et al. [13] have reported a rate of 1% of deep surgical site infections as captured by the NOIS (Norwegian Surveillance System for Healthcare-Associated Infections), which is considered the gold standard in Norway, at 1 year after primary THR. As the definition of PJI does not differ between THRs and TKRs in the NAR, we may assume that our results are equivalent to the reporting rate, suggesting that we capture around 80% of PJIs that are reoperated. As the diagnosis of PJI is usually clinical and not always based on bacterial cultures before a revision, misclassification bias is possible.

Another limitation was a potential unrecorded variation in the timing, duration, and dosage regime of antibiotics used, as well as the type of anesthetic used. We know that over 90% of patients receive antibiotic prophylaxis as recommended by national guidelines [6]. However, timing of the preoperative dose is not recorded on the surgeon form. This is a shortcoming, as it has previously been suggested that timely administration of antibiotic prophylaxis contributes to a lower infection risk but is probably the same in both groups [14].

Finally, the relatively small number of revisions due to infection must be noted. Especially at 3 months, there were only 10 revisions in the clindamycin group and 338 revisions in the cephalosporin group. Therefore, in particular our analysis for 3 months postoperatively must be viewed critically, as we had only a small number of clindamycin cases to compare. The confidence intervals in the Cox analyses are generally quite wide, and there is a risk of a type 2 error (not being able to prove a difference that is actually there due to low power).

Conclusion

We found no difference in risk of revision surgery for PJI when using clindamycin compared with cephalosporins in primary cemented TKRs. It appears safe to continue the use of clindamycin in penicillin- or cephalosporin allergic patients.

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