Chapter 3

RSA prediction of high failure rate for the uncoated Interax TKA confirmed by meta-analysis

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Abstract

In a previous radiostereometric (RSA) trial the uncoated Interax tibial components had shown excessive migration compared to HA-coated and cemented tibial components. It was predicted that this type of fixation would have a high failure rate. The purpose of this systematic review and meta-analysis is to investigate whether the RSA prediction is correct.

We performed a systematic review and meta-analysis to determine the revision rate for aseptic loosening of the uncoated and cemented Interax tibial components.

Three studies were included with a total of 349 Interax total knee arthroplasties (TKA) for the comparison of uncoated fixation with cement. There were a total of 30 revisions: 27 uncoated and 3 cemented components. There was a 3 times higher revision rate of the uncoated Interax components compared to cemented Interax components; OR 3 [95% CI 1.4 to 7.2].

The meta-analysis confirms the prediction of a previous RSA trial. The uncoated Interax components showed the highest migration and turned out to have the highest revision rate for aseptic loosening. RSA appears to enable efficient detection of an inferior design as early as 2 year post-operatively in a small group of patients.

Introduction

Aseptic loosening remains a major reason for revision surgery in Total Knee Arthroplasty (TKA).[1,2] Since revision rates are generally low it is necessary to follow up hundreds if not thousands of patients for a long period of time (10 years) to be able to detect inferior designs.[3]

A method for early detection of aseptic loosening exposing as few patients as possible is therefore of value. Radiostereometric analysis (RSA) enables accurate measurement of migration of prosthetic components relative to the bone[4], which has been shown to be associated with late aseptic loosening.[5-7]

Although these findings are promising and the number for RSA studies is increasing, few studies have actually researched whether the RSA predictions are correct.[5-8] In TKA the question thus remains: Do TKA with increased early migration have higher revision rates for aseptic loosening? We have already shown in a randomized RSA trial that uncoated Interax tibial components have increased early migration compared to HA-coated and cemented tibial components.[9] We predicted that the uncoated components would have a high failure rate. The aim of the present study was therefore to investigate whether this prediction of the previous RSA trial is correct. We performed a meta-analysis to evaluate the failure rate of these components.

Methods

Design of the meta-analysis, and rationale

The design is based on the Cochrane standards and reporting of this meta-analysis is according to the PRISMA guidelines.[10] In order to exclude confounding due to differences in prosthesis design, the meta-analysis is restricted to studies comprising exactly the same implant as the previously published RSA-trial[9]: the cruciate retaining (CR) Interax TKA tibial component, (Howmedica / Stryker, Rutherford New Jersey) with two polyethylene halfbearings. The fixation of the components is either by cement or by bone ingrowth on uncoated or hydroxy-apatite (HA) coated prosthetic surfaces. The cemented components had a diamond surface on the side that was within bone, whereas the uncemented components had a mesh-wire surface (2.25 square millimetres corresponding to circular pore diameter of 1690 micrometers) with or without a HA coating.

The outcome of interest is the number of revisions or recommended revisions for aseptic loosening of the tibial component, for each fixation separately. This outcome will be compared to the early migration results of the RSA-trial [9] which showed increased early migration of the uncoated

tibial component compared to the cemented and HA coated tibial components (Figure 3.1). Uncemented components show high initial migration followed by stabilisation.[11-16] Thus, we also present the migration rate of MTPM (mm/year) determined on the migration measured with the post-operative RSA examination as reference (Table 3.1).

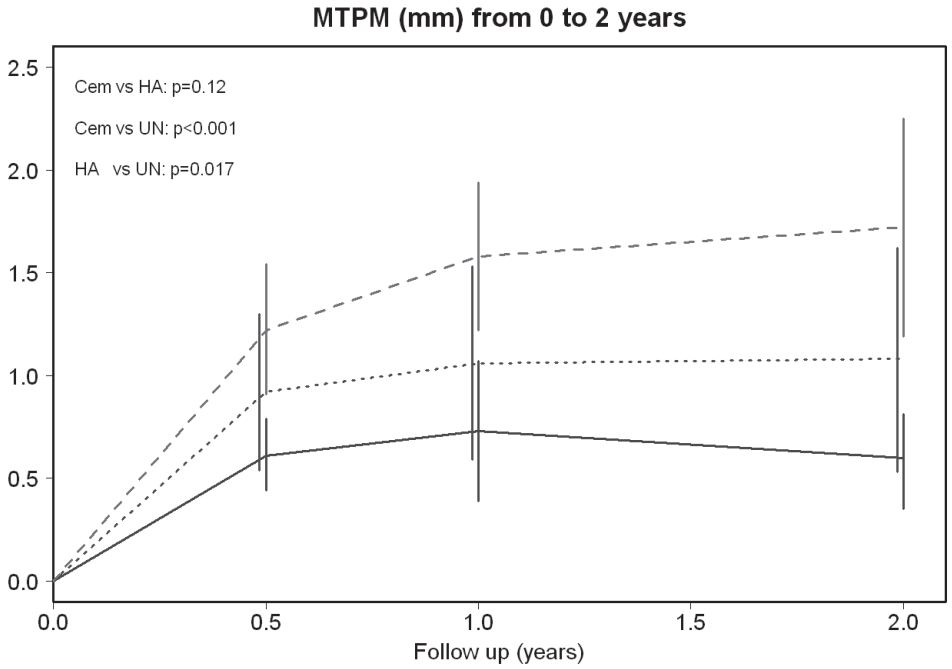

Figure 3.1 Summary of the migration results of the previous RSA trial.[9] The plot shows the mean migration – expressed as Maximal Total Point Motion (MTPM) - with 95% CI for each type of fixation of the tibial components: red dashed line for uncoated; green dotted line for HA-coated and blue solid line for cement. The uncoated tibial components showed the most migration. * mm = millimetre

Literature search

The literature search is the foundation on which a systematic review and meta-analysis is built. Inadequate search strategies have been shown to give biased results.[17] We therefore adopted a thorough search strategy in collaboration with a medical librarian, JWS. The following bibliographies were searched up to and including March 2011: PubMed, EMBASE (OVID version), Web of Science, Cochrane Library, Current Contents Connect, CINAHL (Ebscohost-version), Academic Search Premier (Ebscohost-version). Additionally, the websites of the following medical journal publishers were searched: Elsevier ScienceDirect, WileyBlackwell, Lippincott-Williams & Wilkins, Highwire, Informaworld/ Informahealth, and Springer. To reduce the effect of any publication bias the "gray literature" was searched up to and including March 2011: WHO

International Clinical Trials Registry Platform, clincialtrial.gov and the proceedings of the major conferences (NOF, AAOS, EFORT, ESSKA, ISTA). Furthermore, the bibliographies of included studies were hand searched for relevant publications. Also, various lesser known databases were searched, e.g. ScienceGov and OAIster. Finally, Google Scholar was searched.

The search involved among others the all fields- and fulltext-options to screen if the following component was mentioned anywhere in a manuscript: *"Interax"* and relevant abbreviations and extensions. Since "Interax" is a registered brand name of a particular TKA model, it was assumed to be spelled out the same way in the text of a manuscript irrespective of the language used. We did not use any language restrictions

Table 3.1: Mean migration rate of MTPM expressed in mm / year.

	Cemented		HA-coated		Uncoated	
Migration Rate*	Mean	95%CI	Mean	95%CI	Mean	95%CI
0 to 6 months	1.22	0.88 - 1.57	1.84	1.07 - 2.61	2.45	1.82 - 3.10
6 to 12 months	0.24	-0.34 - 0.82	0.27	-0.02 - 0.57	0.60	0.06 - 1.15
12 to 24 months	-0.12	-0.31 - 0.07	0.03	-0.12 - 0.18	0.19	0.02 - 0.35

* The uncoated components showed the highest migration rate. The migration rate was determined on the migration measured with the post-operative RSA examination as reference.
0 to 6 months: Cem vs HA p= 0.16; Cem vs UN p = 0.01; HA vs UN p= 0.15 (GLMM)

Study selection

All studies were subjected to the following inclusion criteria:

1) The study comprises an original patient cohort treated with the Interax TKA (Howmedica, Rutherford, New Jersey).
2) The cruciate retaining Interax prosthesis with halfbearings is used (Posterior stabilised Interax and Interax ISA versions are excluded).
3) The type of fixation of the tibial component and the number of knees receiving this type of fixation is adequately reported.
4) Number of revisions or recommended revision for aseptic loosening of the tibial component is reported for each fixation separately.
5) At least two fixation types are compared.

Two reviewers, BGP and MJN, independently subjected all studies to these five inclusion criteria. In cases where the title and abstract were inconclusive, the full text article was obtained. Any disagreement between the reviewers was resolved by re-examination and subsequent discussion

to reach a consensus. Randomized Controlled Trials (RCT) as well as observational studies were considered for inclusion.

Quality Assessment and Data extraction

The quality of each included study was independently appraised by two reviewers, BGP and MJN, using the Jadad Scale.[18] The same reviewers independently extracted relevant data for each included study using a standardized form including demographic data, number of TKA in each fixation group, number of revisions for aseptic loosening in each fixation group, and loss to follow up. Any disagreement between the reviewers was resolved by re-examination and subsequent discussion for consensus.

Statistical analysis

Before considering a meta-analysis (pooling of data), we investigated whether it was appropriate to pool the data. Studies should be similar in design and patient population. In addition, the variability in effect size between studies should not exceed those expected from sampling error: low heterogeneity is desirable. Heterogeneity was assessed by calculating the I^2-statistic, which is appropriate in case of a small number of studies.[19] Publication bias was assessed with a funnel plot.[20] Meta-analysis was performed with Peto Odds Ratio (OR) fixed effect pooling and Mantel-Haenszel random effects pooling for the risk difference (RD) and number needed to treat (NNT).[21] The NNT was defined as the number of cemented tibial components that would have to be implanted in order to prevent 1 revision as compared to when uncoated components were implanted. We used RevMan software.

Results

Study selection & study characteristics

The search strategy resulted in 268 unique hits of which 4 studies could be included (Figure 3.2).[22-25] Two papers were published in the English language[23,25], one in German[24] and one in French[22] (Table 3.2). Three studies compared the cemented component to the uncoated one.[22,24,25] One of these studies [24] was part of a thesis [26], which we used for more details. One of these studies[25] was the long term follow-up of the RSA-trial[9] and reported 3 revisions (2 uncoated and 1 cemented) for aseptic loosening of the tibial component.

Since only one study with 18 TKA [23] compared the HA-coated tibial component to the uncoated one, no pooling was performed for this comparison. The funnel plot did not show any publication bias.

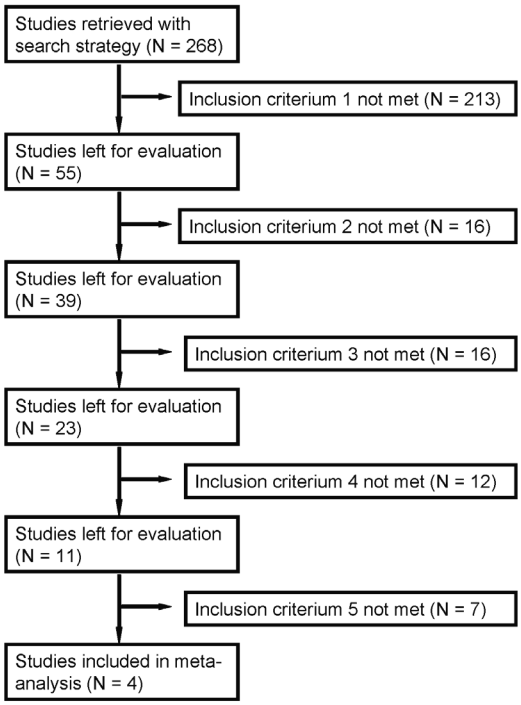

Figure 3.2 Flow diagram providing details on study selection. In case the title and abstract were insufficiently conclusive, the full text article was obtained.

Table 3.2 Characteristics of included studies

	Cemented vs uncoated			HA-coated vs uncoated
Study	Pijls 2011	Gicquel 2000	Stukenborg 2000	Petersen 2005§
Type	RCT	RCT	OBS	RCT
Number TKA	68	96	209	18
females (%)	55 (81)	NS (75)	166 (79)	15 (83)
OA (%)	18 (26)	NS (97)	NS (67)	18 (100)
RA (%)	49 (72)	NS (3)	NS (26)	0 (0)
Mean age at operation (years)	66	73	68	76
Mean FU (years)	7.6	2.3	6.8	2
Operation period	1993-1998	1993-1995	1991-1994	-
Deaths (%)	28 (42)	6 (6)	39 (19)	1 (5.5)
Lost to FU (%)	1 (1.5)	20* (20)	3 (1.4)	1 (5.5)
Jadad Quality Score**	3	3	1	2

*20 cases were lost to follow-up: 8 cemented cases and 12 uncoated cases
** Maximal attainable score is 3 because the evaluation of revision on the x-ray cannot be blinded.
§ Since Petersen et al is the only study evaluating HA-coated versus uncoated and includes only 18 patients, no meta-analysis could be performed for the HA-coated versus uncoated comparison.
RCT = Randomized Controlled Trial
OBS = Observational Study
NS = Not Stated

Uncoated versus cemented tibial component

349 TKA compose the meta-analysis of uncoated versus cemented components. There were 30 revisions of the tibial component for aseptic loosening of which 27 were for the uncoated components compared to 3 for the cemented component.

The odds of revision due to aseptic loosening of the uncoated tibial component was 3.1 times higher as compared to the cemented tibial component: pooled Odds Ratio (OR) 3.1 [95% CI 1.4 to 7.2] (Figure 3.3). The pooled risk difference was 7% [95% CI 3% to 12%] in favour of the cemented component. The number needed to treat (NNT) was 14 in favour of the cemented components [95% CI to 8 to 33]. This means that for every 14 patients treated with a cemented Interax tibial component, 1 revision for aseptic loosening is prevented compared to the uncoated component.

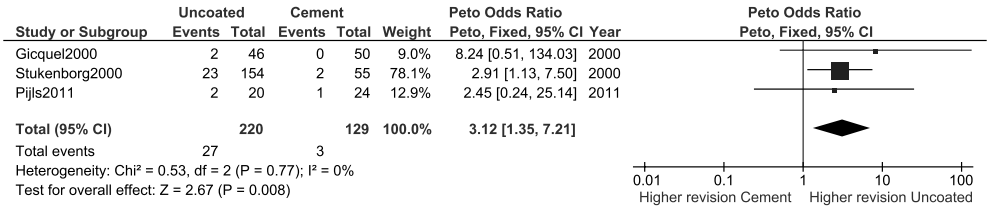

Figure 3.3 Forest plot summarising the pooled effect size of cemented versus uncoated tibial components. As shown there was a significantly 3.1 times higher revision rate for the uncoated Interax tibial components compared to the cemented ones.

Risk of bias within studies

The sequence of randomization as well as concealment of allocation was described and appropriate in two studies.[22,25] In one study [23] randomization was performed but the method and concealment not adequately described and in another study [24] no randomization was performed. In the non-randomized study the decision for implanting either a cemented or an uncoated uncemented tibial component was made by the surgeon during the operation leading to confounding by indication-because cemented components were used for cases with reduced bone quality.[24] This confounding would lead to a possible underestimation of the revision rate of the uncoated uncemented tibial component. Thus, the higher revision rate for the uncoated components compared to the cemented ones may have been an underestimation of the true revision rate.

In all studies blinding was a potential source of bias. Since evaluation of X-rays is essential for the indication of a revision and the presence or absence of cement cannot be masked on the X-ray, blinding – if possible at all– was not performed in any of the studies.

The number of withdrawals and dropouts was adequately described in all studies. The number of lost to follow-up (8 cemented and 12 uncoated) was high in study by Gicquel et al(Table 3.2).[22] All three studies which compared cemented versus uncoated components included all patients consecutively during study inclusion period and thus reduced the possibility of selection bias.[22,24,25]

Discussion

Uncoated versus Cemented Components

Our aim was to investigate whether the predictions of a previous Radiostereometric Analysis (RSA)-trial were correct. Since the uncoated Interax components had shown the highest migration, it was predicted that this type of fixation would have a high failure rate.[9] The results of the meta-analysis show a significant 3 times higher revision rate for the uncoated uncemented component compared to the cemented tibial component. Thus the prediction of the previous RSA-trial was correct: the uncoated tibial components showed the highest migration and had the highest revision rate for aseptic loosening. The uncoated tibial components also continued to migrate after 1 year, whereas the HA-coated components stabilized after 1 year. This is in accordance with a recent report by Wilson et al, who showed that tibial components can give solid fixation despite high levels of initial migration.[27]

In the RSA trial, the high degree of migration of the uncoated uncemented tibial components was identified within 2 years in a small group of 44 patients (24 in the cemented group and 20 in the non-coated group) compared to the 349 in the meta-analysis. This emphasizes the value of RSA for the early detection of inferior TKA designs in a small series of patients.[5-7]

It is noteworthy that none of the individual traditional clinical studies with large numbers of patients and medium term or long term follow-up reported a significant difference in revision rates between the uncoated uncemented and cemented Interax tibial component.[22,24] Only when the results of these studies were combined in a meta-analysis setting did the high revision rate in the uncoated components became clearly visible.

Uncoated versus HA-coated

One of the selected studies compared the uncoated tibial component to the HA-coated component.[23] This study involved only 18 patients followed for 2 years. Because of the short follow-up and small patient cohort it was not appropriate to perform a meta-analysis for the uncoated versus HA-coated components. The uncoated Interax tibial component has been withdrawn from the market after the results of the RSA trial were published. Since the HA-coating migrates less than the uncoated tibial component, a beneficial effect of the HA coating

is expected. Less migration of a HA component compared to the non-coated component for the Interax CR has also been demonstrated by Østgaard et al.[28] Their migration results were similar to those of our RSA trial, despite differences in patient characteristics: all their patients were suffering from osteoarthritis, compared to 30% osteoarthritis and 70% rheumatoid arthritis in our RSA trial.

Strengths and limitations

Our search strategy was thorough and complete. This is underscored by the fact that we found two studies that have been published in non-English literature. Although our research question was highly specialized, i.e. fixation of a single type of TKA, we were still able to include three studies. This is not uncommon for orthopaedic meta-analysis even in Cochrane reviews.[29]

The included studies were of moderate quality mostly due to issues with blinding for the fixation method, which is a general problem of any study comparing cemented with uncemented components and not specific to the present meta-analysis.

Publication bias generally favours the newly introduced treatment[30]: the uncoated uncemented fixation in this case. Since the studies included in this meta-analysis did not find a positive effect for the uncoated components, publication bias was probably not a major factor here. Thus, we are confident that our conclusion is correct: the uncoated tibial component of the Interax has a higher revision rate for aseptic loosening.

The I-statistic was 0%, so there was no indication for statistical heterogeneity. Despite differences in patient demographics, surgical technique or study design all OR's are on the same side, i.e. showed higher –although not individually significantly – revision rates for the uncoated component and this confirms the predictions of the RSA trial.

Future Perspectives

More than a decade ago Liow and Murray [31] and Muirhead-Allwood [32] called for a more evidence-based evaluation and clinical introduction of (new) prosthetic designs and fixations. Malchau [33] proposed a phased evidence based introduction of new designs. Recently, a renewed call for concrete steps has been made towards such a evidence-based clinical introduction.[34,35] A disastrous design can be detected early post-operatively in a small group of patients by RSA, which therefore has the potential to play an important role in the clinical introduction of new models and fixation methods in total knee arthroplasty. For example, in vitro testing machine studies, should be followed by two year RSA studies in small cohorts in different institutions worldwide, followed by larger comparative studies after which introduction to the market can be started.[33] The latter also involving follow-up in national registries. In this way a more phased prosthesis introduction to the market is guarantied, as is currently the standard for pharmacological agents.

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Authors Contributions

The following authors designed the study (SM, BGP, RGN, ERV), designed the search strategy for the literature search (JWS), performed the study selection (BGP, MJN), appraised the quality of the literature (BGP, MJN) analyzed the data (BGP, SM), wrote the initial draft manuscript (ERV, BGP, JWS, MJN) and ensured accuracy of data and analysis (SM, RGN). Critical revision of the manuscript was performed by all authors.

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