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**Mortality after total knee arthroplasty: A systematic review of incidence, temporal trends
and risk factors**

Abstract

Background: To determine a contemporary estimate of the risk of mortality following total knee arthroplasty (TKA), including the identification of temporal trends, common causes, and modifiable and non-modifiable risk factors.

Materials and methods: Systematic review, meta-analysis and meta-regression. Searches of MEDLINE, AMED, CAB Abstracts, Embase, for studies in any language published between 2006 and 2016 reporting 30 or 90 day mortality following TKA, supplemented by contact with authors.

Results: Thirty-seven studies with mortality data from 15 different countries following 1.75 million TKAs contributed to this review. The pooled Poisson-normal random-effects meta-analysis estimate of 30 and 90 day mortality are 0.20% (95% confidence interval 0.17 to 0.24) and 0.39% (0.32 to 0.49). Both estimates have fallen over the study period ($p < 0.001$). **Meta-regression using median year of surgery as a moderator shows that 30 and 90 day mortality following TKA fell to 0.10% (0.07 to 0.14) and 0.19% (0.15 to 0.23) in 2015.** The leading cause of death is cardiovascular disease.

Conclusions: There is a worldwide ongoing secular decline in mortality following TKA. Improved patient selection, perioperative care and a healthy population effect may account for this observation. Efforts to further reduce mortality should be targeted at reducing cardiovascular events following TKA.

Level of evidence: I

Introduction

All surgery carries risk of some kind, including death. Reporting of 30 day mortality is preferred to in-hospital mortality due to differences in hospital discharge practices.^{1,2} Mortality up to 90 days is also widely reported. The rarity of mortality in the immediate postoperative period makes it difficult to investigate. However, risk of death is of paramount importance to patients, their significant others and to healthcare providers. The risk of postoperative death needs to be accurately quantified and conveyed to patients in order to inform decisions about treatment options. In addition, modifiable patient and surgical risk factors should be identified, so that measures can be taken to address them. A study of data between 2003 and 2011 from the National Joint Registry for England and Wales showed a marked decline in mortality following TKA in England and Wales.³

We aim to characterise trends in mortality, identify modifiable and non-modifiable risk factors, and the leading causes of death. We hypothesise that early postoperative mortality following TKA is falling globally and aim to use meta-regression to predict a contemporary estimate of 30 and 90 day mortality.

Materials and methods

The study outcomes of interest to this review were 30 and 90 day mortality following primary TKA. Small studies where no mortality was observed were excluded. Studies presenting only in-hospital mortality, or other timeframes not of interest to this study were excluded. Studies investigating mortality within specific subgroups of the overall population of those undergoing primary TKA were excluded (e.g. simultaneous bilateral TKA, patients undergoing revision surgery, extremes of age, exclusively non-cardiac patients). Studies where hip and knee

arthroplasty mortality data were combined and could not be separated were excluded. To prevent double counting, datasets which were presented in multiple publications were only included once. Numerous studies report data from the American College of Surgeons National Surveillance Quality Improvement Project (NSQIP).⁴⁻⁹ To prevent double counting of NSQIP data within this review, three studies with overlapping data collection periods were excluded from pooled statistical analyses. Unique secondary findings of these studies have however been discussed in the narrative part of this review.

Our review team used a rigorous systematic approach, as described in the Cochrane Handbook¹⁰ and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines,¹¹ for the conduct and reporting of this review. This review was registered on the *** **Blinded by JBJS** *** database following preliminary searches, registration number: *** **Blinded by JBJS** ***.

Search strategy

We searched Ovid MEDLINE 1946 to 16th August 2016, AMED (Allied and Complementary Medicine) 1985 to August 2016, CAB Abstracts 1973 to 2016 Week 31, and Embase 1980 to 2016 Week 33. Searches were performed on 16th August 2016, and included abstracts and studies published in any language. Using controlled vocabulary, we searched the terms, “mortality”, “knee”, and “replacement or arthroplasty”. Given the likely temporal association with mortality, and our aim to provide a contemporary estimate of mortality, searches were subsequently limited to studies published in the period between 2006 and 2016. We also searched the reference lists of articles identified by this search strategy and included additional studies deemed relevant.

Screening

A total of 731 records were identified from searching the literature; two experienced reviewers (***** Blinded by JBJS *****) independently screened the titles and abstracts of these records to identify potentially relevant articles for inclusion in this systematic review. After screening, 37 studies were included in this review.

Data extraction and risk of bias assessment

Data were extracted regarding the proportion of patients who had died at either 30 or 90 days postoperatively. Where adjusted or manipulated mortality data were reported, we contacted authors to request unadjusted rates and those who responded and provided additional data are acknowledged. Study and participant characteristics were also recorded (cohort size, country of study, median year of study data collection, mean age of patients, proportion of female patients, type of database used, inclusion/exclusion criteria, and risk of bias assessment). We also noted the causes of death, risk factors for mortality and other adverse events. The characteristics of included studies are available in appendix 1.

Risk of bias was assessed using relevant parts of the Newcastle-Ottawa Quality Assessment Scale: Representativeness of the exposed cohort, ascertainment of exposure, assessment of outcome, and adequacy of follow up of cohorts. Two authors independently assessed risk of bias (***** Blinded by JBJS *****).

Statistical analysis

We used the median year of data collection for each individual study for pooled analyses. Due to the rarity of mortality as an outcome after TKA, as well as heterogeneity in global healthcare, meta-analyses and meta-regressions were conducted using a Poisson-normal model with random effects. Log transformed incidence rates were used as the effect measure. This approach has been shown to perform well in rare event studies.¹² Effect estimates for individual and pooled studies

are summarised in forest plots and heterogeneity was assessed using the I^2 statistic to quantify inconsistency.¹³ All statistical analyses were performed using the metafor package¹⁴ within the R statistical environment.¹⁵

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses to identify the sources of heterogeneity. Study size (>50,000, <50,000), median year of data collection (<2004, 2004-2006, 2007, >2007), geographical origin (USA, Europe, rest of the world), and health insurance status (Medicare, other) were used to stratify the data in an attempt to identify sources of heterogeneity. Meta-regressions with median year of data collection as a variable were conducted.

Source of funding

No funding was received for this study.

Results

We included 37 studies of mortality after TKA from fifteen different countries in four continents where unadjusted 30 or 90 day mortality rates were recorded or made available by the authors.^{3-9,16-45} Of these, 27 studies published between 2006 and 2016 reported 30 day mortality. Due to overlapping data, 3 were excluded and the remaining 24 of these studies were pooled. These included 1,753,449 TKAs performed between 1991 and 2014. The pooled 30 day Poisson-normal random-effects estimate of mortality over the study period was 0.20% (95% confidence interval 0.17 to 0.24), see figure 1. The pooled 90 day estimate of mortality was 0.39% (0.32 to 0.49), according to seventeen studies published between 2006 and 2016 including 700,981 TKAs performed between 1991 and 2014, see figure 2.

Three studies reported a secular decline in mortality observed within their cohorts.^{3,25,40} Using meta-regression, a strong correlation towards a secular reduction in mortality was observed when the median year of surgery for each individual study was used as a moderator ($p < 0.000005$), see figure 3. **Log transformed incidence rates were used with a Poisson-normal random-effects model to show that 30 day mortality following TKA in 2015 was 0.10% (0.07 to 0.14).**

Heterogeneity fell from 95% to 88% with this model suggesting that significant variation in global healthcare still exists. The trend for 90 day mortality was similar ($p < 0.001$). **Meta-regression modelling shows that 90 day mortality following TKA in 2015 was 0.19% (0.15 to 0.23), see figure 4.**

There were no differences in mortality between continents when meta-regressions included origin of study as a moderator ($p > 0.6$). Controlling for the secular trend towards declining mortality in meta-regressions comparing continent of study further reduced the statistical significance ($p > 0.9$).

The period of increased mortality risk following TKA has been described in four studies.^{3,30,35,45} Risk of mortality is highest in the first ten days³⁰ then returns to preoperative baseline rates within 21 days,³⁰ thirty days,^{35,45} or 45 days.³ Postoperative mortality was five times higher in the first 30 days compared with the same period prior to surgery, and when corresponding 90 day periods were analysed the post-operative mortality rate was double that of the equivalent pre-operative period.³⁵ In a similar study, 30 day mortality for the age category of 61 to 70 years tripled postoperatively from baseline rates.³⁰

Cardiovascular causes, particularly myocardial infarction were cited as the commonest cause of death in all studies where cause of death was reported.^{4,28,35,38,41} Two multivariate adjusted studies identify a prior cardiac event as a significant risk factor for postoperative 90 day

mortality (OR 3.0, 95% CI 1.7 to 5.4),⁴⁰ and 45 day mortality (hazard ratio 3.46, 95% CI 2.81 to 4.14).³ Pulmonary embolus and cerebrovascular accident appear to be the next most common causes of death.^{35,41} With time, other unrelated causes of death become increasingly prevalent. For example, in a study of 90 day mortality, malignancy accounted for 14% of deaths.³⁵ Diabetes mellitus was identified as a medical comorbidity in 18.2% of patients undergoing TKA in a study by Belmont and colleagues from the USA. On multivariate logistic regression analysis, controlling for known risk factors for mortality, a diagnosis of diabetes was still associated with increased odds of mortality (OR = 2.99, 95% confidence interval 1.35 to 6.62).⁴ Seven studies reported increasing age as an independent risk factor for 30 day^{5,30,31,33,45} and 90 day^{36,40} mortality following TKA, when controlling for co-morbidities and other confounders. Male gender appeared to be an important risk factor for mortality at 30 and 90 days **compared with female gender** (odds ratio 1.9 and 1.7, p<0.001), in a multivariate analysis controlling for age and comorbidities in over 200,000 TKAs,⁴⁵ confirmed by similar odds ratios in three other studies.^{30,36,40} Ethnicity did not appear to confer a difference in 30 day mortality,^{19,45} however at longer term follow up (60 to 180 days) lower mortality was observed in Asian patients on multivariate analysis.⁴⁵ Being mildly overweight appeared to confer a protective effect following TKA. Models adjusted for other comorbidities reveal lowest mortality in the BMI category 26-30 kg/m² (hazard ratio 0.69, 95% confidence interval 0.54 to 0.88) when referenced to a normal BMI of 19–25 kg/m².³ Smaller studies have not been able to identify an association between mortality and BMI.^{4,9} Cerebrovascular disease, liver disease and renal disease conferred statistically significant hazard ratios of mortality of 3.4, 7.2, and 2.2 respectively in the study by Hunt and colleagues.³

North America is represented in 21 studies, Europe in 11 studies, Asia in three studies and Australia in two studies.

Overall there was a low risk of bias within the studies included in this review, however most studies were performed in a subset of the overall population undergoing TKA, e.g. Medicare or NHS patients only. A summary of the risk of bias assessment is presented in table 1.

Discussion

This analysis identifies a strong worldwide temporal decline in 30 and 90 day mortality following TKA. Although causality cannot be determined, a possible explanation for this decline may be related to improvements in healthcare over the past twenty years. For this trend towards decreasing mortality to continue, healthcare providers will need to address the major cause of early post-operative mortality, identified as cardiovascular disease in our study.

Another possible explanation for declining mortality could be related to improving health and life expectancy of the population. The study by Hunt and colleagues showed that mortality following TKA fell at a faster rate than that expected when compared with the general population.³ Although the results of our study may indicate improvements in population life expectancy, it appears that this may not fully explain the trends we observe. Other studies comparing postoperative mortality with the general population are at risk of underestimating the risk associated with surgery due to a selection bias towards operating on healthy patients.

Significant variation in the reported mortality following TKA is observed worldwide. This may be due to differences in the underlying populations or the delivery of healthcare. It is unlikely that differences in study design would account for the observed heterogeneity. All of the available studies report retrospective cohorts or retrospective analysis of prospectively collected

data. Although the risk of bias was low in most studies, and it appeared that adequate processes were followed to ascertain the mortality status of patients at 30 and 90 days, there remains a greater potential for under rather than over-reporting mortality. This may have the effect of reducing the mortality estimates we present.

The identification of modifiable risk factors is of paramount importance to healthcare providers, and efforts to address the risk from cardiovascular disease, diabetes and extremes of BMI should be encouraged. The protective effect of being mildly overweight has been identified in studies of mortality in other disciplines and has been termed the obesity paradox.^{46,47} Age and male gender have also been confirmed as independent risk factors for mortality.

In summary, TKA is a safe procedure associated with low rates of mortality. A strong international secular trend towards declining mortality has emerged. Efforts to reduce cardiovascular and diabetes related risks may reduce mortality further.

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Figure Legends

Figure 1: Forest plot of Poisson-normal random-effects model for studies reporting 30 day mortality ordered by median year of study data collection.

Figure 2: Forest plot of Poisson-normal random-effects model for studies reporting 90 day mortality ordered by median year of study data collection.

Figure 3: Meta-regression bubble plot of 30 day mortality against median year of study data collection.

Figure 4: Meta-regression bubble plot of 90 day mortality against median year of study data collection.