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Appendix

Using Cost to Define the Noninferiority Margin

The cost associated with a revision of a total knee replacement varies considerably based on severity/complexity. Using data from 2005-2006 in Bozic et al.[1] estimated that the average total cost of the revision to be $56,087 at the higher end (corresponding to replacement of all primary knee components). We were unable to find published reports of cost associated with antibiotic cement (ABC), but the average cost differential at our institution for a patient with ABC vs. without for a cemented femur, tibia and patella is $308 (2 bags of cement). Holding all other costs for the primary TKA constant, the primary procedure for those receiving ABC would therefore be an additional $308 compared to regular cement.

In order to calculate the noninferiority margin we sought to identify the difference in septic revision rates between regular cement and ABC that would correspond to a cost of ABC being completely offset by the cost of a septic revision (i.e., cost difference of zero between the two treatment groups when factoring costs of both the primary and revision procedures). To calculate the difference, if we assume a 1.000% risk of septic revision in the regular cement group, then the total cost for 10,000 TKA would be $5,608,700 (10,000*0.01*56,087). For there to be a cost difference of close to zero when comparing 10,000 regular cement to 10,000 ABC, we found the septic revision rate for the ABC group would need to be approximately 0.451% ([10,000*308]+[10,000*0.00451*56,087]=$5,609,524). This corresponds to a risk difference of -0.549% (ABC septic revision rate of 0.451% - regular cement septic revision rate of 1%) and is the noninferiority margin used in this study.

Calculating a Risk Difference from Cox Proportional Hazard Models

Noninferiority hypotheses are tested by first estimating survival for the group not receiving antibiotics in cement (NABC) at each of three discrete points in time (90 days, 1 year, 3 years), $\hat{S}_{NABC}(t)$, using a propensity score weighted cement group stratified Cox model. At a fixed time, survival for the group receiving antibiotics in cement (ABC) is calculated by $\hat{S}^{*}_{ABC}(t) = \hat{S}_{NABC}^{\exp(\hat{\beta}(t))}(t)$ and a risk difference is estimated as $\hat{S}^{*}_{ABC}(t) - \hat{S}_{NABC}(t)$. Similarly, a lower bound of the risk difference can be calculated by using the lower bound of the hazard ratio, $\hat{S}^{**}_{ABC}(t) - \hat{S}_{NABC}(t)$, where $\hat{S}^{**}_{ABC}(t) = \hat{S}_{NABC}^{\exp\left(\hat{\beta}(t) - 1.96 * \widehat{SE}\left(\hat{\beta}(t)\right)\right)}(t)$.

We allowed for the possibility that the effect of the cement grouping may not be constant over time, hence our $\hat{\beta}(t)$ notation above. One commonly used approach is a step function for $\hat{\beta}(t)$ using non-overlapping time periods (e.g., (0-1], (1-2]…). However, this is not ideal in the current

study given a desire to estimate risk in overlapping time periods. For example, 90 days is imbedded within 1 year. Therefore, we estimated three separate propensity score weighted Cox models with time-dependent effects (using cluster robust standard errors), in each instance varying the binary partition of time (e.g., 0-90 days vs > 90 days). In this way we are able to obtain the hazard ratio estimates for 0-90 days, 0-1 year, 0-3 years, which are used to for the 90-day, 1-year and 3-year risk difference point estimates/lower bound calculations, respectively. Parameter estimates in these calculations are aggregated across multiple imputed data using Rubin's rule.[2]

Binomial Regression

Binomial regression models with an identity link and cluster robust standard errors can also be used to estimate the risk difference. One drawback of this binary endpoint approach is missing data. Excluded from analyses are implantations not experiencing DSSI or revision due to infection in the 90 days following surgery but who did experience death (n=199), health insurance member terminations (n=237), revision for non-infection related reasons (n=124), or had incomplete follow-up due to surgery occurring after 10/3/2016 (n=3232).This is a substantial loss of information, and even greater for longer duration endpoints, therefore this approach is only adopted for the 90-day infection outcome for the full sample. Using a propensity score weighted binomial regression model with identity link gives a percent risk difference of 0.11%, 95% CI=-0.05%-0.26%, *P* =0.176. These results are comparable to the survival analysis. Again, the value of the lower bound of -0.05% is well above the noninferiority margin.

References

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