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Role of Modifiable Risk Factors in Postoperative Infections, Following Joint Arthroplasty.

Luana Johnson
Lynchburg University, johnson_la@lynchburg.edu

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Luana A. Johnson, MPAS. PA-C

Lynchburg College

Department of Physician Assistant Medicine

Doctor of Medical Science Program

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Abstract

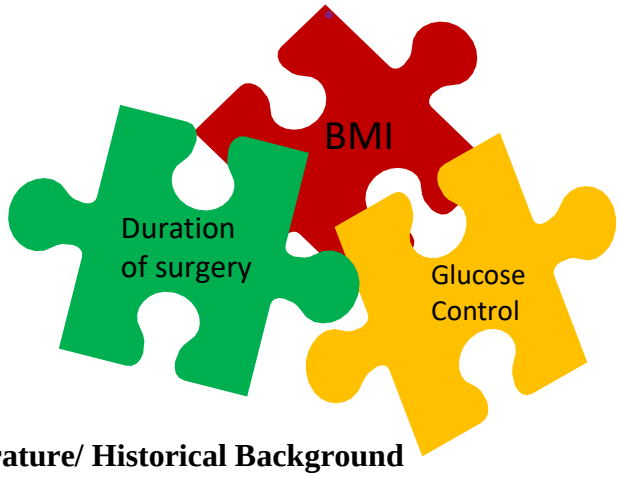
As the American population ages, osteoarthritis (OA) will also have more of an impact. Once, people believed that disability was an unavoidable effect of aging, but this belief as changed as older American expect to stay as active as possible, for as long as possible. These factors have sparked an increased demand for elective total hip arthroplasty, (THA), and total knee arthroplasty, (TKA). These procedures have high success rates and are considered relatively safe and effective[1,2]; "According to the Academy of Orthopaedic Surgeons, (AAOS), serious complications, such as knee infections, occur in less than two percent of patients[3]". However, when infections occur, the results can have devastating consequences for the patients. This project will focus on three modifiable risk factors, that seem to be associated with an increased risk of developing postoperative infections: obesity, poor glycemic control, and long operative times. [4,5,6]

Keywords: postoperative infection, operative time, risk factors, patient and surgical factors, prevention, joint arthroplasty, glycemic control, obesity, BMI.

Introduction

As the American population ages, people are no longer content to remain sedentary, they wish to remain active for as long as possible and continue to enjoy the activities they have always done, such as golfing and walking, without being limited by their osteoarthritis. More and more people are deciding to undergo total hip and total knee arthroplasty. As predicted by Kurtz et.al, (2007), by 2030 the demands for primary total hip arthroplasty is expected to grow by 174% to 572,000.[1] The demand for total knee arthroplasty is expected to grow by 673% to 3.48 million procedures. Hip and knee arthroplasties are successful elective procedures, with greater that 95% survival, at 10-year follow up.[1] Even with conservative figures of only .2-2% [2,7], of these cases going on to develop postoperative infections, this becomes a problem of astounding proportions. The purpose of this paper is to identify patient and surgical characteristics that are more likely to result in postoperative infections. By identifying these traits one can better patient-select candidates for elective joint replacement, follow at-risk patients more closely during their hospital stay, and most importantly try to modify the risk factors themselves. Ultimately, the goal of identifying these patient and modifiable surgical traits that can be modified, will help decrease the number of post-operative infections. Figure 1.

Modifiable Risk Factors to Help Prevent Post-Operative Infections



Review of the Literature/ Historical Background

We live in a current health system, in which reducing complications has become more important than ever, as surgical site infections (SSI) are part reportable hospital-acquired conditions, and their presence can lead to decreased reimbursements.[8,9,10] Medicare reimbursements are often tied in to patient performance, therefore accurate patient selection becomes more essential than

ever. As indicated by this study by Kapalia et al., 2014, when discussing periprosthetic joint infection, following total knee arthroplasty: "The patients who had PJIs had significantly longer hospitalizations[2] (5.3 vs. 3.0 days), more readmissions[2] (3.6 vs. 0.1), and more clinic visits[2] (6.5 vs. 1.3) when compared to the matched group." The mean annual cost was significantly higher in the infected cohort ($116,383; range, $44,416 to $269,914) when compared to the matched group[2] ($28,249; range, $20,454 to $47,957)."

We should also strive be good stewards of medical services, and those resources should be allocated with prudence. Since the introduction of joint replacement procedures, a significant drop in infection was noted with the advent of laminar flow ventilation, using body-exhaust suits, and prophylactic antibiotics.[11] However, there has been little reduction in infection rates since, despite the introduction of new technology e.g. antibiotic-laden cement, preoperative skin preparation, disposable draping, etc. Therefore, let us examine patient and surgical specific risks for developing postoperative infections.

How can one predict which patients are at greater risks for developing post-operative complications? How about a computer program to better predict 30-day complications, following total knee and hip arthroplasty? This study by Edelstein et. al, 2015, attempted to use the American College of Surgeons Risk calculator, (originally used by colorectal surgeons, in 2009), to predict which patients were at greater risk to develop postoperative complications. Basically, the program uses CPT codes for planned procedures and patient specific data, e.g.) age, sex, functional status, wound class, American Society of Anesthesiologist (ASA) class etc., it then returns the risk estimates for complications, as well as well as expected length of hospital stay, and predicted chance of patient needing other than at home discharge from hospital, nursing home, or rehab facility. The study looked at Medicare patient who had undergone elective hip or knee arthroplasty, between 2009-2012, data of the final 1066 patients was then submitted to statistical analysis. The study compared the information obtained from the computer tool to actual rates for those specific complications, and it found that: the risk calculator had "acceptable performance in predicting discharge to nursing home", but was not statistically able to predict postoperative complications,[12] or to link risk for 30 day readmission,[12] when using "narrow Odds Ratio, (OR) or Confidence Interval, (CI), and a strong c-statistic value >.0.8" This might have been because the patient sample was too narrow, the Medicare patients did not have the same characteristics as the ones in this particular setting, the risk calculator lacked variables of relevance to lower extremity arthroplasty, or just not able to predict, based on preoperative data inputted.

As evidenced by the above study, predicting which patients will do well following surgery, vs, those who will have complications, is no easy task. It would be beyond the capabilities of this study to focus on all possible post-operative complications, therefore the author has chosen to focus on post-operative injections, but even here, it is extremely difficult to predict which patients will develop a postoperative infection following lower limb arthroplasty, as dozens of risk factors have been implicated.[13] George et. al., 2017, divided these risk factors into three categories: *1*) patient related risk factors e.g.) sex, weight, co-morbidities, nutritional status, etc., *2*) risk factors related to the surgical environment, such as room temperature/ humidity, operative time, timing of prophylactic antibiotics, etc., and finally, *3*) post-surgical risk factors, such as if the patient received a blood transfusion, or developed post-operative complications like cardiac arrhythmias, or urinary tract infections, (UTIs). As previously discussed, infections, especially peri-prosthetic joint infections (PJI), are difficult to treat, costly, and exert a physical, emotional financial toll on patients, providers, and facilities, therefore prevention is key.

A recent article in the Journal of Arthroplasty looked at the impact of patient and surgical factors on the rate of postoperative infection, after total hip arthroplasty, (THA). Data on 91,585 THAs, performed between 2000- and 2014 were analyzed. Factors associated with periprosthetic joint injections, (PJI), leading to revision of the joint arthroplasty, within a twelve-month period, were identified using univariate analysis. Factors found to be associated ($P<.10$) with revision for PJI at six and twelve months, were then further analyzed to test for independent association, using stepwise multiple logistic regression analysis. Smith et al., (2018), concluded that morbidly obese patients, (BMI over 40), had a "4-fold increased rate of infections",[14] as compared to patients with BMI under 35. This study also found that "obesity was an independent factor,[14] with a 3-fold increased risk of revision in morbid patients compared to those with a BMI under 35 kg/m^2. "One of the strengths of the sheer number of patients analyzed. As for weaknesses, this study was conducted in New Zealand, and looked at data on New Zealanders; this may or may not correlate to American patients. As with all other ethical "harm studies" a randomized control study could not be done, therefore one relies on the statistics.

Another large study, from Korea, also found some of the same risk factors.[15] This was another retrospective cohort study, that looked at data from 26 hospitals participating in the Korean Nosocomial Infection Surveillance System, (KONIS), from 2006-2009, for patients that had undergone total knee, and total hip arthroplasty. They identified surgical site infections (SSIs), in 2.35% of 6,848 cases. Statistical multivariate analysis was then applied to the data. It uncovered that diabetes mellitus, revision surgery, prolonged operative time, (above the 75th

percentile), and need of surgery as result of trauma were independent risk factors for total and severe SSI after THA.[15] (The study also revealed that male sex and operating room without artificial ventilation were independent risk factors for total and severe SSIs, following TKA). This was again a large study, some of the associated weaknesses are inherent to what we're studying; that it does not avail itself to randomized control studies, and again correlation of foreign studies is unknown.

There are literally dozens of risk factors associated with joint arthroplasties, many worthy of their own scholarly paper. The author has chosen to focus on three easily identifiable, and potentially reversible risk factors: Weight and glycemic control are patient-related risk factors, whence length of surgery is, to some extent, a modifiable provider- related risk factor. (For the record, all discussed arthroplasties should be considered primary joint arthroplasties, as revision surgeries have their own distinct characteristics, and are beyond the scope of this project).

Obesity

More people throughout the world are being classified as obese,[16] this is especially a problem in the United States.[17] According to the World Heath Organization (WHO), a body mass index (BMI) of ≥ 30 kg/m^2 is defined as obese, and ≥ 40 kg/m^2 morbidly obese.[18] In 2015, Liu et al., attempted to answer if obesity had a deleterious effect on total hip arthroplasty; earlier studies had yielded equivocal findings, therefore the question of obesity as negatively affecting the outcomes of lower extremity arthroplasty, remained controversial. This was a meta-analysis of prospective cohort studies, in which they searched PubMed, Embase, Web of Science, and the Cochrane Library. They reviewed fifteen different studies, and compared outcomes between those of BMI <30, 30-40, and >40 kg/m^2, they specifically wanted to compare the groups for outcomes in *1*) "overall complication rates: incidence of dislocation, deep infection, and osteolysis", *2*) functional outcome, and *3*) operative time and length of hospitalization. The results as pertinent to infection rates, found that "obese patients, appeared to undergo a higher deep infection rate than non-obese patients,[19] (RR 2.92, 95% CI, CI 0.74-11.49, P=0.13). This study even if not a Randomized Controlled Trial (RCT), was a systematic review, which is as good as it gets, for trying to answer this type of question. Some weaknesses include that the number of THA discussed in each of the fifteen studies ranged from 50-2495, therefore some of these studies had a small number of subjects, some issues such as diabetes, and nutritional status were not accounted for, which might have skewed the results, finally when ten out of the fifteen studies in question were plotted in a funnel plot, a mild asymmetry was detected, which could account for a slight publication bias.

Another recent systemic review and meta-analysis by Sun K, and Li H, 2017, confirmed that as compared with normal BMI patients (≤ 30), patients with higher BMI had an increased risk of postoperative (and perioperative) complications.[20] Another recent multivariate statistical analysis of the New Zeeland Surgical Site Infection Improvement Programme data revealed that there was a significant association between deep infections and BMI >40 kg/m^2(OR 1.7, 95% CI 1.05-2.74), for patients who had undergone THA[21], an similar results for greater chance of deep infection for patients who underwent TKA, and had a BMI >40 (OR 1.94, 95% CI: 0.63-5.70).[21] Some authors speculate that obese patients have more co-morbidities than non-obese patients, thus leading to greater complication rates.[22]

Operative Time

In the surgical field, there has always been an informal belief that complications seem to increase along with operative time, the rationale entails that the longer the patient's open incision is exposed to the environment, the greater the change of bacterial contamination. The author wanted to provide some date to back this belief. In a 2006 article from the Hospital Special Surgery Journal, Peersman et al, (2006), did a retrospective analysis of 6.489 patient, who had undergone total knee replacement surgery, between 1993-1999, 113 infected patients were matched with 236 controls, variables were then statistically controlled. Patients without infections had surgeries that lasted 94 ±28 min., while patients who developed infections had surgical times of 127±45 min.[23] ($p<0.001$). Operation time also had positive correlations with weight ($r = 0.3$, $p < 0.001$,), and with body mass index ($r = 0.3$, $p < 0.001$).[23] This study was interesting because it showed a link between obesity and longer operative time, (which are both independent factors for increased risk of infections), the authors tried to positively compensate for the fact that this was a retroactive cohort study, by matching the infected patients with the controls, as much as they could. One potential weakness is that the study focused solely on patients who had undergone knee arthroplasty at The Hospital for Special Surgery, in NYC. Patients who choose to have surgery in that facility might differ in other respects i.e.) more affluent, better infirmed than the general patient population?

A recent systematic review of the data, by Cheng, Chen et al, 2017, confirmed the earlier Peersman at al. results. They reviewed 81 prospective and retrospective studies, looking at operative duration, and then performed three meta-analyses where odds ratios were pooled by hourly operative time thresholds, increments of operative times, and surgical specialties. Their systematic review showed that in the majority of studies, prolonged surgery was associated with a statistically significant increased chance of SSIs,[24]: 100% (3/3) of RCTs, 89% (16/180 of prospective cohort studies, and 86% (49/57) of retrospective cohort

and case control studies (Cheng & Chen, 2017). (Definitions of "increased operative time" ranged from 11-30%, greater than the mean overall operative time calculated across studies). Pooled analysis revealed that chance of developing a SSI increased by twofold in surgeries exceeding operative cutoff times of two, three, and four hours, and increased by a three-fold in surgeries greater than five hours.[24] Across surgical subspecialties, there was an 80% increase in chance of developing a postoperative infection when surgeries lasted more than three hours.[24] Several other studies noted that an extended operative time was the most important, or only , risk factor for developing post-operative infections.[25,26,27] The Cheng and Chen study also revealed that there was a linear relation between chances of developing a SSI and operative time; the magnitude of the odds ratio increased along with operative time increments[24]: 5% for every 10 minutes of surgery, 13% for every 15 minutes, 17% for every 30 minutes, and a whopping 37% for every 60 minutes of surgery. (Figure 2)

(Figure 2) Chances of Developing a Surgical Infection and Operative Time

Magnitude of Odds Ratio (%)	Operative Time Increments (min)
5	10
13	15
17	30
37	60

Within surgical specialties, some of the highest likelihood effect measures were reported in orthopaedic surgery (odds ratio [OR] of 7.40 if surgery exceeded 3 hours.[28] In conclusion, procedures with longer than expected operative durations (i.e., >95% confidence interval [CI] of expected surgical time), had a significant greater risk of complications, vs. shorter lasting procedures had lower associated risk of complications.[29]

Glycemic Control

Obesity is associated with type II diabetes mellitus; as obesity in this country increases, it also makes sense that more of those obese/ diabetic patients would be potential candidates for lower extremity joint arthroplasty. It's worthwhile to explore how being diabetic and having poor glycemic control, affects the odds of developing a periprosthetic joint injection. Mraovic et.al., 2011, explored whether hyperglycemia and diabetes mellitus were associated with

infection that required surgical intervention, following total knee and hip arthroplasty. They reviewed a computerized database, for patients who had undergone THA and TKA, between 2000-2008. Patients were divided into infected group, (101 patients), and non-infected group, (1,847). The data was then analyzed using t, Chi-squared and Fisher's exact test. The study revealed that the diabetic patients had a much higher rate of infection,[30] (225 vs. 9%, $p < .001$). Infected patients also had significantly higher blood glucose, (BG), levels preoperatively, BG (112 ± 36 vs. 105 ± 31 ml/dl, $p = .043$, and postoperatively, BG (154 ± 37 vs. 138 ± 31 ml/dl, $p = < .001$. "Postoperative morning hyperglycemia, (BG > 200 mg/dl), increased the risk for infection more than two-fold.[30]" Most interestingly, even patients without a history of diabetes, who had postoperative hyperglycemia, had a significant risk for developing an infection.[30] Potential weaknesses arise in that all the information was from patients undergoing joint replacement surgery in one institution, also, it was not known how well matched the two infected and uninfected groups were, in terms of other characteristics.

In 2013, Han SH and Kang SB, looked at wound complications, including early postoperative deep infections, in 167 TKA diabetic patients, and discovered wound complications in 6.6% of patients, and incidence of deep infections in 4.2%; logistical regression revealed that having a preoperative HbA1C ≥ 8 % was an independent risk for developing wound infections[31] (OR 6.07; 95% CI, 1.12-33.0). Another study, by Fisichella et al, 2014, looked at a group of 486 patients who had undergone total knee, or total hip arthroplasty, out of these patients, 84 patients were identified as having a superficial and/or deep surgical site infection were identified and compared them with 203 uninfected patients (control group). The authors looked at diabetes as a risk factor, (BMI, smoking, age, and ASA status were also considered), and upon analyzing the results, discovered that the infected patients had significantly high serum glucose levels (preoperative and postoperative) in comparison with the control group[32] (odds ratio = 8.7). These finding were replicated in 2015, by Reategui D, et al., who found a correlation between postoperative hyperglycemia (glucose>=126mg/dl) in total knee arthroplasty (TKA) patients and greater medical and infectious complications[33]; 11.24% of diabetic patients in the study, with the 126 mg/dl glucose or greater, had postoperative infections[33] (OR 1.76, $p<0.006$).

Limitations

I consider the main limitation of this scholarly project to be the validity and reproducibility of the studies being evaluated by my literature review; as in most "harm" type studies, the methods involved are retrospective and prospective cohort studies, which have been subjected to statistical analysis, therefore it's not always possible to draw direct conclusions from the presented results, as one

might with randomized control studies. One must also accept that the data acquisition was free of bias, that the cohorts were otherwise well-balanced, and that the statistical analysis was fundamentally sound.

Implications for Patient Care

The target population is, of course, the patient undergoing elective, (lower extremity), total joint arthroplasty, for they are the ones ultimately most impacted by the unfortunate occurrence of developing a postoperative infection. Developing a peri-prosthetic joint infection can cause prolonged pain and disability,[34,35] can cause depression, lack of trust in the medical profession, as well as economic burdens.[36,37,38] In older patients, peri-prosthetic joint infections have also been linked with increased mortality rates.[39,40] Identifying patient that may be at greater risk for developing infections would be of great interest to the primary care physicians who are charged with "clearing'' the patient prior to surgery, and to medically manage them postoperatively. Once at-risk patients are identified, they could be medically optimized by better controlling their glucose levels and by initiating weight-loss measures, as needed. Orthopaedic surgeons/ surgical physician assistants would also be greatly interested in the findings of this paper, as they are always striving for ways to maximize surgical outcomes and decrease complications.

Anesthesia providers may be interested in this study, as they manage the patient in the peri-operative period and may provide interventions to minimize/mitigate the effect of these risk factors, (i.e., perioperative hyperglycemia, and possibly aid in decreasing operative times by better pre-operative planning in conjunction with the surgeon, and other members of the surgical team). Finally, this effort may be of interest to hospitals and hospital administrators, as identifying and preventing postoperative infections affects our health care delivery system on many levels: *1*) patient selection; surgeons may choose not to operate on patients that are obese or have poorly controlled diabetes as they're more prone to getting infected, *2*) surgical approval by insurance companies may be denied if patients have these high-risk traits, or delayed until these risk factors are corrected, *3)* Medicare reimbursement rates may be affected by increased length of stay, and re-admissions; as each post-operative joint infection has tremendous economic ramifications.

Conclusion

The demand for elective lower extremity joint arthroplasty is expected to increase, over the next twenty years, as the population continues to age. By 2029, when all members of the baby boomer cohort will be 65 years and over, more than 20 percent of the total U.S. population will be over the age of 65.[41] During

the literature review and discussion sections of this work, the author has hopefully succeeded in presenting high BMI, long operative times and poor glycemic control as independent variables associated with greater chance of developing postoperative infections, following total joint arthroplasty. We have also discussed the physical, emotional and economic damage associated with postoperative infections. Interestingly enough, some studies have also shown these factors to be interrelated: A 2013 study by Liabaud et al. in which 272 patients who had undergone a TKA, showed a direct linear relationship between MBI and operative time[42,43]; for every 1 kg increase in BMI, the operative time increases by 0.933 minute. Many studies have linked obesity to type II diabetes,[44,45,46] which create another level of linkage among these risk factors. The good news is that these factors can be at least partially modified, or its affects mitigated by meticulous pre-operative planning, patient life-style counseling, and pharmaceutical modifications, as needed.

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