Operative Start Time Does Not Affect Post-Operative Infection Risk

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Abstract

Background: Surgical care is delivered 24 h a day at most institutions. Alarming, some authors have found that certain operative start times are associated with greater morbidity and mortality rates. This effect has been noted in both the public and private sector. Although some of these differences may be related to process, they may also be caused by the human circadian rhythm and corresponding changes in host defenses. We hypothesized that the time of day of an operation would impact the frequency of certain post-operative outcomes significantly.

Methods: Cases at a single tertiary-care center reported to the American College of Surgeons National Surgical Quality Improvement Program over a 10-year period were identified. Operative start times were divided into six-hour blocks, with 6 AM to noon serving as the reference. Standard univariable techniques were applied. Multivariable logistic regression with mixed effects modeling then was used to determine the relation between operative start times and infectious outcomes, controlling for surgeon clustering. Statistical significance was set at $p < 0.01$.

Results: A total of 21,985 cases were identified, of which 2,764 (12.6%) were emergency procedures. Overall, 9.7% ($n = 2,142$) of patients experienced some post-operative infectious complication. Seventy percent of these infections ($n = 1,506$) were surgical site infections. On univariable analysis considering all cases, nighttime and evening operations had higher rates of post-operative infections than those in performed during the day (9.1% from 6 AM to noon; 9.7% from noon to 6 PM; 14.8% from 6 PM to midnight; and 14.4% from midnight to 6 AM; $p < 0.001$). On multivariable analysis, operative start time was not associated with the risk of post-operative infection, even when emergency cases were considered independently.

Conclusion: Our data suggest that operative start times have no correlation with post-operative infectious complications. Further work is required to identify the source of the time-dependent outcome variability observed in previous studies.

SURGICAL CARE is provided 24 h a day. Some studies have suggested that the time of day at which a procedure is performed significantly impacts patient outcomes [1–4]. Other studies have not demonstrated an increase in morbidity or mortality rates depending on start times [5–7].

Human beings have circadian variations in several acute illnesses, including ventricular tachyarrhythmia, myocardial ischemia/infarction, and stroke [8]. Small animal models have demonstrated that circadian regulatory mechanisms play an important role in both the humoral and innate immune responses [8–12]. Given the circadian regulation of immune function, studies evaluating surgical time of day and clinically relevant infectious outcomes are surprisingly few.

The purpose of this study was to evaluate the potential role of operative start time on clinically relevant outcomes: 30-

day mortality rate, complications, and post-operative infection. Our hypothesis was that a significant variability in patient outcomes exists depending on the operative start time.

Patients and Methods

The American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) database was queried for all procedures performed between January 1, 2003, and December 31, 2012 at our institution. The ACS NSQIP-defined patient demographics and co-morbidities were recorded. All variables recorded in the ACS NSQIP Risk Calculator were organized according to Bilimoria's description with a few additions and modifications [13]. Hypoalbuminemia (serum albumin < 3.0 g/dL) was recorded. When serum albumin was not available,

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TABLE 1. DEMOGRAPHICS AND CO-MORBIDITIES

	<i>Operative start period (%)</i>				p
	00:00–05:59	06:00–11:59	12:00–17:59	18:00–23:59	
Number	564	12,376	7,779	1,266	
Patient age (y)					
≤64	72.7	69.4	67.4	69.6	0.003 ^{b,d}
65–74	12.9	18.4	18.2	17.1	0.009 ^{a–c}
75–84	11.5	9.8	10.4	9.3	0.004 ^d
≥85	2.8	3.1	4.0	4.0	0.009 ^d
Sex: Female	51.6	58.9	58.3	51.1	<0.0001 ^{a,b,e,f}
Body mass index (BMI)					
Underweight (BMI <18.5)	18.1	5.5	5.9	16.7	<0.0001 ^{a,b,e,f}
Normal weight (BMI 18.5–24.9)	23.6	27.3	27.1	25.8	0.18
Overweight (BMI: 25.0–29.9)	24.7	27.5	27.7	24.3	0.03 ^{e,f}
Obese I (BMI 30.0–34.9)	13.1	16.8	16.4	14.1	0.01 ^{a,b,e,f}
Obese II (BMI 35.0–39.9)	8.2	9.0	8.4	7.2	0.11
Obese III (BMI ≥40.0)	12.4	14.0	14.5	12.1	0.08
Hypertension	41.1	50.7	52.9	47.6	<0.0001 ^{a–f}
Cardiac event	0.9	0.5	0.8	1.5	<0.0001 ^{d–f}
Congestive heart failure	1.6	0.4	0.8	2.0	<0.0001 ^{a,d–f}
Ventilator dependent	5.9	0.5	1.3	5.5	<0.0001 ^{a,b,d–f}
Dyspnea	12.8	21.2	21.5	16.2	<0.0001 ^{a,b,e,f}
Current smoker	27.8	23.9	25.1	29.5	<0.0001 ^{a,e,f}
COPD	5.9	3.8	4.1	5.8	0.001 ^{a,b,e,f}
Diabetes mellitus					
IDDM	7.3	7.2	8.0	7.7	0.15
NIDDM	6.4	10.7	10.7	9.7	0.008 ^{a–c}
Renal Insufficiency	1.2	0.1	0.2	0.9	<0.0001 ^{a,b,d–f}
Hemodialysis	3.9	2.0	2.7	4.4	<0.0001 ^{a,d–f}
Ascites	5.7	1.2	2.2	2.9	<0.0001 ^{a–c}
Corticosteroid use	6.9	5.2	6.4	6.6	0.003 ^{d,e}
Functional status: Independent	77.1	90.1	88.6	76.5	<0.0001 ^{a,b,d–f}
Disseminated cancer	3.9	3.4	3.5	3.6	0.92
Albumin					
Normal (>3.0 g/dL)	71.8	65.8	67.6	67.3	0.002 ^{a,b,d}
Hypoalbuminemic (<3.0 g/dL)	28.2	34.3	32.4	32.7	0.002 ^{a,b,d}
Unknown	12.8	31.2	26.7	18.1	<0.0001 ^{a–f}
Pre-operative infection					
SIRS	19.3	1.4	2.6	10.4	<0.0001 ^{a–f}
Sepsis	7.6	0.8	1.6	6.0	<0.0001 ^{a,b,d–f}
Septic shock	6.2	0.3	1.1	5.1	<0.0001 ^{a,b,d–f}

Categorical variables are listed as N (%).

Listed p values reflect statistical significance of group as a whole. Statistical differences between individual groups are delineated by superscript based on the following key:

a=significant difference between 00:00–05:59 and 06:00–11:59 groups.

b=significant difference between 00:00–05:59 and 12:00–17:59 groups.

c=significant difference between 00:00–05:59 and 18:00–23:59 groups.

d=significant difference between 06:00–11:59 and 12:00–17:59 groups.

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f=significant difference between 12:00–17:59 and 18:00–23:59 groups.

COPD=chronic obstructive pulmonary disease; IDDM=insulin-dependent diabetes mellitus; NIDDM=non-insulin-dependent diabetes mellitus; SIRS=systemic inflammatory response syndrome.

albumin status was marked as “unknown.” The recording of functional status within ACS NSQIP changed over the study period, so this variable was dichotomized to either independent or non-independent functional status. Work Relative Value Units (RVU) were used as a surrogate for case complexity in the absence of Current Procedural Terminology (CPT)-specific linear risk models. Operative duration was recorded in minutes. Operative year was categorized into two-year groups. Operative start times were divided into four six-hour blocks starting at midnight (00:00–05:59; 06:00–11:59; 12:00–17:59; 18:00–23:59). Cardiothoracic and vascular cases were identified by a

single variable. Transplant patients and candidates were similarly identified. The individual surgeons performing each operation were noted, and a random number was assigned to each surgeon to avoid bias. Our outcomes were death within 30 days, any ACS NSQIP-defined serious complication, and any post-operative infection [13].

Standard univariable analysis using χ^2 and Kruskal-Wallis methods was used to compare groups. Multivariable logistic regression was performed on all outcomes using random effects modeling to account for clustering within surgeon. All variables were included a priori to create non-parsimonious

TABLE 2. UNIVARIABLE PROCEDURE DATA

	<i>Operative start time (%)</i>				p
	<i>00:00–05:59</i>	<i>06:00–11:59</i>	<i>12:00–17:59</i>	<i>18:00–23:59</i>	
Emergency	93.8	4.8	10.1	67.2	<0.0001 ^{a–f}
Cardiothoracic or vascular	6.6	14.4	16.7	13.0	<0.0001 ^{a–d,f}
Transplant	0.9	3.4	4.5	1.0	<0.0001 ^{a,b,e,f}
Incision class					
Clean	12.9	51.5	46.2	19.5	<0.0001 ^{a–f}
Clean-contaminated	33.0	39.7	39.9	39.4	0.01 ^{a–c}
Contaminated	20.9	4.3	6.1	15.2	<0.0001 ^{a–f}
Dirty/infected	33.2	4.5	7.8	25.9	<0.0001 ^{a–f}
American Society of Anesthesiologists class					
1	13.3	5.5	4.5	9.2	<0.0001 ^{a–f}
2	34.6	49.1	43.7	34.2	<0.0001 ^{a,b,d–f}
3	32.6	40.7	44.7	39.1	<0.0001 ^{a–f}
4	17.0	4.5	6.8	15.5	<0.0001 ^{a,b,d–f}
Operative Year					
2003–2004	24.3	19.7	18.4	30.4	<0.0001 ^{a–f}
2005–2006	25.2	19.8	19.3	21.3	0.004 ^{a,b}
2007–2008	19.0	20.0	20.5	18.0	0.2
2009–2010	15.8	20.3	20.3	15.5	<0.0001 ^{a,b,e,f}
2011–2012	15.8	20.3	21.6	14.9	<0.0001 ^{a,b,d–f}
Operative duration (min)	81 (55–124)	125 (79–195)	120 (75–180)	86 (54–135)	<0.0001 ^{a,b,d–f}

Continuous variables are listed as median (interquartile range). Categorical variables are listed as N (%).

Listed p values reflect statistical significance of group as a whole. Statistical differences between individual groups are delineated by superscripts based on the following key:

a = significant difference between 00:00–05:59 and 06:00–11:59 groups.

b = significant difference between 00:00–05:59 and 12:00–17:59 groups.

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f = significant difference between 12:00–17:59 and 18:00–23:59 groups.

regression models. Statistical significance was set at $p < 0.01$. All statistical analysis was conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

We identified 21,985 procedures performed by 50 surgeons over a 10-year period. Of these, 2,764 (12.6%) were emergency operations. Only 1,830 (8.3%) of the cases were performed during the night or in the early morning hours. The results of our univariable analysis of patient demographics

and co-morbidities are included in Table 1. Differences in demographics and co-morbidities fell along generally predictable lines. Patients who were operated on during the night or in the early morning hours tended to be more acutely ill and had more pre-operative co-morbidities. Surgical case data are listed in Table 2. Notably, there was a trend toward fewer overnight operations at the end of the study.

Univariable outcomes are listed in Table 3. Not surprisingly, operations performed at night or in the early morning hours had significantly higher rates of any complication, death, and post-operative infection.

TABLE 3. OUTCOMES

	<i>Total</i>	<i>Operative start time (%)</i>				p
		<i>00:00–05:59</i>	<i>06:00–11:59</i>	<i>12:00–17:59</i>	<i>18:00–23:59</i>	
30-Day mortality rate	452	8.2	1.4	2.3	5.0	<0.0001 ^{a–f}
Any complication	3,094	24.1	12.6	14.3	22.5	<0.0001 ^{a,b,d–f}
Post-operative infection	2,142	14.4	9.1	9.7	14.8	<0.0001 ^{a,b,e,f}

Categorical variables are listed as N (%).

Listed p values reflect statistical significance of group as a whole. Statistical differences between individual groups are delineated by superscripts based on the following key:

a = significant difference between 00:00–05:59 and 06:00–11:59 groups.

b = significant difference between 00:00–05:59 and 12:00–17:59 groups.

c = significant difference between 00:00–05:59 and 18:00–23:59 groups.

d = significant difference between 06:00–11:59 and 12:00–17:59 group.

e = significant difference between 06:00–11:59 and 18:00–23:59 groups.

f = significant difference between 12:00–17:59 and 18:00–23:59 groups.

TABLE 4. SELECTED RESULTS OF MULTIVARIABLE REGRESSION MODELS^a

<i>All cases</i>			
<i>Operative start time</i>	<i>30-Day mortality</i>	<i>Any complication</i>	<i>Post-operative infection</i>
00:00–05:59	1.28 (0.72–2.30)	1.07 (0.76–1.50)	0.96 (0.65–1.41)
06:00–11:59	Reference	Reference	Reference
12:00–17:59	1.18 (0.86–1.63)	1.07 (0.95–1.21)	1.03 (0.89–1.18)
18:00–23:59	0.81 (0.49–1.35)	1.08 (0.85–1.38)	1.07 (0.82–1.41)
C statistic	0.86	0.78	0.77
<i>Emergency cases only</i>			
<i>Operative start time</i>	<i>30-Day mortality^b</i>	<i>Any complication</i>	<i>Post-operative infection</i>
00:00–05:59	–	1.03 (0.68–1.56)	0.99 (0.62–1.18)
06:00–11:59	–	Reference	Reference
12:00–17:59	–	1.04 (0.72–1.49)	1.00 (0.67–1.50)
18:00–23:59	–	1.10 (0.76–1.59)	1.13 (0.76–1.70)
C statistic	–	0.78	0.72

^aResults listed as odds ratios with 99% confidence intervals.

^b30-day mortality rate model not completed because of over-fitting.

Selected results of our multivariable analysis are listed in Table 4. After adjusting for pre-operative risk factors, there was no independent association between operative start times and the risk of death within 30 days, any complication, or post-operative infection. The multivariable analysis was repeated post hoc using only emergency operations. Again, we did not identify an independent association between operative start times and the risk of any complication or post-operative infection. We were not able to repeat the analysis for death because of significant model over-fitting with only emergency cases.

Discussion

Several recent studies have highlighted the role that circadian regulation plays in the innate immune response to acute injury and infection. Leukocyte counts differ with the time of day, with peaks during typical periods of rest (at night for human beings and during the day for rodents) [8]. Macrophages exhibit circadian variability in phagocytic activity [9]. One study demonstrated that mice receiving intraperitoneal injection of *Listeria monocytogenes* demonstrate greater bacterial clearance when injected later in the day than in those injected in the early portion of the day [14]. Scheiermann et al. demonstrated that mice receiving a lethal dose of lipopolysaccharide (LPS) exhibit better survival rates when injected during daylight hours rather than at night [15]. A computational model of human endotoxemia similarly suggested that the immune system is most sensitive to LPS around midnight and least sensitive in the early morning [16]. Even for an established infection, the inflammatory response follows a diurnal course, peaking during daylight hours [17]. Our univariable analysis data support the hypothesis of circadian variability in infectious outcomes after surgery. In two studies, Kelz et al. similarly demonstrated significant variation in post-operative infectious complications on univariable analysis but did not evaluate infection as a specific outcome in a multivariable model [2,3]. Infections in their studies remain bundled within the overall morbidity models. After adjusting for co-variables, we did not identify a difference in infectious outcomes based on operative time of day.

Kelz et al. published two studies of the effects of operative start times on outcomes, within the Veterans Affairs system and in the private sector. Both studies demonstrated that for all cases, operative start time was independently associated with increased morbidity but not greater mortality rates [2,3]. However, when subdivided into emergency and elective cases, operative start time was independently associated with the morbidity for emergency cases (but not for elective), as well as deaths for elective, but not emergency, cases [3]. Notably, these studies used different statistical methods: Stepwise regression vs. hierarchical regression with random effects modeling, which may account for the subtle differences between these two analyses. Our findings are more in line with those of Sessler et al. and Tan et al., who did not demonstrate a difference in morbidity or mortality rates with respect to operative start time, season, or moon phase [6,7]. Similarly, George et al. demonstrated no difference in the one-year survival rate of thoracic organ transplantation based on the time of day the transplant was performed [5].

It is worth noting that both of the studies by Kelz et al. had substantially larger sample sizes (>145,000 and >56,000 cases) than either our study or the studies by Sessler, Tan, or George and their colleagues, which each had fewer than 28,000 cases. This result suggests that our study may have been underpowered to detect the differences observed in the analyses by Kelz et al. Assali et al. and Badiyan et al. each demonstrated a time-of-day-dependent variation in outcome with fewer than 500 cases in each, but both these studies focused on a single specific intervention [1,4]. Perhaps if we had narrowed our analysis to a single operation, we might have observed, a significant effect. However, the purpose of this study was to evaluate a large cross-section of surgical procedures. Our data suggest that, in general, there is no difference in the risk according to the operative time of day.

Is operative time of day the correct variable to evaluate the influence of circadian immunologic variation? Lipopolysaccharide, tumor necrosis factor- α , interleukin-1 β , and interferon- γ all disrupt circadian mechanisms [8,9]. These disruptions prolong the rest phase and present as exhaustion

and fatigue in human beings [8]. It is not clear to what degree these feedback mechanisms affect host susceptibility to infection. The timing of a patient's operative intervention may not correlate well with the onset of inflammation or infection, which may have prompted the intervention. It may be reasonable to infer that, in general, a patient's receiving an operation at night or early in the morning causes a greater disturbance in baseline physiologic rhythms than those who receive an operation during the day. This inference may not apply as well to emergency cases. Additionally, we currently have no data to demonstrate any potential circadian rhythm disturbance in this retrospective study, and further evaluation is needed to clarify these relations. However, there is no doubt that surgical intervention is a significant physiologic stressor and represents a marked change from the patient's previous state. Therefore, we believe it is reasonable to use operative time of day to evaluate circadian susceptibility to post-operative infection. Similar studies in the past have focused on the presumed effect of operative time of day on the surgeon. We may not be able to control for the effects of surgeon fatigue, but our use of random intercept modeling helps to minimize the influence of the surgeon on our estimated odds ratios. Ultimately, operative start time may not be the ideal variable to study circadian infectious outcomes, but it is a reasonable place to start. More work is needed to clarify the interaction between our circadian regulatory mechanisms and clinically relevant infectious outcomes.

Our study has several important limitations. First, this is a single-institution study, so our results may not be broadly generalizable. Second, as a retrospective analysis, the results are subject to the observation bias inherent in studies of this type. Third, despite analyzing more than 21,000 cases, our study may have been underpowered to detect more subtle differences in outcomes at our selected statistical threshold. However, if larger samples are required to overcome a type II error, we believe that any effect may have little clinical relevance compared with other patient risk factors.

Conclusion

We performed an analysis of operations performed at a single tertiary-care facility over a 10-year period. Although our univariable analysis demonstrated some degree of variability in post-surgical outcomes depending on the time of day, we did not demonstrate a similar effect with our multivariable analysis. Our data suggest that operative start time is not independently associated with the 30-day mortality rate, any complication, or post-operative infection. Further work is needed to evaluate the role that circadian rhythm plays in surgical outcomes, particularly with regard to infectious complications.

Author Disclosure Statement

The conception and design of the study were performed by CAG and RGS. Data acquisition was the responsibility of CAG. Analysis and interpretation was conducted by CAG and RGS. Manuscript drafting and editing for important intellectual content was carried out by all the authors.

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