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Dose-response association of operative time and surgical site infection in neurosurgery patients: A systematic review and meta-analysis

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Key Words:

Operative time
Surgical site infection
Meta-analysis
Craniotomy**Background:** The association of operative time and surgical site infection (SSI) in neurosurgery patients is unclear. We therefore, through a systematic review and meta-analysis, sought to clarify the association.**Methods:** We performed a systematic search of the PubMed and Embase databases, from January 1, 1966, to December 26, 2018, for published articles. We used random effects generalized least squares regression models to combine study-specific relative risks (RR) and 95% confidence intervals (CI), and performed a sensitivity analysis by excluding 1 study at a time to assess the stability of results and potential sources of heterogeneity. We used the Egger (from plotting to test) to assess publication bias.**Results:** A total of 5 articles, with 231,915 individuals and 6,726 SSI cases, were included. The summary RR for SSI after craniotomy were 1.67 (95% CI, 1.13–2.20), with high versus low operative time, and 1.34 (95% CI, 1.15–1.53), with each 1-hour increase in operative time. On sensitivity analysis, no individual study had an excessive influence on the pooled effect. We found no evidence of publication bias by the Egger test ($P = .464$) and Egger's plotting.**Conclusions:** Prolonged operative time can increase the SSI risk for neurosurgery patients. Intensive interventions should be taken to decrease operative duration.

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A large amount of clinical evidence has demonstrated that neurosurgery could improve neurological outcomes (eg, traumatic brain injury,¹ brain edema,² malignant infarction of the middle cerebral artery,^{3,4} and ischemic stroke⁵) and decrease the associated mortality rate. Generally considered a straightforward surgical procedure, the complications associated with cranioplasty have been underestimated for many years.⁶ Surgical site infection (SSI) is 1 of the most common complications of health care–associated infections, accounting for 31% of all such infections among hospitalized patients.⁷

With neurosurgery, although SSI is relatively infrequent (0.8%–6.6%), its occurrence causes significant mortality, morbidity, and economic burden.^{8–12} In the United Kingdom, a cost analysis of SSI

after craniotomies estimated an additional average cost of £9,283 for each SSI case.¹³ Therefore, identifying people at high risk of SSI is indispensable for effective prevention strategies, which could help halt the inexorable increase in SSI and decrease the cost of health care.

Several factors can contribute to the incidence of SSI. In the meta-analysis reported by Martin et al,¹⁴ of 13 studies, diabetes mellitus was considered an independent risk factor of SSI, with multiple surgical procedure types. A systematic review including 57 studies reported reduced fitness, patient frailty, and complexity as risk factors for SSI.¹⁵ In addition, operative time is mentioned as a significant predictor of SSI in several reviews.^{15–17} In contrast to some factors mentioned previously, operative time represents a modifiable risk factor. However, there is poor understanding and some debate about the relation between increasing operative time and SSI with neurologic surgery.^{11,18} Therefore, we performed the study to review the association between operative time and SSI in neurosurgery patients.

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METHODS

Literature search and selection

To identify potentially relevant studies, we searched PubMed and Embase, from January 1, 1966, to December 26, 2018, restricting the search to studies involving humans and published in English. The main search terms were: 'Infection' AND ('neurosurgery' OR 'craniotomy') AND ('operative time' OR 'operative duration') with the search fields 'title/abstract' and 'MeSH terms.' In addition, we reviewed the reference lists from retrieved articles for other relevant studies.

Studies were included if the exposure of interest was operative time. The outcome of interest was SSI in neurosurgery patients, and adjusted relative risk (RR) or odds ratio (OR) estimates with 95% confidence intervals (CI) were provided. If more than 1 study was found for the same population, only the latest publication was included in the analysis. Two investigators (C.H. and Q.S.) independently conducted the literature search to identify studies.

Data extraction

Two investigators (C.H. and Q.S.) independently extracted the following data from each study: the first author's last name, publication year, country where the study was performed, mean participant age, number of participants and SSI cases, study design, and adjusted RR or OR estimates with corresponding 95% CIs for each category of operative time. For the dose-response analysis, we extracted the number of SSIs and participants as well as RR or OR (95% CI) for each category of operative time. For each study, we assigned the median operative time for each category to each corresponding RR or OR estimate. If the upper boundary of the highest or lowest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. We extracted RR or OR estimates that reflected the greatest degree of control for potential confounders. Last, if study result units were reported in minutes, the results were converted to hours for consistency in presenting results and ease of interpretation.

Studies meeting the above criteria were assessed by the Newcastle-Ottawa Scale, which measures study quality based on selection, comparability, and exposure, giving a maximum of 9 stars.

Statistical analysis

Heterogeneity of studies was estimated by the Q test. A random effects model was used to calculate the summarized ORs and RRs of SSI estimates according to the results of the Q test. If the number of cases in each category was missing, these data were inferred on the

basis of the number of total cases and the reported effect size. Study-specific RR or OR estimates were calculated per 1-hour increase in operative time. Effect measures typically included ORs; however, a small number of studies reported RRs according to the presence or absence of infection. In this meta-analysis, the term "RR" was used as a generic term for ORs and RRs.¹⁹ The DerSimonian and Laird random-effects model was used to pool the study-specific RR estimates per 1-hour increase in operative time. To explore the sources of heterogeneity, we performed subgroup analyses by location, study design, and number of SSI cases. Additionally, we performed a sensitivity analysis by excluding 1 study at a time to assess the stability of results and potential sources of heterogeneity. Publication bias was evaluated by the Egger test and Egger's plotting. Statistical significance was set at $P < .05$. Statistical analyses were performed using Stata (version 12.1 software; Stata Corp LLC, College Station, TX).

RESULTS

Characteristics of studies

Among the 63 articles identified, 5^{18,20-23} were included in the final analysis (Supplementary Fig S1; 231,915 individuals and 6,726 SSI cases). Table 1 shows the study details.

Association between operative time and SSI in neurosurgery patients

The summary RR for high versus low operative time was 1.67 (95% CI, 1.13-2.20), but with substantial heterogeneity ($I^2 = 95.4%$; $P < .001$; Fig 1). The summary RR for SSI after craniotomy was 1.34 (95% CI, 1.15-1.53) for each 1-hour increase in operative time and also with high heterogeneity ($I^2 = 94.6%$; $P < .001$; Fig 2).

Subgroup and sensitivity analyses and publication bias

Table 2 shows the results of the subgroup analyses. In general, the association was consistent in most analyses. The heterogeneity seemed lower for studies with $\geq 1,000$ SSI cases ($I^2 = 0.5%$) and retrospective studies ($I^2 = 0.0$). However, no significant changes of heterogeneity occurred in other subgroup analyses.

In sensitivity analysis, no individual study had an excessive influence on the pooled effect. We found no evidence of publication bias by the Egger test ($P = .464$) and the Begg test.

DISCUSSION

To our knowledge, the present study represents the largest and most comprehensive evaluation of the association between operative

Table 1
Characteristics of included studies

First author	Year	Country	Mean age (years)	N	SSI cases	Study design	Operative time	Adjusted RR (95% CI)	NOS score
Karhade ²⁰	2016	United States	58	132,063	2,377	Prospective study	<82 min	1	8
							82-128 min	1.262 (1.095-1.454)	
							128-200 min	1.444 (1.255-1.661)	
							>200 min	2.035 (1.777-2.330)	
Bekelis ²¹	2016	United States	62.9	94,744	3,885	Retrospective study	<130 min	0.72 (0.61-0.83)	8
							130-163 min	0.82 (0.73-0.93)	
							164-201 min	1	
							202-265 min	1.16 (1.04-1.30)	
							>265 min	2.07 (1.86-2.31)	
Chiang ¹⁸	2014	United States	52	416	104	Prospective study	mean in min	1	7
Hardy ²²	2010	United States	—	114	57	Retrospective study	>225 min	1.6 (0.9-2.6)	7
Korinek ²³	2005	France	51	4,578	303	Prospective study	1 h	1.430 (1.005-2.050)	7
							1 h	1.16 (1.09-1.24)	9

CI, confidence interval; NOS, Newcastle-Ottawa Scale; RR, relative risk; SSI, surgical site infection.

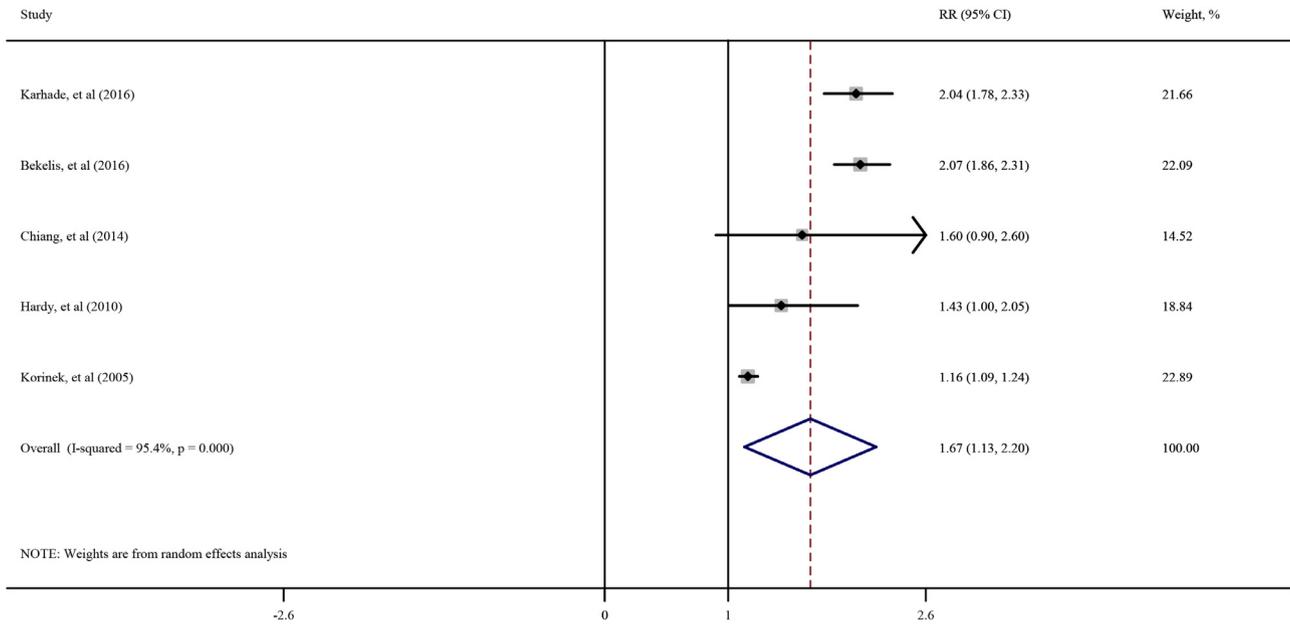


Fig 1. Risk of surgical site infection with high versus low operative time. CI, confidence interval; RR, relative risk.

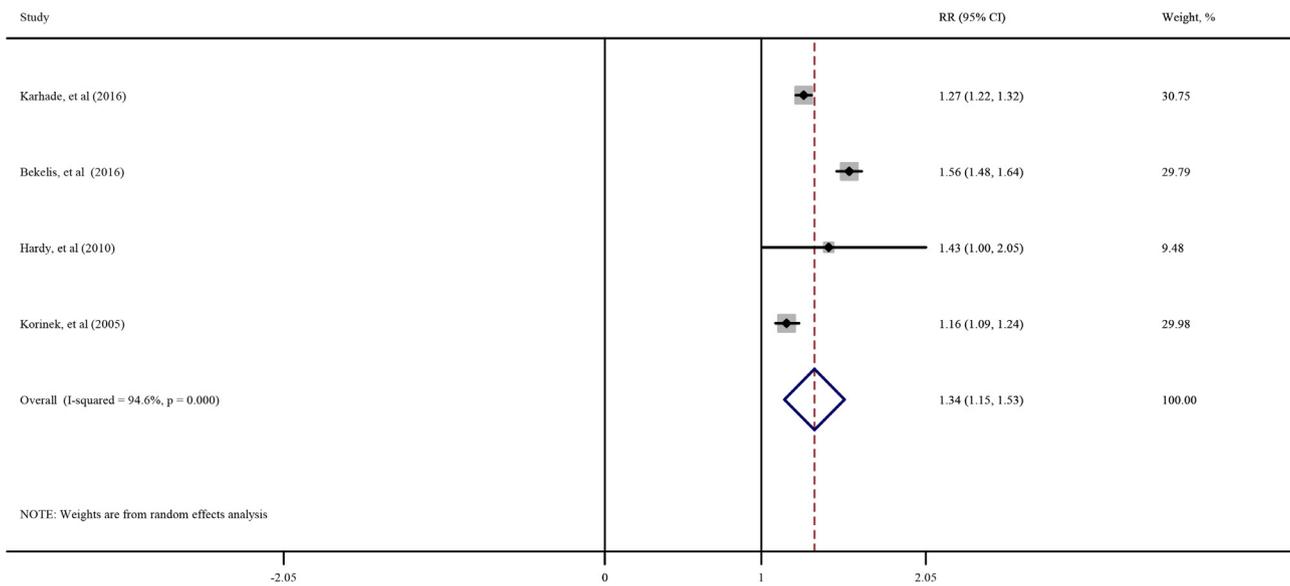


Fig 2. Risk of surgical site infection per 1-hour increase in operative time. CI, confidence interval; RR, relative risk.

Table 2

Dose-response subgroup analysis of operative time and SSI risk in neurosurgery patients

	N	RR (95% CI)	I ² (%)	P value
All studies	4	1.34 (1.15-1.53)	94.6	<.001
Location				
United States	3	1.42 (1.16-1.67)	94.5	<.001
France	1	1.16 (1.09-1.24)	—	—
Study design				
Retrospective	2	1.56 (1.48-1.64)	0	.630
Prospective	2	1.22 (1.11-1.33)	82.5	<.001
Cases				
<1,000	2	1.17 (1.09-1.25)	97.2	<.001
≥1,000	2	1.41 (1.13-1.70)	0.5	.316

CI, confidence interval; RR, relative risk; SSI, surgical site infection.

time and SSI risk in the postoperative neurosurgical population. We found a linear, positive association between increase in operative time and risk of incident SSI after craniotomy, with a 34% increase in RR per 1-hour increase in operative time. Notable, the findings have important clinical implications.

The results are consistent with a meta-analysis that also found a positive association between operative time and SSI risk with neurologic surgery.²⁴ In contrast to the previous meta-analysis,²⁴ we explored the association between operative time and risk of SSI after neurosurgery quantitatively (high vs low, per 1-hour increase).

We recognize that many factors are associated with increased time in the operating room, and although some of the parameters that increase operative time can be modifiable, others may not. Unlike certain neurological patient risk factors, operative time is an independent risk factor for SSI that may be partially modifiable. For

neurological patients with longer targeted or unexpected surgery times, strict adherence to infection prevention measures is essential.^{25–27} A study from the Tennessee Surgical Quality Collaborative demonstrated a greater risk of SSI for procedures with longer-than-expected operative duration and a lower risk for procedures with shorter-than-expected operative duration.²⁸ Preoperative planning, surgical team familiarity, and optimizing work flow can help reduce the time spent during the surgery.^{29,30} Therefore, intensive interventions should be targeted to time of neurologic surgery.

The exact mechanism of increased SSI incidence because of prolonged operative time is not fully understood; however, several studies have provided some suggestions. With increased operative time, open incisions for patients are exposed to the environment longer, therefore, increasing the risk of bacterial contamination. Longer operative time predisposes incisions to tissue desiccation, which may also increase the probability of contamination.^{31,32}

The main strengths of our meta-analysis include numerous, well-established studies from a range of geographic locations; a large number of included participants and SSI events in neurosurgery patients; and detailed adjustment for a wide range of potential confounding risk factors that allowed us to evaluate the independent contributions of different levels of operative time to SSI risk. The included studies were of high quality, and we found no significant publication bias in the included studies.

Some potential limitations of this meta-analysis should be mentioned. Operative duration could be influenced by numerous factors. However, most included studies adjusted for mainly influential factors in the multivariable regression model. Therefore, the effect of operative duration might be relatively limited. Heterogeneity among included studies is unavoidable in all meta-analyses. To discover potential sources of heterogeneity, we performed various subgroup analyses and found the association did not vary by subgroup analysis, which suggests that the findings are robust for SSI. SSI definitions varied between surveillance programs and potentially between hospitals within programs. Despite the different definitions, they have similar ability to predict outcomes influenced by SSI.¹⁶ We did not perform restricted cubic spline analysis because of limited studies. The possible nonlinear associations could be ascertained in further studies.

CONCLUSIONS

This study demonstrates comprehensively that prolonged operative time can increase the likelihood of developing SSI after neurologic surgery. Given the importance of SSIs on patient outcome and health care economics, hospitals should focus on reducing operative time. Intervention strategies should be considered in light of other possible risk factors for SSI.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.ajic.2019.05.025>.

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