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Title

Time to Surgery for Open Hand Injuries and the Risk of Surgical Site Infection: A Prospective Multicentre Cohort Study

Abstract

Whether delaying surgery increases the risk of infection in open hand injuries is an important but unresolved topic. This prospective cohort study included 983 consecutive adults with open hand injuries treated surgically over 1 year. The risk ratio (RR) for surgical site infection was estimated by logistic regression. The median time from injury to surgery was 20 hours (range, 4 -90). Forty-one patients (4%) developed an infection. The risk of infection was not affected by the time to surgery (adjusted RR 1.0 [95% CI: 1.0 to 1.0]) or preoperative antibiotics (adjusted RR 1.8 [95% CI: 0.2 to 13]) which were provided to 95% of patients. Skin loss increased the risk of infection (adjusted RR 2.6 [95% CI: 1.3 to 5.0]). Delaying surgery for open hand injuries by 4 days does not appear to increase the risk of surgical site infection.

Level of evidence: 1

INTRODUCTION

Surgical teaching perpetuates the dogma that traumatic open hand injuries should undergo urgent surgery to reduce the risk of infection. This goal is important because surgical site infection (SSI) is a common and costly complication (Gibson et al., 2014; Zimlichman et al., 2013) occurring after 1-35% of operations for trauma to the hand (Angly et al., 2012; Berger, 2011; Berk et al., 1988; Baker and Lanuti, 1990; Juon et al., 2014; Morgan et al., 1980; Wormald et al., 2017; Zehtabchi et al., 2012).

A recent systematic review showed no association between the time from open hand injury to surgery (in the Emergency Room) and the subsequent risk of SSI (Zehtabchi et al., 2012). However, there were several limitations: the sample sizes of the parent studies were small, which might bias the estimates; few patients were subject to the delays (over 24 hours) that commonly occur in clinical practice; all studies employed arbitrary thresholds of time, which presents a number of statistical issues; and no studies adjusted for potential confounders (Angly et al., 2012; Juon et al., 2014). A more recent study (Pavan et al., 2018) provided important data concerning patients waiting more than 24 hours for surgery after hand trauma. However, it too was weakened by the use of an arbitrary time threshold and did not control for potential confounders. The purpose of the present study was to investigate the association between time to surgery and SSI, whilst avoiding the methodological weaknesses of previous studies.

METHODS

This prospective multicentre cohort study was conducted between 1 April 2018 and 1 April 2019 in two tertiary care Plastic and Hand Surgery centres in the UK.

We included consecutive adults (>16 years of age) with traumatic open unilateral hand injuries distal to the distal wrist crease who underwent surgery. We excluded patients with active infection, burns, an ischaemic digit or hand or amputated part for which replantation / revascularization was attempted.

The primary outcome was surgical site infection (SSI) requiring any form of medical and / or surgical treatment, within 28 days of surgery. This study was designed to investigate whether the time from injury to surgery affects the risk of SSI and consequently data on numerous other exposures and potential confounders were collected in accordance with our protocol including patient demographics, the mechanism and pattern of injury, the preoperative assessment and interim management, operative findings and interventions and the occurrence of any surgical site infection requiring treatment within 28 days. All patients were subject to at least one follow-up wound check postoperatively (between 2 and 10 days, depending on the injury and surgery) by specialist plastic surgery nurses within the hospital; if there were concerns over SSI then a doctor was consulted. If multiple doctors assessed a patient, then the grade of the most senior doctor was recorded. SSI was defined pragmatically and according to the judgement of the assessing doctor. Any of the following were sufficient to define SSI: erythema, swelling and pain beyond that which is expected postoperatively or purulent discharge from the wound,

The protocol specified the analysis of time as a continuous predictor although no such data existed on which to base a power calculation. Therefore, to guide recruitment, our proxy power calculation was based upon prior studies which used arbitrary thresholds of time to define early versus delayed surgery, reporting an approximate 3% difference in infection rates between early and delayed cases(Angly et al., 2012; Berger, 2011; Berk et al., 1988; Baker and Lanuti, 1990; Juon et al., 2014; Morgan et al., 1980; Zehtabchi et al., 2012). So, to detect a 3% difference in the rate of infection between early and late surgical groups, with 90% power, a 5% level of significance and two clusters with an (assumed) intraclass correlation coefficient of 0.1, we estimated that n≈895 individuals would be required.

<u>Statistical analysis</u>

Data were analysed using Stata v15. The overall rate of missing data was <1% with data points missing completely at random. Proportions were compared using the chi-squared or Fisher's exact test when the assumptions of the former were violated. Continuous data were skewed so have been summarized by the median and interquartile range (IQR). Differences in the time to surgery between groups was estimated by non-parametric regression. As the outcome of SSI is rare, we used the risk ratio (RR). Multivariable logistic regression was used to estimate the risk of surgical site infection; the co-variables in the multivariable model were selected according to our protocol and handled as follows: smoking status, a co-morbid diagnosis of diabetes, a dirty wound and the traumatic loss of skin were binary; the mechanism of injury was categorical and time was continuous. In our protocol, preoperative immobilization and topical antiseptic solutions were intended to be in the multivariable model but they had to be omitted because of multicollinearity. Multicollinearity describes a strong correlation between predictor variables, which is undesirable for several reasons. The use of preoperative antibiotics (as a binary variable) was explored as an effect modifier (also known as an interaction term) and visualized through marginal effects plots; in this case the interaction term was used to explore whether antibiotics were specifically beneficial to a subset of patients with delayed surgery, diabetes, skin loss or high-risk mechanisms of injury. There was no adjustment for clustering because estimates from mixed-effects logistic regression (Appendix 1, available online) were not substantially different. The effect of specifying thresholds of times to surgery (24-hour intervals) was explored using restricted cubic splines and no meaningful threshold was identified, so time was modelled linearly. To improve the robustness of the estimates, multivariable models were bootstrapped using lossless non-parametric resampling with replacement, with 1000 iterations. 95% confidence intervals were generated. In order to counteract for problems arising from multiple comparisons, the family-wise error rate was revised down according to Šidák's correction to $p<0.002$.

RESULTS

Overall, 983 patients with surgically managed open hand injuries were included. Table 1 shows the baseline characteristics. Patients more commonly injured the dominant hand (OR 1.5 [95% CI:1.0 to 2.1], p=0.029). The median time from injury to assessment was 3 hours 28 minutes (range, 60 minutes to 46 hours). The median time from injury to surgery was 20 hours (range, 4-90). There was no difference in the time from injury to surgery between groups (Table 2).

Forty-five patients (5%) did not receive preoperative antibiotics. Of the 938 given preoperative antibiotics, 125 (13%) received flucloxacillin, 772 (82%) co-amoxiclav, 26 (3%) clarithromycin and 14 (2%) clindamycin. The provision of antibiotics at the time of assessment was not associated with age (p=0.180), sex (p=0.328), smoking status (p=0.137), a co-morbid diagnosis of diabetes (p=0.681), the mechanism of injury (p=0.147), the cleanliness of the wound (contaminated versus dirty; p=0.760), the number of digits injured (p=0.917) or time from injury to assessment (p=0.359).

Forty-one patients (4%) developed an infection within 28 days of surgery. SSI was most commonly diagnosed by doctors in foundation or core surgical training years (n=26), rather than specialty training registrars (n=8) or consultants (n=7). The treatments for SSIs included a course of oral antibiotics (n=33), admission for intravenous antibiotics only (n=2) or admission for intravenous antibiotics and re-operation (n=6). Multinomial logistic regression showed no statistically significant difference in the treatment strategies of the different grades of doctor who diagnosed SSI. In the 41 patients who developed SSI the microbiological cultures yielded no growth (47%), *Staphylococcus aureus* (43%), *Staphylococcus epidermidis* (5%) and anaerobes (5%).

The time from injury to surgery was not associated with the risk of postoperative infection (Table 3 and Figure 1). Skin loss increased the risk of SSI threefold in both the univariable and multivariable models, suggesting that skin defects might be an important and independent risk factor for surgical site infection. This was observed despite the fact that patients with skin loss were treated surgically 1 hour 45 minutes sooner than others (95% CI: 42 minutes to 2 hours; p<0.001; Supplementary

Figure 1S, available online). The time to surgery was not different for patients with diabetes (median difference 39 minutes [95% CI: -2 hours to 1 hour], p=0.831; Supplementary Figure 2S, available online). The time from injury to surgery was not different between the mechanisms of injury (p=0.620; Supplementary Figure 3, available online). No estimates were substantially altered by bootstrapping.

Overall, we observed no significant interaction between the time to surgery and provision of preoperative antibiotics (adjusted RR 1.0 [95% CI: 1.0 to 1.0]) which means that preoperative antibiotics did not affect the risk of infection after surgery. Furthermore, preoperative antibiotics did not change the risk of SSI in patients with diabetes (Figure 2), different mechanisms of injury (Figure 3) or skin loss (Figure 4). No estimates were substantially altered by bootstrapping.

DISCUSSION

This study shows that the occurrence of infection in open hand injuries managed operatively is low and is in keeping with previous reports (Murphy et al., 2016; Pavan et al., 2018; Zehtabchi et al., 2012). Moreover, delays of up to 4 days from injury to surgery do not appear to increase the risk of surgical site infection. Further, our data show no apparent benefit from preoperative antibiotics and no greater risk of SSI for patients with diabetes or crush injuries, contrary to popular belief. The only factor which appeared to independently increase the risk of SSI was skin loss.

Surgical teaching has perpetuated the concept that early debridement of a traumatic wound reduces the risk of infection. However, a systematic review (Zehtabchi et al., 2012) showed that the time from injury to surgical treatment (in the Emergency Department) was not related to the risk of infection; studies included in this review were of low quality and the findings of each individual were heterogenous, meaning that a robust conclusion could not be drawn. Furthermore, all patients were treated within 24 hours (which does not represent typical practice), surgical treatment in the Emergency Department may not be comparable to surgery within the operating theatre and all included studies had major statistical limitations (principally the use of an arbitrary time cut-off and failure to control for potential confounding). More recently, the work of Pavan and colleagues (2018) addressed the lack of information about surgery more than 24 hours after injury; their retrospective cohort study found the overall infection rate to be low (3%) and suggested that the proportion of patients with SSI was higher in those operated more than 24 hours after injury (5% vs 2%). However, there was again no adjustment for potential confounding, and the chosen cut-off of 24 hours is arbitrary and introduces many well recognized problems. As with previous studies, the dichotomization of a continuous variable (e.g. time in hours) leads to the loss of information, reduction in statistical power and inflates the risk of a Type 1 error. Additionally, dichotomization may misclassify individuals around the cut-off point (e.g. individuals operated at 23.5 versus 24.5 hours after injury are very similar but will be categorized differently by using an arbitrary threshold of 24 hours) and this results in loss of information about the distribution between exposure and outcome (Lang and Altman, 2013). Although Pavan et al. (2018) used a post-hoc Monte-Carlo simulation to estimate the effect of time on infection, with time grouped into 1 hour intervals, a more robust design would measure time as a continuous variable (as we did) and bootstrap the final model to work within the limits of the observed data (Lang and Altman, 2013; Moons et al., 2015). Therefore, our study adds higher quality, prospectively collected data and agrees with the findings of most studies (Zehtabchi et al., 2012) that the time from injury to surgery appears to be unrelated to the risk of infection. Also, we add data to show that SSI appears to be independent of many commonly cited risk factors (Table 3). Nevertheless, we recognize that our sample contained patients with a variety of injuries, that antibiotic use was variable and highly prevalent, and there may be factors which we have failed to consider which might affect the estimates.

The use of perioperative antibiotics did not appear to affect the risk of infection (Table 3 and Figure 4). However, the confidence interval around this adjusted estimate is wide, which is probably because 95% of patients received antibiotics and the rate of infection was small, meaning that the model is likely to be underpowered at this level. To improve the precision of our estimate, we bootstrapped the multivariable model with 1000 iterations although this still yielded null findings; with an allocation ratio of 19:1 any observational study is likely to yield imprecise estimates, so a different design might be needed, perhaps in the form of a randomized trial. Nevertheless, our findings are in agreement with the comprehensive work by Murphy et al. (2016) which, although based on moderate quality evidence, found that antibiotics do not reduce the risk of infection in simple open hand injuries treated surgically. However, several studies (including studies of bites, open fractures and crush injuries) did not meet the inclusion criteria for their review, so translation to other injury patterns may be limited. All patients reported by Morgan et al. (1980), Juon et al. (2014) and Pavan et al. (2018) received perioperative antibiotics and their overall occurrences of infection were 1%, 5% and 3%, respectively. The infection rates in Morgan et al. (1980) and Pavan et al. (2018) are slightly lower than we found and that have been reported in other similar studies. This may be due to several reasons: the lack of information on the pattern of injury and treatment makes inferences difficult (Morgan et al., 1980); and the strict criteria for infection (all four signs of erythema, tenderness, swelling and purulent discharge) applied by Pavan et al. (2018) might underestimate the prevalence of wounds treated for suspected infection in everyday practice. In contrast, the prospective study by Baker and Lanuti (1990) reported that infection occurred more frequently in those treated with antibiotics (4% versus 1%) although this might be explained by their more liberal approach to the diagnosis of infection, which permitted the presence of pus, lymphangitis, cellulitis or increasing tenderness to constitute a diagnosis. Although we have altered the policy concerning the use of pre- and perioperative antibiotics to improve antimicrobial stewardship in our centres, there is still disagreement between hand surgeons about the role of prophylactic antibiotics in open hand injuries. This should be addressed in large-scale, well-designed studies, for the benefit of patients and global health.

We observed several clinically important negative findings about purported risk factors for SSI, which may be due to limitations in the study design. A diagnosis of diabetes was not associated with the risk of infection, which may be a Type 2 error owing to few cases or represent currently improved glycaemic control. We expected crush and bite injuries to confer a higher risk of infection (Henton and Jain, 2012) although this was not observed; however, this area requires further investigation before clinicians alter their practice. We also expected patients with multiple injured digits to be at higher risk of infection although this too was not borne out in the data.

As with any study, we were unable to prevent loss of patients to follow-up but believe this is likely to be small because the prevalence of SSI was in keeping with previous reports (which suggests that most, if not all, patients with hand infections were detected or re-directed to our services). We used a definition of infection which was based on the actions of the treating clinician, which might not represent the true prevalence of SSI in this population and may not be generalizable.

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Figure legends

Figure 1. Boxplot of the incidence of surgical site infection by hours from injury to surgery. The line bisecting the box represents the median, the limits of the box are the interquartile range (IQR) and the whiskers are 1.5 x IQR.

Figure 2. A marginal effects plot showing that the provision of preoperative antibiotics does not affect the risk of surgical site infection (SSI) in patients with or without diabetes. The red and blue lines represent the risk of SSI over time in each group and the coloured regions are their 95% confidence intervals. Note that the difference between the lines is negligible to begin with (<0.01%) and the lines ultimately converge meaning that antibiotics do not reduce the risk of infection over time in diabetics treated surgically.

Figure 3. A marginal effects plot showing that the provision of preoperative antibiotics does not affect the risk of surgical site infection (SSI) in patients with sharp lacerations, crush injuries or bites. The red, blue and green lines represent the risk of SSI over time per mechanism and the coloured regions are their 95% confidence intervals. Note that the difference between the lines is tiny to begin with (i.e. the difference in infection risk between groups is barely perceivable) and ultimately all three lines converge meaning that antibiotics do not appear to affect the risk of infection over time.

Figure 4. A marginal effects plot showing that the provision of preoperative antibiotics does not affect the risk of surgical site infection (SSI) in patients with skin loss. The red and blue lines represent the risk of SSI over time for each group and the coloured regions are their 95% confidence intervals. The difference between the lines is sustained over time which means that skin loss increases the risk of SSI over time; however, the confidence intervals for the effect of antibiotics overlap, meaning that antibiotics do not appear to affect this risk when patients are managed surgically.

Supplementary Figure 1S (available online). Boxplot of the incidence of surgical site infection for with with and without skin loss, by hours from injury to surgery. The line bisecting the box represents the median, the limits of the box are the interquartile range (IQR) and the whiskers are 1.5 x IQR.

Supplementary Figure 2S (available online). Boxplot of the incidence of surgical site infection for with with and without diabetes, by hours from injury to surgery. The line bisecting the box represents the median, the limits of the box are the interquartile range (IQR) and the whiskers are 1.5 x IQR.

Supplementary Figure 3S (available online). Boxplot of the incidence of surgical site infection for the different mechanisms of injury, by hours from injury to surgery. The line bisecting the box represents the median, the limits of the box are the interquartile range (IQR) and the whiskers are 1.5xIQR.