Prevention

1.1. PREVENTION: HOST FACTORS

Authors: Carlos A. Sánchez Correa, Mustafa Citak, Carl Haasper, Niklas Unter Ecker

QUESTION 1: What is the relationship between smoking and infection in fracture procedures? Is smoking history or only current smoking important? Does nicotine cessation at time of fracture reduce complication rates?

RECOMMENDATION: Smoking seems to increase the risk of infection in fracture procedures. The importance of smoking history versus current smoking status is unknown. It is also unknown if nicotine cessation (smoking) at time of fracture treatment reduces complication rates.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Smoking has been seen to have a negative effect in physiological and biological pathways. It interferes with the coagulation cascade (smokers clot faster), it impairs vascular function, and also interferes with the immune system (alters neutrophil function, migration and action) [1–5]. Even after smoking cessation, neutrophil phagocytic function continues to be impaired. Monocyte and macrophage correct function are key to prevent infection caused by *S. aureus* or *E. coli*, two of the most common infection-causing pathogens [3,4]. Smoking also affects the proliferative and remodelling phases of healing [6] by compromising epidermal regeneration and neovascularization and by causing decrease in perfusion and oxygenation [7,8].

The relationship between smoking and complications after fracture procedures has been widely studied [9,10]. Available literature suggests that smoking increases the overall incidence of complications including the risk for non-union and surgical site infection (SSI) [9–14]. Although the latter has not been consistent throughout studies, many authors continue to investigate this relationship.

Some available studies have not found smoking to be a definitive risk factor for infection [9–14]. One case control study that compared 140 smoking and 133 non-smoking patients with open tibia fractures suggested that infection might be multifactorial and not related to a single event [11]. A different prospective cohort study evaluating patients with limb-threatening open tibia fractures showed that current smokers were twice as likely to develop an infection compared to non-smokers (odds ratio (OR) 2.2; $p = 0.05$) [12]. That same study observed that previous smokers, compared to non-smokers, did not show any difference in terms of infection risk (OR 1.00; $p = 0.99$). Court-Brown et al. evaluated 178 patients who underwent fixation after calcaneal fractures [15]. They evaluated factors associated with infection including time to surgery, level of experience of the attending, smoking and type of wound closure. None of these were shown to be associated with infection. A randomized control trial allocated 105 smokers with a fracture requiring surgical treatment to a quit-smoking group ($n = 50$) or a non-quit-smoking group ($n = 55$) [16]. They found that the odds for presenting with a complication (superficial infection being the most common) was 2.51 times higher in the group that continued smoking compared to those who quit smoking, although this did not reach statistical significance. With similar findings, a recent systematic review found that there was no increased risk in smokers either for superficial or deep infection ($p = 0.13$ and $p = 0.33$, respectively) [14]. In terms of deep infection, retrospective studies have evaluated intramedullary nailing of tibia shaft fractures [17], open reduction and internal fixation (ORIF) of pilon fractures [18] and ORIF of acetabular fractures [19]. These concluded that there is no statistical significance related to smoking and increased infection rates. The most recent published study also showed that there was no statistically significant increased risk of infection in relation to smoking ($p = 0.45$) [20].

There is also evidence suggesting that smoking clearly increases the risk of infection in fracture procedures. Nasell et al. [13] evaluated 906 patients with ankle fractures that developed deep wound infections. They reported that these were more likely to be smokers than non-smokers (4.9% versus 0.8%; $p < 0.001$). They concluded that smoking was a risk factor associated with both deep and superficial wound infections (OR 6.0 and 1.7, respectively). Morris et al. [21] published a retrospective cohort study that included 302 bicondylar tibia plateau fractures treated with ORIF. Smoking was identified as the most important risk factor for deep infection (OR 2.40; $p = 0.02$). That same year Ovaska et al. [22] published a prospective cohort study that included 1,923 ankle surgeries with 131 deep surgical site infections. Smoking was shown to be statistically significant relative to infection in both the univariate (OR 4.0; $p = 0.004$) and multivariate analyses (OR 4.1; $p = 0.017$).

Two additional studies evaluated smoking-related complications in lower limb fractures. One consisted of a retrospective cohort study that included 519 patients with distal tibia fractures [23]. Smoking was associated with overall complications including infection (OR 3.40; $p = 0.039$). The second evaluated 30-day postoperative complications after ankle fracture fixation in a prospective cohort study [24]. They concluded that among the predictors for major local complications (deep wound infection and reoperation) peripheral vascular disease, open wound, contaminated wound classification and smoking (OR 2.85; $p = 0.0031$) were the strongest. Evidence from the last two years reveal smoking as an independent risk factor for

wound infection, as presented in a retrospective study managing 1,320 elbow fractures [25] and a case-control study from 318 calcaneal fractures [26]. In the first study, only smoking was found to have an association with infection after multivariate analysis (adjusted OR = 2.2; p = 0.023); the second study revealed that higher body mass index, delayed operation and active smoking (OR 19.497, p < .001) represented an increased risk for wound infection after ORIF.

Despite the conflicting evidence found in the literature, smoking seems to have a negative effect on overall complications and health and could potentially lead to an increased risk of infection. It is well-established that smoking has a detrimental effect on tissue healing and cellular pathways. Nonetheless, the current literature lacks the high-level evidence to state a direct relationship between these two factors. The recommendation provided here is inconclusive.

REFERENCES

[1] Wannamethee SG, Lowe GDO, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J. 2005;26:1765–1773. doi:10.1093/eurheartj/ehi183.

[2] Casey RG, Joyce M, Roche-Nagle G, Cox D, Bouchier-Hayes DJ. Young male smokers have altered platelets and endothelium that precedes atherosclerosis. J Surg Res. 2004;116:227–233. doi:10.1016/S0022-4804(03)00343-3.

[3] Zappacosta B, Martorana GE, Papini S, Gervasoni J, Iavarone F, Fasanella S, et al. Morpho-functional modifications of human neutrophils induced by aqueous cigarette smoke extract: comparison with chemiluminescence activity. Luminescence. 2011;26:331–335. doi:10.1002/bio.1233.

[4] Stringer K, Tobias M, O'Neill HC, Franklin CC. Cigarette smoke extract-induced suppression of caspase-3-like activity impairs human neutrophil phagocytosis. Am J Physiol Lung Cell Mole Physiol. 2007;292:L1572–L1579. doi:10.1152/ajplung.00325.2006.

[5] Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US). How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. 2010.

[6] Wong LS, Martins-Green M. Firsthand cigarette smoke alters fibroblast migration and survival: implications for impaired healing. Wound Repair Regen. 2004;12:471–484. doi:10.1111/j.1067-1927.2004.12403.x.

[7] Sørensen LT, Jørgensen S, Petersen LJ, Hemmingsen U, Bülow J, Loft S, et al. Acute effects of nicotine and smoking on blood flow, tissue oxygen, and aerobe metabolism of the skin and subcutis. J Surg Res. 2009;152:224–230. doi:10.1016/j.jss.2008.02.066.

[8] Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. Ann Surg. 2012;255:1069–1079. doi:10.1097/SLA.0b013e31824f632d.

[9] Fang C, Wong TM, Lau TW, To KKW, Wong SSY, Leung F. Infection after fracture osteosynthesis - part I: pathogenesis, diagnosis and classification. J Orthop Surg. 2017;25:1–13. doi:10.1177/2309499017692712.

[10] Sloan A, Hussain I, Maqsood M, Eremin O, El-Sheemy M. The effects of smoking on fracture healing. Surgeon. 2010;8:111–116. doi:10.1016/j.surge.2009.10.014.

[11] Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. Injury. 2001;32:61–65. doi:10.1016/S0020-1383(00)00121-2.

[12] Castillo RC, Bosse MJ, MacKenzie EJ, Patterson BM, Burgess AR, Jones AL, et al. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. J Orthop Trauma. 2005;19:151–157. doi:10.1097/00005131-200503000-00001.

[13] Nåsell H, Ottosson C, Törnqvist H, Lindé J, Ponzer S. The impact of smoking on complications after operatively treated ankle fractures-a follow-up study of 906 patients. J Orthop Trauma. 2011;25:748–755. doi:10.1097/BOT.0b013e318213f217.

[14] Scolaro JA, Schenker ML, Yannascoli S, Baldwin K, Mehta S, Ahn J. Cigarette smoking increases complications following fracture: a systematic review. J Bone Joint Surg Am. 2014;96:674–681. doi:10.2106/JBJS.M.00081.

[15] Court-Brown CM, Schmidt M, Schutte BG. Factors affecting infection after calcaneal fracture fixation. Injury. 2009;40:1313–1315. doi:10.1016/j.injury.2009.03.044.

[16] Nåsell H, Adami J, Samnegård E, Tønnesen H, Ponzer S. Effect of smoking cessation intervention on results of acute fracture surgery. J Bone Joint Surg Am. 2010;92:1335–1342. doi:10.2106/JBJS.I.00627.

[17] Metsemakers WJ, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. Injury. 2015;46:740–745. doi:10.1016/j.injury.2014.12.018.

[18] Molina CS, Stinner DJ, Fras AR, Evans JM. Risk factors of deep infection in operatively treated pilon fractures (AO/OTA: 43). J Orthop. 2015;12:S7–S13. doi:10.1016/j.jor.2015.01.026.

[19] Li Q, Liu P, Wang G, Yang Y, Dong J, Wang Y, et al. Risk factors of surgical site infection after acetabular fracture aurgery. Surg Infect (Larchmt). 2015;16:577–582. doi:10.1089/sur.2014.134.

[20] Sun Y, Wang H, Tang Y, Zhao H, Qin S, Xu L, et al. Incidence and risk factors for surgical site infection after open reduction and internal fixation of ankle fracture. Medicine. 2018;97:e9901. doi:10.1097/MD.0000000000009901.

[21] Morris BJ, Unger RZ, Archer KR, Mathis SL, Perdue AM, Obremskey WT. Risk factors of infection after ORIF of bicondylar tibial plateau fractures. J Orthop Trauma. 2013;27:e196–e200. doi:10.1097/BOT.0b013e318284704e.

[22] Ovaska MT, Mäkinen TJ, Madanat R, Vahlberg T, Hirvensalo E, Lindahl J. Predictors of poor outcomes following deep infection after internal fixation of ankle fractures. Injury. 2013;44:1002–1006. doi:10.1016/j.injury.2013.02.027.

[23] Ren T, Ding L, Xue F, He Z, Xiao H. Risk factors for surgical site infection of pilon fractures. Clinics. 2015;70:419–422. doi:10.6061/clinics/2015(06)06.

[24] Belmont PJJ, Davey S, Rensing N, Bader JO, Waterman BR, Orr JD. Patient-based and surgical risk factors for thirty-day post-operative complications and mortality following ankle fracture fixation in hospitalized patients. J Orthop Trauma. 2015;29:476–482. doi:10.1097/BOT.0000000000000328.

[25] Claessen FMAP, Braun Y, van Leeuwen WF, Dyer GS, van den Bekerom MPJ, Ring D. What factors are associated with a surgical site infection after operative treatment of an elbow fracture? Clin Orthop Relat Res. 2016;474:562–570. doi:10.1007/s11999-015-4523-3.

[26] Su J, Cao X. Risk factors of wound infection after open reduction and internal fixation of calcaneal fractures. Medicine. 2017;96:e8411. doi:10.1097/MD.0000000000008411.

Authors: Kazuhiko Matsushita, Paul Stangl

QUESTION 2: What is the role of nutritional supplementation (NS) in avoiding infection in acute fracture cases?

RECOMMENDATION: (1) Evidence does not support the role of NS for avoiding infections in well-nourished individuals. (2) However, the literature has stated that in patients with a nutritional deficiency or catabolic state restoring nutritional parameters might reduce the risk of infection.

LEVEL OF EVIDENCE: (1) Limited, (2) Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Evidence in the available literature demonstrats that malnutrition is a significant clinical and public health problem. Several clinical trials present NS as a global effort in medicine, with applications in different specialties to improve the general condition of patients