Biomedical Research 2017; 28 (4): 1883-1889 *ISSN 0970-938X*
www.biomedres.info

The effects of preoperative smoking cessation on the healing of fractures and postoperative complications: A systematic review and meta-analysis.

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Abstract

Introduction: Smoking is a known risk factor for fracture healing and postoperative complications. However, most evidence upon the association between bone healing and smoking was investigated in retrospective studies or laboratory-based animal studies. This meta-analysis evaluated the clinical efficacy of preoperative smoking cessation on the healing of fractures and postoperative complications.
Evidence acquisition: MEDLINE, EMBASE, CNKI and the Cochrane Database were retrieved for identifying relevant study. Four studies, including three Randomized Controlled Clinical Trials (RCTs) and one Non-Randomized Concurrent Controlled Trial (NRCCTs), involving a total of 510 patients, were included.
Evidence synthesis: In the patients with preoperative smoking cessation, the risk of overall postoperative complications was lower (Risk Ratio (RR) 0.37; 95% Confidence Interval (CI) 0.26 to 0.52; P=0.49) when compared with the patient without smoking cessation. Preoperative smoking cessation reduced the risk of wound-related complications ((RR) 0.21; 95% (CI) 0.11 to 0.39; P=0.42), recurrent surgery ((RR) 0.23; 95% (CI) 0.08 to 0.67; P=0.42) and additional complications ((RR) 0.41; 95% (CI) 0.25 to 0.67; P=0.85). One NRCCT showed that the risks of fracture non-union (P=0.03) and osteomyelitis (P=0.49) in the patients with preoperative smoking cessation were reduced.
Conclusion: Our study supports the role of preoperative smoking cessation on orthopaedic surgery outcomes.

Keywords: Preoperative smoking cessation, Fractures healing, Postoperative complications, Meta-analysis.

Accepted on October 3, 2016

Introduction

Smoking continues to induce serious health consequences worldwide. A large amount of evidence supports the fact that smoking is associated with chronic diseases and cancer [1]. Similarly, smokers have been observed to have higher rates of fracture non-union and other serious postoperative complications [2,3]. Additionally, a recent estimate of worldwide health-related costs has showed that smoking related complications caused $193 billion extra costs, annually [4]. In orthopaedic surgical procedures, the effects of smoking on bone healing and postoperative complications are inconsistent. There were non-significant trends between increased hospital stay and fractures union, increased postoperative rates of superficial and deep infections [5]. Smoking cessation is widely believed to be an effective measure to decrease the incidence of postoperative complications including: general morbidity, wound complications, general infections, pulmonary complications, neurological complications, and admission to the Intensive Care Unit (ICU) [6,7]. Furthermore, longer periods of smoking cessation provide better surgery outcomes [8]. During the last few years, some researches have shown that smoking cessation improving bone healing and reducing preoperative complications in various orthopaedic surgical procedures [2,3,9,10]. Following the recent evidences in the published literature, we investigated the associations between smoking cessation and the healing of fractures and the development of postoperative complications by conducting a meta-analysis of Randomized Controlled Trials (RCTs) and Non-Randomized Concurrent Control Trial (NRCCT).

Evidence Acquisition

Literature search

A systematic search of the databases MEDLINE, EMBASE, China National Knowledge Infrastructure (CNKI) and the Cochrane Database for all the original published studies was conducted up to February 2016. The flow of selecting studies

for this systematic review and meta-analysis is shown in Figure 1. The relevant search terms were 'smoking' and 'cessation'; 'smoking' and 'abstinence'; 'cigarette' and 'cessation'; 'postoperative' or 'pre-operative'; 'bone' and 'healing'; 'fracture' and 'healing' or 'complications'. All manuscripts were reviewed to select those that met the requirements.

Study selection

Published studies were eligible for meta-analysis if they met the following criteria: (1) Type of research: Randomized Controlled Trials (RCTs) and Non-Randomized Concurrent Control Trial (NRCCT); (2) Participants: patients who underwent orthopaedic surgery including open reduction and internal fixation, hip or knee arthroplasty and who had a record of smoking status and history; (3) Intervention: preoperative smoking cessation, including all types of preoperative smoking cessation therapy; (4) Outcomes: radiologically-confirmed union of fracture. Overall rates of preoperative complications and the incidence of each complication were described; (5) full texts should be available.

Data extraction

The following information was independently extracted by two authors, including basic information (including authors and year of publication), study design, fracture location, treatment method (operation technique and others), number of participants, interventions, smoking status, history of diseases, preoperative smoking cessation period and follow-up duration. Disagreements were resolved by consensus.

Cochrane collaboration's tool was used to assess the risk of bias in each RCT, to provide a qualification of risk of bias. For analysis of the NRCCTs, we used the Methodological Index for Non-Randomized Studies (MINORS) guidelines to assess the methodological quality [11]. The MINORS guidelines consisted of 12 indexes: every item has two scores and the total score is 24; when the score is $\geq$ 16 points this indicated a high quality study; otherwise the quality was low (<16 points).

Levels of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rate the level of evidence and strength of recommendation [12]. GRADE profiler 3.6 software was used to create the evidence profile.

Evidence synthesis

All statistical analysis was performed using the Cochrane Review Manager 5.3 software to generate forest plots and assess the heterogeneity of the included studies. The effect was measured as Risk Ratio (RR) with 95% Confidence Intervals (CIs), and pooled estimates were computed according to a fixed-effects model. Chi^2 and I^2 statistic were used to qualified heterogeneity, so that $I^2 \leq 25\%$ and Chi^2 ($P>0.5$) indicated no evidence of heterogeneity. Sensitivity analysis was performed to explore possible explanations for heterogeneity. The robustness of the main results was tested by removing each single study in turn. The results from only RCTs were pooled by meta-analysis to ensure appropriate statistical outcomes analysis both clinically and statistically.

Results

Search results

We identified seven potentially relevant studies including 5 Randomized Controlled Trials (RCTs) and 2 Non-Randomized Concurrent Control Trials (NRCCT) of preoperative smoking cessation and bone healing. Of these seven studies, three were excluded because the operative procedure contained not only orthopaedic procedures but also general surgery or other surgical procedures [6,7], or the patients undergoing orthopaedic surgery were second-hand smokers [13]. The four left studies [2,3,9,10] including three RCTs and one NRCCT were chosen for the final analysis (Figure 1). The characteristics and quality assessment of each study are presented in Table 1.

These four studies were performed in the USA [2], Denmark [9], Sweden [3], and China [10], respectively, during the period between 2002 and 2014. The total number of patients in each study ranged from 105 to 187. The quality of each RCT was assessed by the Cochrane bias risk assessment tools (Table 2). According to the Methodological Index for Non-Randomized Studies (MINORS) evaluation criteria [11], only the NRCCT scored 20 points. The items of deduction were summarized as follows: 1) loss rate in the follow-up was greater than 5% in both 'preoperative smoking cessation' group (14.6%) and the 'continued smoking ' group (23.8%); 2) no prospective calculation on the sample size (Table 3).

Overall incidence of postoperative complications

Meta-analysis of the three RCTs [3,9,10] was performed using a fixed-effects model ($P=0.49$; $I^2=0\%$). The results of overall incidence of postoperative complications shown that there were the patients with preoperative smoking cessation did not have an overall increased rate of postoperative complications. Moreover, it was significantly lower compared with the patients without preoperative smoking cessation (RR, 0.37; 95% CI, 0.26-0.52; $P<0.01$; Figure 2).

Rate of wound-related complications

Meta-analysis of wound-related complications in three RCTs [3,9,10] was performed using a fixed-effects model ($P=0.42$; $I^2=0\%$). The results showed that wound-related complications (including: haematoma, superficial infection, subfascial infection) of patients with smoking cessation was significantly lower compared with the patients without smoking cessation (RR, 0.21; 95% CI, 0.11-0.39; $P<0.01$; Figure 3).

Rate of secondary surgery

Meta-analysis of the secondary surgery rate of the three RCTs [3,9,10] was performed using a fixed-effects model ($P=0.42$; $I^2=0\%$). The results showed that the smoking cessation

significantly decreased the secondary surgery rate (RR=0.23; 95% CI, 0.08-0.67; P<0.01; Figure 4).

Rate of other postoperative complications

Meta-analysis of other postoperative complications rate of the three RCTs [3,9,10] was performed using a fixed-effects model (P=0.85; I^2=0%). The patients with preoperative smoking cessation had a lower incidence of other postoperative complications (including: respiratory insufficiency, cardiovascular insufficiency, renal insufficiency, gastrointestinal bleeding, deep venous thrombosis and pulmonary embolus) compared with the patients without smoking cessation (RR, 0.41; 95% CI, 0.25-0.67; P<0.01; Figure 5).

Rate of fracture non-union and osteomyelitis

The NRCCT [2] showed that the patients with preoperative smoking cessation had a lower incidence of fracture non-union than the patients without preoperative smoking cessation (RR=0.46; 95% CI, 0.23-0.93; P=0.03). In addition, the incidence of osteomyelitis was lower in the patients with preoperative smoking cessation compared with the patients without preoperative smoking cessation, although this difference was not statistically significant (RR=0.78; 95% CI, 0.39-1.56; P=0.49).

GRADE profile evidence

The included RCTs had same outcome indicators which were overall incidence of postoperative complications, rate of wound-related complications and rate of secondary surgery. In addition, the rate of fracture non-union was determined in NRCCT. Table 4 shows the outcome levels classified by GRADE system.

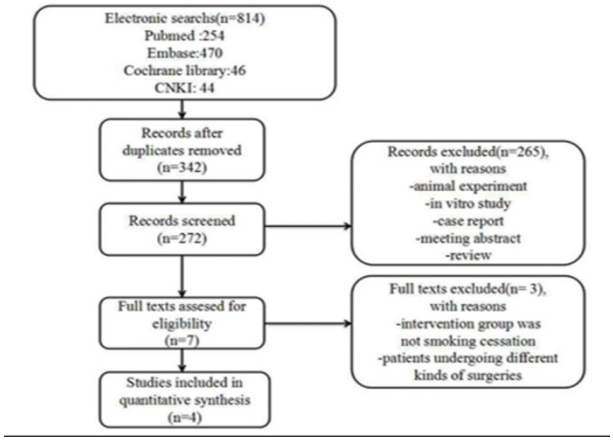

Figure 1. *Flow chart of the literature search and selection process.*

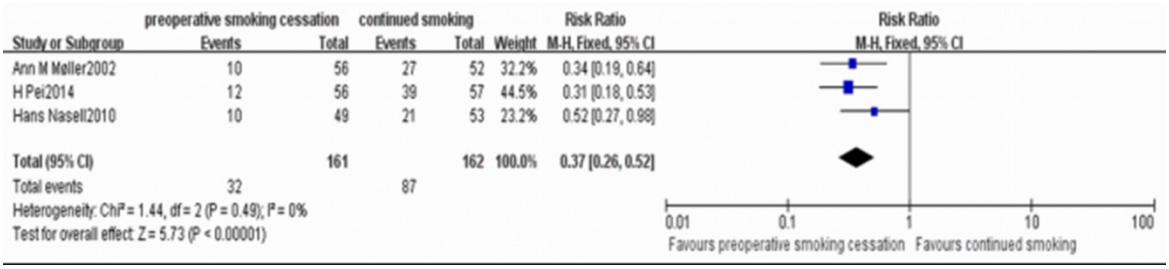

Figure 2. *Forest plot of Risk Ratio (RR) with confidence intervals for overall postoperative complications.*

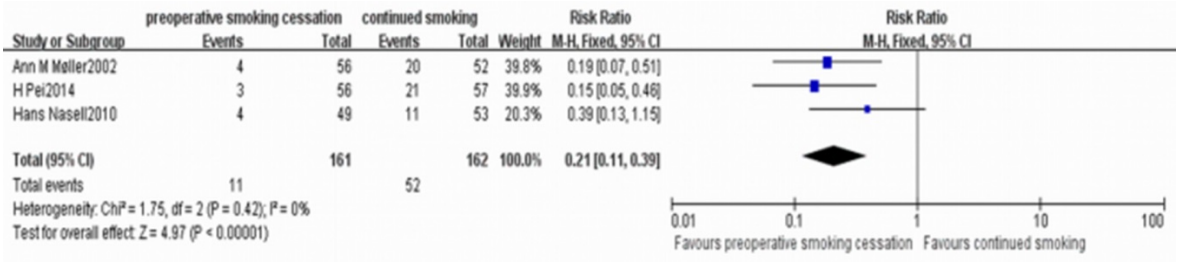

Figure 3. *Forest plot of risk ratio (RR) with confidence intervals for wound-related complications.*

Table 1. *Characteristics of included studies.*

First author	Study design	Surgery/ Fracture location	Treatment method (operation technique and others)	No.of patients	Male sex (%)	Mean age (y)	Smoking status	Interventions	Preoperative smoking cessation period	History of disease	Follow-up period post-surgery
Moller	RCT	Knee Hip	Knee/hip replacement	108	43	IG: 66 (41-83)	IG:15 (5-30)	IG: received smokers smoking	6-8 week	Chronic heart disease	4 week

						CG: 64 (30-85)	cigarettes per day; (11-65) pack years[#] CG:15 (3-30)cigarettes per day; (1-102) pack years	cessation 6-8 week preoperatively CG: smokers did not receive any intervention before surgery		Chronic obstructive Lung disease Diabetes mellitus	
Nasell	RCT	Ankle Hip Tibia/knee Foot Upper extremity	Open reduction internal fixation Closed reduction internal fixation Closed reduction external fixation Hip/Shoulder arthroplasty	104	30	IG: 54.7 ± 2.2 CG: 51.5 ± 2.0	IG: 21.5 ± 11.8 cigarettes per day; 12.8 ± 5.7 pack years CG:21.5 ± 16.2 cigarettes per day; 13.2 ± 6.3 pack years	IG: smokers received smoking cessation 6 week preoperatively CG: smokers did not receive any intervention before surgery	6 week	Heart disease Lung disease Diabetes mellitus Depression High blood pressure	12 week
Pei	RCT	Knee Hip	Knee/Hip replacement	113	100	IG: 67 ± 8 CG: 65 ± 9	IG: 15 cigarettes per day; 35 pack years CG: 15 cigarettes per day; 37 pack years	IG: smokers received smoking cessation 4 week preoperatively CG: smokers did not receive any intervention before surgery	4 week	Chronic heart disease Chronic obstructive lung disease Diabetes mellitus	Not reported
Castilo	NRCCT	Lower extremity below the distal femur excluding foot	Fracture debridement Antibiotic coverage Fracture stabilization Early soft tissue coverage Stimulation procedures[§]	187	73	33.4	IG: ex-smoker CG:100 or more cigarettes over the course of one's lifetime	IG: information on time since quitting smoking was not quantitative[$] CG: smokers did not receive any intervention before surgery	Month/decades	Not reported	2 years

IG: preoperative smoking cessation group; CG: continued smoking group;#: smoking years × daily consumption=20; §: bone grafting, rod dynamization, repeat reamed nailing (exchange nail), fibular osteotomy, and ultrasound/electrical stimulation for fractures with bone loss or non-union; $: quitting months or decades;

Table 2. *Risk of bias assessment for randomized control trial.*

First author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blanding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Moller	+	-	-	+	+	+	?
Nasell	+	+	?	+	+	+	?
Pei	+	+	+	+	+	+	?

"+"=Low risk of bias; "-"=High risk of bias; "?"=Unclear risk of bias.

Table 3. *Methodological quality assessment for non-randomized concurrent control trial.*

First author	Castilo
A clearly stated aim	+
Inclusion of consecutive patients	+
Prospective collection of data	+

Endpoints appropriate to the aim of the study	+
Unbiased assessment of the study endpoint	+
Follow-up period appropriate to the aim of the study	+
Loss to follow-up less than 5%	-
Prospective calculation of the study size	-
Adequate control group	+
Contemporary groups	+
Baseline equivalence of groups	+
Adequate statistical analyses	+

Every item has two scores and the total score is 24. "+"=Add two scores; "-"=No score.

Table 4. *Grade profile evidence.*

	Fracture non-union	**Overall incidence of postoperative complications**	**Wound-related complications**	**Secondary surgery**	**Other postoperative complications**	**Osteomyelitis**
Studies design and no. of consisting studies	NRCCT/1	RCT/3	RCT/3	RCT/3	RCT/3	NRCCT/1
Risk of bias	Serious	Serious	Serious	Serious	Serious	Serious
Inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency	No serious inconsistency
Indirectness	No serious indirectness	No serious indirectness	No serious indirectness	No serious indirectness	No serious indirectness	No serious indirectness
Imprecision	Serious	No serious imprecision	No serious imprecision	No serious imprecision	No serious imprecision	Serious
Other considerations	None	None	None	None	None	None
Preoperative smoking cessation	9/82 (11%)	32/161 (19.9%)	11/161 (6.8%)	4/161 (2.5%)	19/161 (11.8%)	11/82 (13.4%)
Continued Smoking	25/105 (23.8%) CI (0.32 to 0.93)	87/162 (53.7%)	52/162 (32.1%)	17/162 (10.5%)	46/162 (28.4%)	18/105 (17.1%)
Relative effect	RR 0.46 (from 17 fewer to 183 fewer)	RR 0.37 CI (0.26 to 0.52)	RR 0.21 CI (0.11 to 0.39)	RR 0.23 CI (0.08 to 0.67)	RR 0.41 CI (0.25 to 0.67)	RR 0.78 CI (0.39 to 1.56)
Absolute effect	129 fewer/1000 (from 17 fewer to 183 fewer)	1000 (from 258 fewer to 397 fewer)	1000 (from 196 fewer to 286 fewer)	81 fewer/1000 (from 35 fewer to 97 fewer)	168 fewer/1000 (from 94 fewer to 213 fewer)	1000 (from 105 fewer to 96 fewer)
Quality	⊕⊕○○ Low	⊕⊕⊕○ Moderate	⊕⊕⊕○ Moderate	⊕⊕⊕○ Moderate	⊕⊕⊕○ Moderate	⊕⊕○○ Low
Importance	Critical	Critical	Important	Important	Important	Important

Discussion

Four studies were included in this systematic review, including three Randomized Controlled Clinical Trials (RCTs) and one Non-Randomized Concurrent Controlled Trial (NRCCT), involving a total of 510 patients. We have conducted the first systematic review and meta-analysis to evaluate the effect that smoking cessation is beneficial to the postoperative outcome of orthopaedic surgical patients. In our study, the results showed that in the patients with preoperative smoking cessation, the risk of overall postoperative complications was lower that the patients without preoperative smoking cessation. Furthermore, preoperative smoking cessation reduced the risk of wound-related complications, recurrent surgery and additional complications. The NRCCT study demonstrated that the risks of fracture non-union and osteomyelitis in the patients with preoperative smoking cessation were reduced. These findings support the previously published reports on the benefits of smoking cessation prior to orthopaedic surgery [3,9,10]. It is also reported that smoking is associated with a significantly increased risk of aseptic loosening of prosthesis, deep infection and all-cause revisions after total hip arthroplasty [14]. However, these findings were in contrast to the results of Castilo et al. [2] who showed that the incidence of postoperative complications in patients who ceased smoking

preoperatively were not reduced (RR=0.54, P>0.05) compared with the patients who continued to smoke.

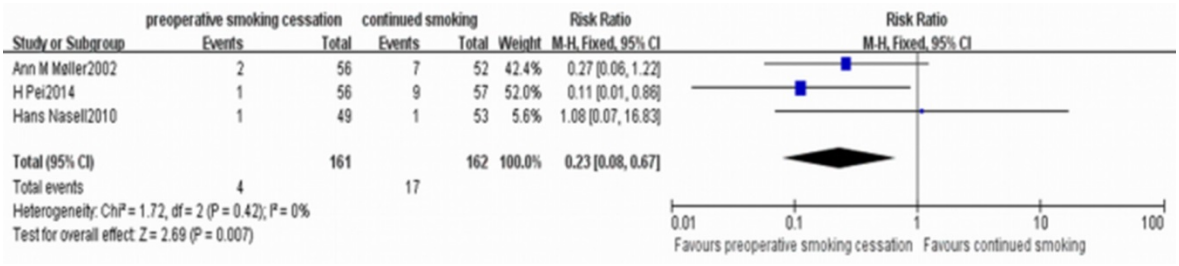

Figure 4. *Forest plot of Risk Ratio (RR) with confidence intervals for secondary surgery.*

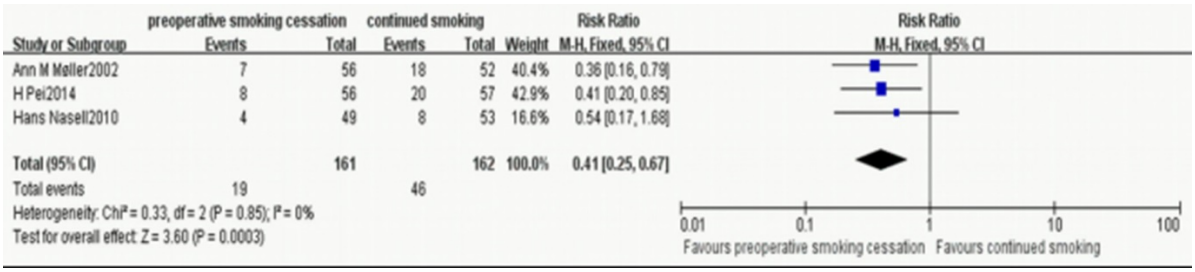

Figure 5. *Forest plot of Risk Ratio (RR) with confidence intervals for other postoperative complications.*

Most previous studies that have shown the harmful effects of smoking were either epidemiological studies of patient populations or laboratory-based animal studies. Smoking studies using animal models have shown that nicotine and other components of cigarette smoke impede the healing of bone fractures by inhibiting the expression of genes for bone growth factors such as Bone Morphogenetic Proteins (BMPs), Transforming Growth-Factor beta (TGF-β) and Platelet-Derived Growth-Factor (PDGF) in a dose-dependent way [15-19]. In terms of clinical evaluation on the effects of smoking in orthopaedic patients undergoing surgery, as this study has shown, there has been little evidence-based, controlled clinical research.

The inconsistencies in the findings of the clinical literature have recently been highlighted by the systematic review and meta-analysis of data conducted by Scolaro et al. [5] nineteen clinical studies which showed that time to achieve union of fractures and the incidence of superficial and deep postoperative infections was not prolonged in smokers when compared with non-smokers. The reasons for the different results may be due to the variations in trial design and quality, including confounding factors of metabolic bone disease diseases, alcohol use, neurological and psychiatric medications use, for example.

Recent developments in orthopaedic surgical techniques have refined surgical procedures combined with new therapies, for example, the application of tissue-engineered bone in treating fracture non-union, and improvement of postoperative treatment, which reduced the incidence of fracture non-union and postoperative complications. The preoperative smoking cessation should be recommended to reduce morbidity and in-hospital mortality following general surgery, vascular surgery, cardiothoracic surgery and, in our view, orthopaedic surgery.

The present study has provided further evidence that preoperative smoking cessation is beneficial to bone healing and may reduce the incidence of complications following orthopaedic surgery. However, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system used in the study analysis, the quality of the evidence was only intermediate or low.

There were some limitations in this study. First, the number of published studies is small. There is a lack of allocation concealment and blinding in these studies. The imprecision of meta-analysis may be caused by un-conforming to the Optimal Information Size (OIS) standards. As a key indicator, the rate of fracture union was only performed in the non-randomized trial. Second, the way of recording cigarette consumption (per day/year) varies in these studies. There were also differences of periods of preoperative smoking cessation, surgical technique and the clinical outcomes among these studies.

Further prospective large-scale, multi-center, randomized controlled clinical trials are still needed to evaluate the relationship between smoking and outcome in orthopaedic surgery.

In conclusion, current evidence supported by this study indicates that for smokers who are planning to undergo orthopaedic surgery, preoperative smoking cessation does not increase the rate of fracture non-union, but can decrease the incidence of postoperative complications, reduce health care expenses and hospital stay.

Conflict of Interest

The authors declare no conflict of interests.

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