International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Study of Impact of Tobacco Smoking on Wound Healing in Abdominal Surgery

Dr. Ayushi Sharma[1], Dr. Gambheer Singh[2], Dr. Mayank Devangan[3]

[1, 2, 3]Raipur Institute of Medical Sciences, Raipur, Chhattisgarh, India

Abstract: ***This study investigates the effect of tobacco use on wound healing in patients undergoing abdominal surgeries. Conducted at the Department of Surgery of Raipur Institute of Medical Sciences, the research included 240 patients, equally divided between tobacco users and non-users. Key metrics for wound healing, such as granulation tissue appearance, wound length reduction, and healing time, were analyzed. The findings revealed that smokers experienced delayed granulation tissue formation, slower wound healing, and a higher incidence of complications, including surgical site infections and the need for additional surgical interventions. These results underscore the detrimental impact of tobacco on post-operative wound recovery and support the importance of smoking cessation to optimize surgical healing outcomes.***

Keywords: tobacco, wound healing, abdominal surgery, complications, smoking cessation

1. Introduction

Acute wounds normally heal in an orderly and efficient manner, and progress smoothly through the four distinct, but overlapping phases of wound healing: haemostasis, inflammation, proliferation and remodelling. The process of wound healing is complex and involves a variety of specialized cells, such as platelets, macrophages, fibroblasts, epithelial and endothelial cells. These cells interact with each other and with the extracellular matrix. In addition to the various cellular interactions, healing is also influenced by the action of proteins and glycoproteins, such as cytokines, chemokines, growth factors, inhibitors, and their receptors. Each stage of wound healing has certain milestones that must occur in order for normal healing to progress. Many factors can interfere with one or more phases of this process, thus causing improper or impaired wound healing [1].

Role of tobacco smoking is well known for lung cancer, coronary heart disease and vascular disease. However, the association between cigarette smoking and delayed wound healing is less well recognized in clinical practice [2]. The detrimental effects of smoking on wound healing were first reported in 1977 by Mosely and Finseth [3], who observed impaired healing of a hand wound in a smoker with arteriosclerosis.

Nicotine exerts several specific effects that can influence wound healing. First, proliferation of red blood cells, fibroblasts, and macrophages is diminished [4]. Fibroblasts and macrophages are responsible for transporting healing substances to the wound area and producing scarring. Second, nicotine has been associated with increased platelet adhesiveness, which causes microclots and decreases micro-perfusion [3]. Third, even while the tissue is becoming deprived of oxygen and blood flow, nicotine produces cutaneous vasoconstriction. This vasoconstriction results from the release of adrenal and peripheral catecholamines, which also increase heart rate, blood pressure, and oxygen demand [5]. Wound healing also requires enzyme formation. Taken together, the effects of these toxic substances clearly have the potential to undermine the conditions required for expeditious wound repair and healthy scar formation.

Thus, on the pathophysiological levels, association between tobacco and delayed wound healing is well recognized, however extensive controlled studies are yet to be performed. The present hospital bases analytical study thus aimed at evaluating the role of tobacco on wound healing characteristics using age and gender matched controls.

Aim and Objectives

Aim

To evaluate the impact of tobacco on rate of wound healing in cases undergoing abdominal surgeries.

Objective

1) To compare the wound healing among tobacco users and non-users in terms of wound healing rate.
2) To compare the incidence of surgical site infections among tobacco users and non-users.

2. Material and Methods

Study Area

Department of Surgery of Raipur Institute of Medical Sciences.

Study Population

Cases undergoing abdominal surgeries at our hospital and giving informed consent.

Study Design

Hospital based analytical study

Sample Size

Sample size was calculated using formulae:

$n= (Z\alpha/2 + Z\beta) \times PQ * 2 /d2$

n- Sample size

$Z\alpha/2$ – Z value at 5% error (1.96)

$Z\beta$ – Z value at 20% (0.84)

P- (p1+p2)/ 2

Q – 1-P

P1 - Prevalence of wound healing problems in smokers (47.9%) [34]

P2 - Prevalence of wound healing problems in non-smokers (14.8%) [34]
d – effect size (taken as 10%)
n – $\frac{(1.96+0.84) * 0.313 * 0.687 * 2}{(0.1)^2}$
n- 120
So, we took 120 subjects in each group i.e. tobacco users and non-users.

Study Duration
Two years

Cases
1) Patient age > 18 years
2) Both gender
3) All surgical wounds of Abdominal surgeries – (Immediate post op wounds)
4) History of tobacco smoking/ chewing > 6 months
5) Nutritional status – average - good

Controls
1) Patient age > 18 years
2) Both gender
3) All surgical wounds of Abdominal surgeries – (Immediate post op wounds)
4) No history of tobacco smoking/ chewing
5) Nutritional status – average - good

Exclusion Criteria
1) Patient with infected wound
2) Patient with dirty infected wound
3) Patients with chronic wound
4) Age < 18 years
5) Immunocompromised patients (DM, HIV, HBsAg positive, HCV, chemotherapy / radiotherapy, cachexic)
6) Not giving informed consent or able to maintain follow up.

Methodology
Study was commenced after approval from institutional ethical committee and taking informed consent from patients. Study included 120 cases and 120 controls i.e. tobacco users and non-users. All the study participants were those undergoing abdominal surgical incision wound in our hospital.

A detailed history, clinical examination and relevant investigations will be performed in all patients. For cases, history regarding duration of tobacco use, its form and amount (in terms of pack years) were asked and recorded in a pre-designed case record form.

Wound length was determined by manual tracing method. All patients received standardized wound management according to the institute protocol and regular follow up will be maintained.

Complete wound healing is defined as complete epithelialization of the tissue defect. Wound Healing Time is defined as the number of days required to achieve complete wound healing.

Manual Tracing for wound area [37]
Prior to tracing and photography, the wound margins were made as clear as possible. The wounds were undressed and any debris, slough, and necrotic tissue removed. The wound and surrounding tissue were then cleaned with saline and dried. We then place a transparent film over the wound and trace the outline with a permanent marker. The tracing was then placed on a metric grid, and the number of squares of a known area counted to get the wound surface area.

Primary Study Outcome
- Time for appearance of granulation tissue
- Time for complete wound healing
- Wound complications including surgical site infection, necrosis, dehiscence and requirement of surgical intervention like debridement or secondary skin closure.

Statistical Analysis
All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test. Quantitative data was represented using Mean ± SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A p-value < 0.05 was taken as level of significance. Results were graphically represented where deemed necessary. SPSS Version 26.0 was used for most analysis and Microsoft Excel 2021 for graphical representation.

3. Discussion

Tobacco smoking is widely recognised for its association with lung cancer, coronary heart disease, and vascular disease. Nevertheless, the correlation between cigarette smoking and impaired wound healing is not widely acknowledged in clinical settings [2]. In 1977, Mosely and Finseth [3] were the first to report the harmful impact of smoking on the process of wound healing. They discovered that a smoker with arteriosclerosis experienced poor healing of a hand wound. Nicotine has various distinct effects that can impact the process of wound healing. Initially, the growth of red blood cells, fibroblasts, and macrophages is reduced [4]. Fibroblasts and macrophages play a crucial role in delivering healing chemicals to the wound site and generating scar tissue. Furthermore, nicotine has been linked to heightened platelet adhesion, resulting in the formation of microclots and a reduction in micro-perfusion [3].

Furthermore, despite the tissue experiencing a lack of oxygen and blood flow, nicotine induces cutaneous vasoconstriction. The vasoconstriction occurs due to the secretion of adrenal and peripheral catecholamines, which also elevate heart rate, blood pressure, and oxygen need [5]. Enzyme production is also necessary for wound healing. Collectively, the impacts of these poisonous substances undoubtedly possess the capability to undermine the necessary conditions for prompt wound healing and the production of a healthy scar.

Therefore, at the pathophysiological levels, the connection between smoke and delayed wound healing is widely acknowledged, but comprehensive controlled studies have

not yet been conducted. This study conducted at the hospital aims to evaluate the impact of smoke on wound healing features.

Study included 120 subjects in each group i.e. tobacco users and non-users. A detailed history, clinical examination and relevant investigations will be performed in all patients. Wound length was determined by manual tracing method. Complete wound healing is defined as complete epithelialization of the tissue defect. Wound Healing Time is defined as the number of days required to achieve complete wound healing.

Baseline Data

Mean age of smokers and non-smokers was comparable i.e. 54.03 years vs 53.18 years (p-0.51). Study included 92.5% males and 7.5% females. Males were predominant in both smokers and non-smokers group (89.2% vs 95.8%; p-0.08).
Manassa EH et al. [34] observed mean age of cases as 49.8 years with 91.7% males in their study.
Siana JE et al. [33] observed mean age as 43 years (range 24-65 years) with predominantly males (94%).

Wound Healing & Smoking

Both clinical observations and controlled studies seem to confirm a relationship between the known effects of the toxic constituents of cigarettes at the vascular and cellular levels and delayed wound healing in smokers. Slower healing has been noted in smokers with wounds resulting from trauma or disease, as well as those recovering from surgical procedures. The medical literature contains extensive reports documenting slower healing of duodenal ulcers in smokers [29], and dental professionals have long been familiar with the delayed healing of oral wounds in smokers.

In present study, mean length of wound was comparable between the groups at baseline (5.87 vs 5.55 cm; p-0.199). At day 7, mean length of wound was lower in non-smokers group as compared to smoker group (2.81 vs 3.32 cm; p<0.01). The difference was significant till the 21 days follow up (1.84 vs 2.01 cm; p<0.01).

Granulation tissue appearance was significantly earlier in non-smokers group as compared to smoker group (7.43 vs 8.31 days; p<0.01). Healing was significantly faster in non-smokers group as compared to smoker group (21.36 vs 23.85 days; p<0.01).

Siana JE et al. [33] aimed to see if there was any difference in the skin healing of smokers as opposed to non-smokers and studied 120 women admitted consecutively for laparotomy sterilisation. When the incision was in the midline the scars in the smokers measured 7.4 mm averagely as compared with 2.7 mm in non-smokers (p<0.01). There was a corresponding tendency in transverse incisions.

Sørensen LT et al. [35] aimed to clarify the evidence on smoking and postoperative healing. The pooled adjusted odds ratios (95% CI) was 2.07 (1.53-2.81) for healing delay.

Complication & Secondary surgical procedures

Incidence of complications was more in smokers' group (25.8% vs 10.8%). Incidence of SSI was 25.8% in smokers as compared to 10.8% among non-smokers while wound dehiscence was seen in 2 cases of smoking group (1.7%). Secondary Surgical Procedures were required in 10.8% cases of smoking group as compared to 0.8% cases of non-smoking group (p<0.01).

Manassa EH et al. [34] studied the effects of smoking on wound healing. The rate of wound problems and wound dehiscence showed a statistical difference between smokers and nonsmokers (p < 0.01); 47.9 percent of the smokers showed wound healing problems before hospital discharge versus 14.8 percent of the non-smokers. SSIs rate was 12.7% in smokers as compared to 5% in non-smokers (p<0.01).

Sørensen LT et al. [35] observed the pooled adjusted odds ratios (95% CI) as 3.60 (2.62-4.93) for necrosis, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications. In their meta-analysis, four randomized controlled trials observed that smoking cessation reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]).

Inoue Y et al. [36] aimed to examine the association between smoking and perioperative complications of laparoscopic abdominal surgery. total number of postoperative complications was higher in all groups of smoking than in non-smoking group, independent on preoperative smoking cessation.

To summarize, in the current investigation, it was found that smoking tobacco had a significant and detrimental effect on the healing process of wounds in patients who were undergoing abdominal surgery. In smokers, the emergence of granulation tissue was significantly delayed, and the healing process was also significantly slowed down. The rate of post-operative wound complications was also shown to be considerably greater among smokers in comparison to non-smokers. As a result of the findings of the current study, we have come to the conclusion that quitting smoking is absolutely necessary prior to surgical procedures in order to facilitate the healing of surgical wounds.

4. Results

Table 1: Distribution of study groups

Group	N	%
Non-Smoker	120	50.00%
Smoker	120	50.00%
Total	240	100.00%

Present study aimed to evaluate the impact of tobacco on rate of wound healing in cases undergoing abdominal surgeries. Study included 120 subjects in each group i.e. tobacco users and non-users.

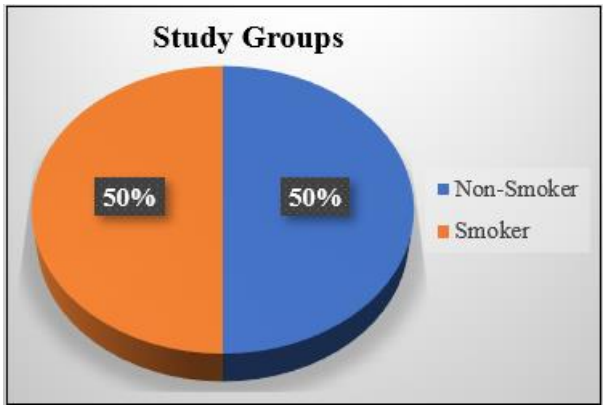


Table 2: Mean age comparison among study groups

Parameter	Group	N	SD	SD	p-value
Age in years	Non-Smoker	120	53.18	6.43	0.51
	Smoker	120	54.03	4.33	

Mean age of smokers and non-smokers was comparable i.e. 54.03 years vs 53.18 years (p-0.51).

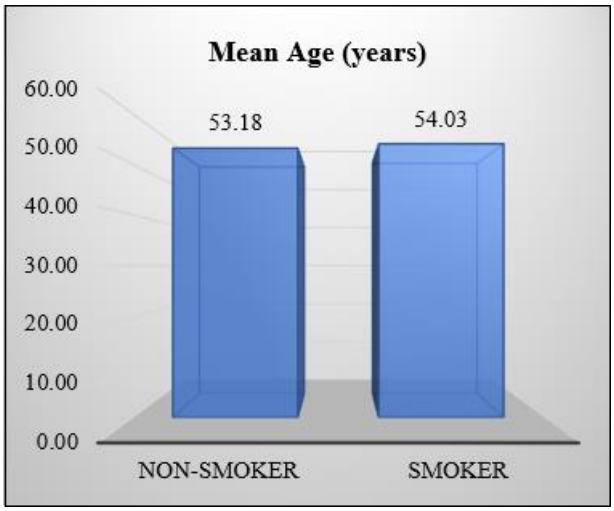


Table 3: Gender comparison among study groups

Gender	Group		Total
	Non-smoker	Smoker	
Female	5	13	18
	4.2%	10.8%	7.5%
Male	115	107	222
	95.8%	89.2%	92.5%
Total	120	120	240
	100.0%	100.0%	100.0%
p- value - 0.08			

Study included 92.5% males and 7.5% females. Males were predominant in both smokers and non-smokers group (89.2% vs 95.8%; p-0.08).

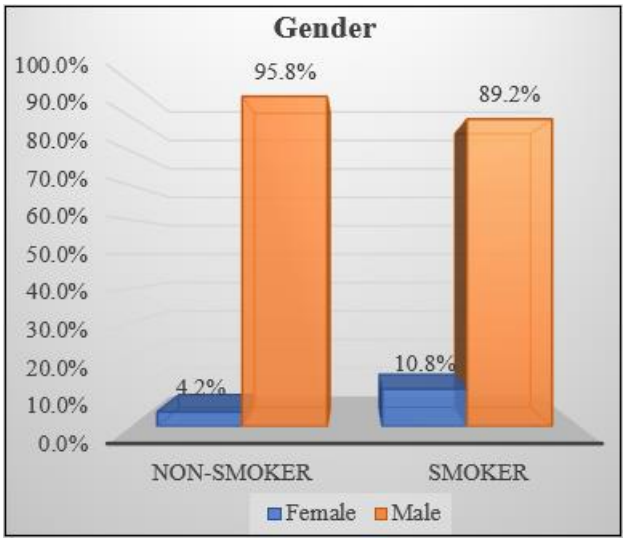


Table 4: Mean comparison of wound length among study groups

Wound length	Group	N	SD	SD	p-value
Day 1	Non-Smoker	120	5.55	1.76	0.199
	Smoker	120	5.87	2.08	
Day 7	Non-Smoker	120	2.81	1.03	<0.01
	Smoker	120	3.32	1.39	
Day 14	Non-Smoker	120	2.02	0.72	<0.01
	Smoker	120	2.29	0.83	
Day 21	Non-Smoker	83	1.84	0.52	<0.01
	Smoker	94	2.01	0.65	

Mean length of wound was comparable between the groups at baseline (5.87 vs 5.55 cm; p-0.199). At day 7, mean length of wound was lower in non-smokers group as compared to smoker group (2.81 vs 3.32 cm; p<0.01). The difference was significant till the 21 days follow up (1.84 vs 2.01 cm; p<0.01).

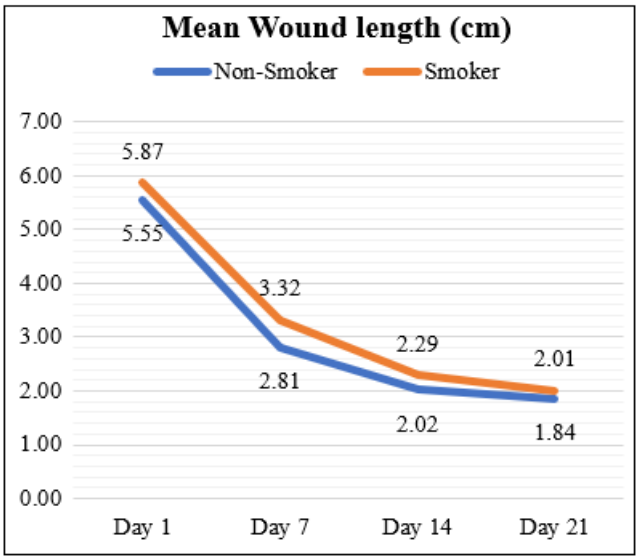


Table 5: Mean time for appearance of granulation tissue in study groups

Parameter	Group	N	SD	SD	p-value
Granulation tissue appearance (days)	Non-Smoker	120	7.43	1.50	<0.01
	Smoker	120	8.31	2.11	

Granulation tissue appearance was significantly earlier in non-smokers group as compared to smoker group (7.43 vs 8.31 days; p<0.01).

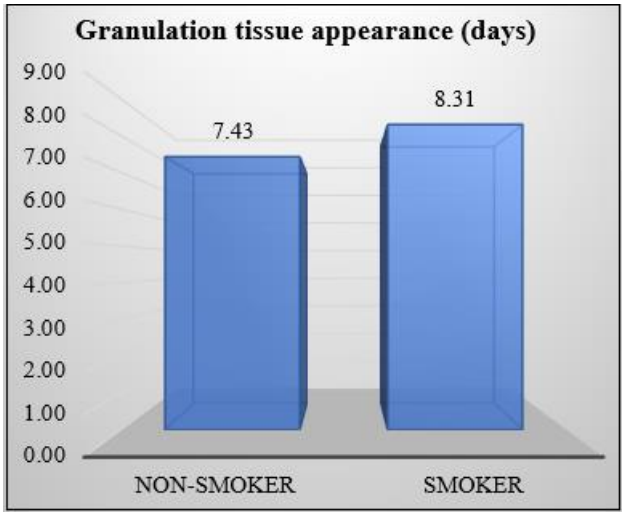


Table 6: Comparison of mean healing time between study groups

Parameter	Group	N	SD	SD	p-value
Healing Time (days)	Non-Smoker	120	21.36	4.13	<0.01
	Smoker	120	23.85	5.03	

Healing was significantly faster in non-smokers group as compared to smoker group (21.36 vs 23.85 days; p<0.01).

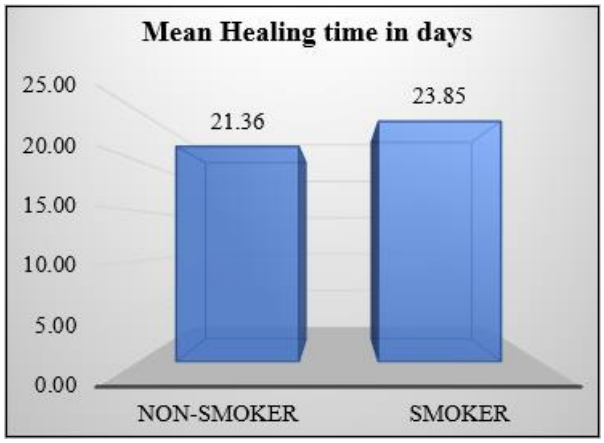


Table 7: Comparison of complication rate among study groups

Complications	Group		Total
	Non-smoker	Smoker	
None	107	89	196
	89.2%	74.2%	81.7%
SSI	13	29	42
	10.8%	24.2%	17.5%
SSI, Dehiscence	0	2	2
	0.0%	1.7%	0.8%
Total	120	120	240
	100.0%	100.0%	100.0%
p- value <0.01			

Incidence of complications was more in smokers' group (25.8% vs 10.8%). Incidence of SSI was 25.8% in smokers as compared to 10.8% among non-smokers while wound dehiscence was seen in 2 cases of smoking group (1.7%).

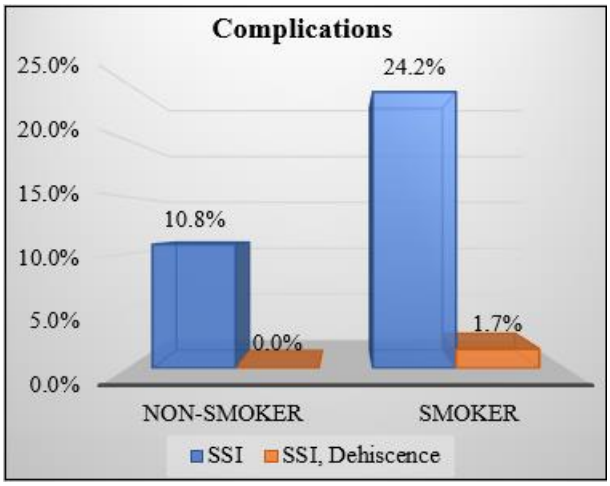
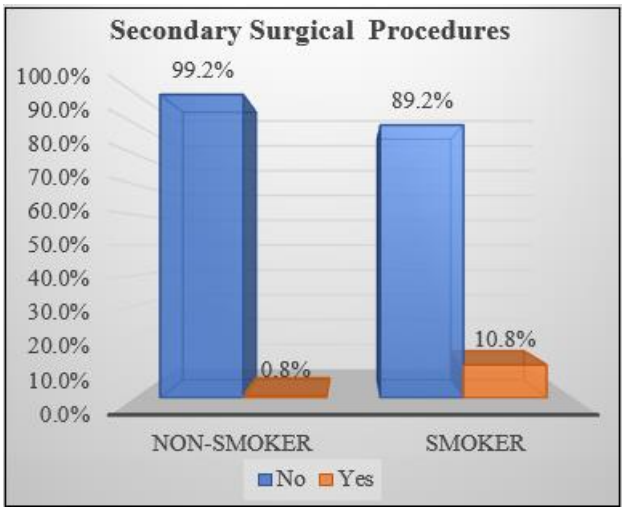


Table 8: Requirement of Secondary Surgical Procedures among study groups

Secondary Surgical Procedures	Group		Total
	Non-smoker	Smoker	
No	119	107	226
	99.2%	89.2%	94.2%
Yes	1	13	14
	0.8%	10.8%	5.8%
Total	120	120	240
	100.0%	100.0%	100.0%
p- value < 0.01			

Secondary Surgical Procedures were required in 10.8% cases of smoking group as compared to 0.8% cases of non-smoking group (p<0.01).

Table 9



5. Conclusion

This case-control research was conducted with the purpose of determining the effect that tobacco use had on the rate of wound healing in patients who were having abdominal operations. Tobacco smoking has been shown to have a considerable and detrimental effect on the healing process of wounds in patients who are undergoing abdominal surgery, according to studies that were conducted. In smokers, the emergence of granulation tissue was significantly delayed, and the healing process was also significantly slowed down. The risk of post-operative wound complications was also

shown to be considerably greater among smokers in comparison to non-smokers. As a result of the findings of the current study, we have come to the conclusion that quitting smoking is absolutely necessary prior to surgical procedures in order to facilitate the healing of surgical wounds.

6. Summary

A hospital based comparative study was conducted at Department of Surgery of Raipur Institute of Medical Sciences. Study aimed to evaluate the impact of tobacco on rate of wound healing in cases undergoing abdominal surgeries. Cases undergoing abdominal surgeries at our hospital and giving informed consent were included. Study included 120 subjects in each group i.e. tobacco users and non-users. A detailed history, clinical examination and relevant investigations will be performed in all patients. Wound length was determined by manual tracing method. Complete wound healing is defined as complete epithelialization of the tissue defect. Wound Healing Time is defined as the number of days required to achieve complete wound healing. Following observations were made during the study:

1) Mean age of smokers and non-smokers was comparable i.e. 54.03 years vs 53.18 years (p-0.51).
2) Study included 92.5% males and 7.5% females. Males were predominant in both smokers and non-smokers group (89.2% vs 95.8%; p-0.08).
3) Mean length of wound was comparable between the groups at baseline (5.87 vs 5.55 cm; p-0.199). At day 7, mean length of wound was lower in non-smokers group as compared to smoker group (2.81 vs 3.32 cm; p<0.01). The difference was significant till the 21 days follow up (1.84 vs 2.01 cm; p<0.01).
4) Granulation tissue appearance was significantly earlier in non-smokers group as compared to smoker group (7.43 vs 8.31 days; p<0.01).
5) Healing was significantly faster in non-smokers group as compared to smoker group (21.36 vs 23.85 days; p<0.01).
6) Incidence of complications was more in smokers' group (25.8% vs 10.8%). Incidence of SSI was 25.8% in smokers as compared to 10.8% among non-smokers while wound dehiscence was seen in 2 cases of smoking group (1.7%).
7) Secondary Surgical Procedures were required in 10.8% cases of smoking group as compared to 0.8% cases of non-smoking group (p<0.01).

Conflict of Interest / Sponsorships –

No Conflict of Interest and Sponsorships

References

[1] Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010 Mar;89(3):219-29.
[2] Mosely LH, Finseth F. Cigarette smoking: impairment of digital blood flow and wound healing in the hand. Hand 19n; 9: 97-101.
[3] Silverstein P. Smoking and wound healing. The American journal of medicine. 1992 Jul 15;93(1):S22-4.
[4] Sherwin MA, Gastwirth CM. Detrimental effects of cigarette smoking on lower extremity wound healing. J Foot Surg 1990; 29: 84-7.
[5] Nolan J, Jenkins RA, Kurihara K, Schultz RC. The acute effects of cigarette smoke exposure on experimental skin flaps. Plast Reconstr Surg 1985; 75: 544-9.
[6] Wade CI, Streitz MJ. Anatomy, Abdomen. StatPearls [Internet]. 2020 Jan 17.
[7] Lambert G, Samra NS. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 27, 2020. Anatomy, Abdomen and Pelvis, Retroperitoneum.
[8] Selçuk İ, Ersak B, Tatar İ, Güngör T, Huri E. Basic clinical retroperitoneal anatomy for pelvic surgeons. Turk J Obstet Gynecol. 2018 Dec;15(4):259-269.
[9] Ahluwalia HS, Burger JP, Quinn TH. Anatomy of the anterior abdominal wall. Oper Tech Gen Surg. 2004 Sep 1;6(3):147-55.
[10] Bernier-Latmani J, Petrova TV. Intestinal lymphatic vasculature: structure, mechanisms and functions. Nature reviews Gastroenterology & hepatology. 2017 Sep;14(9):510-26.
[11] Schultz GS, Chin GA, Moldawer L, et al. Principles of Wound Healing. In: Fitridge R, Thompson M, editors. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists [Internet]. Adelaide (AU): University of Adelaide Press; 2011. 23. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534261/
[12] Bates-Jensen B. New pressure ulcer status tool. Decubitus 1990; 3 (3): 14-5.
[13] Bates-Jensen BM, Vredevoe DL, Brecht ML. Validity and reliability of the Pressure Sore Status Tool. Decubitus 1992; 5 (6): 20-8.
[14] Bates-Jensen BM. The pressure sore status tool: an outcome measure for pressure sores. Top Geriatric Rehabil 1994; 9 (4): 17-34.
[15] Thomas DR, Rodeheaver GT, Bartolucci AA, Franz RA, Sussman C, Ferrell BA, Cuddigan J, Stotts NA, Maklebust J. Pressure ulcer scale for healing: derivation and validation of the PUSH tool. The PUSH Task Force. Adv Wound Care 1997; 10 (5): 96-101.
[16] Utility of the Sussman Wound Healing Tool in predicting wound healing outcomes in physical therapy. Adv Wound Care 1997; 10 (5): 74-7.
[17] Ferrell BA, Artinian BM, Sessing D. The Sessing Scale for assessment of pressure ulcer healing. Journal of the American Geriatric Society 1995; 43: 37-40.
[18] Krasner D. Wound Healing Scale, version 1.0: A proposal. Adv Wound Care 1997; 10 (5): 82-5.
[19] Houghton PE, Kincaid CB, Campbell KE, Woodbury MG, Keast DH. Photographic assessment of the appearance of chronic pressure and leg ulcers. Ostomy/Wound Manage 2000; 46 (4): 20-30.
[20] Emparanza JL, Aranegui P, Ruiz M y cols. A simple Severity index for pressure ulcers. Journal of Wound Care 2000: 9 (2): 86-90.
[21] Sanada H, Moriguchi T, Miyachi Y, Ohura T, Nakajo T, Tokunaga K, Fukui M, Sugama J, Kitagawa A. Reliability and validity of DESIGN, a tool that classifies pressure ulcer severity and monitors healing. J Wound Care 2004; 13 (1): 13-18.
[22] Mishra S, Mishra MB. Tobacco: Its historical, cultural, oral, and periodontal health association. J Int Soc Prev Community Dent. 2013 Jan;3(1):12-8.

[23] Mosely LH, Finseth F. Cigarette smoking: impairment of digital blood flow and wound healing in the hand. Hand 19n; 9: 97-101.
[24] The health consequences of smoking: cardiovascular disease. A report of the surgeon general. Rockville, Maryland: U.S. Department of Health and Human Services, 1983.
[25] Sherwin MA, Gastwirth CM. Detrimental effects of cigarette smoking on lower extremity wound healing. J Foot Surg 1990; 29: 84-7.
[26] Nolan J, Jenkins RA, Kurihara K, Schultz RC. The acute effects of cigarette smoke exposure on experimental skin flaps. Plast Reconstr Surg 1985; 75: 544-9.
[27] Mosely LH, Finseth F, Goody M. Nicotine and its effect on wound healing. Plast Reconstr Surg 1978; 61: 570-5.
[28] Rees TD. The acute effects of cigarette smoke exposure on experimental skin flaps: a discussion. Plast Reconstr Surg 1985; 75: 550-l.
[29] Piper DW, McIntosh JH, Hudson HM. Factors relevant to the prognosis of chronic duodenal ulcer. Digestion 1985; 31: 9-16.
[30] Siana JE, Rex S, Gottrup F. The effect of cigarette smoking on wound healing. Stand J Plast Reconstr Surg 1989; 23: 207-9.
[31] Rees TD, Liverett DM, Guy CL. The effect of cigarette smoking on skin-flap survival in the face lift patient. Plast Reconstr Surg 1984; 73: 911-5.
[32] Riefkohl R, Wolfe JA, Cox EB, McCarty KS Jr. Association between cutaneous occlusive vascular disease, cigarette smoking, and skin slough after rhytidectomy. Plast Reconstr Surg 1986; n: 592-5.
[33] Siana JE, Rex S, Gottrup F. The effect of cigarette smoking on wound healing. Scandinavian Journal of Plastic and Reconstructive Surgery. 1989 Jan 1;23(3):207-9.
[34] Manassa EH, Hertl CH, Olbrisch RR. Wound healing problems in smokers and non-smokers after 132 abdominoplasties. Plast Reconstr Surg. 2003 May;111(6):2082-7; discussion 2088-9.
[35] Sørensen LT. Wound healing and infection in surgery: the clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Archives of surgery. 2012;147(4):373-83.
[36] Inoue, Y., Katoh, T., Masuda, S. et al. Perioperative complications of abdominal surgery in smokers. J Anesth. 202; 34 712–718.
[37] Harding KG. Methods for assessing change in ulcer status. *Adv Wound Care.* 1995;8(4) suppl:37–42.