JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2020, VOL. 54, NO. 6, 352–357
https://doi.org/10.1080/2000656X.2020.1781141

ARTICLE

Complications in skin grafts when continuing antithrombotic therapy prior to cutaneous surgery requiring skin grafting: an observational study

Lone Jørgensen[a], Reem Dina Matzen[b], Elin Albertsdottir[c] and Lene Birk-Sørensen[d]

[a]Clinic for Surgery and Cancer Treatment and Clinical Nursing Research Unit, Aalborg University Hospital, Aalborg, Denmark; [b]Department of Plastic and Reconstructive Surgery, Aalborg University Hospital, Aalborg, Denmark; [c]Department of Plastic and Breast Surgery, Zealand University Hospital, Aalborg, Denmark; [d]Department of Plastic and Reconstructive Surgery, Aalborg University Hospital, Aalborg, Denmark

ABSTRACT

Use of anticoagulants is common and practice regarding continuation or discontinuation of the medication peri-operatively for cutaneous surgery lacks evidence-based consensus. Therefore, we aimed to do a prospective observational study with patients who were referred to cutaneous surgery and needed full thickness or split skin grafting and using antitrombotic or non-antitrombotic therapies. Data on patients characteristics, diagnosis, location of surgery and surgery performed, antithrombotic medication and complications in skin grafts were collected. Skin grafts were traced on a transparent film and areas of unhealed skin graft were marked. All patients were routinely followed-up on days 5–7 postoperative. Chi-square test, Fisher's exact test or Mann-Whitney U-test were used to compare patients taking antitrombotic medication with patients receiving no antitrombotic therapy. In addition, associations were calculated for treatment with the different antithrombotic therapies. No severe bleeding requiring blood transfusion or re-operation was observed in this study. The results showed no statistically significant difference between patients who continued treatment with antithrombotic therapy compared with patients having no antithrombotic treatment regarding sub graft hematomas or graft take. Continuing antithrombotic monotheraphy with acetylsalicylic, clopidogrel, warfarin or fish oil in relations to cutaneous surgery do not seem to increase risk of haematoma or graft lost.

ARTICLE HISTORY
Received 20 February 2020
Revised 5 May 2020
Accepted 5 June 2020

KEYWORDS
Skin grafts; antithrombotic therapy; cutaneous surgery

Introduction

With an ageing population, the number of people diagnosed with cutaneous carcinomas is rising and so is the number of people requiring treatment with anticoagulants [1]. Antiplatelet and anticoagulant therapies, such as aspirin, warfarin and clopidogrel have been used for decades with the benefit of decreasing morbidity and mortality associated with tromboembolic events. At our department, it was stardard procedure to recommend patients to discontinue antithrombotic medicine prior to cutaneous surgery including skin grafts. This was to minimize the theoretical risk of wound healing problems due to haematomas. The risk of inducing thromboembolic events when pausing antithrombotic medicine lead us to change standard procedure and instead of recommending discontinuation, we recommended to continue the use of the given therapy. We therefore wanted to study whether we were right in believing that the use of anticoagulant does enhance the risk of wound healing problems when performing skin grafting.

The preoperative management of anticoagulants is a common dilemma faced by surgeons where the risk of bleeding has to be weighed up against the risk of thromboembolic events if the medication is discontinued. Adding to further complexity is the expanding number of drugs with anticoagulant properties. A systematic review with more than 14.000 patients of which over 5000 patients received anticoagulant or antiplatelet medicine showed no increase in haemorrhagic complications in patients taking aspirin monotherapy, but evidence was conflicting regarding warfarin and clopidogrel monotherapy [2]. One study showed a ten-fold increased postoperative bleeding rate requiring interventions [3] while another study displayed no difference in bleeding complications between controls and patients with an INR < 3 taken warfarin [4]. In addition, the systematic review showed no increase in wound infection or graft failure and no affected cosmetic outcome was demonstrated [2]. However, life-threatening thromboembolic complications are rare but have been related to perioperative discontinuation of anticoagulant medicine [5,6]. Several studies have reported severe complications accociated with pre-operative anticoagulant discontinuation in the context of cutaneous surgery, including pulmonary embolism and clotted prosthetic aorta valve in patients with pre-existing cardiovalscular disease, who had withhold antitrombotic medication during Mohs surgery [7]. Another serious event was stroke [8,9]. According to most studies, the recommendations are to continue anticoagulant treatment prior to cutaneous surgery as patients do not demonstrate worse overall outcomes compared with patients who are not taking anticoagulant [10–13]. However, there is a risk of underestimating the number of thrombotic events as most patients are referred directly to the emergency room and not to the outpatient clinics where surgery was performed, leading to a number of underreported cases [10]. According to Isted *et al.*, risk assessment is necessary in all patients as thromboembolic events carried high morbidity and even mortality when such events happened [2]. A systematic review suggests that use of antithrombotic therapy can increase

CONTACT Lone Jørgensen lojo@rn.dk Clinic for Surgery and Cancer Treatment and Clinical Nursing Research Unit, Aalborg University Hospital, Sdr. Skovvej 5, Aalborg, 9000, Denmark

the risk of non-life threatening bleeding complications in skin grafts. However, graft failure was rare and given the risk of thrombotic events, the review recommend continuing all medically necessary antithrombotic therapy [13]. The limitations of this review are the small sample sizes and the level of evidence why studies with more participants are needed. Therefore, the purpose of this prospective observational study was to determine the risk of postoperative bleeding or wound healing complications among patients in anticoagulation treatment compared with patients who are not receiving anticoagulation treatment prior to minor cutaneous surgery requiring skin grafting.

Materials and methods

Study design and participants

A prospective observational study with patients undergoing surgery at the Department of Plastic and Reconstructive Surgery at Aalborg University Hospital in Denmark was conducted. Inclusion criterias were patients, who were referred to cutaneous surgery with full thickness or split skin grafting. In addition, the excision shold be performed on the levels of subcutis or perichondrium. All sizes of excisions were included from January 2015 to December 2016. Exclusion criterias were patients having a pace maker, needed skin graft on bare bone and patients with an INR above 3.5.

Indications, surgical procedure and follow-up

Prior to surgery all patients were sent a letter instructing them to continue with their anticoagulant treatment unless a physician recommended otherwise. However, some of the patients who had prior surgery were customed to discontinue anticoagulant treatment. At the day of surgery ID number, age, gender, antithrombotic therapy, whether or not treatment was discontinued, and for how long time it was discontinued was registered on a standardized sheet. INR was measured if the patient was in Warfarin or Phenoprocouman treatment. Data on co-morbidities such as diabetes, hypertension, prior radiotherapy of the area, current treatment with immunosuppressive medications, intake of fish oil, active smoking, disease (benign tumour, carcinoma, malignant melanoma), depth of excision, split skin graft or full thickness skin graft, location of surgery (head/neck, upper extremity, trunk, lower extremity) were collected.

The surgeons were instructed to secure profound haemostasis before applaying skin grafts. All skin grafts were either sutured or stapled on the defects to permit appropriate adherence to the surrounding tissue. The bolus layer of bandage consisted of a silver Vaseline gaze, two layers of Vaseline gaze and a piece of foam tied down with sutures. Split skin grafts were hand- or maschine meshed with a mesh hole per 1–2 cm^2 (Figures 1–4).

The skin grafts were inspected five to seven days post operatively. On a standardized study sheet it was registered if there was any sign of infection or hematoma. The skin graft was traced on a transparent film and areas of the unhealed skin graft were marked on the drawing (Figures 5–6).

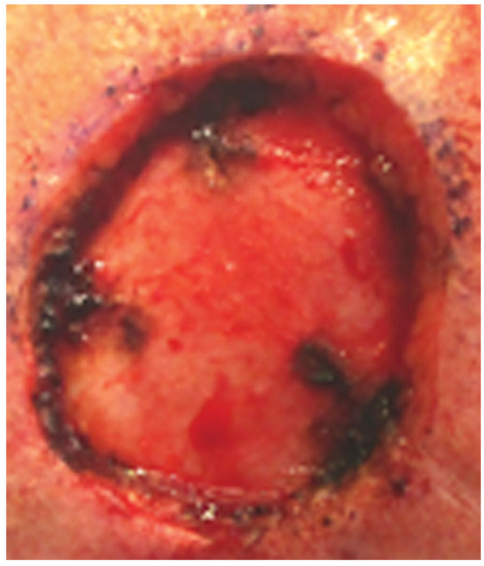

Figure 2. Perioperative photo after removal of the skin cancer.

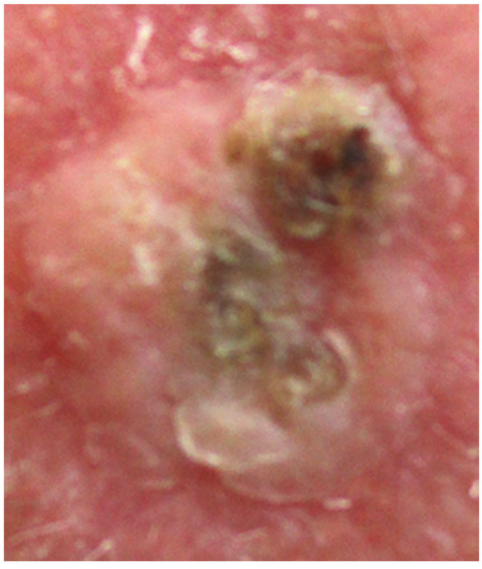

Figure 1. Example of a skin cancer on the scalp.

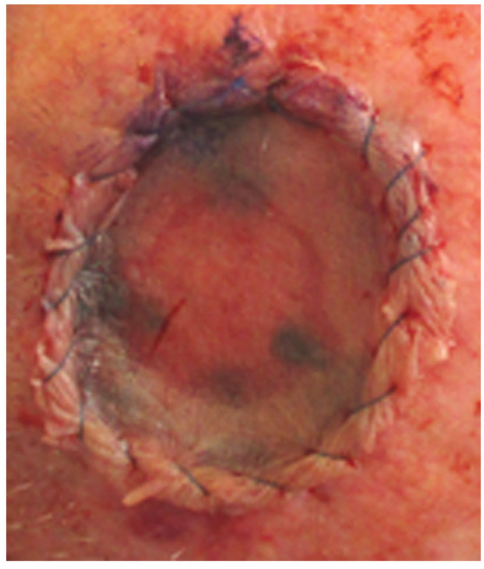

Figure 3. Perioperative photo after the defect was sutured.

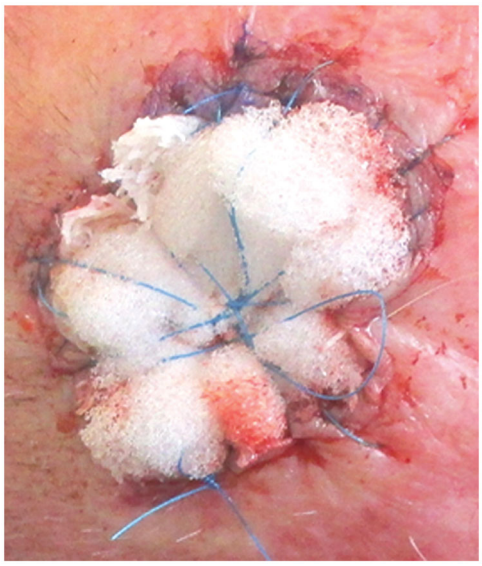

Figure 4. Perioperative photo after a piece of foam was tied down.

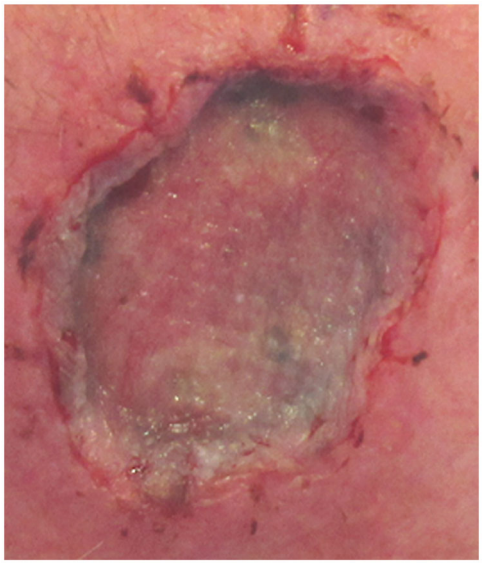

Figure 5. Photo of the skin graft on the postoperative day 5–7.

Statistical analysis

Data were entered into REDCap (Research Electronic Data Capture) [14]. A calculations of strength showed that a minimum of 154 patients was necessary. Chi-square test, Fisher's exact test or Mann-Whitney U-test were used to compare the group of patients taking antitrombotic medication and patients taking no antitrombotic drugs. Associations were calculated for treatment with the different antithrombotic therapies. A result was considered statistically significant if $p < 0.05$. The drawings to record unhealed skin grafts were traced with computer software, where the graft take area percentage was calculated [15]. The statistical analysis were performed using Stata version 12.1.

Ethical considerations

Approval from the Danish Data Protection Agency, The Northern Region of Jutland was obtained (ID 2008-58-0028). According to Danish law, this study does not need approval from the National Committee on Health Research Ethics. Patients received oral and written information and all participants gave informed consent. All data was stored in a secure location only accessible by the authors.

Figure 6. Photo of the transparent film where the skin graft was traced showing no graft failure

Results

A total of 172 patients having 187 skin grafts were included in this study. Average size of the skin grafts was 1278 mm^2 ranging from 52 mm^2 to 14283 mm^2.

The number of skin grafts where patients were prescribed antithrombotic therapy were 111, and 76 patients had no prescribed anti-thrombotic therapy. The 111 transplants were split into groups depending on the kind of anti-thrombotic treatment the patient received at the time of surgery and then split further into sub groups based on whether or not they had discontinued their treatment prior to surgery (Figure 7).

Patients characteristics are summarized in Table 1. Skin grafts were most commonly performed in order to mend a defect after excision of basal cell carcinoma (52.4%), and the second most common were excision of squamous cell carcinoma (21.9%). Most of the surgeries were performed in the face (57.7%) and scalp (20.8%). In addition, 52.9% were split skin grafts and 47.1% were full thickness grafts (Table 2).

No severe bleeding requiring blood transfusion or re-operation was observed in this study. The only bleeding observed was a minor hematoma under some of the skin grafts. In Table 3, the numbers of complications in form of infection or hematoma are listed for each group categorized by the type of anticoagulant therapy.

In the no anti-thrombotic treatment group, there were 17 (22%) skin grafts with hematoma out of 76. In the group that continued acetylsalicylic acid, hematoma was seen in six (21%) of the skin grafts out of 29. In patients discontinuing acetylsalicylic acid, there was hematoma in two (12%) out of 17 skin grafts. In patients who continued treatment with clopidogrel prior to surgery, no hematoma was observed. In the group of patients who continued warfarin therapy, hematoma was observed in six out of 22 (27%) skin grafts. In the group of patiens taking fish oil as a dietary supplement, hematoma was found in seven (33%) out of

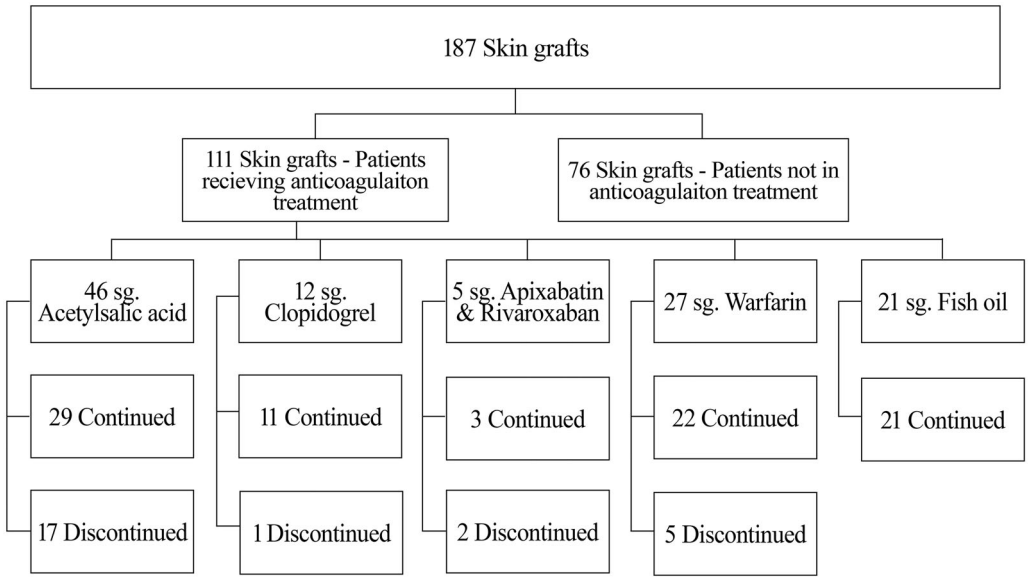

Figure 7. Overview of study population.

Table 1. Participants´ characteristics.

Variable	*N* (%)
Average age at time of operation, years ± SD	74.6 ± 12.8
Male	92 (53.5%)
Female	80 (46.5%)
Immunosuppressive therapy	13 skin grafts
Hypertension	97 skin grafts
Diabetes	27 skin grafts
Previous radiation therapy of the area	12 skin grafts
Current smoker	30 skin grafts
Fish oil	21 skin grafts

Table 2. Procedure characteristics.

Parameter	*N* (%)
Skin grafts included:	187 (100%)
Skin grafts where the patient was in no anti thrombotic treatment or paused	97 (51.9%)
Skin grafts where the patient was in antithrombotic treatment	90 (48.1%)
Diagnosis:	
Basal cell carcinoma	98 (52.4%
Squamous cell carcinoma	41 (21.9%)
Melanoma	5 (2.7%)
Benign tumours	19 (10.2%)
Other	24 (12.8%)
Localization:	
Scalp	39 (20.8%)
Face	106 (56.7%)
Upper extremities	12 (6.4%)
Neck and trunk	4 (2.1%)
Lower extremities	26 (13.9%)
Surgery performed:	
Anaesthesia	
Local anaesthesia	178 (95.2%)
General anaesthesia	9 (4.8%)
Depth of excision	
Subcutis	106 (56.7%)
Fascia	81 (43.3%)
Skin grafting	
Split skin graft	99 (52.9%)
Full thickness skin graft	88 (47.1%)
Average size of skin graft	1278 mm^2
First look at skin graft post operatively	
<5 days	3 (1.6%)
5–7 days	181 (96.8%)
>7 days	3 (1.6%)

21 skin grafts. The difference between the groups in antithrombotic therapy compared to the control group (no anti thrombotic therapy) was not significant. Table 4 illustrates the distribution of percentages with regard to graft take in every group.

Discussion

The results showed no statistically significant difference between patients who continued treatment with antithrombotic therapies including acetylsalicylic acid, clopidogrel, and warfarin and fish oil, compared with patients having no antithrombotic treatment regarding the amount of hematomas or graft take. Although we saw a high percentage of haematomas that did not seem to have any influence on graft take.

To date, there is no national guidelines when it comes to recommendations for patients in antithrombotic treatment prior to cutaneous surgery requiring skin grafts. However, it is of great importance that the indication of discontinuation of antithrombotic treatment is based on strong evidence as discontinuation can result in severe consequences for the patient including death [10]. The literature shows that the risk of severe post-operative bleeding is low when continuing antithrombotic therapies [11,13]. Our study supports previous findings as we saw no case of severe bleeding that needed interference of clinician or blood transfusion. The risk of bleeding due to medication with aspirin seems to be negligible while taken warfarin, the risk may be increased. A two-fold increase appears likely, however a greater increase is more likely due to statistical reasons arising from the rareness of severe events and small numbers of included patients [16,17]. Even though our study showed no statistically significant results, there is a higher proportion of patients continuing Acetylsalicylic acid, Clopidogrel and Warfarin that develop haematoma compared to patients discontinuing these medcamentations. However, it may be due to the small number of included patients. Thus, patients taken Clopidogrel or Warfarin represent a particular high-risk group of patients. Given the potential sequalae of a thromboembolic event, it would be recommended to continue this therapy in all patients undergoing minor cutaneous surgery. Another way to prevent bleeding complications may be the use of fibrin glue for split skin grafting fixation, which has shown

Table 3. Complications in skin grafts on patients continuing antithrombotic therapy vs. no antithrombotic therapy.

Variables	Skin grafts Total (%)	Hematoma under skin grafts (%)	Infected skin grafts (%)
Skin grafts, no antithrombotic therapy	76	17 (22%)	10 (13%)
Skin grafts, in antithrombotic therapy	111	16 (14.4%)	12 (10.8%)
Acetylsalicylic acid	46	8	4
A) continued	29 (63%)	6 (21%)	2 (7%)
B) discontinued	17 (37%)	2 (12%)	2 (12%)
Clopidogrel	12	1	4
A) continued	11 (92%)	0 (0%)	4 (36%)
B) discontinued	1 (8%)	1 (100%)	0 (0%)
Apixaban, Rivaroxaban	5	1	2
A) continued	3 (60%)	1 (33%)	1 (33%)
B) discontinued	2 (40%)	0 (0%)	1 (50%)
Warfarin	27	6	2
A) continued	22 (81%)	6 (27%)	2 (9%)
B) discontinued	5 (19%)	0 (0%)	0 (0%)
Fish oil:	21	7	3
A) continued	21	7 (33%)	3 (14%)

Table 4. Distribution percentage of graft take within the groups.

% graft take	No antithro.[a]	Acetyl. con[b]	Acetyl. dis[c]	Clopi-dogrel. con[d]	Clopi-dogrel. dis[e]	Apixaban/ Rivarox, con[f]	Apixaban/ Rivarox. dis[g]	Warfarin con[h]	Warfarin dis[i]	Fish oil	Grand Total Grafts
0–10	2	1		3							6
10–20				1							1
30–40								1			1
40–50	2							1		2	5
50–60	1	1	1								3
60–70	2	1						1			4
70–80	5						1	1			7
80–90	1	1	1					2		3	8
90–100	63	25	15	7	1	3	1	16	5	16	152
Grand Total Grafts	76	29	17	11	1	3	2	22	5	21	187

[a]No Anti trombotic therapy, [b]Acetylsalicylic acid continued, [c]Acetylsalicylic acid continued, [d]Clopidogrel continued, [e]Clopidogrel discontinuied, [f]Apixaban/Rivaroxiban continued, [g]Apixaban/Rivaroxiban discontinued, [h]Warfarin continued, [i]Warfarin discontinued.

promising results when compared with traditional fixation methods such as skin stabler or suture [18,19] as used in our study. The main factor that reduces graft take and survival for skin grafts is a lack of adhesion to the recipient due to the presence of haematoma or seroma that inhibits revascularisation. However, to prevent graft failure requires the handling of more components: 1) preoperative patient factors such as nutrition and wound bed preparation 2) surgical factors such as good harvesting technique, stabilazation of the graft to avoid shearing and adequate hemostasis of the wound bed to avoid hematoma formation and 3) postoperative wound care such as skin graft anchored to ensure stability [20]. If these components are not taken into account, graft take may be compromised.

Bleeding after surgery is inconvenient and may expose patients to additional procedures or may affect final cosmetic outcome, but postoperative bleeding from a surgical procedure holds a lower consequence than heart or brain ischemia that may happen during discontinuation of antithrombotic therapy. Withholding antitrombotic therapy for skin surgery exposes patients to the potentially risk of thrombosis and may therefore not be advised. However, even though patients in our study explicitly were informed to continue their antithrombodic medicine regardless of which drug they were taken, 76 of 172 patients still discontinued their antithrombotic drugs. This may be due to being used to discontinue antithrombotic therapy when having surgery, which may have increased the risk of thromboembolic events as patients are told that it is imperative to immobilize the skin graft by limiting physical activity to avoid rebleeding, haematoma or dehiscence in the early postoperative period. However, a careful balance must be achieved between graft protection and preservation of motion. Nevertheless, it is then important to express clearly to the patients that it is essential to continue antithrombotic treatment due to potential risky conseqences when discontinuing. Meticulous surgical technichs, adequate wound dressings, and communication with the patients about signs of postoperative bleeding may prevent complications associated with taken antitrombotic medications [21].

In conclusion, our data showed that continuing monotherapy with acetylsalicylic acid, clopidogrel, warfarin or fish oil did not seem to increase the risk of hematoma or graft loss.

The limitation of this study is the limited number of patients taking newer drugs, such as factor Xa inhibitors or direct thrombin inhibitors. Therefore, our conclusion can thus not be extrapolated to these patients. Another limitation is that a substantial part of the patients in antithrombotic treatment discontinued their medication prior to the operation despite of being instructed to do so. It may also have been beneficial to follow-up on patients entended the five to seven days post-operatively.

Disclosure statement

The authors report no conflicts of interest.

ORCID

Lone Jørgensen https://orcid.org/0000-0002-4197-3066

References

[1] Adelborg K, Grove EL, Sundboll J, et al. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. Heart. 2016;102(23):1883–1889.

[2] Isted A, Cooper L, Colville RJ. Bleeding on the cutting edge: a systematic review of anticoagulant and antiplatelet continuation in minor cutaneous surgery. J Plast Reconstr Aesthet Surg. 2018;71(4):455–467.

[3] O'Neill JL, Taheri A, Solomon JA, et al. Postoperative hemorrhage risk after outpatient dermatologic surgery procedures. Dermatol Surg. 2014;40(1):74–76.

[4] Harbottle M, Telfer M, Hunjan PS, et al. Bleeding complications in cutaneous surgery for patients on warfarin who have skin cancer of the head and neck. Br J Oral Maxillofac Surg. 2014;52(6):523–526.

[5] Liu X, Lammers L, Nelemans PJ, et al. Preoperative management of antithrombotic medication in Mohs micrographic surgery. Acta Derm Venereol. 2015;95(7):845–847.

[6] Cook-Norris RH, Michaels JD, Weaver AL, et al. Complications of cutaneous surgery in patients taking clopidogrel-containing anticoagulation. J Am Acad Dermatol. 2011;65(3):584–591.

[7] Alam M, Goldberg LH. Serious adverse vascular events associated with perioperative interruption of antiplatelet and anticoagulant therapy. Dermatol Surg. 2002;28(11):992–998; discussion 998.

[8] Kimyai-Asadi A, Jih MH, Goldberg LH. Perioperative primary stroke: is aspirin cessation to blame? Dermatol Surg. 2004;30(12 Pt 2):1526–1528. discussion 1528–1529.

[9] Heard LK, Shanahan C, Maggio KL. Complications with new oral anticoagulants dabigatran and rivaroxaban in cutaneous surgery. Dermatol Surg. 2017;43(4):597–599.

[10] Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. J Am Acad Dermatol. 2003;48(2):233–237.

[11] Koenen W, Kunte C, Hartmann D, et al. Prospective multicentre cohort study on 9154 surgical procedures to assess the risk of postoperative bleeding - a DESSI study. J Eur Acad Dermatol Venereol. 2017;31(4):724–731.

[12] Otley CC. Continuation of medically necessary aspirin and warfarin during cutaneous surgery. Mayo Clin Proc. 2003;78(11):1392–1396.

[13] Jarjis RD, Jorgensen L, Finnerup K, et al. Complications in skin grafts when continuing antithrombotic therapy prior to cutaneous surgery requiring skin grafting: a systematic review. J Plast Surg Hand Surg. 2015;49(3):129–134.

[14] Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–381.

[15] Dobbs E. SketchAndCalc. [Accessed 2004, 2019; Published 2011]. Available from: www.SketchAndCalc.com.

[16] Nast A, Ernst H, Rosumeck S, et al. Risk of complications due to anticoagulation during dermatosurgical procedures: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2014;28(12):1603–1609.

[17] Eichhorn W, Kluwe L, Heiland M, et al. Lack of evidence for increased risk of postoperative bleeding after cutaneous surgery in the head and neck in patients taking aspirin. Br J Oral Maxillofac Surg. 2014;52(6):527–529.

[18] Reddy KS, Chittoria RK, Babu P, et al. Effectiveness of fibrin glue in adherence of skin graft. J Cutan Aesthet Surg. 2017;10(2):72–75.

[19] Han HH, Jun D, Moon SH, et al. Fixation of split-thickness skin graft using fast-clotting fibrin glue containing undiluted high-concentration thrombin or sutures: a comparison study. Springerplus. 2016;5(1):1902.

[20] Tan WXE, Lee JT, Kang GCW, et al. Reverse alphabetical grafting: an innovation to ensure successful split-thickness skin grafting. Plast Reconstr Surg Glob Open. 2019;7(7):e2317.

[21] Palamaras I, Semkova K. Perioperative management of and recommendations for antithrombotic medications in dermatological surgery. Br J Dermatol. 2015;172(3):597–605.