King et al., Arch Surg Oncol 2017, 3:4
DOI: 10.4172/2471-2671.1000128

Archives of Surgical Oncology

Research Article OMICS International

Multiple Anticoagulant Use Increases Wound Complications Following Resection of Lower Extremity Soft Tissue Sarcomas

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Abstract

Objectives: Prevention of thromboembolic complications is a concern in patients who undergo resection of Soft Tissue Sarcomas (STS). The risk of thrombosis must be balanced with the increased risk of haemorrhage and wound healing complications in this difficult patient population. In this study we aim to determine if multiple anticoagulant use increases the risk of post-operative Major Wound Complications (MWC) in STS of the lower extremity.

Material and methods: Between 2000-2015, 134 patients with localized STS of the lower extremity underwent limb-salvage surgery. Patient and treatment variables, including anticoagulant use, wound outcomes, and thrombotic events were reviewed. Predictors for MWC were evaluated using the fisher exact test for Univariate (UVA) and logistic regression for Multivariate Analysis (MVA).

Results: The overall MWC rate in this patient population with lower extremity and buttock tumours was 35%. The MWC rate in patients on ≥2 anticoagulants were 60% versus 24% in patients taking <2 anticoagulants (p<0.001). Patients on warfarin had a higher MWC rate, 61%, versus those not taking warfarin, 28% (p=0.004). On MVA, warfarin use (p=0.02, OR 3.6) On MVA, ≥2 anticoagulants (p<0.001, OR 4.3) and warfarin use (p=0.02, OR 3.6) were found to have an increased propensity for MWCs.

Conclusion: Patients administered, ≥2 anticoagulants and warfarin use was associated a higher risk of post-operative MWCs. Anticoagulants used for DVT prophylaxis were not associated with an increased risk of MWC alone, but only when combined with other anti-coagulants.

Keywords: Thrombosis; Anticoagulant; Multivariate analysis; Thromboembolic

Introduction

Wound healing is a dynamic process that involves multiple mechanisms and can be affected by a variety of exogenous factors. The wound healing cascade involves several mechanisms which include inflammation, cell proliferation, matrix deposition, and matrix remodelling [1,2]. The use of anticoagulants is a common practice in patients undergoing major orthopaedic surgeries, especially in the resection of Soft Tissue Sarcomas (STS). Patients are typically administered anticoagulants such as heparin and Low Molecular Weight Heparin (LMWH), in addition to mechanical prophylaxis the day prior to or immediately after surgery to prevent thromboembolic events [3-5]. Although it is critical to prevent venous thromboembolism after surgery and minimize the risk of fatal Pulmonary Embolism (PE), there has been data to suggest that anticoagulant use leads to the increased risk of Major Wound Complications (MWCs) post-operatively [6-14]. Factors that have been demonstrated in the literature to contribute to post-surgical MWCs in patients with STS, include, but are not limited to, lower extremity tumours, tumour proximity to skin surface, tumour size, patient age, and pre-operative radiation therapy [6-12].

The issue of anticoagulation is complicated in the subset of patients who undergo major orthopaedic surgeries that require additional anticoagulant use due to pre-existing medical co-morbidities. It remains to be determined if these patients are at increased propensity for post-operative MWCs as well. The aim of this retrospective study was to determine whether patients who are inherently at a higher risk of MWCs with lower extremity tumours have a compounded risk of post-surgical MWCs when taking anticoagulants after STS resection. In addition, the effect of MWCs between various classes of anticoagulants, including heparin, LMWH, warfarin, clopidogrel, and aspirin was examined. The ultimate goal is to help define the risks associated with anticoagulant use in soft tissue sarcoma patients to help determine the optimal anticoagulant strategy for these patients to maximize outcomes.

Materials and Methods

All investigators completed training in both human research and patient privacy and obtained approval from the Institutional Review Board (IRB). Patient records from the orthopaedic oncology database and tumour registry at the Medical College of Wisconsin were then reviewed for all cases of STS of the lower extremity between 2000 and 2015. Pathology review was done at the time of initial diagnosis. Patients were staged according to the 2009 American Joint Committee on Cancer (AJCC) system seventh edition. One hundred and thirty-four patients were identified in our database who met the inclusion criteria.

Exclusion criteria included metastatic disease on initial presentation, age <18 years old, STS of locations other than the lower extremity or buttock, recurrent sarcomas, and small subcutaneous tumours. Patients who did not have complete medical records including treatment information and a pathology report, and follow-up of less than 6 months were also excluded. Histopathologic types demonstrating

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Received July 17, 2017; **Accepted** August 07, 2017; **Published** August 14, 2017

Citation: King DM, Bedi M, Hackbarth DA, Neilson JC (2017) Multiple Anticoagulant Use Increases Wound Complications Following Resection of Lower Extremity Soft Tissue Sarcomas. Arch Surg Oncol 3: 128. doi: 10.4172/2471-2671.1000128

rhabdomyosarcoma, extraosseous primitive neuroectodermal tumour, Kaposi's sarcoma, angiosarcoma, and aggressive fibromatosis were also excluded.

All patients were discussed at a multidisciplinary tumour board consisting of surgical and orthopaedic oncologists, medical and radiation oncologists, radiologists and pathologists. Treatment recommendations from this tumour board were presented to the patient. Radiotherapy and Chemotherapy Radiation was typically recommended in patients who had deep, intermediate to high grade tumors or those patients that had tumours near neurovascular bundles or had positive margins. Patients received a median preoperative radiation dose of 50 Gy and median post-operative radiation dose of 60 Gy using 3D-conformal radiation or Intensity-Modulated Radiotherapy (IMRT). Chemotherapy was recommended and administered in patients who were typically <70 years of age, with large (>5 cm), deep, and high-grade lesions. Chemotherapy was delivered prior to radiation therapy, using Adriamycin and ifosfamide for 2 to 3 cycles. Surgery Limb-sparing resection was performed in all patients either as the sole management or 4 to 6 weeks after radiotherapy. Wide surgical resection was performed by fellowship trained musculoskeletal oncologists grossly through normal tissue planes with sacrifice of arteries or veins that were involved by tumor. Preservation of neurovascular structures was performed when possible. The goal of surgery was to achieve negative margins (R0). Vascular or reconstructive plastic surgeons were involved in cases that required vascular reconstruction, difficult wound closures and free flap reconstructions.

Anticoagulant use data was obtained through medical records and included information on patient and tumour characteristics, past medical history, medications, including anticoagulant use. Anticoagulant use for thromboembolic prophylaxis included warfarin, heparin and LMWH. Anticoagulant use by patients for medical co-morbidities included aspirin (ASA), warfarin and Clopidogrel. Patients had to have been on anticoagulants for their co-morbidities prior to their surgery. Patients who were not taking the above medications at the time of their diagnosis were recorded as non-users. Rationale for anticoagulant use: It was felt that patients undergoing major resection of lower extremity sarcomas should receive standard orthopaedic anticoagulation according to the Antithrombotic Therapy and Prevention of Thrombosis Guidelines [15]. These recommendations included warfarin or LMWH depending on provider preference. During the study period, ASA was not considered adequate prophylaxis alone to prevent thromboembolic events, so additional anticoagulants were added to the post-operative regimen. Additionally, many patients placed on warfarin were bridged with LMWH until therapeutic. The length of anticoagulation varied among practitioners, but typically was maintained for 3 to 4 weeks following surgical resection. Statistical Analysis Clinical, pathologic and treatment characteristics for MWC were assessed and summarized in Table 1. Wound outcomes were a dichotomous variable. The fisher exact test was used for Univariate Analysis (UVA). If a variable had a p-value of less than 0.25, then it was used in the multivariate model. A logistic regression analysis was used for Multivariate Analysis (MVA). For all analysis, type I error was maintained at 0.05 and all tests were two-sided.

Patients at the institution were monitored with the following protocol. Follow-up care was coordinated through the medical oncologists in a multidisciplinary clinic, in conjunction with surgical oncology, radiation oncology, and interventional radiology. An MRI of the primary site and a PET/CT or a CT of the chest, abdomen, and pelvis was obtained for initial staging. Follow-up included an interval history, physical exam and imaging with and CT of the chest, abdomen and pelvis every 3 to 6 months to monitor for disease progression. MRI of the primary tumour was also acquired every 4-6 months or if any localized symptoms ensued. Follow-up occurred until the patient died or decided to pursue hospice measures.

Age	≤70 >70	106 (79%) 28 (21%)
Gender	F M	60 (45%) 74 (55%)
Performance Status (KPS)	80-100 ≤70	110 (82%) 24 (18%)
Cardiovascular Disease	No Yes	121 (90%) 13 (10%)
Diabetes	No Yes	121 (90%) 13 (10%)
Smoking History	No Yes	88 (66%) 46 (34%)
Stage	I II III	25 (19%) 22 (16%) 87 (65%)
Size	<10 cm ≥10 cm	67 (50%) 67 (50%)
Location	Proximal Lower Extremity Buttock Distal Lower Extremity	102 (76%) 11 (8%) 21 (16%)
Grade	Low Intermediate High	31 (23%) 9 (7%) 94 (70%)
Histology	Undifferentiated Liposarcoma/ Leiomyosarcoma Myxofibrosarcoma Synovial Spindle cell Other	33 (25%) 43 (32%) 21 (16%) 7 (5%) 11 (8%) 19 (14%)
Neoadjuvant Chemotherapy	No Yes	88 (66%) 46 (34%)
Timing of RT	No RT Preoperative RT Post-operative RT	12 (9%) 114 (85%) 8 (6%)
Flap Reconstruction	No Yes	83 (62%) 51 (38%)
Anticoagulation	Coumadin ASA Plavix No anticoagulation	23 (17%) 35 (26%) 1 (1%) 75 (56%)
Post-operative Anticoagulation	Heparin LMWH	12 (9%) 94 (70%)
Number of Anticoagulants	<2 ≥2	92 (69%) 42 (31%)

Table 1: Clinical, pathologic, and treatment characteristics.

Post-operative MWCs were defined as those requiring re-operation for wound management within 4 months following limb-salvage surgery. Patient variables evaluated included age, gender, Karnofsky Performance Status (KPS), presence or absence of cardiovascular disease, diabetes, and smoking history. Use of anticoagulants prior to and after surgical management was also assessed. Anticoagulants investigated included aspirin, Clopidogrel, warfarin, heparin and low-molecular weight heparin. Tumour variables assessed included size and location of primary disease. Treatment variables included chemotherapy and radiation to the primary tumour.

There were 151 patients in the soft tissue sarcoma dataset. Of these, 134 presented with lower extremity tumours and were eligible for analysis, underwent definitive resection, and were followed at the treating institution. Patient demographics, tumour and treatment variables are listed in Table 1. Staging of patients was performed using the American Joint Committee on Cancer (AJCC) guidelines. The

mean age at diagnosis for patients presenting with stage I-III disease was 56 (range: 19-91). The majority of patients had high grade tumours (70%).

Statistical software MedCalc (Version 15.6; MedCalc Software bvba, Ostend, Belgium) was used for all data analysis. The fisher exact test was used for univariate analysis (UVA). If a variable had a p-value of less than 0.25, then it was used in the multivariate model. A logistic regression analysis was used for Multivariate Analysis (MVA). For all analysis, type I error was maintained at 0.05 and all tests were two-sided. A probability of <0.05 was accepted as statistically significant.

Results

Median follow-up was 3.9 years. The overall MWC rate in patients with lower extremity and buttock tumours was 35% (48/134). Of these, 21 (44%) patients developed wound dehiscence and necrotic wounds, 14 (29%) patients had delayed wound healing, 10 (21%) patients developed infection, and 3 (6%) patients developed post-operative hematomas. Of the patients who were administered heparin post-operatively, 3 (25%) developed MWCs compared to 37 (32%) who were not administered heparin (p=0.75). Of the patients who were administered LMHWH post-operatively for thromboembolic prevention, 32 (34%) developed MWCs compared to 11 (31%) who were not administered LMWH (p=0.84). However, of the patients who were on ASA prior to and at the time of resection, 18 (51%) developed MWCs post-operatively versus 27 (28%) who were not taking ASA (p=0.02). The post-operative MWC rate was 61% in patients on warfarin prior to and at the time of surgery versus 28% in patients not taking warfarin (p=0.004). All patients who took Clopidogrel for medical conditions developed post-surgical MWCs, however this was not statistically significant (p=0.32). Moreover on MVA, of the anticoagulants, only warfarin was found to have an increased propensity for MWCs (p=0.02, 95% CI 1.2563 to 10.3011, OR 3.6).

There were 23 patients who were taking warfarin at the time of surgery, and 12 of these patients were bridged with Low Molecular Weight Heparin (LMWH). Of those that were bridged, 83% developed wound complications compared to 36% of patients who were not on warfarin and not bridged with LMWH (p=0.036, OR 6.6).

STS patients who were on at least two anticoagulants at the time of wide local excision had an increased rate of post-surgical MWCs, 60 compared to 24% who were only taking or administered one anticoagulant or less (p<0.001). On MVA, patients who were administered 2 or more anticoagulants (p<0.001, 95% CI 1.8963 to 9.7052, OR 4.3) had an increased risk of post-surgical MWCs. There were no other variables that predicted for MWCs on MVA.

Increasing age (p=0.03) and proximal lower extremity tumours (p=0.02) were the only additional variables that contributed to an increased risk of post-operative MWCs on UVA (Table 2). Five patients developed venous thromboembolism and 4 patients developed pulmonary embolism in the 3 months following the surgical resection (Table 3).

Variable	P
Age	0.01
Sex	NS
Performance Status	NS
Diabetes	NS
Cardiovascular Disease	NS
Smoking History	NS
Tumor Location	0.02
Tumor Size	NS
Chemotherapy	NS
Reconstructive Flap at Time of Surgery	NS
Timing of RT	NS
ASA	0.02
Warfarin	0.004
Clopidogrel	NS
Heparin	NS
LMWH	NS
Multiple Anticoagulants (≥2)	<0.001

Table 2: Predictors of post-operative wound complications.

Patient	1	2	3	4
Symptomatic?	No	Yes	Yes	Yes
Wound Complication	No	Yes	No	Yes
Anticoagulation	LMWH	Heparin	LMWH	Coumadin+LMWH

Table 3: Summary of patients who developed post-operative pulmonary embolism.

Discussion

Wound healing is a complex cascade of reactions that occur at various time points and involve the interaction of a multitude of growth factors, proteins, blood and extracellular components. These processes begin with the inflammatory period, followed by the proliferative and maturational phases. Although various factors may be predominant in each phase, there is overlap pertaining to the interaction of these components to ensure proper healing occurs [1,2]. In the inflammatory phase, growth factors such as transforming growth factor, epidermal growth factor, insulin-like growth factor, and vascular endothelial growth factor are present, along with multiple complements (C3 and C5) and other cytokines (tumour necrosis factor). In the proliferative phase, epithelial cells and granulation will occur along with angiogenesis by many similar factors that are present in the inflammatory phase in addition to fibroblast growth factor, platelet-derived growth factors, angiogenin, angiotrofin and thrombospondin. The last phase, maturation, involves scar formation which implicates many of the components above [16-20]. Although many internal factors contribute to wound healing, other mechanisms may impact this phenomenon, including environmental interactions [21].

The epigenetic means of patients' environment may produce various changes in the expression of DNA and genes that lead to the dysregulation of the wound healing cascade [21]. Studies have shown that modifying epigenetic markers impact the level and healing and thus affect the propensity for wound complications. These processes may be triggered by trauma, such as surgery, and other environmental stresses that lead to DNA and protein modification [21-23]. For instance, in the inflammatory phase, epigenetic mechanisms contribute to the commencement and continuation of processes by regulation of factors that are produced. However, certain environmental influences may affect elements through genetic modification and lead to inhibition of the initial stage of wound healing. Similarly, in the proliferative and maturation phases, epigenetic change due to exogenous and endogenous components could lead to downregulation of various aspects of the cascade and poor wound healing [21-23]. In the present study, the exogenous factor of anticoagulation may have led to the modification of DNA and protein expression in the wound healing cascade [24].

Several studies have assessed the impact of anticoagulant use on post-surgical MWCs; however, there has been little data on the consequences of anticoagulation on MWCs in the setting of STS. It

is known that patients who have malignancies are at an intrinsically higher risk of thromboembolic events. This presumed increased risk in sarcoma patients' results in a desire for aggressive anticoagulation by co-managing oncology and medical providers. While it is imperative to prevent the incidence of thromboembolic events through the use of effective anticoagulants with a low risk profile [25-27], the potential wound complications associated with aggressive anticoagulation are largely uncharacterized. In this retrospective study, STS patients taking 2 or more anticoagulants and those taking warfarin prior to and after surgery had a higher incidence of MWCs. To date, this is the only study that has correlated this clinical outcome with anticoagulant use for thromboembolic prevention in STS patients.

There is a paucity of information on multiple anticoagulant use or even single agent anticoagulant use and wound outcomes in other disease settings, particularly in an oncologic population. Our study has shown that regardless of the class of drug, patients who took at least 2 anticoagulants in the post-operative setting also a 4.3 times increased risk of MWCs. This study is the first to show an impediment of the use of multiple anticoagulants in patients with STS post-operatively. This phenomena, however, has been established in the dermatologic setting. Bordeaux et al. prospectively assessed dermatologic surgical complications in patients who were on antiplatelet or anti-coagulant medications. In this study of 1911 patients, 38% were on antiplatelet or anti-coagulants, and 8% were on ≥2 forms of therapy. Patients on Clopidogrel and warfarin had over 40 times more risk of bleeding complications (p=0.03), such as hematoma or speri- or post-operative haemorrhage, compared to those who were on single agent treatment [18].

The present study also revealed that patients with lower extremity STS on warfarin had more than 3 times the risk of post-operative MWCs. The influence of anticoagulation and wound healing is attributed to the mechanism of action of the various classes of drugs. Warfarin inhibits the synthesis of vitamin K factors II, VII, IX and X, and thus prevents fibrin deposition which occurs in the proliferative and maturational phases of the wound cascade. Moreover, warfarin is a vitamin K antagonist, which is an essential vitamin in the clotting phase of wound healing [7]. Heparin, in combination with anti-thrombin, inhibits factors IX, X, Xa, XI, and XII in the coagulation cascade. Both warfarin and heparin are thought to affect wound healing by inhibiting the formation of fibrin [7,28,29]. ASA irreversibly inhibits platelet aggregation and reduces the inflammation in wounds mediated by the metabolites of arachidonic acid [7,30]. Although the biochemical interaction of these medications differ, they have each been shown to impact wound healing such that there is an increased risk of infection, time to heal, development of hematoma, and wound dehiscence when administered [7,10,11].

Perhaps the most abundant data on the impact of anticoagulant therapy on MWCs comes from the orthopaedic population. Wang et al. utilized the Global Orthopaedic Registry to review the incidence of complications in 3,755 patients who underwent total hip or knee arthroplasty [4]. The rates of thromboembolism, infections, bleeding and other complications were assessed in patients taking warfarin or LMWH for prophylaxis. This study demonstrated that compared to warfarin, the administration of LMWH led to higher rates of post-operative bleeding (2% versus 6%, respectively), re-operations (1.3% versus 2.3%, respectively), transfusions (22% versus 29%, respectively), and surgical site infections (0.6% versus 1.6%, respectively) [4]. Contrary to this analysis, our study revealed that patients who were on warfarin had a higher risk of post-surgical MWCs (p=0.02, 95% CI 1.2563 to 10.3011, OR 3.6) and there was no statistically significant increase in MWCs in patients who were administered LMWH alone in the post-operative setting (p=0.83). Parvizi et al. assessed factors that contributed to sepsis and subsequent revision after 78 patients underwent joint arthroplasty [31]. Variables reviewed included co-morbidities, and medications including anticoagulants. All patients were administered warfarin initiating on the day of surgery and for 6 weeks post-operatively, with a goal International Normalized Ratio (INR) of 1.5. In this study, the INR was significantly higher in patients who developed post-operative infection (p=0.03). Moreover an INR of >1.5 at the time of discharge was shown to lead to higher rates of MWCs compared to those patients with an INR of ≤1.5 (22% versus 8%, respectively, p=0.005). The authors also noted that patients who received heparin as an alternative to warfarin had a higher predilection for hematomas, persistent drainage and delayed wound healing [31]. Our retrospective analysis did not allow us to accurately determine INR levels of our patients at discharge. A prospective analysis would allow us to better determine this potential relationship. Lastly, Bordeaux et al. not only discerned that ≥2 antiplatelets and anti-coagulants led to increased bleeding complications in dermatologic surgeries, but also that warfarin use had a significantly higher risk of bleeding complications such as hematoma and haemorrhage [28]. This finding has been echoed in other studies evaluating post-operative complication in the cutaneous setting [28,32,33].

Limitations of this study include its retrospective nature and the consequent potential for patient heterogeneity and selection bias. Moreover, assessment of anticoagulants, including those used for medical co-morbidities was assessed through electronic medical record alone and there was no verification of administration of these medications other that what was indicated in the patient chart. Doses and compliance or regularity were not established and although complete records in terms of MWCs, treatment and patient characteristics were assessed, there were instances when medication reconciliations were not available and thus data pertaining to these medications were not analyzed. Lastly, the sample size of this cohort was relatively small and heterogeneous in nature inserting other potential bias into the analysis a prospective study incorporating other medications that may impede wound healing, such as non-steroidal anti-inflammatories, steroids, and immunosuppressants in addition to more detailed reporting of anticoagulant use would potentially shed further light on variables that influence post-operative MWCs.

Conclusion

Patients on ≥2 anti-coagulants following lower extremity sarcoma resection had a higher rate of post-operative MWCs. Additionally, patients on warfarin following resection had higher MWC rates than patients placed on LMWH or heparin alone for the prevention of venous thromboembolism. As such, caution should be taken in patients on other anticoagulants for added co-morbidities. Further studies with a larger sample are needed to corroborate these findings.

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Citation: King DM, Bedi M, Hackbarth DA, Neilson JC (2017) Multiple Anticoagulant Use Increases Wound Complications Following Resection of Lower Extremity Soft Tissue Sarcomas. Arch Surg Oncol 3: 128. doi: 10.4172/2471-2671.1000128