Antithrombotic drugs and the risk of bloody punctures in regional anesthesia - a retrospective registry analysis

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ABSTRACT

Introduction The risk of bleeding during regional anesthesia implementation in patients on antithrombotic therapy remains poorly characterized. We; therefore, analyzed bloody tap rates and adjusted ORs comparing patients who take antithrombotic medications with those who do not.

Methods 65,814 qualifying regional anesthetics (2007–2019) from the Network for Safety in Regional Anesthesia and Acute Pain Therapy registry were included in a retrospective cohort analysis. Procedures in patients who took antithrombotic drugs were compared with procedures in patients who did not. The primary outcome was bloody puncture, defined as any kind of blood aspiration during placement. Secondarily, we considered timely discontinuation of thromboprophylaxis and the impact of various drug classes. As a sensitivity analysis, we used propensity matched groups.

Results Patients on antithrombotic therapy were more likely to have a bloody puncture during peripheral nerve block implementation (adjusted OR 1.60; 95% CI 1.33 to 1.93; p<0.001) irrespective of whether therapy was discontinued. In contrast, bloody neuraxial blocks were no more common in patients who took antithrombotic medications (adjusted OR 0.95; 95% CI 0.82 to 1.10; p=0.523) so long as they were paused per guideline. Across both peripheral and neuraxial blocks, concurrent use of more than one platelet and/or coagulation cascade inhibitor nearly doubled the odds (adjusted OR, 1.89; 95% CI 1.48 to 2.40; p<0.001).

Discussion Patients on antithrombotic therapy receiving peripheral blocks are at increased risk for bloody punctures irrespective of discontinuation practice. Patients having neuraxial blocks are not at increased risk so long as antithrombotics are stopped per guidelines. Patients who take combined medications are at especially high risk. Guidelines for discontinuing antithrombotic treatments for neuraxial anesthesia appear to be effective and should possibly be extended to high-risk peripheral blocks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Relevant bleeding complications in regional anesthesia are rare. Bloody tap may be an initiating event for bleeding complications.

WHAT THIS STUDY ADDS

⇒ Preblock antithrombotic drug use influences the odds of bloody tap as a surrogate indicator.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data may influence future guidelines on regional anesthesia and antithombotic drug use.

INTRODUCTION

Regional anesthesia has become increasingly popular both for anesthesia and postoperative analgesia. Although the benefits of regional anesthesia are often apparent, bleeding complications are feared, especially in patients on antithrombotic medications. Given the variety of antithrombotic agents, there remains uncertainty about their perioperative use in patients having regional anesthesia, especially for peripheral blocks.

For neuraxial blocks, there are national and international guidelines that specify how long various antithrombotic medications should be paused before epidural or spinal puncture.[1–4] Suggestions are available for individual drugs, but not for various combinations. Bleeding complications consequent to peripheral nerve blocks are usually considerably less serious than those that occur during neuraxial blocks, and consequently, peripheral blocks are often performed in anticoagulated patients. Nevertheless, bleeding consequent to peripheral block insertion can cause reversible or persistent sensory and motor deficits, prolonged and complicated hospital stays, need for transfusions, and even death from hemorrhage.[3 5–7] We currently lack specific guidelines for peripheral regional blocks in patients taking antithrombotic drugs, presumably because there is little evidence on which to base decisions. Consequently, preoperative management of antithrombotic drugs for peripheral blocks is largely based on clinician's assessment of block site compressibility, adjacent vascularity, and the potential consequences of bleeding.[1–3] Approaches to a more differentiated risk assessment for peripheral nerve and interfascial plane blocks have recently been published by the Canadian Anesthesiologists' Society, and also by the European Society of Anesthesiology and Intensive Care jointly with the European Society of Regional Anesthesia and Pain Medicine.[3 8]

Vascular puncture can be indicated by blood becoming visible in the needle hump, catheter or syringe. Even if not every bloody puncture may

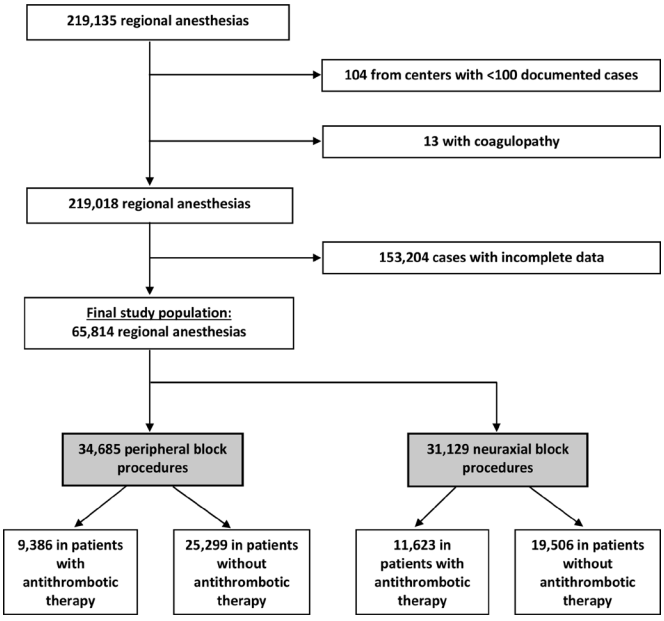

Figure 1 Flow chart of case selection.

lead to a serious complication,[8] the risk of a poor neurological outcome in spinal hematoma is almost quadrupled after a bloody tap.[9] For peripheral blocks, no risk data for a negative outcome after bloody puncture have been described to date. However, it is also evident that most serious complications are described for blocks with a high bloody tap risk such as the psoas compartment block.[8 10] Given the rarity of clinical meaningful bleeding complications (eg, blood transfusion, surgical revision, paraplegia caused by epidural bleeding, neurological impairment caused by peripheral hematoma), bloody taps are often used as a surrogate parameter for an initiating event. Especially in patients receiving thromboprophylaxis, there are many case reports of bleeding complications.[5–7 11] Thus, if intraoperative antithrombotic medications need to be administered and epidural catheter insertion was bloody, guidelines recommended to postpone surgery or to discuss it.[1 2] The incidence of vascular punctures is regularly investigated in studies as a variable of interest and it was shown to be influenced by ultrasound guidance[12–14] and to vary with puncture site[8 10] or patients' state of consciousness during regional anesthesia implementation.[15]

So far, there are no data showing a direct relationship between antithrombotic therapies and bloody taps in regional anesthesia.

We; therefore, analyzed whether antithrombotic medication influences the odds for a bloody puncture during neuraxial and peripheral regional anesthetic implementation using the Network for Safety in Regional Anesthesia and Acute Pain Therapy registry. Our primary hypothesis was that patients taking antithrombotic drugs are at higher odds of having a bloody puncture than those who do not. Our secondary hypotheses were that the odds of a bloody puncture depends on the timing of antithrombotic interruption, and on the classes of antithrombotic drugs used.

METHODS

Based on the submitted study protocol which included a statistical analysis plan, registry data were released on June 4, 2020, by the Scientific Panel of the network (www.net-ra.eu). This article is consistent with the REporting of studies Conducted using Observational Routinely-collected Data guidance.[16]

The Network for Safety in Regional Anesthesia and Acute Pain Therapy was founded in 2007 under the auspices of the German Society for Anaesthesiology and Intensive Care Medicine and the Professional Association of German Anesthesiologists (Nürnberg, Germany). The registry collects perioperative primary data related to regional anesthesia procedures, intravenous patient-controlled analgesia, and combinations thereof.[17] As previously described, each participating hospital uses its own system for documenting regional anesthesia and its acute pain service.[18 19] Since the data of the documented treatments are routine data collected directly at the patient's bedside, they are subjected to on-site quality control. Our registry provides clear definitions of how the individual items are to be collected. These are known to the participating hospitals and should be followed. The data are transmitted to the registry in anonymized form. Uploaded data are not automatically checked for completeness since not all fields are required.

Data extraction

We extracted data from 2007 to 2019, a period that included 219,135 regional anesthetics from 26 hospitals. We restricted our analysis to regional anesthetics from centers that contributed at least 100 cases during the specified period. Procedures in patients with non-drug-induced coagulation disorders were excluded. Qualifying procedures were all initially analyzed, and then separately for peripheral and neuraxial blocks (figure 1).

Data integrity was evaluated according to specific rules that identified and deleted incorrectly entered data and identified cases with missing information. We excluded implausible data for sex (ie, male designation excludes obstetrics), age (range 0–119 year according to the registry restriction *year of birth >1900)*, height and weight (range 30–249 cm and 1–249 kg according to the registry restrictions), body mass index (BMI) (range from 12 to 85 kg/m^2 according to the registry restrictions for height and weight), and creatinine (0–10 mg/dL or <884 µmol/L). Only cases with complete and internally consistent data were used for analysis.

The registry records more than 20 individual antithrombotic drugs which were grouped according to their mechanisms of action into anticoagulants, antiplatelet agents, other antithrombotic drugs, or combinations thereof.

Treating anesthesiologists recorded whether antithrombotic medications were discontinued in a timely manner or did not need to be discontinued, based on current national guidelines.[4 20] Low-dose aspirin was normally continued in accordance with the guideline because a substantive increase in bleeding risk was not expected.[21 22]

For peripheral blocks, there is a single national guideline published in 2005 by the German Society for Anesthesiology and Intensive Care Medicine.[20] It recommends that psoas compartment blocks be handled the same way as epidural blocks. We thus considered psoas compartment blocks to be neuraxial procedures, along with spinal and epidural blocks. For other peripheral and plexus blocks, there is no specific guidance in Germany. Peripheral blocks, however, have been mentioned in international guidelines during the observation period.[1 2] Designation to the two groups 'paused adequately long' or 'not paused adequately long' was therefore a clinical decision by the attending anesthesiologist, presumably based on whether coagulation was thought to remain unimpaired.

For neuraxial blocks, the German national guideline is largely consistent with international guidelines and contains detailed suggestions for discontinuation of all available antiplatelet and

anticoagulant drugs.[4] When drugs were discontinued at or before the recommended times, cases were designated as having been 'paused per guideline'. We assumed that both antithrombotic therapies 'not paused' and 'allowed to continue' would ultimately result in impaired clotting. Both designations were therefore combined into 'not paused per guideline'.

The Network for Safety in Regional Anesthesia and Acute Pain Therapy registry defines a bloody puncture as any blood aspiration through the needle or catheter during regional anesthesia placement. The dichotomous occurrence of a bloody puncture (yes or no) was predefined as our primary event.

Statistical analysis

The primary and secondary analyses complied with the a priori statistical analysis plan that was included in the study protocol submitted to the registry before data were released to the investigators. We predefined potential confounding factors for our primary and secondary analyses including year of surgery, sex, age, BMI, American Society of Anesthesiologists physical status, renal insufficiency, use of sedative drugs or general anesthesia during block performance, puncture site, catheter use versus single shot approach, multiple skin punctures, and use of ultrasound.

For the primary analysis, we identified cases with a documented use of antithrombotic drugs prior to the regional anesthetic block and a reference group without thromboprophylaxis. Our primary outcome was the odds of having a bloody puncture, adjusted for the confounders mentioned above. We initially evaluated the adjusted odds across all documented regional anesthesia procedures, and then separately for peripheral and neuraxial approaches.

Our secondary analysis explored the impact of a guideline-driven pause of antithrombotic therapy on the adjusted odds for bloody punctures. We categorized cases with platelet inhibitor and/or anticoagulant therapy into therapy 'paused per guideline/paused adequately long' or 'not paused per guideline/not paused adequately long' and compared each group to cases in which antithrombotic medications were not used. We also performed a direct comparison of the two groups 'paused per guideline/paused adequately long' and 'not paused per guideline/not paused adequately long'. Additionally, we analyzed the adjusted odds of a bloody puncture with various groups of antithrombotic drugs. Cases were grouped into antiplatelet agents, anticoagulant agents, others, and combined antiplatelet and/or anticoagulant agents, with each being compared with patients who did not take antithrombotic medications. As in our primary analysis, we initially evaluated all regional anesthesia procedures together, followed by independent analyses of peripheral and neuraxial blocks.

We used multivariable logistic regression models for our primary and secondary analyses. Associations were tested using a Wald-type test with 5% type-1-error rate and reported as ORs with 95% CIs. Hosmer-Lemeshow tests evaluated model fit. Testing for multicollinearity showed that variance inflation factors for independent variables were all <1.75. Statistical evaluation was performed using IBM SPSS Statistics V.26 (IBM, USA). Two-sided p values less than 0.05 were considered statistically significant.

We planned to include all qualifying procedures. But we nonetheless conducted a priori sample size estimates to assess practicality of evaluating our primary outcome using PASS 2019 (NCSS, USA). We estimated that 29 612 patients would provide 80% power at a 0.050 significance level (OR 1.2 and R-squared 0.8) in a logistic regression model (assuming 20% of patients took antithrombotic drugs). As the registry contained more than 200 000 cases within the predefined period, the study was considered feasible.

In a post hoc sensitivity analysis, propensity scores were estimated via logistic regression using all potential confounders. Matched pairs were created using nearest neighbor 1–1 matching on the propensity score with caliper 0.1*SD(PS) without replacement via R package 'MatchIt' V.4.3.3. Using the matched data sets for all regional anesthetic procedures, only peripheral, and neuraxial blocks, the treatment effect was estimated by univariable conditional logistic regression analysis and doubly robust adjustment.[23]

Differences in baseline characteristics are expressed as absolute standardized differences, with values <0.1 considered well balanced. Categorical variables are expressed as absolute frequencies and percentages, χ^2 tests were performed to evaluate group differences. Numeric variables (age, BMI) are reported as means and SDs. Group differences were evaluated with Mann-Whitney U tests since variables were not normally distributed.

RESULTS

We considered 219,135 regional anesthesia procedures, but three-quarters were excluded because of missing data, leaving 65,814 for analysis (figure 1). Demographic characteristics and distributions of the clinical and procedural variables for our primary analysis are shown in table 1 (full data available in online supplemental file 1).

There were 34 685 peripheral blocks; 27% of the procedures were done in patients taking anticoagulant and/or antiplatelet drugs. The odds of a bloody puncture was 60% higher when patients took antithrombotic drugs prior to block implementation (table 2, figure 2, >99% power at a 0.050 significance level). A total of 8832 peripheral blocks provided information about discontinuation of the antithrombotic medication of which therapy was judged to be paused adequately in 85%. Antithrombotic therapy strongly increased the odds for a bloody puncture, regardless of whether it was paused per guidelines or not (table 3, figure 2). A total of 9374 peripheral blocks provided information about the drugs used (9% antiplatelet drugs, 82% anticoagulants, 9% combined therapies). After confounder adjustment, the odds for a bloody puncture was increased by 67% for anticoagulants, but not for antiplatelet drugs, and more than doubled for combined therapies (table 4, figure 2, 83% power at a 0.050 significance level).

There were 31,129 neuraxial blocks of which 37% of the procedures were done in patients taking anticoagulant and/or antiplatelet drugs. After confounder adjustment, antithrombotic drugs did not increase the odds of a bloody puncture (table 2, figure 2)—presumably because most were stopped per guidelines. A total of 11,116 neuraxial blocks provided information about discontinuation of the antithrombotic medication, of which therapy was paused per guideline in 89%. Antithrombotic therapy prior to the regional anesthetic block, when paused per guideline, did not increase the odds of a bloody puncture even compared with cases with no antithrombotic therapy (table 3, figure 2). When therapy was not paused per guideline, the odds compared with a guideline-led therapy interruption was significantly increased (table 3, 76% power at a 0.050 significance level), although there was no significant increase compared with cases without antithrombotic therapy (table 3, figure 2). A total of 11,616 neuraxial blocks provided information about the antithrombotic drugs used (7% antiplatelet drugs,

Table 1 Demographic and procedural data

	Patients with thromboprophylaxis	Patients without thromboprophylaxis	P value*†
Sample size, n	21,009	44,805	
Demographic data			
Female sex, n (%)	10,162 (48)	23,830 (53)	<0.001
Mean age (SD) in years	64.0 (15)	58.4 (18)	<0.001
Mean BMI (SD) in kg/m^2	28.2 (6)	28.1 (6)	<0.01
ASA status, n (%)			
ASA 1	1475 (7)	5931 (13)	<0.001
ASA 2	7900 (38)	21,938 (49)	
ASA 3	10,897 (52)	16,349 (37)	
ASA ≥4	737 (4)	587 (1)	
Mean year of surgery (SD)	2012 (3)	2014 (3)	<0.001
Renal insufficiency‡, n (%)	5715 (27)	7244 (16)	<0.001
Procedural data			
Peripheral puncture site, n (%)	9386 (45)	25,299 (57)	<0.001
Neuraxial puncture site, n (%)	11,623 (55)	19,506 (44)	
Awake during block placement, n (%)	9915 (47)	17,949 (40)	<0.001
Sedated/general anesthesia, n (%)	11,094 (53)	26,856 (60)	
Single shot, n (%)	3792 (18)	10,807 (24)	<0.001
Catheter, n (%)	17,217 (82)	33,998 (76)	
Use of ultrasound, n (%)	4221 (20)	15,682 (35)	<0.001
Multiple skin puncture, n (%)	3797 (18)	5742 (13)	<0.001
Bloody tap	626 (3.0)	909 (2.0)	<0.001

*P value compares patients with thromboprophylaxis versus patients without thromboprophylaxis.
†Mann-Whitney U test used to compare means and χ^2 test used to compare proportions.
‡Defined as dialysis or CKD EPI < 60 mL/min/1.73 m².
ASA, American Society of Anesthesiologists; BMI, body mass index; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration estimating equation for eGFR.

85% anticoagulants and 8% were combinations thereof). After confounder adjustment, the odds for a bloody puncture during neuraxial block placement was 77% higher in patients with a combined antithrombotic therapy (table 4, figure 2, 92% power at a 0.050 significance level). The single use of an antiplatelet or anticoagulant drug, mostly stopped per guidelines, did not significantly increase the odds for a bloody puncture.

Sensitivity analysis

Matching resulted in 8220 pairs for peripheral blocks and 9852 pairs for neuraxial blocks. Online supplemental file 1 shows the distribution of variables in the original and matched data sets. After matching, the groups were comparable with respect to covariate balance (absolute SD<0.1 for all variables). Within the propensity matched sample across peripheral blocks, the odds increased about 50% with antithrombotic drugs (OR 1.48; 95% CI 1.19 to 1.82; p<0.001). In contrast, for neuraxial blocks, the odds were unchanged (OR 1.0; 95% CI 0.85 to 1.18; p=0.994, full data available in online supplemental file 2). Results of our propensity-matched sensitivity analysis were therefore similar to those obtained with multivariable regression.

DISCUSSION

The incidence of bloody punctures in our patients was well within the range previously reported which is from 0.9% to 4.4% for peripheral blocks,[15 24–26] and from 0.5% to 3% for neuraxial blocks.[15 24 27] Fortunately, most bloody punctures do not lead to serious complications, but some do.[8 9] For peripheral blocks,

Table 2 Primary outcome: risk of bloody punctures in patients with and without thromboprophylaxis

	Patients with thromboprophylaxis*	Patients without thromboprophylaxis	P value†
Peripheral blocks			
Group size/no of bloody taps (%)	9386/277/3.0	25,299/318/1.3	<0.001‡
Crude OR (95% CI)	2.39 (2.03 to 2.81)	1	<0.001
Adjusted§ OR (95% CI)	1.60 (1.33 to 1.93)	1	<0.001
Neuraxial blocks			
Group size/no of bloody taps (%)	11,623/349/3.0	19,506/591/3.0	0.892‡
Crude OR (95% CI)	0.99 (0.87 to 1.13)	1	0.892
Adjusted§ OR (95% CI)	0.95 (0.82 to 1.10)	1	0.523

*Any kind of antithrombotic medication before regional anesthesia block implementation.
†P value compares patients with thromboprophylaxis to patients without.
‡χ^2 test used to compare proportions.
§Adjusted for year of surgery, sex, age, body mass index, American Society of Anesthesiologists physical status, use of sedative drugs or general anesthesia during block performance, catheter use versus single shot approach, multiple skin punctures, and use of ultrasound.

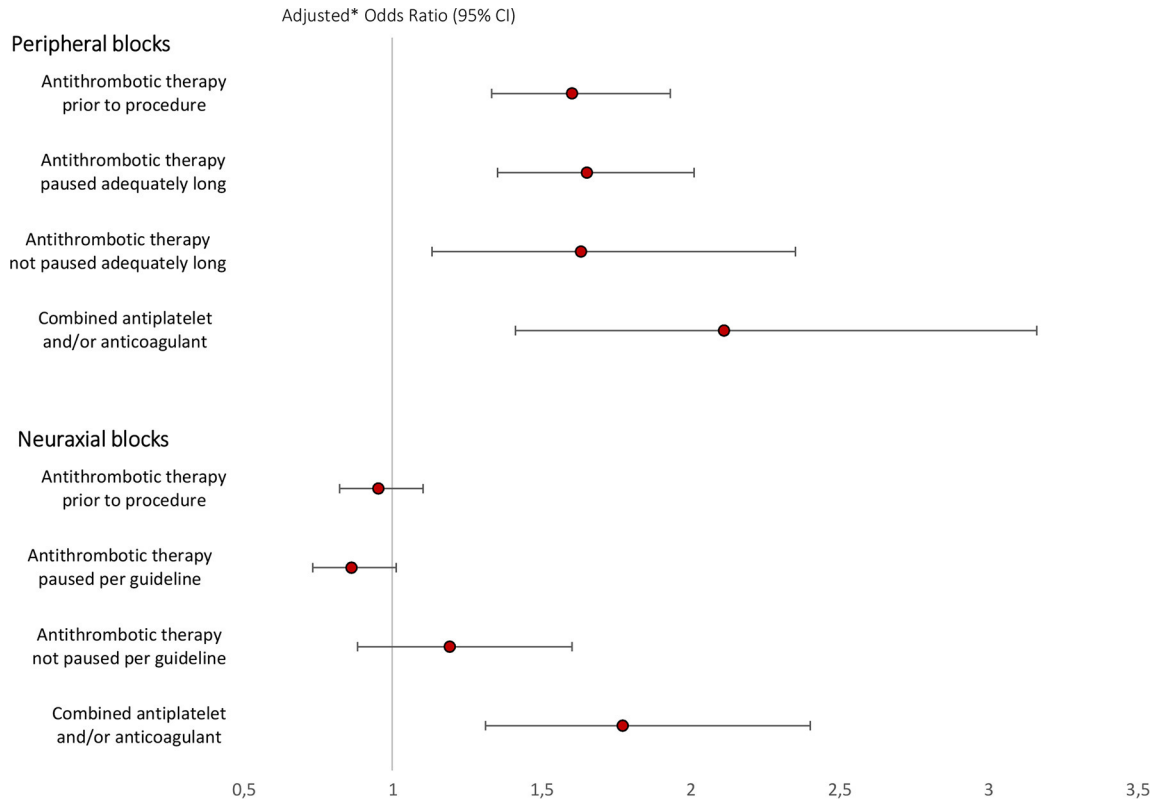

Figure 2 Odds for bloody punctures posed by antithrombotic therapy in regional anesthesia. *Adjusted for year of surgery, sex, age, body mass index, American Society of Anesthesiologistsphysical status, renal insufficiency, use of sedative drugs or general anesthesia during block performance, catheter use vs single shot approach, multiple skin punctures, and use of ultrasound. Comparator: patients without antithrombotic therapy.

the incidence was higher in patients who had an antithrombotic therapy than in those who did not (3% vs 1.3%). Our results are therefore consistent with the logical assumption that antithrombotic therapy can promote bleeding which is supported by many case reports.[5–7 11]

Bloody punctures range from a blood tinged aspirate to brisk bleeding whereas a vascular puncture may remain undetected. We believe that bloody punctures are underreported in clinical routine because the threshold for documenting remains subjective. Since the only objectively conceivable quantification would be an erythrocyte count, almost all publications use a pragmatic approach without exact definition.[28 29] Extrapolation of a surrogate maker such as bloody tap to extremely rare events such as epidural hematoma is not possible even with the large case numbers available in the NET-RA registry at this time. Given the rarity of clinically meaningful bleeding complications, we nevertheless consider it justified to use bloody puncture as a surrogate parameter for an initiating event and

Table 3 Secondary outcomes: risk of bloody punctures in relation to a pause of antithrombotic drugs

	Controls without antithrombotic drugs	Antithrombotic drugs paused*	P value	Antithrombotic drugs not paused	P value
Peripheral blocks					
Group size/no of bloody taps (%)	25,299/318 (1.3)	7502/232 (3.1)	<0.001	1330/35 (2.6)	<0.001
Crude OR (95% CI)	1	2.51 (2.11 to 2.98)†	<0.001	2.12 (1.49 to 3.02)†	<0.001
Adjusted‡ OR (95% CI)	1	1.65 (1.35 to 2.01)†	<0.001	1.63 (1.13 to 2.35)†	<0.01
Crude OR (95% CI)		1		0.85 (0.59 to 1.21)§	0.366
Adjusted‡ OR (95% CI)		1		1.0 (0.67 to 1.48)§	0.997
Neuraxial blocks					
Group size/no of bloody taps (%)	19,506/591 (3.0)	9872/269 (2.7)	0.143	1244/53 (4.3)	0.015
Crude OR (95% CI)	1	0.90 (0.78 to 1.04)†	0.143	1.42 (1.07 to 1.90)†	0.016
Adjusted‡ OR (95% CI)	1	0.86 (0.73 to 1.01)†	0.059	1.19 (0.88 to 1.60)†	0.252
Crude OR (95% CI)		1		1.59 (1.18 to 2.15)§	<0.01
Adjusted‡ OR (95% CI)		1		1.42 (1.03 to 1.97)§	0.033

*Paused was defined as a guideline-driven pause in neuraxial blocks and a pause judged adequate by the treating anesthetist in peripheral blocks.
†Compares patients on antithrombotic medications (paused, respectively, not paused) with controls.
‡Adjusted for year of surgery, sex, age, body mass index, American Society of Anesthesiologists physical status, use of sedative drugs or general anesthesia during block performance, catheter use versus single shot approach, multiple skin punctures, and use of ultrasound.
§Direct comparison of patients in whom antithrombotic medications were paused as defined and of patients without adequate pause.

Table 4 Secondary outcomes: risk of bloody punctures with regard to different antithrombotic drug classes

	Controls without antithrombotics	Antiplatelet drugs	P value*	Anticoagulant drugs	P value*	Combined therapy†	P value*
Peripheral blocks							
Group size/no of bloody taps (%)	25,299/318 (1.3)	855/11 (1.3)	0.939‡	7667/236 (3.1)	<0.001‡	852/30 (3.5)	<0.001‡
Crude OR (95% CI)	1	1.02 (0.56 to 1.89)	0.339	2.50 (2.10 to 2.96)	<0.001	2.87 (1.96 to 4.20)	<0.001
Adjusted§ OR (95% CI)	1	0.76 (0.41 to 1.40)	0.372	1.67 (1.37 to 2.04)	<0.001	2.11 (1.41 to 3.16)	<0.001
Neuraxial blocks							
Group size/no of bloody taps (%)	19,506/591 (3.0)	788/35 (4.4)	0.025‡	9871/262 (2.7)	0.070‡	957/52 (5.4)	<0.001‡
Crude OR (95% CI)	1	1.49 (1.05 to 2.11)	0.026	0.87 (0.75 to 1.01)	0.070	1.84 (1.37 to 2.46)	<0.001
Adjusted§ OR (95% CI)	1	1.18 (0.80 to 1.68)	0.374	0.85 (0.72 to 1.00)	0.047	1.77 (1.31 to 2.40)	<0.001

*P value compares patients with antiplatelet, anticoagulant or a combined therapy to controls without antithrombotic medication.
†Combination of more than one antiplatelet and/or anticoagulant drug.
‡χ^2 test used to compare proportions.
§Adjusted for year of surgery, sex, age, body mass index, American Society of Anesthesiologists physical status, use of sedative drugs or general anesthesia during block performance, catheter use versus single shot approach, multiple skin punctures, and use of ultrasound.

to describe the impact of antithrombotic therapies on bleeding propensity.

Patients receiving antithrombotic therapy had a 60% increase in risk of bloody punctures during peripheral block implementation. This increase in risk was independent of assignment to the 'paused adequately long' or 'not paused adequately long' group by the treating anesthesiologist possibly reflecting the lack of clear timing guidelines for peripheral blocks. Since, according to this definition, no risk reduction by discontinuation became visible, the establishment of specific guidelines based on the available recommendations and risk assessments might be useful.[7 8]

There was no detectable increase in odds for bloody punctures in neuraxial blocks in patients taking antithrombotic medications compared with those who did not, presumably because antithrombotics were paused per guidelines in 89% of patients. In the remaining patients in whom the neuraxial blockade was performed outside guideline recommendations, there was a slight increase in odds. It was non-significant, probably because sample size was small. Furthermore, our information about guideline compliance was only yes or no, and we had no information on when drugs were actually stopped. Because neuraxial bleeding complications are feared, it seems likely that most of the 11% of patients who did not meet guideline recommendations for pausing antithrombotics were only slightly out of compliance. Our results thus suggest that neuraxial anesthesia is safe in patients taking antithrombotics so long as the drugs are stopped per guidelines. Since we are referring to the German guidelines, we would like to compare the relevant points with the US guidelines. In our sample, the most often used anticoagulant drug was low-molecular-weight heparin (78%), the most common antiplatelet drug was low dose aspirin (maximum 100 mg, 7%), and there were 7% combinations of at least two antithrombotics. In this respect, the recommendations in both guidelines are the same. Minor differences, which do not appear to be relevant to this analysis, exist for prophylactic doses of unfractionated heparin (Germany 4 hours, US 4–6 hours), for clopidogrel (Germany 7–10 days, US 5–7 days), and aspirin doses more than 100 milligrams which together accounted for less than 8% of the documented drugs.

Combined administration of drugs with various effects on blood clotting and possibly competing elimination pathways means that clinical effects are difficult to assess. Although current evidence suggests that there is no direct pharmacokinetic interaction between commonly used anticoagulant and antiplatelet drugs,[30 31] we found that combined therapies roughly doubled the odds for both peripheral and neuraxial blocks. Patients on combined therapies therefore appear to be at particular risk, possibly because the guidelines do not specify clear time intervals for these cases.

A limitation of the NET-RA registry is that it gathers anonymized primary data from various hospitals. The associated risk of under-reporting and inaccuracy is therefore hard to estimate but may be substantial. However, we assume that the rate of underreporting and inaccuracy does not differ across the study groups. Using routine data, we had to discard three-quarter of potentially eligible cases because of incomplete or implausible data which surely introduced a degree of selection bias. Since we focused on the main antithrombotic drug acting mechanisms, specific drugs may be underrepresented. Dosing could not be evaluated. Because there are no detailed guidelines for peripheral blocks, interruption of antithrombotic medications depends on anesthesiologists' judgements which may have influenced their assignment to the groups 'paused adequately long' and 'not paused adequately long'. Few patients surely appear more than once in the registry, but because data are anonymous we could not statistically adjust for repeated observations. During the long observation period of 13 years, there was presumably progress in medicine, techniques, and anesthesia methods making more recent cases more relevant.

Conclusions

In summary, bloody punctures during peripheral regional block insertion were more common in patients who took antithrombotic drugs. The increased odds was apparently not influenced by pausing antithrombotic medications, keeping in mind that there are no specific guidelines for peripheral blocks. For neuraxial punctures, the odds did not increase so long as antithrombotic medications were paused per guideline. Bloody punctures were about twice as common in patients who concurrently used at least two platelet and/or coagulation cascade inhibitors. We; therefore, conclude that patients taking antithrombotic drugs are at increased risk for bloody punctures, especially when treatments are not discontinued within recommended pre-procedure periods. Patients who take combined antiplatelet and/or anticoagulant drugs are at especially high risk. Guidelines for discontinuing antithrombotic treatments for neuraxial anesthesia appear to be effective, and should possibly be extended to peripheral blocks with a high risk of bleeding.

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