Chapter 13

Implications of Antithrombotic Therapy in Regenerative Medicine

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1.0 INTRODUCTION

In the Western world, effective public health intervention and health promotion campaigns have resulted in the increased longevity of the population. This has not been without its consequences. Along with increased life span, there has been an escalation in degenerative diseases often accompanied with chronic and debilitating pain. Longevity with a robust quality of life can be found in the promise of regenerative therapies.

It is quite common for patients with degenerative diseases to be on some form of antithrombotic therapy as well as nonsteroidal antiinflammatory drugs (NSAIDs). The key to providing effective regenerative therapy is to minimize the risk of a thromboembolic event and maximize the healing process as well as curtail the use of NSAIDs.

This chapter will discuss contemporary implications of antithrombotic treatment/risks and their safe and efficient administration. It will also cover current literature of established and recently developed recommendations relating to antithrombotics in neuraxial, intraarticular, soft tissue and peripheral nerve injections. Finally, it will discuss the appropriate evaluation and management of the risks with the goal of administering regenerative therapies.

2.0 THROMBOEMBOLIC IMPLICATIONS

Regenerative medicine procedures are elective. The main concerns when considering regenerative medicine for the patient using antithrombotic therapy are hemorrhage from harvesting or deployment site(s) and thromboembolic risks due to discontinuing antithrombotic agents, as well as the potential effects of antithrombotic agents on platelet rich plasma (PRP) and stem cell efficacy (1). As such, the indication for antithrombotic therapy (preventive/therapeutic use for coronary artery disease, deep vein thrombosis, pulmonary embolism, atrial fibrillation, coagulation disorders/thrombophilia) must be considered before stopping these agents (2). It is advisable to consult with the prescribing provider (Primary Care Provider/cardiologist) prior to stopping any antithrombotic therapy. It may also be prudent to refer to a hematologist for bleeding and thromboembolic risk assessment and recommendations.

Regenerative medicine procedures require harvesting and processing of tissue (whole blood, bone marrow, fat) and then redeployment of the harvested tissue into other sites by injection or surgery (3). Both harvesting and redeployment are invasive procedures that could lead to uncontrolled bleeding in patients in receipt of antithrombotic therapy. It is important to assess the risk of bleeding inherent in the procedure before stopping antithrombotic therapy. Bone Marrow aspiration and intraarticular and soft tissue injections, for example, have a low risk of bleeding. Injections in or around the CNS and meninges pose a greater risk for patients on antithrombotic therapy due to potentially catastrophic sequelae of uncontrolled bleeding. The American Society of Interventional Pain Physicians (ASIPP)

(4,5) and American Society of Regional Anesthesia and Pain Medicine (ASRA) (6) have published guidelines for managing antithrombotic medications for interventional techniques.

There is currently very little data assessing the safety of joint injections/aspirations in patients taking antithrombotics. Studies have assessed the safety of intramuscular and other injections for patients who are on antithrombotics (7). Most of the studies that detail complications of taking antithrombotics involved spontaneous hemarthrosis, which was typically both diagnosed and treated via joint aspiration. A prospective analysis study conducted by the Mayo Clinic by Thumboo and O'Duffy (8) analyzed 32 joint or soft tissue aspirations and injections in patients who were taking warfarin sodium. The study revealed no patient-reported complications of joint or soft tissue hemorrhage. They also concluded that this procedure is low risk for hemorrhagic complications.

A separate prospective analysis conducted by Salvati et al (9) investigated 15 patients on oral anticoagulation (OAC) with a joint effusion. Of the 15 patients, two patients experienced hemarthrosis as a complication of the arthrocentesis. Of note, these two patients had supratherapeutic international normalized ratios (INRs) of 3.8 and 5.0, respectively. The authors concluded that anticoagulation should not be an absolute contraindication to arthrocentesis.

Dunn and Turpie investigated thromboembolic events and complications for patients who were taking OAC who also needed to undergo surgery or invasive procedures. The authors reported major bleeding while patients were receiving therapeutic OAC was rare for the following: dental procedures (0.2% [4 of 2,014]), arthrocentesis (0.0% [0 of 32]), cataract surgery (0.0% [0 of 203]), and upper endoscopy or colonoscopy with or without biopsy (0.0% [0 of 111]) (10).

3.0 PHARMACOLOGY OF ANTICOAGULATIVE AGENTS

3.1 NSAIDS and Aspirin

NSAIDs inhibit cyclooxygenase enzymes COX1 and COX2, which inhibit prostaglandin production to decrease the inflammatory response. Thus, NSAIDs have analgesic effects and are used for minimizing pain. Thromboxane A2 is produced via COX1 enzyme activity, which is a potent thrombus activator. Aspirin is an irreversible inhibitor of COX1 and has significant clinical benefits for preventing thrombus formation. In response to Aspirin, more prostacyclin is produced by endothelial cells, but there is no additional thromboxane made as there are no nuclei in platelets, thus, there is a greater percent of prostacyclin to thromboxane, thinning the blood. Elevated bleeding risk is a concern for a small portion of patients, but adverse effects are rare. Prostacyclin (PGI2) synthesis from vascular endothelial cells is dependent on COX2 and has anti-platelet effects. High doses of aspirin reduce PGI2 production which can abolish the anti-platelet effect of low-dose Aspirin. Low-dose Aspirin anti-platelet effects last for 7-10 days, as bone marrow directed platelet renewal is required for clotting to resume. Low-dose Aspirin therapy is well established to reduce the risk of cardiovascular events in patients with acute coronary syndromes, cerebral infarct, or occlusive vascular disease (11).

3.2 ADP Inhibitors

Clopidogrel (Plavix®), Prasugrel (Effient®), Ticlopidine (Ticlid®), and Ticagrelor (Brilinta®) are all ADP inhibitors, which inhibit platelet aggregation.

Clopidogrel is the prototypical thienopyridine drug that inhibits the P2Y12 receptor. The P2Y12 receptor is activated by ADP binding and promotes platelet aggregation. Depending on the dosage schedule, the maximal platelet aggregation inhibitory effects of clopidogrel are reached within 3 to 7 days. After discontinuation, recovery of platelet inhibition occurs after one week (12).

Ticlopidine also belongs to the thienopyridine group and is maximally aggregated after 8 to 11 days of a 500mg per day dosage schedule. After withdrawal of 72 hours there is still a lingering effect as there is an irreversible inhibition of platelet function (13). Prasugrel acts by antagonizing ADP at the platelet's purine receptors, and aggregation is thus noncompetitively and irreversibly inhibited.

A loading dose is usually used for Prasugrel, which results in around half of the platelets being inhibited within the first hour of taking this medication. Following three to five days of therapy,

the steady-state inhibition of platelet aggregation reaches around 70% (14). As a prodrug, prasugrel is rapidly metabolized to active and inactive metabolites. These metabolites have varying elimination rates, although the active metabolites have an elimination half-life of 7 hours, with a wide range of 2-15 hours (15).

Lastly, a distinct ADP inhibitor is Ticagrelor, which directly inhibits P2Y12 receptors (16). While Ticagrelor is metabolized to active metabolites, the original compound is responsible for the majority of the inhibitory effects (17,18). A notable advantage of Ticagrelor is rapid effect, with peak platelet inhibition after 2 to 4 hours of intake (19).These medications undergo hepatic conversion to active metabolites which are then eliminated by the kidneys (20). In addition, glycoprotein IIB/IIIA receptors are less activated, causing a reduction in fibrinogen fixation and platelet crosslinking.

Table 1 shows comparative pharmacokinetics/pharmacodynamics of ADP inhibitors.

3.3 Phosphodiesterase (PDE) Inhibitors

Phosphodiesterase inhibitors include Cilostazol (Pletal®) and Dipyridamole (Persantine®). These medications selectively inhibit phosphodiesterase, which leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) and subsequent reversible inhibition of platelet aggregation (21). Additionally, Dipyridamole blocks thromboxane synthase, the thromboxane receptor, and the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells. This results in increased adenosine in the extracellular space and inhibition of formation of cytokines and proliferation of smooth muscle cells. Absorption of Dipyridamole occurs in the gastrointestinal tract and is pH dependent. Gastric acid suppressors and proton pump inhibitors inhibit absorption, which

Table 1. Comparative pharmacokinetics/pharmacodynamics of ADP inhibitors.

	Clopidogrel (Plavix®)	**Prasugrel (Effient®)**	**Ticlopidine (Ticlid®)**	**Ticagrelor (Brilinta®)**
Target	P2Y12ADP	P2Y12ADP	P2Y12ADP, also inhibits liver CYP2C19 and CYP2B6	P2Y12ADP
Time to Cmax	3-7 days	3-5 days	8-11 days	2-4 hours
CYP metabolism	CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5	CYP450-mediated (primarily CYP3A4 and CYP2B6)	Cytochromes P450	CYP3A4
Bioavailability	>50%	≥79%	>80%	36%
Protein binding	94–98%	Active metabolite: ~98%	98%	>99.7%
Half-life	7-8 hours (inactive metabolite)	~7 hours (range 2 hours to 15 hours)	12 hours (single dose) 4-5 days (repeated dose)	7 hours (ticagrelor), 8.5 hours (active metabolite AR-C124910XX)
Renal elimination	50% kidney, 46% biliary	Urine (~68% inactive metabolites); feces (27% inactive metabolites)	Renal and fecal	Biliary

can be prevented via buffered additives added to the medication (22). An additional advantage of Cilostazol is inhibition of PDE3A, which is selective to vascular smooth muscle cells and results in vasodilatation. Cilostazol is administered at 100mg twice daily and reaches maximum plasma levels after three hours. It is eliminated via hepatic metabolism and is excreted in the urine (23). Thus, Cilostazol is contraindicated in those with severe renal insufficiency.

3.4 Glycoprotein GPIIb/IIIa Inhibitors

A final common component of platelet aggregation is the glycoprotein IIb/IIIa receptor. Specialized medications inhibit this receptor, potently inhibiting platelet aggregation while being reversible (24).

Abciximab (ReoPro®) is a Fab fragment of a humanized monoclonal antibody directed against the GFPIIb receptor. Abciximab inhibits over 80% of ADP-induced platelet aggregation and is given via IV administration. Additionally, thrombin generation is inhibited by Abciximab, which quickly binds to platelets with high affinity.

Eptifibatide (Integrilin®) is a cyclic peptide inhibitor of the fibrinogen binding site on the GPIIb receptor. Tirofiban (Aggrastat®) is an additional glycoprotein IIb/IIIa receptor inhibitor, reaching maximum efficacy after 4 hours of administration, with 50-80% inhibition of platelet aggregation (25). Platelet function normalizes 8 to 24 h after stopping the IV infusion.

3.5 Heparin

Low Molecular Weight Heparins (LMWHs) inhibit the coagulation cascade via binding to antithrombin, which leads to a conformational change of antithrombin, which accelerates inhibition of factor Xa. LMWH has advantages: relatively high bioavailability, longer half-life, and ability for use once per day. Maximum efficacy levels are observed after 3-4 hours post subcutaneous administration, and elimination occurs after 4-6 hours in those with normal renal function (26). High molecular weight heparins (HMWH) catalyze the inhibition of clotting factors IXa, Xa and thrombin by greatly enhancing antithrombin III activity, by causing a conformational change in ATIII exposing its reactive site. Testing is required to determine the dose effect on coagulation via partial thromboplastin time (PTT). HMWH is not absorbed by GI tract due to its large molecular weight, therefore IV or SC injection must be used. The short half-life of HMWH (approximately 1h) means frequent injections or continuous infusion, and it is thus not considered suitable in an outpatient setting.

3.6 Warfarin

Oral anticoagulants inhibit the synthesis of vitamin K-dependent clotting factors, which are factor II, VII, IX, and X. Warfarin blocks the gamma-carboxylation of glutamate residues in prothrombin and factors VII, IX, and X. This results in biologically inactive coagulation factor molecules. Vitamin K epoxide reductase is the enzyme that catalyzes the carboxylation reaction. Therapeutic doses of warfarin inhibit vitamin K epoxide reductase, which prevents the reductive metabolism of the inactive vitamin K epoxide to its active hydroquinone form. Synthesis is the primary target of oral anticoagulants (warfarin), therefore the effects of these medications are not apparent until previously-existing clotting factor turnover has occurred. Factor half-lives vary, from factor VII at 6-8 hours to factor II at 50-80 hours (27). Thus, it has a slow onset of action (8-12 hours) as existing clotting factors must be depleted, and the maximal effect occurs 3-5 days after administration. Warfarin is monitored by prothrombin time and INR, which is a normalized ratio of the patient's PT to that of a control sample (27). Age, female gender, and preexisting medical conditions such as hepatic, cardiac, and renal disease modify the patient's response to warfarin. Asian patients, for example, have higher sensitivity to warfarin and require lower doses than those patients of European descent (27). Dietary changes may alter the patient's clotting ability, and those on Warfarin are advised to avoid grapefruit and cranberry products, eat a consistent amount of leafy greens and other high vitamin K containing foods and are advised to limit herbal supplement intake of garlic, ginger, gingko biloba, ginseng, and fish oil.

3.7 Direct Thrombin Inhibitors

Direct thrombin inhibitors include Dabigatran (Pradaxa®), Argatroban (Acova™), Bivalirudin (Angiomax®), Lepirudin (Refludan®), Desirudin (IPRIVASK®), and Hirudin.

Dabigatran etexilate is an oral anticoagulant and is a prodrug that is converted to dabigatran in the plasma. After an oral dose, the peak effect is reached within 2 to four hours, and plasma half-life is 13 hours on average (28). Dabigatran dose recommendations depend on renal efficacy in the patient receiving the medication. In those with a creatinine clearance of greater than 30mL/minute, 150 mg is taken orally twice daily. For patients with lower creatinine clearance, 75mg twice daily is recommended. Dabigatran's function is via factor inhibition and not clotting factor depletion, thus, the administration of clotting factors is anticipated to be less effective in reversing the effects of dabigatran. Dabigatran is mostly cleared by the kidneys. In those with normal kidney function, Dabigatran is excreted in 1-2 days post-discontinuation. This also depends on renal sufficiency of the patient taking the medication.

Argatroban is a small molecule direct thrombin inhibitor that is administered intravenously. It reaches steady-state plasma concentrations in 1-3 hours and is metabolized via the liver. It has a half-life of 50 minutes and is monitored by PTT. As it is metabolized hepatically, it is a viable alternative for Dabigatran, which is metabolized renally (29).

Bivalirudin works by binding specifically to the catalytic site, in addition to the anion-binding exosite of circulating and clot-bound thrombin. Bivalirudin is cleared by the kidney and thus is dose-dependent on overall renal function. It has as a half-life of 25 minutes in those with normal renal function, but this may be doubled in those with severe renal insufficiency (30).

Desirudin is a subcutaneously administered direct thrombin inhibitor and is indicated for the prevention of venous thromboembolism after total joint replacement. It is recommended that dosage adjustment and aPTT be monitored in patients with moderate-to-severe renal impairment. After IV administration, desirudin is removed rapidly via the renal system, with 90% of the dose removed from the plasma within two hours. Plasma concentrations decline with a mean half-life of 2-3 hours. Subcutaneous administration demonstrates a half-life of 2 hours (31).

Hirudin has specific activity on fibrinogen and binds to and inhibits only activated thrombin, making it an extremely potent direct thrombin inhibitor. Thus, hirudin dissolves the formation of clots and thrombi and has therapeutic value in coagulation disorders. It is also able to act on complexed thrombin and does not alter other serum protein function or activity (32). Hirudin has a half-life of 2-3 hours and is monitored by aPTT, allowing close titration over a wide range of anticoagulative clinical desires. ACT and PT are insensitive for monitoring hirudin (33). Table 2 shows comparative pharmacokinetics/pharmacodynamics of direct thrombin inhibitors.

3.8 Direct Factor Xa Inhibitors:

Direct factor Xa inhibitors such as Rivaroxaban (Xarelto®) have been commonly used in the United States. It has dual renal and hepatic clearance, with around one-third of the drug being active with each route of metabolism. This dual route of clearance makes accumulation less likely than other medications that are solely hepatically or renally cleared. Rivaroxaban is orally administered and has a half-life of 5.7 to 9.2 hours. Plasma protein binding of rivaroxaban is 92-95%. One third of the absorbed dose is excreted in the urine, and two-thirds of the dose is excreted as an inactive metabolite in the feces and urine. Rivaroxaban has the potential for drug interactions with medications that are P-glycoprotein inhibitors and those metabolized by CYP3A4 (34).

Apixaban (Eliquis®) is a specific factor Xa inhibitor like its counterpart, rivaroxaban. It is rapidly absorbed and reaches peak concentrations in 1-2 hours (35,36). Apixaban has an oral availability of 45% and has a relatively complex elimination pathway with both direct renal and intestinal excretion, with the latter being the majority (36,37).

Edoxaban (Savaysa® or Lixiana®) was approved for prevention of venous thromboembolisms following lower limb orthopedic surgery in 2011 and is an oral direct factor Xa inhibitor that inhibits free factor A and prothrombinase activity. It has also been approved for the prevention of stroke and systemic embolism. Peak plasma concentrations are reached 1.5 hours after oral administration, and it has an elimination half-life of 10-14 hours when taken at 60mg once daily. It is excreted via both the hepatic and renal systems (38). It is orally available, and not removed by dialysis.

Table 2. Comparative pharmacokinetics/pharmacodynamics of direct thrombin inhibitor.

	Dabigatran (Pradaxa)	Argatroban (Acova)	Bivalirudin (Angiomax)	Lepirudin (Refludan)	Desirudin (IPRIVASK)	Hirudin
Target	Direct thrombin inhibitor	Direct thrombin inhibitor	Reversible direct thrombin inhibitor	Direct thrombin inhibitor	Direct thrombin inhibitor	Naturally occurring peptide anticoagulant
Time to Cmax	2-4 hours	1-3 hours	2 minutes	4 hours	1-3 hours	3 hours
Metabolism	Metabolized via conjugation into 4 acyl glucuronides, not mediated by CYP450	CYP3A4	Proteolytic cleavage	Lepirudin is thought to be metabolized by release of amino acids via catabolic hydrolysis of the parent drug	Metabolized by stepwise degradation from the C-terminus possibly catalyzed by carboxypeptidase(s) such as carboxypeptidase A	Proteolytic cleavage
Bioavailability	3-7%	100% IV	n/a IV application only	100%	100%	100%
Protein binding	35%	54%	no	n/a	n/a	n/a
Half-life	13 hours	50 minutes	~25 minutes in patients with normal renal function	1.3 hours	2-3 hours	80 minutes
Renal elimination	80% urine	Liver	Yes	Yes	Yes	Renal, about 48% (35% unchanged)
Linear PK	Yes	Yes	Yes	Yes	Yes	Yes

Betrixaban (Bevyxxa®) is a potent oral factor Xa inhibitor that recently received FDA approval. It has exemplified promising results, as it has low hERG affinity and has reduced bleeding risk and prevented thromboembolism in clinical trials for orthopedic knee surgery (39-41). Betrixaban has the smallest percent of renal clearance, is INR/PTT insensitive, and has minimal liver metabolism.

Another selective factor Xa inhibitor, Fondaparinux (Arixtra®) is 100% bioavailable and achieves maximum concentration in 1.7 hours of administration (42). Its extended half-life of 17 to 21 hours allows once-daily dosing (43).

Table 3 shows comparative pharmacokinetics/pharmacodynamics of newer oral anticoagulant agents including Dabigatran, Pradaxa, and Direct Factor Xa inhibitors (44,45).

3.9 Thrombolytic Agents

Fibrinolysis is caused by thrombolytic agents via conversion of plasminogen and thrombi to plasmin in order to destroy clots. These "clot busters" such as recombinant tissue-type plasminogen activator (tPA), streptokinase, urokinase, tenecteplase, and reteplase are enzymes that have effects on both circulating and tissue type plasminogen. The half-life of these thrombolytic drugs is generally a few hours, but the inhibition of plasminogen and fibrinogen may last for up to 27 hours after administration (46).

3.10 Herbal/Alternative Therapies

Garlic has a dose-dependent effect on bleeding, as it contains a compound called Ajoene. Derived from Allicin, the compound that provides garlic's

Table 3. Comparative pharmacokinetics/pharmacodynamics of direct factor Xa inhibitor.

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Edoxaban (Savaysa, Lixiana)	Betrixaban (Bevyxxa)	Fondaparinux (Arixtra)
Target	Xa	Xa	Xa	Xa	Xa
Time to Cmax	1-3 hours	2-4 hours	1-2 hours	3-4 hours	2 hours
CYP Metabolism	15%	32%	NR	NR	n/a
Bioavailability	66%	80%	>45%	34%	100%
Transporter	P-gp	P-gp/BCRP	P-gp	P-gp	P-gp
Protein binding	87%	>90%	55%	60%	94%
Half-life	8-15 hours	9-13 hours	8-10 hours	37 hours	17-21 hours
Renal elimination	25%	33%	35%	<1%	100%
Linear PK	Yes	No	Yes	n/a	Yes

BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR – not reported; P-gp = P-glycoprotein

flavor, Ajoene inhibits granule release and fibrinogen binding and additionally inhibits aggregation of platelets via a variety of mechanisms. Prostacyclin, forskolin, indomethacin, and dipyridamole are all altered via Ajoene's inhibition of granule release (47,48). Ginkgo Biloba has been used for thousands of years, and its mechanism is not entirely understood. Ginkgo is thought to antagonize PAF and collagen leading to inhibition of platelet aggregation, resulting in several reports of spontaneous bleeding. Flavonol glycosides and terpene glycosides have been suggested to be the chemical compounds responsible for the increased bleeding events after intake of this medication (49). Ginseng is commonly used and reduces the effect of warfarin, declining peak INR levels. Ginsenosides are the major active ingredient of ginseng, and possibly induce cytochrome P450 enzymes to increase the metabolism of Warfarin and thus reduce its effect.

4.0 THROMBOEMBOLIC EVENTS

Individuals who stop taking low-dose aspirin with a history of cardiovascular events are at increased risk of non-fatal myocardial infarction when compared with those individuals who continue treatment (50). Discontinuation of aspirin and thienopyridines is associated with an increased risk of serious cardiovascular events including the following: ST, spontaneous MI, and stroke beyond 1-month after coronary stenting (51). Vitamin K antagonists such as warfarin should be clinically correlated with respect to INR values. Therefore, it stands to reason that if antithrombotic therapy is discontinued, there is good evidence to suggest that the risk of thromboembolic events is significantly increased. There is also evidence to suggest that when antiplatelet therapy is continued, there are risks of bleeding and lesser thromboembolic events (4).

There is limited evidence for the discontinuation of antiplatelet therapy with platelet aggregation inhibitors in order to avoid bleeding and epidural hematomas (4). There is also limited evidence to continue antiplatelet therapy (e.g., clopidogrel, ticlopidine, prasugrel) during interventional techniques in order to avoid cerebrovascular and cardiovascular thromboembolic (4).

Clopidogrel and ticlopidine are better at preventing ischemic cerebral infarction, MI, and vascular deaths when compared to aspirin after interventional techniques (52). Thromboembolic events are less common in patients using Prasugrel when compared to ticlopidine and clopidogrel, with noted reductions in the combined rate of death from nonfatal MI and nonfatal stroke (12,53-55).

With respect to newer antithrombotic agents dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) there is limited published literature to suggest whether discontinuation is advisable, to avoid bleeding and epidural hematomas during interventional techniques, or conversely, avoid cerebrovascular and cardiovascular thromboembolic events (56). Renal health seems to be the determining factor in the decision to discontinue

dabigatran, with recommendations varying depending on patient renal function analyses (4). Current recommendations suggest a 2 to 4-day period of discontinuation in individuals with normal function and 5 days in those with impaired renal function before invasive techniques. There is also limited evidence to guide clinical decisions to continue or discontinue unfractionated heparin or LMWH prior to interventional techniques in regards to thromboembolic events.

5.0 BLEEDING RISKS

5.1 Prevalence Data in IPM

There has been significant literature accumulating for interventional techniques and related hemorrhagic risks in recent years (4,5,57-76). In a survey of practice patterns among interventional pain physicians in 2012, Manchikanti et al (57) showed that the majority of physicians discontinued antithrombotic agents; however, this study also showed that there were a significantly higher number of complications related to thromboembolic events of 162 compared to hemorrhagic complications of a total of 55 in this population.

In a systematic review assessing risks and benefits of ceasing or continuing anticoagulant medication for image-guided procedures for spine pain (77), authors evaluating 14 manuscripts which provided applicable evidence. The results shows procedures involving interlaminar access carried a non-zero risk of hemorrhagic complications, regardless of whether anticoagulants were ceased or continued. For other procedures, hemorrhagic complications have not been reported, and case series indicated that they are safe when performed in patients who continue anticoagulants. The results also showed that 3 articles reported the adverse effects of ceasing anticoagulants, with serious consequences, including death. Authors of this manuscript concluded that other than for interlaminar procedures, the evidence does not support the view that anticoagulant and antiplatelet medication must be ceased before image-guided spine pain procedures.

In a prospective evaluation of bleeding risks of interventional techniques in chronic pain, Manchikanti et al (61) assessed the rates of adverse events in patients undergoing interventional techniques on antithrombotic therapy with cessation or without cessation and compared them to a group of patients without antithrombotic therapy. While the results showed differences in milder complications, there were no reports of hemorrhagic complications requiring any type of treatment. In this assessment, the authors studied all types of procedures with 1,227 of 1,831 continuing aspirin compared to 604 of 1,831 discontinuing them. Similarly, they also studied 100 patients on clopidogrel with continuation, whereas, 226 patients were discontinued. Further, there were 128 patients with aspirin and other agents with continuation and 151 were discontinued. The procedures performed included cervical epidural injections with continued aspirin in 249 patients, thoracic epidural in 30 patients, lumbar interlaminar epidural in 128 patients, lumbar transforaminal in 144 patients, whereas, 528 patients for caudal epidural injections, and 148 for percutaneous adhesiolysis. In reference to clopidogrel, it was continued in 10 patients undergoing cervical epidural, one patient with thoracic epidural, 14 patients with lumbar epidural, 44 patients with caudal epidurals, 10 with lumbar transforaminal epidural, and 21 with percutaneous adhesiolysis. There were a large number of facet joint interventions and other treatments. Since then, multiple manuscripts have been published in 2017 (59,60,62,67).

van Helmond et al (60), in a retrospective review, assessed the safety of low to intermediate risk spine procedures in patients with continued antithrombotic therapy. They identified 490 patients of a total of 2,204 patients on antithrombotic medications which included aspirin (N=275), P2Y12 inhibitors (N=129), warfarin (N = 62), heparin (N = 10), factor Xa inhibitors (N = 55), and dipyridamole (N = 1). The procedures included facet joint nerve blocks and facet joint radiofrequency in all 3 regions and sacroiliac joint injections. The authors concluded that there were no hemorrhagic complications in performing these procedures. Goodman et al (59) studied the role of anticoagulant and antiplatelet management for spinal procedures in a prospective descriptive study. They performed procedures in 74 patients, 197 procedures from a total of 4,253 procedures. They reported no clinically evident bleeding events observed in patients on antiplatelet/anticoagulant medications for lumbar transforaminal

epidural injections (N=90), facet joint injections (N=62), lumbar intradiscal procedures (N=11), lumbar sympathetic blocks (N=3), sacroiliac injections (N=5), or in 26 radiofrequency neurotomy procedures. However, similar to van Helmond et al (60), Goodman et al (59) have not performed any epidural injections on patients with continuation of antiplatelet therapy.

Endres et al (67) assessed risks of continuing or discontinuing anticoagulants for patients undergoing interventional procedures. They reported no complications attributable to anticoagulants in 4,766 procedures in which anticoagulants were continued. They only performed lumbar transforaminal injections, lumbar medial branch blocks, trigger point injections, and sacroiliac joint blocks, and they concluded that continuation of anticoagulant therapy seems to be safe. They performed interlaminar epidural injections in 25 patients with continuation of Warfarin and 15 patients with continuation of clopidogrel. They also reported, which is relevant to regenerative medicine, a number of patients undergoing trigger point injections, trochanteric bursa injections, and hip joint injections. Along with 171 patients undergoing sacroiliac joint blocks on Warfarin, 227 patients undergoing trigger point injections, 40 patients with trochanteric bursa injections, and 87 patients with hip joint injections, they also reported 81 patients with clopidogrel undergoing sacroiliac joint blocks, 214 patients with trigger point injections, 50 patients with trochanteric bursa injections, and 52 patients with hip joint injections.

Lavallee et al (66) reported 328 ultrasound guided intramuscular botulinum toxin injections performed in 15 patients, with only 2 subclinical hematomas, resulting in a bleeding complication rate of 0.61% in this patient population. Warner et al (65) in a manuscript describing bleeding and neurological complications in 58,000 interventional pain procedures showed that preprocedural aspirin or nonsteroidal antiinflammatory drug therapy was prevalent in 17,825 procedures or 30.7% of the procedures without significant bleeding complications. They concluded that bleeding complications were rare in patients undergoing low or intermediate risk pain procedures even in the presence of antiplatelet medication. Other studies (62-64) also have assessed bleeding complications in patients undergoing intrathecal drug delivery system implantation, percutaneous spinal cord stimulator trials and implantations, and celiac plexus blocks with identification of no cases of hemorrhagic complications.

Manchikanti et al (58) also reported 2 cases of epidural hematoma following cervical epidural injections and reviewed the literature. They looked at a 16 year span of cervical interlaminar epidural injections with a prevalence rate of 0.0085% with 2 cases of epidural hematoma over 16 years from 223,552 total cases performed in these physicians practice. There also have been multiple other reports of epidural hematoma; however, the majority of these reports are from patients without antithrombotic therapy or that was discontinued according to the guidelines.

5.2 Risks in Regenerative Medicine

As previously discussed, bone marrow aspiration and intra-articular/soft tissue injections have low risks of bleeding, while CNS/meninges related injections produce a higher risk of bleeding. A comprehensive review with literary search was conducted by ASIPP (4), analyzing various guidelines which produced recommendations specific to interventional techniques and the associated risk of bleeding. These recommendations are dependent on multiple factors including the patient's risk factors and the managing physician's opinion. While bleeding risk is present with any interventional procedure, thromboembolic events must be considered equally and clinically correlated in relation to a patient's past medical history, social history, and risk of each relative to these factors.

With respect to NSAIDS and aspirin, there is little to no risk of bleeding in interventional techniques at low doses. High doses of these medications should be evaluated and altered if the clinician correlates their medication status with previous episodes of heavy bleeding (4-6,46). Many patients may be taking additional medications that increase their risk of bleeding or supplements such as SSRIs, fish oil, garlic, and many others. Phosphodiesterase inhibitors also do not increase the risk of bleeding significantly in intervention-

al techniques, however they may or may not be discontinued in accordance with patient history (4-6,46). Platelet aggregation inhibitors such as ticlopidine, clopidogrel, and prasugrel have been suggested to be discontinued 7 to 10 days before interventional techniques. While some studies have shown 3 days to be effective, the ASRA consensus is at least one week's period of time before a CNS related injection (4-6,46).

Warfarin is more complicated in regards to discontinuation, as much of the clinical decision making depends on a patient's INR achieved during therapy and trends associated with INR over the past few months. For high-risk interventional techniques such as interlaminar epidural injections, warfarin may need to be discontinued until INR of 1.5 or less is achieved. For lower risk procedures, an INR of 2 is an appropriate level to achieve before undergoing these techniques (4-6,46). There is limited evidence to suggest that unfractionated or low molecular weight heparins should be discontinued prior to interventional techniques, but the current suggestion is 12 hours of discontinuation before CNS related injection.

Similar to INR values in Warfarin, renal function values significantly alter clinical decision making in relation to Dabigatran (Pradaxa). In procedures with a high risk of bleeding, creatinine clearance greater than 50 mL per minute in patients allows a 2 to 4 day period of discontinuation. However, in those with 50 mL per minute and less, a period of 4 to 5 days is currently suggested before CNS related interventional techniques.

6.0 EFFECTS OF ANTITHROMBOTIC THERAPY ON PRP AND STEM CELL EFFICACY

The significance of an integral platelet surface membrane cannot be understated, given that it allows for the appropriate dissemination of healing biological proteins and growth factors essential in regenerative medicine. The biochemical pathways of the coagulation cascade are key in that disruption of platelet surfaces or prematurely activated platelets may cause the limited efficacy of the clinical procedure (1). Furthermore, with the recent advent of mesenchymal stem cell (MSC) technology in regenerative medicine, it is important to consider the viability of these cells in the context of antithrombotic therapy. To that end, the effects of heparin on ex vivo MSCs recovered from bone marrow showed that supplementation of even low doses of heparin could adversely impact the growth and differentiation potential of this pleiotropic cell type (78). Therefore, it is important to evaluate bone marrow tissue in patients receiving heparin treatment particularly if ex vivo expansion hMSCs is to occur.

The use of platelet-rich plasma (PRP) is increasing due to its ligament and tendon healing potential. It is also considered to be a natural alternative to surgery. However, anticoagulants and antiplatelet drugs are commonly used in patients who are candidates for receipt of PRP. Alternatively, the use of an anticoagulant, while not taken systemically, is required to process PRP to prevent automatic activation. Since antithrombotic agents influence the stability of platelets, they are, therefore, likely to exert an effect on PRP efficacy as well and should be ceased at a suitable timeframe preceding injection therapy (1). PRP has been shown to significantly improve the proliferation of differentiated cells, enhance synthesis of collagen, and prompt angiogenesis and revascularization, all of which aid regeneration. The seminal study by Sutherland and colleagues (79) in 2005 eloquently demonstrated the utility of autologous MSCs in regenerative medicine using sheep through reconstruction of stem cell tissue-engineered heart valves.

The healing influence of the dispensation of PRP depends on the bioactive amalgams such as cytokines and growth factors that are being released (via activation and aggregation) precisely to the location of the injury. The characteristic of the platelets confined in autologous PRP (mainly exhibited by the potential of activation and aggregation of platelets) may be essential (80).

NSAIDs are depicted to have negative influences on platelets such as inhibition of activation, a decrease in storage of alpha granules, and aggregation of platelets. The negative impact of these medications on platelet activation and aggregation may be significant since a substandard quality of autologous PRP is emitted post-NSAID therapy. The coherent substantial inhibition of platelet function such as aggregation acquired post stimulation using arachidonic acid within the NSAID

designated study group was found to be regardless of duration and type of NSAID ingestion and the blood compendium technique used for PRP formulation (80). Without the NSAIDs intake, such effects could not be observed in the healthy control group. NSAID's impede cyclo-oxygenase–mediated oxygen utilization and therefore prevent platelet activation and aggregation (83). Moreover, bioactive compounds such as transforming growth factor–β, growth factors, and platelet factor 4 stored in the alpha granules, cannot be released adequately if NSAIDs bar this pathway, and platelet function is drastically compromised. Thus, such stipulations validate the hypothesis that autologous PRP generated after NSAID intake is of inferior attribute, and therefore, may negatively influence the healing outcomes.

NSAIDs are essential to control pain in the posttraumatic setting. While NSAIDs can interfere with bone healing, some contradict these findings (81). Although NSAID analgesic potency is well documented, clinicians continue to questions the associated safety issues. A 2012 study of the effects of NSAIDs on bone healing in animals reveal very mixed results (81). However, the conclusion of the authors correctly notes that the "lack of evidence does not constitute the absence of an effect" and further cautions that the clinician should [continue to] treat NSAIDs as a risk factor for bone healing impairment and should be avoided in high-risk patients" (81).

Ramsook and Danesh (1) described issues related to PRP injections and antithrombotic therapy. They discussed the importance of understanding the intrinsic and extensive pathways of the coagulation cascade and that any disruption of this mechanism may result in prematurely activated platelets and therefore limited efficacy. They also made clear that antithrombotic agents affect platelet stability and will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. Overall, the general rules appear to be the same for antithrombotic and anticoagulant agents similar to utilization in interventional techniques as described above.

However, there is a significant paucity of literature in regards to the safety, efficacy, and timing of PRP injections in patients with concomitant antithrombotic therapy. The importance of an intact platelet surface membrane allows for the appropriate release of the healing bioproteins and growth factors granting PRP therapy its efficacy. Antithrombotic agents that affect the stability of platelets will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. With future research, appropriate guidelines may be established not only for PRP, but also for stem cell therapy.

7.0 SAFE AND EFFICIENT ADMINISTRATION OF REGENERATIVE MEDICINE

If it is deemed advisable that antithrombotic therapy should be halted (even temporarily), then thromboembolic risk determines if bridging is necessary. "Heparin bridging" involves discontinuing warfarin 4-5 days prior to a procedure while using subcutaneous low molecular weight heparin (LMWH) to maintain anticoagulation until the day prior to the procedure. This mitigates thromboembolic risk during the time the patient is off warfarin by effectively shortening the amount of time the patient is not anticoagulated. LMWH has a shorter half-life than warfarin and can be discontinued the day prior to the procedure.

Bridging with subcutaneous low-molecular-weight heparin (LMWH) is appropriate and reliable. For patients who have chronic kidney disease, the LMWH should be decreased in dose or substituted by intravenous unfractionated heparin. For AF patients, the AHA advocates a once-daily therapeutic dose of LMWH, with half the dose to be taken at dawn of the day before the procedure (82). Moreover, therapeutic LMWH should be taken up again 24 to 72 hours post procedure, dependent on the bleeding risk of the technique. Warfarin therapy ought to be resumed when viable. It is vital to consider that bridging could lead to unexpected post-op bleeding after anticoagulants are resumed.

International guidelines reflect the differing views on the safe interval between cessation of antithrombotic therapies and implementation of neuraxial and peripheral procedures, and for the re-introduction of the therapeutic drug regimen.

While two to three half-life intervals might be adequate in patients who are at excessive threat of venous thromboembolism (VTE) or stroke, an in-

terval of four to six half-lives amid the cessation of the drug and neuraxial injection is reliable in the majority of patients at a low-level risk of thrombosis (83). However, in patients with kidney disease, the interval should be calculated on creatinine clearance. In particular instances, laboratory monitoring of the antithrombotic effect is applicable, and reversal agents may be suitable when a hemostatic function requires rapid restoration.

8.0 CONCLUSION

No doubt, the advancement of technology has contributed to the development of regenerative medicine. It is the new frontier offering new hope and options to those who have been suffering from a disease process or injury and who feel that conventional therapies have not yielded satisfactory results. Pain providers are in a unique position to avail themselves of this type of treatment in aiding the inherent healing processes of the body.

Medical manipulation of hemostasis and thrombosis is critical to safe and efficient procedures that are frequently performed under neuraxial and disc injection. International guidelines, including ASRA, have differing recommendations on the safe interval between discontinuation of antithrombotics and performance of invasive procedures and between the interventional procedure and re-introduction of the therapeutic drug regimen. However, a consistent theme from recent evidence demonstrates a requirement for close consultation with hematology and pain services. Furthermore, the clinician should be vigilant for warning signs of epidural hematoma and consider a reversal of the antithrombotic drug by administration of platelets. The guidelines presented here should be a useful memory aid for prevention of adverse events such as a neuraxial hematoma following epidural/intrathecal/spinal injections and perineural hematoma ensuing peripheral nerve procedures.

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