4 Drugs in Neurovascular Intervention

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Abstract

Neuroendovascular procedures are associated with a risk of immediate or delayed thromboembolic and ischemic complications. Anticoagulants and antiplatelet agents are widely used to lower the risk of perioperative thromboembolic events in neuroendovascular surgery. Immature embolization of the aneurysmal sac, protrusion of coils, balloon remodeling, or stenting maneuvers may lead to acute thrombus formation by platelet activation. Antiplatelet therapy prior to procedures has significantly lowered the risk of thromboembolic complications in stent-assisted coil embolization of cerebral aneurysms. Although several antithrombotic therapeutic options are available, optimized antithrombotic management in neuroendovascular surgery is not well defined. Appropriate antiplatelet agents, anticoagulants, dosing, and duration of treatment have not been adequately determined. The present chapter provides our experiences of available antithrombotic agents, focusing on practical aspects of their use in different clinical settings.

Keywords

Antiplatelet drug · P2Y12 inhibitors · GPI IIb/IIIa · heparin · Antithrombotic drug

4.1 Introduction

The field of neurovascular intervention is expanding rapidly. Newer instruments and better techniques optimized by the use of drugs have resulted in better outcomes. More number of neurologists, neurosurgeons, and radiologists are undertaking this field as their career choice [1]. Multiple ongoing trials are presenting new evidence in management [2, 3]. Hence, updated knowledge about drugs used in neurovascular intervention techniques is important. This chapter deals with drugs used in intervention procedures.

4.2 Fibrinolytic Agents

Sudden occlusion due to thrombus formation results in acute ischemic stroke. Early intervention with fibrinolytic agents in carefully selected patients results in re-establishing blood flow. Figure 4.1 shows the mechanism of fibrinolytic

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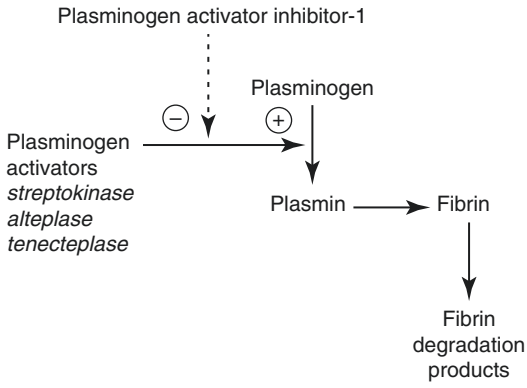

Fig. 4.1 Mechanism of fibrinolytic drugs

agents. Fibrinolytic drugs activate plasminogen to plasmin, thus degrading insoluble fibrin to fibrin degradation products causing lysis of clot. Currently, Alteplase and Tenecteplase are approved for use in acute ischemic stroke [4]. Compared to first-generation streptokinase, these agents generally do not cause antigenic reactions [5].

4.2.1 Alteplase

Recombinant tissue-type plasminogen activator (rtPA or alteplase) is more fibrin specific than streptokinase [6]. It has a short half-life (3–4 min), so need to be given as a continuous intravenous infusion. Patient needs to be admitted to intensive care or stroke unit for monitoring. Prior CT scan of brain should be done to rule out intracranial hemorrhage. Alteplase is given as 0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of the dose given as bolus over 1 min. Initially approved for use during 3 h of ischemic stroke, it is also recommended for select patients within 3 and 4.5 h of ischemic stroke after ECASS III trial [7]. BP monitoring and neurological assessment should be done every 15 min during infusion. During infusion or within 24 h after infusion, if the patient develops a severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, infusion should be discontinued (if IV alteplase is being administered) and emergency head CT scan should be done to rule out intracranial hemorrhage. AHA/ASA 2019 guidelines on acute ischemic stroke management describe detailed indications and contraindications for use of alteplase [8]. Important eligibility recommendations for use of alteplase are window period within 3 h, window period between 3 and 4.5 h in carefully selected patients, age group above 18 years, blood pressure < 185/110 mmHg, and blood sugar level above 50 mg/dL. In patients with blood pressure > 185/110 mmHg, careful lowering of BP can be done using Labetalol (10 mg IV followed by continuous IV infusion 2–8 mg/min), Nicardipine (5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h), or Clevidipine (1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached, maximum 21 mg/h). Potential contraindications for use are previous ischemic stroke, severe head trauma, and intracranial/intraspinal surgery within 3 months. Alteplase should not be given to patients who have received treatment doses of low molecular weight heparin within last 24 h. Patients who are taking thrombin/factor Xa inhibitors should not be given alteplase till laboratory tests such as aPTT, INR, platelet count, eccrine clotting time, thrombin time, and factor X assay are normal. It is important to note that patients who taking antiplatelet monotherapy prior to stroke should be given alteplase as benefits outweigh the risk of bleeding. In case the patient develops orolingual angioedema during alteplase infusion, discontinue infusion, maintain airway, administer IV methylprednisolone (125 mg), IV diphenhydramine (50 mg), IV ranitidine (50 mg), or famotidine (20 mg). If there is a further increase in angioedema, give epinephrine (0.1%; 0.3 mL subcutaneously). Management of symptomatic intracranial bleeding secondary to alteplase requires more intensive approach. Alteplase infusion must be stopped, emergency CT scan of Brain should be done to confirm hemorrhage [9]. Such patients should be given Cryoprecipitate (10 U infused over 10–30 min), Tranexamic acid (1000 mg IV infused over 10 min), or e-aminocaproic acid (4–5 g over 1 h, followed by 1 g IV) until bleeding is controlled.

4.2.2 Tenecteplase

(TNK-t-PA) It is derived from alteplase, differing in its fibrin binding specificity, plasma half-life (20 min), and resistance to Plasminogen Activator Inhibitor-1 [10]. Tenecteplase has higher fibrinolytic potency on platelet-rich clots than its parent molecule. It is given in a dose of 0.4 mg/kg as single bolus administration. Extend IA TNK trial showed Tenecteplase (0.25 mg/kg, max 25 mg) was non-inferior to alteplase in restoring perfusion large vessel occlusion of intracranial cerebral artery (internal carotid artery, basilar artery, and middle cerebral artery) [11]. Overall functional outcome was better with tenecteplase. There was no significant difference in the incidence of cerebral hemorrhage.

4.3 Antiplatelet Agents

Platelets play a central role in achieving hemostasis. Platelet activation, followed by aggregation and adhesion to vascular endothelium lead to formation of a clot which is subsequently stabilized by coagulation cascade. Collagen, vWF (Von-Willibrand factor), and other platelet activators like ADP (Adenosine diphosphate) mediate this process. ADP acts on adenosine-specific receptor, P2Y12, present on platelet plasma membrane and activates G protein-coupled expression of GP IIb-IIIa receptors on platelet surface which cause platelet aggregation [12]. Neurointervention procedures like intraluminal stenting, coiling of aneurysms, and flow diversions have potential for thromboembolic events during or after the procedure. Platelet inhibitors prevent platelet activation, aggregation, or adhesion, thereby preventing clot formation and propagation. Pre-procedure antiplatelet drugs are administered to prevent thrombosis in stenting and flow diverters [13]. Other treatment options for preventing or treating thromboembolic events include intravenous unfractionated heparin and thrombolytics. Various classes of antiplatelet agents have different targets as shown in Fig. 4.2.

4.3.1 Aspirin

Prostaglandin pathway involving cyclooxygenase enzyme leads to formation of thromboxane

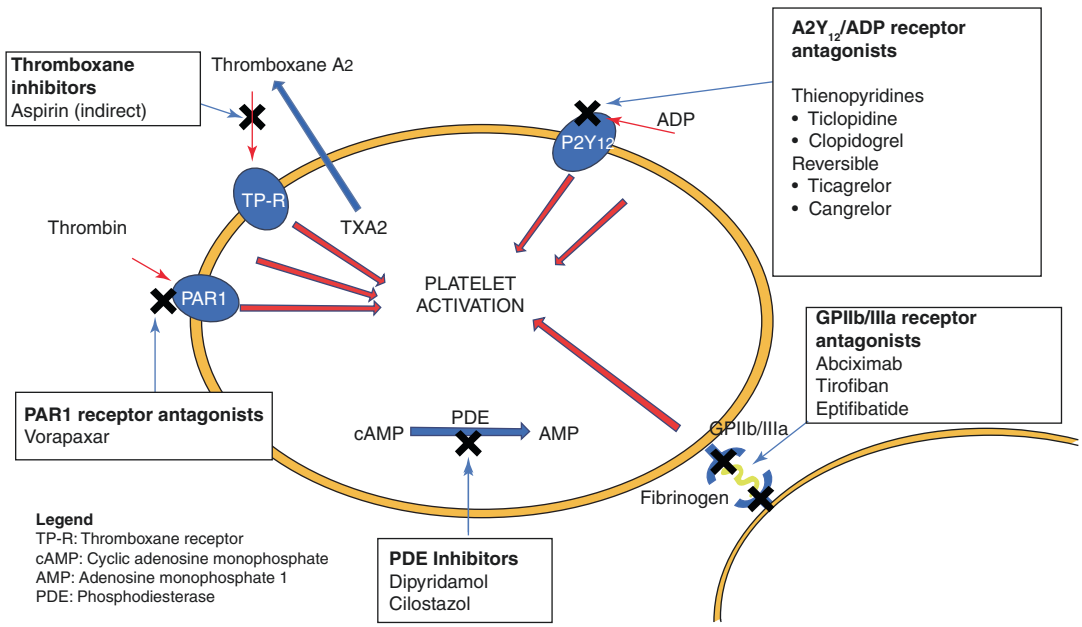

Fig. 4.2 Mechanism of action of antiplatelet agents

A2, which is a potent platelet aggregator. Aspirin is irreversible, non-selective cyclooxygenase inhibitor. It has more specificity for COX 1 receptors than COX 2 receptors. It is most widely available, frequently used, and extensively backed by clinical trials for its use in intervention and stroke treatment. It has onset of action within 15–30 min and its effect on platelets lasts for 8–10 days due to irreversible inhibition [14]. Doses used during neurointervention typically range from 81 to 325 mg daily (Table 4.1). Most neurovascular interventionists start Aspirin 3–5 days before stenting procedure, but some consider it before 14–21 days. In case of hemorrhage, platelet transfusion may be considered to reverse the effects of aspirin. Common side effects include gastritis and ulceration.

4.3.2 ADP Antagonists/P2Y12 Inhibitors

ADP acts on P2Y1 and P2Y12 receptors concomitantly to activate platelets and cause aggregation. Thienopyridines (Clopidogrel, Ticlopidine, and Prasugrel) cause irreversible and competitive inhibition of P2Y12 receptors [15]. These are prodrugs that gets metabolized in vivo to form active form of drug, thus delaying onset of action. Loading dose is required to hasten to onset of action. Cytochrome P450 polymorphism, specially CYP2C19 polymorphism found in Asian population, causes different metabolism and clopidogrel resistance or hypo-responders [16]. Yet, this polymorphism is not consistently associated with increased thromboembolic events so routine testing of polymorphism by genetic testing is not required.

Clopidogrel is most commonly used with aspirin in dual antiplatelet therapy as it is most tolerated thienopyridine, with lesser side effects than ticlopidine and prasugrel [15]. It has a half-life of 7–8 h and onset of action is 2–4 h. It is given as 75 mg daily dose with 300–600 mg loading dose at onset of therapy. It causes lesser gastrointestinal bleeding than aspirin, but causes diarrhea, nausea, and vomiting. Ticlopidine is not a commonly used drug clinically due to its side effects profile, which includes marrow suppression, rarely thrombotic thrombocytopenic purpura (TTP), cholestatic jaundice, and colitis.

Prasugrel has a faster onset of action and more potent inhibition of platelet activation [17]. It causes more bleeding related complications than clopidogrel offsetting its benefits clinically. It can be used in those patients with clopidogrel resistance or in those unable to tolerate clopidogrel as a first-line agent. Usual dose regimens for intervention use are 5–10 mg daily with a 20–60 mg loading dose.

Ticagrelor is a noncompetitive antagonist of P2Y12 receptor [18]. It is not influenced by CYP polymorphisms. Ticagrelor has a median onset of action of 1.3–2 h. Commonly, it is used in patients who have thromboembolic complications in carotid stents or flow diverters. It is used as dual antiplatelet therapy with aspirin in suspected clopidogrel resistance. It is started with loading dose of 180 mg with daily maintenance of 90 mg twice a day. Commonest side effect requiring discontinuation of drug is respiratory discomfort.

4.3.3 GP IIb/IIIa Inhibitors

GP (glycoprotein) IIb-IIIa receptors are present on platelet plasma membrane which on activation bring about conformational change exposing binding sites for fibrinogen, vWF, and adhesion molecules [19]. GP IIb-IIIa inhibitors are highly potent, fast-acting antiplatelet agents. These are mostly used as rescue therapies in the treatment of acute thrombosis during or immediately after procedure.

Abciximab is a monoclonal antibody directed at the GPIIb-IIIa receptor [19]. It is administered intravenously (IV) or intra-arterially (IA). A bolus of 250 μg/kg inhibits platelet aggregation by 80% at 15 min post-administration. Platelet function reverses 50% in 48 h after stopping infusion. The effect of abciximab is reversed by platelet transfusion in case of life-threatening bleeding. The drug is cleared by reticuloendothelial system, so no dose adjustment is required in case of renal failure. Profound thrombocytopenia

Table 4.1 Drugs and doses commonly used in neuroendovascular surgery

No.	Drugs	Doses	Remarks
1	Aspirin (irreversible inhibitor cyclooxygenases 1 & 2)	Loading dose 325 mg PO maintenance doses ranging from 81 to 325 mg daily	• Onset 7–60 min. • At least 3–5 days prior to carotid or intracranial stenting • Many practitioners may start therapy as long as 14–21 days prior to a procedure • In emergency neuroendovascular interventions in which pre-procedure aspirin therapy is not possible, loading doses have varied from 200 to 650 mg
2	Clopidogrel (Plavix) (irreversible inhibitor P2Y12 ADP receptor)	Loading dose: 300 or 600 mg, followed by 75 mg daily	• Onset 2 h • Duration of action 3–7 days
3	Ticagrelor (Brilinta) (reversible inhibitor P2Y12 ADP receptor)	Loading dose: 180 mg, followed by 90 mg bid	• Onset 30 min • Duration of action 12–24 h • Dose should not be missed. • No problem of drug resistance compared to clopidogrel
4	Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)		
	(A) Abciximab (irreversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 0.25 mg/kg IV rapid bolus followed by 125 μg kg/min infusion (to a maximum of 10 mg/min) for 12 h.	• Onset 2 h • Duration of action 48 h • Can be reversed, if needed, with platelet transfusion • Drug is a monoclonal antibody
	(B) Eptifibatide (Integrilin) (reversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 180 μg/kg IV bolus Then a second 180 μg/kg IV bolus 10 min After the first bolus, followed by 2 μg/kg infusion for 12 h	• Onset immediate • Plasma half-life 2.5 h • Duration of action 2–4 h • Cannot be reversed with platelet transfusions
	(C) Tirofiban (reversible inhibitor glycoprotein IIb/IIIa receptor)	Dose: 25 μg/kg IV bolus. Then 0.15 μg/kg infusion for 12–24 h	• Onset 5 min • Half-life 2-h • Duration of action 3–8 h • Cannot be reversed with platelet transfusions
5	Prasugrel (irreversible inhibition of ADP receptor P2Y12)	Loading dose: 60 mg, followed by 10 mg QD	• Have better platelet inhibition than clopidogrel but higher bleeding rate

(continued)

Table 4.1 (continued)

No.	Drugs	Doses	Remarks
6	Heparin	Flush and irrigation—adult—10000 unit/L Pediatric (age < 6 years)—2000 unit/L. The initial bolus dose for an adult is about 60–80 μ/kg followed by 20–40 μ/kg every hour for long procedures. Pediatric loading dose is 50 unit/L	• Half-life: 90 min • Monitoring: ACT of 250–350 s, monitored every hour during procedure; APTT monitored every 6 h • Reversal: Protamine sulfate, 1 mg for 100 units (not to exceed 50 mg total)
7	Atropine	0.5–1 mg or 0.04 mg/kg IV q5min, Max. 3 mg	• Half-life: 2–3 h (>2 years and adults); 7 hr. (<2 years); 10 h (65–75 years) • Onset: Rapid (IV/IM)
8	Fentanyl	1–2 μg/kg IV bolus or 25–100 μg/dose PRN or 1–2 μg/kg/h by continuous IV infusion or 25–200 μg/h	• For analgesia and sedation. • Use undiluted or diluted in 250 mL of D5W
9	Nitroglycerin (NTG)	100 to 200 μg is commonly given intra-arterially to prevent artery spasm	• Treatment of catheter-induced vasospasm • It has an immediate effect and has a short duration of action of 3 to 5 min
10	Protamine	1 mg for 100 units	• Not to exceed 50 mg
11	Acetylcysteine	Tab 600 mg B.D	• Treatment of patients with renal insufficiency
12	Flumazenil		• Reversal of benzodiazepines
13	Furosemide		• Management of elevated intracranial pressure
14	Glucagon	To inhibit motility of stomach and small bowel: 0.2–0.5 mg IV over 1 min or 1 mg IM To inhibit motility of colon: 0.5–0.75 mg IV over 1 min or 1–2 mg IM	• Control of gastric motility during spinal angiography
15	Mannitol	20%;0.5 to 1.5 g/kg IV infused over 30–60 min; may repeat q6-8hr	• Management of elevated intracranial pressure
16	Milrinone	Loading 0.1 mg/kg IV Followed by continuous IV infusion of 0.75 μg/kg/min for 7 to 10 days	• Used for vasospasm in SAH
17	Ondansetron	4 to 16 mg	• Antiemetic • IV, IM, oral
18	Alteplase (tPA)	0.9 mg/kg IV; not to exceed 90 mg total dose; administer 10% of the total dose as an initial IV bolus over 1 min and the remainder infused over 60 min	• Rule out contraindication for tPA • Powder for injection (reconstitute before use) Dosage forms: 50 mg, 100 mg

caused by the drug needs monitoring during treatment.

Eptifibatide is a cyclic heptapeptide derived from rattlesnake venom [20]. It binds reversibly to GPIIb-IIIa receptor. A bolus dose of 180 μg/kg intravenously achieves over 80% inhibition of platelet function in 15 min. Platelet function recovers by 50% in 4 h after stopping the infusion. Eptifibatide has renal clearance, so dose adjustment is needed in case of renal failure.

Tirofiban binds reversibly to the GPIIb-IIIa receptor [21]. It has a faster onset of action. A bolus dose of 0.4 μg/kg causes 90% inhibition of platelet aggregation after 10-40 min. Platelet function returns to near baseline within 4–8 h of stopping of the infusion. Tirofiban is also renally cleared, so dose must be adjusted in patients with renal failure.

4.3.4 Phosphodiesterase Inhibitors

Cilastazol and dipyridamole act as phosphodiesterase (PDE) inhibitors [22]. PDE inhibitors, through cAMP and cGMP mediated metabolism inhibition decreases platelet activation. It has secondary effect of vasodilation. Cilastazol is in cardiac setting along with aspirin and clopidogrel but it can cause tachycardia and arrhythmia [23]. It is contraindicated in cardiac failure.

Antiplatelet therapy remains cornerstone in periprocedural management in intracranial, extracranial stenting, flow diverter placement, and placing Woven EndoBridge (WEB) Device™ [13]. In patients who are undergoing extracranial angioplasty and stenting, dual antiplatelets; aspirin, and clopidogrel are started 5 days before the planned procedure [24]. Appropriate antihypertensive medications are given to control blood pressure to prevent procedure-related complications like bleeding and cerebral hyperperfusion syndrome. During the procedure, Atropine 0.5 mg IV is given prior to dilation angioplasty to prevent baroreceptor-induced bradycardia and hypotension [25]. If a patient develops bradycardia (HR < 60 bpm), Atropine is administered 0.75 mg IV bolus dose. Post procedure, patients should receive dual antiplatelets aspirin (150 mg once a day) and clopidogrel (75 mg once a day) with high dose statin for 30 days, followed by continuation of aspirin (150 mg once a day). Other treatment options post procedure includes aspirin 325 mg once a day, or a combination of aspirin 81 mg once a day and ticagrelor 90 mg twice a day for 30 days followed by continuing aspirin thereafter.

In patients who are undergoing intracranial angioplasty-stenting and flow diverter placement, dual antiplatelets; aspirin (150 mg once a day) with clopidogrel (75 mg once a day) are given 5 days prior to procedure. Strict medical management to maintain blood pressure below 140 mmHg systolic (<130 mmHg in diabetic patients), low-density lipoprotein (LDL) below 70 mg/dl is an important part of management in patients with intracranial atherosclerotic diseases.

Prior to placing WEB device, patients can be administered single antiplatelet; aspirin 150 mg once a day 5 days prior or loading dose of aspirin 300 mg on the day of procedure [13]. In post-procedure management, dual antiplatelet therapy is not universally employed when using the WEB. Some interventionists consider aspirin 75–100 mg daily and clopidogrel 75 mg daily for 3 months, especially when an adjunctive stent or endoluminal flow diverter is used.

4.4 Anticoagulating Agents

Coagulation factors along with platelets form stable clot. Exposure to tissue factor or denuded endothelial surface activates coagulation cascade, forming activated factor X (Xa). This factor converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. Insoluble fibrin forms clot, which further propagates to achieve hemostasis. Figure 4.3 demonstrates coagulation cascade and site of anticoagulation drugs. This topic limits discussion to heparin which is most commonly used in intervention procedure.

Heparin inhibits thrombosis by preventing Factor X activation [26]. The overall risk of thromboembolic complications during neurointerventional procedures is significant.

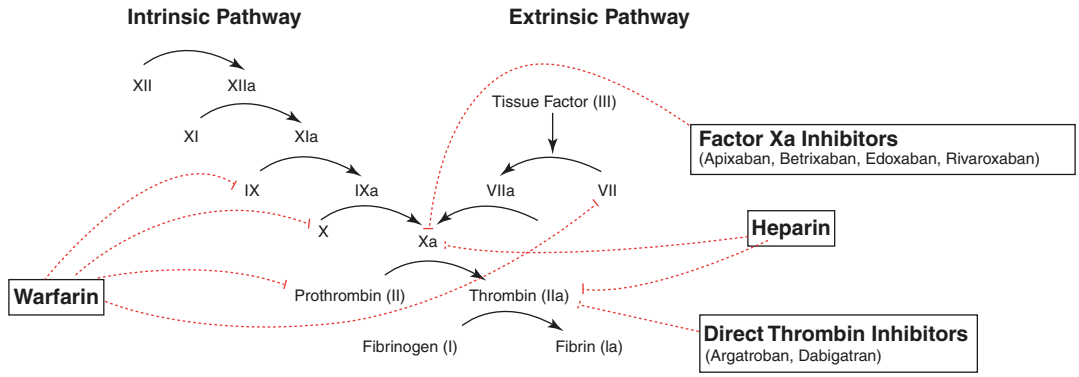

Fig. 4.3 Coagulation cascade and site of anticoagulation drugs

Anticoagulation with unfractionated heparin is standard for most procedures. Anticoagulation during diagnostic cerebral angiograms is usually done, but with a lower dose. The only exception to the use of heparin is in subarachnoid hemorrhage where anticoagulation is deferred until one or two coils are deployed to secure the aneurysm. All the catheters and sheaths should be continuously flushed with heparinized saline (3000–5000 Units in 1 L normal saline) to prevent clot formation. Dosing for flush and irrigation during procedure in adults is 10,000 units/L and in pediatric (age < 6 years) is 2000 units/L. The initial bolus dose for adult is about 60–80 μ/kg followed by 20–40 μ/kg every hour for long procedures. Pediatric loading dose is 50 units/L. Half-life of heparin is 90 min. Monitoring of heparin therapy is done by measuring activated clotting time (ACT), which is kept between 250 and 350 s. It is monitored every hour during a prolonged procedure. During diagnostic digital subtraction angiography (DSA), heparin is given at the dose of 20 mg/kg IV [26]. Bleeding is the commonest side effect. Heparin effects are reversed by Protamine sulfate (1 mg for 100 units of heparin, not to exceed 50 mg total). Partial thromboplastin time should be monitored at 5–15 min after dose, followed by 2–8 h afterward. Protamine sulfate has an independent weaker anticoagulant tendency in higher doses. Heparin is contraindicated in patients with a known allergic tendency to this drug and in patients with a history of heparin-induced thrombocytopenia.

Alternatives to heparin include Argotraban, Bivalirudin, lepirudin, and danaparoid [27]. They are used in patients with heparin-induced thrombocytopenia requiring anticoagulation.

4.5 Treatment of Vasospasm: (Chemical Angioplasty)

Following class of drugs are used to treat vasospasm in subarachnoid hemorrhage.

(A) Calcium Channel Blocker: Nimodipin, Nicardipin, Verapamil
(B) Phosphodiesterase inhibitors: Papavarin, Milrinone
(C) Nitroglycerin (NTG)

Calcium channel blockers are commonly used as intra-arterial vasodilators. No single agent has been shown to be more efficacious than others. Intra-arterial infusion of these agents can be used to treat vessels that cannot be dealt with, or are difficult to treat with balloon angioplasty, such as distal branches and the A1 segment.

Nicardipine (dose 0.5 to 40 mg) is diluted in 0.9% NaCl (without heparin) to a concentration of 0.1 mg/mL [28]. It is injected 1 mL through the micro Catheter to a maximal dose of 5 mg per

vessel. Nicardipine precipitates in heparinized saline, so the system should be flushed with saline without heparin before and after injecting nicardipine. Angiographic improvement is demonstrable in almost all arteries, neurologic improvement occurs in around 42% of patients. Nicardipine causes transient intracranial pressure (ICP) elevation.

Nimodipine (dose 0.8 to 3.2 mg) is a preferred drug for intra-arterial injection [29]. Nimodipine is diluted in saline to 25% concentration. Slow infusion at the rate of 2 mL/min is done, with each vessel infused for 10–30 min. Total dose is per vessel is 1–3 mg and total dose per patient is 5 mg. Clinical improvement is observed in about 76% of patients. Blood pressure needs to be monitored as hypotension is a major side effect. Nimodipine is also be used for irrigation during procedures through guiding catheter to prevent artery to go into spasm (10–15 mL in 1 L pressure bag).

Verapamil (dose 2 to 120 mg) is diluted as 5 mg vial with normal saline to a concentration of 1 mg/mL [30]. It is injected as 10–20 mg per vessel for a maximum of 20 mg per carotid. Transient hypotension and bradycardia are side effects. Neurological improvement is seen in 29% of patients.

Papavarin (dose 200–400 mg), once a popular intraarterial drug, now has fallen out of favor because of short-lived effect and dramatic rise of intracranial pressure, decreased brain oxygenation, and incidences of ischemic infarctions of infused territories [31]. It is administered as 300 mg at a rate of 3 mL/min.

Nitroglycerine (dose 30 microgram in individual artery) is used intra-arterially, but can cause raised intracranial pressure and hypotension [32].

Milrinone (dose 2.5–24 mg), acts by inhibiting phosphodiesterase 3 causing vasodilation and also has inotropic properties (inodilator) [33]. It is used as a loading dose of 0.1 mg/kg Iv followed by infusion of 0.75 μg/kg/min for 7–10 days. It can cause hypotension and hypokalemia.

4.6 Radial Artery Cocktail

It is used to prevent spasm of artery during radial access. It contains 10 mL of saline with Heparin (5000 IU), Verapamil (2.5 mg), Lidocaine (2%, 1 mL), and Nitroglycerine (0.1 mg) [34].

Contrast Agents and Treatment of Contrast-Induced Nephropathy and Allergic Reactions Nonionic contrast agents are safer and less allergenic than ionic preparations [35]. Most commonly used contrast agent in cerebral angiography is Iohexol (Omnipaque®, GE Healthcare, Princeton, NJ). It is a low osmolality, nonionic contrast agent, and is relatively inexpensive. It is used as 300 mg I/mL in diagnostic angiograms and 240 mg I/mL in neurointerventional procedures. Patients with normal renal function can tolerate as much as 400–800 mL of Omnipaque®.

Maximum tolerable volume of 300 mg I/mL nonionic contrast agent is calculated by formula—Weight in kg × 5 (adults) or 4 (children)/serum creatinine (mg/dl).

Contrast-induced nephropathy (CIN) remains most worrisome issue clinically [36]. Clinically significant contrast-induced nephropathy is considered if serum creatinine rises by 0.5 mg/dl or 25% above baseline during 48–72 h following contrast injection. In severe cases, serum creatinine continues to rise for 5–10 days, sometimes requiring dialysis. Incidence of CIN increases with serum creatinine level, 0% at <1.5 mg/dl, 50–75% at 1.6–4.5 mg/dl, to 90–100% at >4.5 mg/dl. Risk factors for CIN include age above 60 years, serum creatinine level above1.5 mg/dl, diabetes mellitus, dehydration, hypertension, hyperuricemia, cardiovascular disease and use of diuretics, and in patients having paraproteinemias.

Methods to reduce risk of CIN include reduction in use of contrast, use of Visipaque™ (270 mL I/mL) instead of Omnipaque™, oral hydration (water, 500 mL prior to the procedure and 2000 mL after the procedure), intravenous

hydration (0.9% NaCl), intravenous hydration with sodium bicarbonate. Acetylcysteine (600 mg orally twice a day, one the day before and on the day of the procedure) is an antioxidant functioning as a free radical scavenger. It also stimulate intrarenal vasodilation. Acetylcysteine has been shown to reduce serum creatinine elevation in patients undergoing radiological procedures using nonionic, low-osmolality contrast material. Prophylactic administration of acetylcysteine (600 mg PO twice a day) and 0.45% saline IV, before and after administration of the contrast agent, has been shown to decrease serum creatinine compared to patients receiving saline only. Sodium bicarbonate infusion has also been shown to reduce rates of CIN. Sodium bicarbonate (150 mEq) in 1 L of 5% dextrose is infused at 3 mL/kg/h for 1 h prior to procedure, at 1 mL/kg/h through procedure, and for 6 h after procedure. Incidence of CIN can be decreased by hydration with 0.45% saline or 0.9% saline beginning 12 h before and continuing 12 h after angiography.

Contrast allergy is one of the commonest side effects noted [37]. Prednisolone 50 mg orally (or hydrocortisone 200 mg IV) is given 13, 7, and 1 h prior to contrast injection. Diphenhydramine (50 mg IV, IM, or PO 1 h prior to contrast injection) is also used. Steroids should be given at least 6 h prior to the procedure [38]. Administration less than 3 h prior to the procedure does not reduce the risk of an adverse reaction.

4.7 Statins (Hypolipidemic Therapy)

Atherosclerotic diseases manifestation including transient ischemic attack and stroke need high-dose statin therapy use to reduce further risk. Atorvastatin 80 mg daily or Rosuvastatin 20 mg daily have been advised [38].

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