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Case Series

A Case Series on Drug Induced Bleeding in Patients Hospitalized with Severe COVID-19

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Abstract

In critically ill patients bleeding complications may have serious consequences. DIB is one of the dreadful complications occurring involving COVID-19 therapeutics. It can be potentiated by concomitant use of drugs, which can lead to an iatrogenic disease. Our objectives are to describe the predictors of major bleeding and nature of DIB. Herein we present a case series of five patients with COVID-19 having prolonged hospitalization as all of them were on mechanical ventilatory support and reported to have DIB. The most likely causation appears to be effects of glucocorticoids, anticoagulants, antiplatelet drugs given concomitantly putting a critically ill patients into the risk of developing such bleeds. We concluded this causality as "Possible category" according to WHO-UMC causality categories.

Keywords: *Drug Induced Bleeding; Iatrogenic; Anti-Coagulants; Steroids; Anti-Platelets*

Abbreviations

DIB: Drug Induced Bleeding; GIB: Gastrointestinal Bleeding; ICU: Intensive Care Unit; VTE: Venous Thromboembolism

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible respiratory virus, has become a worldwide pandemic with over 172,242,495 confirmed cases globally including 3,709,397 deaths, reported to WHO [1]. By late April, India passed 2.5 million active cases and was reporting an average of 300,000 new cases and 2,000 deaths per-day [2].

The majority patients with COVID-19 either are asymptomatic or result in only mild disease. However, considerable percentage of patients, develop a respiratory illness requiring hospitalization, and such infections can progress to critical sickness with hypoxemic respiratory failure requiring prolonged ventilatory support [3]. Advanced age, associated comorbidities such as diabetes, hypertension, cardiovascular disease, chronic lung disease and multiple drug therapy are known to be associated with undesirable clinical outcomes. Specific laboratory abnormalities such as elevated C-reactive protein, Interleukin-6, D-dimer, ferritin, LDH, and troponin are known to be associated with worse clinical outcomes [4,5].

COVID-19 is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death. The disease is also associated with inflammation and a prothrombotic state, with

increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer. According to the treatment guidelines by National Institutes of Health, for hospitalized patients of COVID-19, Dexamethasone has been found to improve survival in patients who require supplemental oxygen. Therefore, the use of dexamethasone is strongly recommended in this setting. They should also receive prophylactic dose anticoagulation for VTE [6,7].

DIB is a recognized entity and can be potentiated by concomitant use of drugs. It can involve GIB, nosebleeds, bruising, heavy menses or rectal bleeding [8]. GIB has been described in 2% - 13% of patients hospitalized with COVID-19. As the clinical course of the disease evolves, with many patients having protracted hospital stays, an increase in GIB has created new challenges for the medical fraternity [9].

Herein we present a case series of five patients with COVID-19 having prolonged hospitalization as all of them were on mechanical ventilatory support and reported to have DIB. The most likely causation appears to be effects of glucocorticoids, anticoagulants, antiplatelet drugs given concomitantly putting a critically ill patients into the risk of developing such bleeds. This can be termed as an unwanted and undesired drug-drug interaction.

Case Details

All five patients had RTPCR positive for SARS-CoV-2, who were brought to the emergency department of our hospital with COVID-19 symptoms. They all needed mechanical ventilatory support and were managed by Inj. Remdesivir, anti-coagulants, steroids, antacids, anti-emetics, antibiotics and other supportive medications. During prolonged hospital stay DIB was observed in all of them. Eventually their condition deteriorated and they all succumbed due to acute respiratory failure predisposed by bilateral COVID-19 pneumonitis and septicaemia.

Case 1

An 83-year-old hypertensive female complained of cough for 7 days, difficulty in breathing for 4 days, and fever for 2 days. On examination she was conscious, and vitals were: BP-132/70 mm Hg, PR-84/min, RR-32/min, Temperature - within normal limits and SPO_2-84% on room air. After admission she was put on BIPAP support with SPO_2-98% on NIV PSV-12, F-18, PEEP-5, and FIO_2-100%. She was a known case of hypertension since 5 years and was on medication.

Considering her clinical course intravenous Heparin 5000 IU BD started from the day of admission, but on Day 4 of hospitalization due to alteration in coagulation profile Heparin was stopped, and after that the values got normalized Inj. LMWH 0.6 CC BD subcutaneously was started on Day 9 of hospitalization. Again, on Day 14 there were significant alteration in coagulation profile and LMWH was withheld. On Day 15 she had a complaint of right upper limb swelling for which surgery reference was done and was diagnosed as having right hand cellulitis. Her clinical condition worsened on each passing day, hence Inj. Dexamethasone 8 mg IV BD started. On Day 19 urine routine examination showed presence of blood and many red cells, suggestive of haematuria. On Day 24 stool examination showed presence of occult blood. Patient was given a total 2 units of PCV and 8 units of PRC in view of low haemoglobin and platelet count. Relevant laboratory investigations are depicted in table 1.

Investigations	Day 1 (Heparin commenced)	Day 4 (Heparin stopped)	Day 9 (LMWH commenced)	Day 14 (LMWH stopped)	Day 24 (Occult blood in stool)
Hb (12 - 18 g/dl)	11.6	10.9	10.2	10.1	7.8
Platelet count (130 - 400 kU/L)	251	355	324	223	68
PT (12 - 16)	13.5	17.9	16.4	40	16
INR (0.8 - 1.2)	0.97	1.32	1.2	3.13	1.17
aPTT (20 - 35 sec)	22.6	>140	30	>140	24.5
D-dimer (< 0.5)	1.92	>20	3.93	2.36	3.24
CRP (< 5 mg/L)	119.4	83.28	19.81	7.6	67.6

Table 1: *Laboratory findings.*

Case 2

A 67-year-old hypertensive and diabetic female complained of fever for 5 days. On examination she was conscious, and vitals were: BP-130/80 mm Hg, PR-111/min, RR-16/min, Temperature-100 F and SPO_2-92% on room air. She was a known case of diabetes and hypertension since 8 years and was on medication. She had a past history of cerebrovascular accident (CVA) 3 years back and for that was taking Tab. Clopidogrel 75 mg OD since then. On admission her SPO_2 was 98% on oxygen 4 L/min.

Considering her clinical course Inj. LMWH 0.6 CC BD subcutaneously and Inj. Methylprednisolone 40 mg BD was started from the day of admission. Her oxygen requirement gradually increased and on day 4 of hospitalization she was shifted to ICU. Her SPO_2 was 98% on HFNC 40 L/min and FIO_2-100%. On day 9 she complained of oral and nasal bleeding which was spontaneous in onset for which Inj. Tranexamic Acid 500 mg TDS, Inj. Hemocoagulase 1 ml TDS, and Inj. PCV 1 unit were given. On day 11 urine routine examination showed presence of blood and many red cells, suggestive of haematuria. Inj. LMWH, Tab. Clopidogrel, and Inj. Methylprednisolone were withheld. Her clinical condition worsened on each passing day, so was put on mechanical Ventilation. On day 19 considering her clinical presentation Inj. Heparin 25K in 50 CC normal saline intravenous infusion and Inj. Dexamethasone 8 mg IV BD was started, but had to be withheld due to thrombocytopenia and sepsis. On day 24 stool examination showed presence of occult blood. Patient was given a total 6 units of PCV and 4 units of PRC in view of low haemoglobin and platelet count. Relevant laboratory investigations are depicted in table 2.

Investigations	Day 1 (LMWH commenced)	Day 11 (LMWH stopped)	Day 19 (Heparin commenced)	Day 21 (Heparin stopped)	Day 24 (Occult blood in stool)
Hb (12 - 18 g/dl)	11.5	9.9	8.4	6.2	6.8
Platelet count (130 - 400 kU/L)	150	147	116	82	42
PT (12 - 16)	13.6	18.4	17	24.6	22.8
INR (0.8 - 1.2)	0.99	1.36	1.25	1.84	1.7
aPTT (20 - 35 sec)	28.7	27.1	50.2	>140	37.8
D-dimer (< 0.5)	0.54	3.7	3.79	2.08	3.53
CRP (< 5 mg/L)	8.28	92.28	123.7	175.87	170.59

Table 2: *Laboratory findings.*

Case 3

A 20-year-old male complained of fever for 6 days, cough for 5 days, and difficulty in breathing for 2 days. He was transferred from a referral hospital and was receiving Inj. LMWH 0.6 SC BD, Inj. Methylprednisolone 40 mg BD, and Tab. Ecosprin 75 mg OD for 2 days. On examination he was conscious and vitals were: BP-130/86 mm Hg, PR-76/min, RR-26/min Temperature-within normal limits and SPO_2-84% on room air. He had a past history of bleeding per rectum 2 months back for which he was treated conservatively. On admission he was put on NRBM support with SPO_2-93% on oxygen 15 L/min.

Considering his clinical presentation, the medications he was already receiving were continued from the day of admission. On day 3 of hospitalization his oxygen requirement increased further with SPO_2 90% on HFNC 55 L/min and FIO_2-100% and Inj. Methylprednisolone 240 mg in 50 CC intravenous infusion started at the rate of 2 ml/hour in view of raised C reactive protein. On day 5 bleeding per rectum was found for which surgery and gastro-medicine reference was done. Stool examination showed presence of occult blood suggestive of melena. Inj. LMWH and Tab. Ecosprin was withheld and Inj. Vitamin K 3 ml IV stat followed by 1 ml IV OD for 3 days, Inj. Tranexamic

Acid 500 mg IV BD, Inj. Hemocoagulase 1 ml IV TDS were started and bleeding per rectum was corrected. His clinical condition worsened on each passing day, hence intubated and was put on mechanical Ventilation. On day 11 on the bases of significantly altered coagulation profile fibrinogen 305 mg/dL (150 - 400 mg/dL), fibrin degraded products > 20 (< 5 considered normal) Inj. Heparin 25K in 50 CC normal saline intravenous infusion restarted, but after 2 days of administration examination showed maroon coloured stool and presence of occult blood and was diagnosed as upper GIB. Inj. Heparin and Inj. Methylprednisolone were withheld and Inj. Albumin 20% IV OD, Inj. Somatostatin 3 mg in 50 CC normal saline 4ml stat followed by 4ml/hour, Inj. Tranexamic Acid 500 mg IV BD, Inj. Hemocoagulase 1 ml IV TDS were started. Patient was given a total 8 units of PCV and 4 units of FFP in view of low haemoglobin. Relevant laboratory investigations are depicted in table 3.

Investigations	Day 1 (LMWH commenced)	Day 5 (LMWH stopped)	Day 8 (Heparin commenced)	Day 11 (Heparin stopped)	Day 13 (Occult blood in stool)
Hb (12 - 18 g/dl)	14.5	13.6	12.4	7.8	5.5
Platelet count (130 - 400 kU/L)	200	189	208	221	204
PT (12 - 16)	12	16.1	17.5	17.8	19.7
INR (0.8 - 1.2)	0.86	1.18	1.29	1.31	1.46
aPTT (20 - 35 sec)	34	26	26.4	26.7	23.8
D-dimer (< 0.5)	2.4	1.94	>20	11.33	7.88
CRP (< 5 mg/L)	9.6	79.12	9.92	32.05	9.29

Table 3: *Laboratory findings.*

Case 4

A 58-year-old hypertensive female complained of fever for 7 days and difficulty in breathing for 3 days. She was transferred from a referral hospital and was receiving Inj. LMWH 0.6 CC SC BD, Inj. Methylprednisolone 40 mg BD, Tab. Ecosprin 75mg OD for 3 days. On examination she was conscious, and vitals were: BP-110/70 mm Hg, PR-62/min, RR-38/min, Temperature-within normal limits and SPO_2-68% on room air. On admission she was put on BIPAP support. She was a known case of hypertension since 8 years and was on medication.

Considering her clinical presentation, the medications she was already receiving were continued from the day of admission. On day 5 of hospitalization, she complained of oral and nasal bleeding which was spontaneous in nature and bleeding per rectum. Inj. LMWH and Tab. Ecosprin were withheld and Inj. Vitamin K 3 ml IV stat followed by 1 ml IV OD for 3 days, Inj. Tranexamic Acid 500 mg IV BD, Inj. Hemocoagulase 1 ml IV TDS were started. Her clinical condition worsened on each passing day, hence was put on mechanical Ventilation. On day 12 Inj. Dexamethasone 24 mg IV OD and Inj. Heparin 25K in 50 CC normal saline intravenous infusion started, but after 4 days of administration nasal bleeding was observed and stool examination showed presence of occult blood, Inj. Heparin and Inj. Methylprednisolone were withheld. Patient was given a total 8 units of FFP and 6 units of PCV in view of low haemoglobin. Relevant laboratory investigations are depicted in table 4.

Investigations	Day 1 (LMWH commenced)	Day 5 (LMWH stopped)	Day 12 (Heparin commenced)	Day 16 (Heparin stopped)	Day 17 (Occult blood in stool)
Hb (12 - 18 g/dl)	10.9	6.8	10.2	9.1	7.9
Platelet count (130 - 400 kU/L)	181	170	86	64	59
PT (12 - 16)	18.2	15.8	16	13.7	24.5
INR (0.8 - 1.2)	1.34	1.15	1.18	1.2	1.85
aPTT (20 - 35 sec)	27.5	87.8	31.2	25.2	24.2
D-dimer (< 0.5)	1.83	2.89	11.76	2.12	1.92
CRP (< 5 mg/L)	63.6	12.9	201.7	138.9	252.7

Table 4: *Laboratory findings.*

Case 5

A 78-year-old hypertensive and diabetic female complained of cough for 2 days and difficulty in breathing for 1 day. On examination she was conscious, and vitals were: BP-140/84 mm Hg, PR-109/min, RR-20/min, Temperature-within normal limits and SPO_2-84% on room air. She was a known case of hypertension and diabetes since 15 years and was on medication. On admission he was put on NRBM support with SPO_2-99% on oxygen 10L/min.

Considering her clinical presentation Inj. Heparin 25K in 50 CC normal saline intravenous infusion at 2 ml/hour and Inj. Dexamethasone 24 mg IV OD started from the day of admission. Her clinical condition worsened, hence was put on mechanical Ventilation. On day 6 of hospitalization, she developed purplish coloured ecchymotic patch over lateral aspect of right leg for which dermatology reference was done. Inj. Dexamethasone was given intermittently according to her clinical presentation. On day 9 due to altered coagulation profile Inj. Heparin was withheld, and again restarted 3 days after correction of the same. On day 16 on proctoscopic examination, per rectum bleeding was observed and Inj. Heparin was withheld. Stool examination showed presence of occult blood. Patient was given a total 6 units of PCV in view of low haemoglobin. Relevant laboratory investigations are depicted in table 5.

Investigations	Day 1 (Heparin commenced)	Day 9 (Heparin stopped)	Day 12 (Heparin recommenced)	Day 16 (Heparin stopped)
Hb (12 - 18 g/dl)	9.2	7.5	9.4	8.8
Platelet count (130 - 400 kU/L)	152	151	182	205
PT (12 - 16)	15.4	18.2	12.9	21.3
INR (0.8 - 1.2)	1.12	1.34	0.93	1.59
aPTT (20 - 35 sec)	26.7	>140	32.1	34
D-dimer (< 0.5)	2.36	1.61	2.58	1.2
CRP (< 5 mg/L)	7.23	137.76	229.68	24.79

Table 5: *Laboratory findings.*

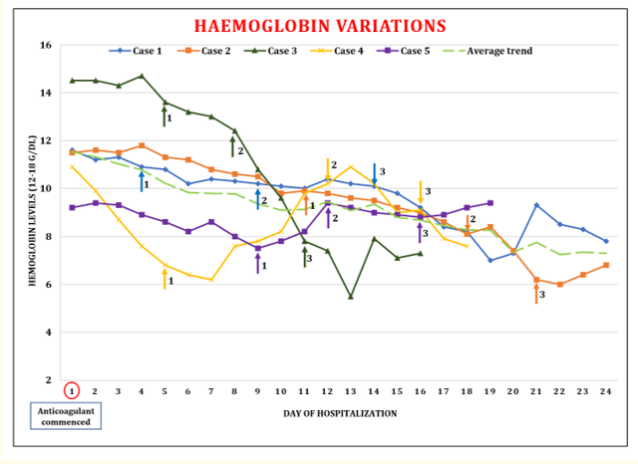

Figure 1: *Graph depicting Haemoglobin variation during hospitalization (Arrow 1: Anticoagulant stopped; Arrow 2: Anticoagulant recommenced; Arrow 3: Anticoagulant stopped; Dash line showing the average trend of haemoglobin levels of all patients which is a decreasing trend).*

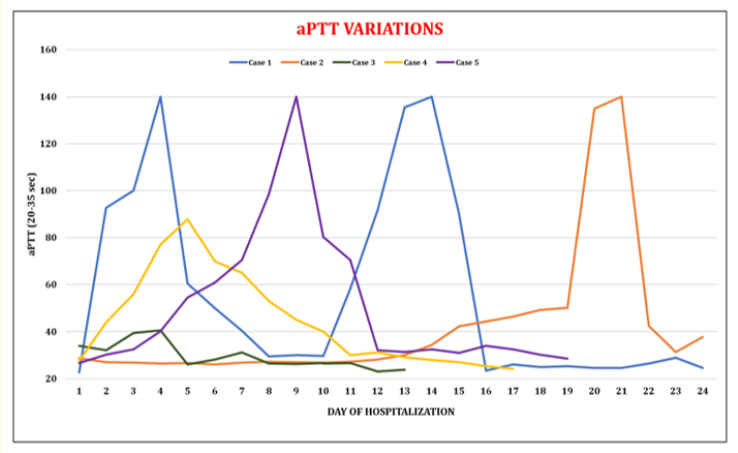

Figure 2: *Graph depicting aPTT variation during hospitalization.*

Discussion

DIB is one of the dreadful complications involving COVID-19 therapeutics. Five cases discussed here involved GIB as well as bleeding from other sites. Considering their clinical presentation, they were treated with concomitant drugs as discussed. Studies have reported varying incidences of VTE in patients with COVID-19. A meta-analysis of studies in hospitalized patients with COVID-19 found an overall VTE prevalence of 14.1% (95% CI, 11.6 - 16.9) [10]. Hence prescribers might adopt an aggressive approach regarding prevention of this life-threatening complication. Anticoagulant therapy includes Heparin and other oral as well as parenteral anticoagulants like Dabigatran, Rivaroxaban, Apixaban have been prescribed in almost all COVID-19 patients due to critical nature of the disease.

Heparin is a powerful and instantaneously acting anticoagulant, which inactivates clotting factors of the intrinsic and common pathways of coagulation. Low concentrations of heparin prolong aPTT without significantly prolonging PT. Heparin specifically inhibit platelet function by disrupting the formation of fibrin and platelet plug reinforcement. As Heparin interferes with haemostasis; the major untoward effect of heparin is bleeding from deeper organs which is observed in 1% - 5% of patients treated with intravenous Heparin. Conditions such as recent surgery, trauma, peptic ulcer disease, or platelet dysfunction due to concomitant administration of aspirin or other antiplatelet drugs are associated with increased risk of bleeding [11,12].

A meta-analysis performed by an American Society of Haematology guidelines panel compared the odds of bleeding and thrombotic outcomes in patients with COVID-19 treated with prophylactic dose anticoagulation versus in those treated with intermediate or therapeutic dose anticoagulation. Overall, the odds of VTE and mortality were not different between the patients treated with prophylactic dose anticoagulation and those treated with higher doses of anticoagulation. In critically ill patients, intermediate or therapeutic dose anticoagulation was associated with a lower odds of pulmonary embolism (OR 0.09; 95% CI, 0.02 - 0.57) but a higher odds of major bleeding (OR 3.84; 95% CI, 1.44 - 10.21) [13].

Because the patients have cytokine storm, they were receiving high doses of glucocorticoids namely Dexamethasone and Methylprednisolone. Glucocorticoids have been reported to have varied adverse effects especially on gastric mucosa. They increase the ulcer risk when administered at a high dose for prolonged periods in susceptible individuals. Various experimental studies in the past have demon-

strated its ulcerogenic property which is due to inhibition of housekeeping prostaglandins. They have stimulatory effect on gastric secretion and have been reported to degranulate the mast cell to release histamine which may be responsible for increased acid secretion [14].

A multicentred study done by Lauzier., *et al*. showed that approximately 6% of critically ill patients developed major bleeding who had received heparin thromboprophylaxis. Therapeutic anticoagulation, prolonged aPTT, or lower platelet count were one of the independent predictors of major bleeding. Association between type of heparin for thromboprophylaxis (unfractionated or low molecular weight) and increased risk of bleeding was not found. Patients who had major bleeding were found to have a significantly increased rate of blood product transfusion, increased duration of mechanical ventilation, longer ICU and hospital lengths of stay, and increased mortality [15].

In our case series all five patients with COVID-19 and associated complications needed prolonged hospital stay and also mechanical ventilatory support. As a line of management concomitant use of anticoagulants, steroids and antiplatelet drugs further increased the bleeding risk. They all had GIB along with bleeding from other sites, as Case 1 had haematuria while Case 2 and 4 had oral and nasal bleeding. We also observed thrombocytopenia in Case 1,2 and 4 and prolonged aPTT. Figure 2 shows the prolongation of aPTT which was significantly prolonged in case 1, 2, and 5 (>140 seconds). Their clinical outcome was poor and eventually all five of them succumbed. On the basis of complete blood count, coagulation profile and stool examination report physician suspected DIB.

A study done by Gutermann IK., *et al*. concluded that there is no clear advice about how to proceed after the episode of acute bleeding due to the lack of clear clinical practice guidelines in an emergency room setting. This complicates patient care because the extra time needed for clinicians in the respective medical specialties to discuss patient's situation can delay critically needed emergency care especially amidst a pandemic [16]. Therefore, we are in the process for formulating evidence-based guidelines to manage covid related complications. Physicians should be vigilant against DIB which could be iatrogenic (physician or drug induced) but in this worst present pandemic wave, they should not be held responsible as the disease spectrum is yet not fully elucidated.

Conclusion

Evidence based guidelines for management of thrombotic events associated with COVID-19 are in pipeline which would help the physician to decide the need for appropriate anticoagulation. These eventful outcomes then be minimized.

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Conflict of Interest

None declared.

Ethical Approval

Not required.

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