Original Article

Evaluation of Use and Safety of Using Parentral Anti-Coagulants in Critically Ill Patients in Tertiary Care Hospital, India

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Abstract

Objective: to find out the appropriateness of prescribing different types of parenteral anticoagulants in critically ill patients and identifying the patterns of thromboprophylaxis. **Methodology:** This cross-sectional prospective study of on appropriateness of prescribing anti-coagulants has been carried out in a number of 213 patients. The study was conducted over 6 months (February to July 2016) at the Tertiary Care Hospital, India. As per inclusion criteria, from the day of admission to the day of discharge the patient's treatment charts have been followed. Guidelines for the use of anti-coagulants have been summed up and checked up during the prognosis of treatment. Mechanical prophylaxis of VTE and Pharmacological prophylaxis have been studied. The mismatch of guidelines and the treatment is being followed and adherence with the guidelines is undertaken. **Result:** The appropriateness of prescribing anti-coagulants have been determined based on the patterns of thromboprophylaxis, out 0f 213 patients, 172 patients received UFH ,65 patients was on Enoxaparin, and no one were on Fondaparinux. The evaluations are been made with respect to guidelines, the mean ratio which follows the guidelines identified as just 47.31%, where some have filtered through the certain diagnostic criteria .The risk over VTE has also evaluated .The outcome measures shows that prescribing appropriate regimen will endorse the risk of VTE .The cost effectiveness of management of VTE prophylaxis has been studied ,the data shows more effectiveness is shown by Enoxaparin, as the QOL has improved. **Conclusion:** This study revealed appropriateness of prescribing in VTE prophylaxis the best and effective for improving the prescription pattern and QOL of patients. In this study, the diagnostic criteria and guidelines mandatory for choosing the appropriate regimen for thromboprophylaxis have been considered, where being evaluated, cost effectiveness of each drug are also studied. Possible recommendations have been made.

Keywords: VTE, Anti-Coagulants, Thromboprophylaxis, Heparin, UFH

INTRODUCTION

The past decade has seen an increase in anticoagulant consumption worldwide. In the United States alone, more than 6 million patients who are on anticoagulants are in danger of entanglements from the same. [1] The explanation behind this is twofold. In the first place, with expanding life span, we are seeing an expanding number of patients giving cardioembolic strokes, which adds to around 15–30% of strokes. Atrial fibrillation is a significant hazard factor for the same. [2, 3] This has brought about the utilization of anticoagulants trying to forestall apoplexy and thromboembolism (venous thromboembolism and ischemic strokes), all around answered to be the first reason for grimness and mortality. [4] Second, given the accommodation (absence of the need of standard checking), constrained medication cooperations and demonstrated viability in apoplexy decrease, direct oral anticoagulants (DOAC) are progressively being endorsed rather than warfarin. [1] The powerlessness to modify dosing to ideal "remedial impact" may confine the capacity to screen for draining danger due to over anticoagulation. With this across the board use of anticoagulants, clinicians are progressively prone to experience patients with significant draining occasions. A few randomized controlled preliminaries over the previous decade contrasting diverse DOAC operators and warfarin have revealed significant draining confusions with both agents. [5]

Heparin was discovered by McLean in 1916. More than 20 years later, Brinkhous and associates demonstrated that heparin requires a plasma cofactor for its anticoagulant

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activity; this was named antithrombin III by Bundgaard in 1968 but is now referred to simply as antithrombin (AT). During the 1970s, Rosenberg, Lindahl, and others clarified the systems liable for the heparin/AT cooperation. It is presently realized that the dynamic community serine of thrombin and other coagulation compounds is restrained by an arginine responsive focus on the AT atom and that heparin ties to lysine destinations on AT, delivering a conformational change at the arginine receptive focus that changes over AT from a moderate, dynamic thrombin inhibitor to an exceptionally fast inhibitor.AT binds covalently to the active serine center of coagulation enzymes; heparin then dissociates from the ternary complex and can be reutilized. Subsequently, it was discovered that heparin binds to and potentiates the activity of AT through a unique glucosamine unit contained within a Penta saccharide sequence, the structure of which has been confirmed. A synthetic Penta saccharide has been developed and is undergoing clinical evaluation for prevention and treatment of venous thrombosis. [6]

The 2 favored courses of organization of unfractionated heparin (UFH) are ceaseless intravenous (IV) implantation and subcutaneous (SC) infusion. At the point when the SC course is chosen, the underlying portion must be adequate to conquer the lower bioavailability related with this course of organization. On the off chance that a quick anticoagulant impact is required, the underlying portion ought to be joined by an IV bolus infusion, in light of the fact that the anticoagulant impact of SC heparin is postponed for 1 to 2 hours. In the wake of entering the circulation system, heparin ties to various plasma proteins, which diminishes its anticoagulant movement at low focuses, in this manner adding to the changeability of the anticoagulant reaction to heparin among patients with thromboembolic scatters and to the research facility wonder of heparin obstruction. Heparin additionally ties to endothelial cells and macrophages, properties that further confuse its pharmacokinetics. Authoritative of heparin to von Willebrand factor additionally hinders von Willebrand factor–subordinate platelet work. Heparin is cleared through a blend of a quick saturable system and much more slow first-request components. The saturable period of heparin freedom is credited to authoritative to endothelial cell receptors and macrophages, where it is depolymerized. The more slow, unsaturable system of leeway is to a great extent renal. At remedial portions, a significant extent of heparin is cleared through the quick saturable, portion subordinate system. This energy make the anticoagulant reaction to heparin nonlinear at restorative dosages, with both the force and term of impact rising excessively with expanding portion. Along these lines, the obvious natural half-existence of heparin increments from 30 minutes after an IV bolus of 25 U/kg to an hour with an IV bolus of 100 U/kg and 150 minutes with a bolus of 400 U/kg. [7, 8]

The antithrombotic action of fondaparinux sodium is the aftereffect of antithrombin III (ATIII)- intervened specific hindrance of Factor Xa. By specifically authoritative to ATIII, fondaparinux sodium potentiates (around multiple times) the natural balance of Factor Xa by ATIII. Balance of Factor Xa interferes with the blood coagulation course and in this way represses thrombin arrangement and clots improvement. Fondaparinux sodium doesn't inactivate thrombin (actuated Factor II) and has no known impact on platelet work. At the suggested portion, fondaparinux sodium doesn't influence fibrinolytic action or draining time. [8, 9]

Materials and Methods

The study was conducted in the Department of Critical Care (HICU, ICU, ICCU), Tertiary care hospital, Manipal, Karnataka, India. The study was conducted from February to July 2016. This study included 213 randomly selected male and female patients who admitted in critical care units under different specialties with any of the parenteral anti-coagulants. The newly admitted patient's case sheets were routinely reviewed for the purpose of this study. All the relevant data including patient information, physician orders, name, dose, time and administration of medication where entered on a predefined data collection form that was designed for this particular study. The predefined data collection form has designed with patient demographics, along with the medically relevant information. Alternatively, these case charts were reviewed for appropriateness of prescription, capture of relevant information in case sheet, contraindications, drug interactions and adverse drug events. The changes and the daily notes in the case sheets were followed until the patient was discharged or shifted to other wards. The prescription guidelines, Micromedex, lexicomp, Medscape and reference books were used as tools to review the prescription and case charts. The data was stored confidentially and was subjected to further analysis using appropriate software. Data were abstracted until death or ICU discharge, collected demographics and baseline characteristics (age, sex, Acute Physiology and Chronic Health Evaluation (APACHE), medical vs. surgical status, ICU admitting diagnosis), and relevant clinical outcomes (deep vein thrombosis, pulmonary embolism, major bleeding, heparin-induced thrombocytopenia, mortality). Venous thromboembolism events were diagnosed by the treating physicians based on clinical judgment and objective testing. Pharmacologic prophylaxis (UFH, LMWH, Fondaparinux), mechanical prophylaxis (antiembolic stockings, pneumatic compression devices), therapeutic anticoagulation, antiplatelet treatments, and use of inferior vena cava filters were captured daily, as well as factors potentially modulating prescribing such as laboratory values (for example, platelet count), outcomes (for example, bleeding), confirmatory tests (for all venous thromboembolism events), and process of care variables (for example, mobility). We additionally recorded attributes of taking an interest habitat, including the quantity of ICU beds, the nearness of a devoted apoplexy administration, injury administration or ICU quality improvement group, and whether thromboprophylaxis was controlled utilizing preprinted arranges or mechanized doctor request section.

Result and Discussion

The study period was 180 days. All the inpatients to the critical care units as per the inclusion criteria have been studied for current data. The study population consisted of 213 patients observed during the same 121 days of observation period. Out of which, 118 were male patients (55.39%) and 95 (44.60%) were female. Out of them 45 were smoking, 18 were alcoholic, 23 were smoking and alcoholic, 105 were neither alcoholic nor smokers and 22 have not mentioned about it. 118 were male patients (55.39%) and 95 (44.60%) were female. the interactions found in our study were 58. Out of them 34 (58.62) interactions were found in male and 24 (41.37) were found in female category. table 1

Table 1: Gender Categorization of Interactions

AGE (years)	NO. OF INTERACTION (n = 58)	PERCENTAGE% (n = 58)
30-39	5	8.62%
40-49	8	13.79%
50-59	11	18.96%
60-69	14	24.13%
70-79	12	20.68%
80-89	8	13.79%

In this study, 23 (10.79%) patients were found to be having on interaction, 14 (6.57%) patient were observed to have 2 interactions, 8 (3.75%) patients were found to have 3 interactions, 6 (2.81%) patients were found to have 4 interactions, 3 (1.40%) with 5 interactions, 3(1.40%) with 6 interactions and only 1(0.46) patient with 7 interaction out of 213 cases was observed.

Table 2: Drug-Drug interaction Observed in the anticoagulants Agents

Drug	Interacting drug	frequency	Effect	Severity	management
Enoxaparin	Aspirin Clopidogrel	7	May inhance the anticoagulant effect of enoxaparin.	Moderate	Increase monitoring diligence for signs and symptoms of bleeding if these agents are used concomitant.
Heparin	Aspirin	23	May inhance the anticoagulant effec of heparin.	Major	The risk of bleeding appears to be increased and should be monitored accordingly.
	Losartan Olmesartan Telmisartan	15	Heparin may inhance the hyperkalemic effect of angiotensin II receptor blockers.	Moderate	Monitoring serum potassium concentrations closely in patients receiving angiotensin II antagonists in combination with heparin.

The interactions observed with anticoagulants in this study were found to be 23 (39.65%) major interaction and 22 (37.93%) moderate interactions out of 58 interactions. table 2

Table 3: Safety Evaluation

Event	Enoxaparin	Heparin	Total
Death	1	3	4
(re)MI	0	3	3
RA with ECG changes	3	5	8
RA required urgent revascularization	4	7	11
Major bleeding	1	5	6
Minor bleeding	2	6	8
Showing abnormal lab data's	3	8	11
Total	14	37	51

For this study, most commonly prescribed parenteral anti-coagulants are being considered. Unfractionated Heparin, Low-Molecular Weight Heparin (Enoxaparin) are being studied in the progress of current study. The statistics of the same are depicted below. table 3

Table 4: depicts the different diagnosis of study population

Diagnosis of The Population	No. Of Population	% Of Total Population
Renal Failure	13	6.10%
Cardiac Emergencies and Post-Surgical Measures	17	7.98%
Ccf	23	10.79%
Dengue and Thrombocytopenia	6	2.81%
Hypoglycemia and Endocrine Emergencies	14	6.57%
Malaria, TB, MRSA, Typhoid Fever and All Infectious Disease	16	7.51%
Multi Organ Failure	26	12.20%
Poison Ingestion & Snake Bites	4	6.71%
Post Operational Care	27	12.67%
Sepsis, Respiratory Disorders	32	15.02%
Post Trauma Measures	9	4.22%
Stroke, Cerebral Hemorrhages	21	9.85%
Epilepsy	5	2.34%
Total	213	100%

Among different diagnosis, 173 people are treated with UFH. A vial of 2500 units is being dispensed for each prescription, it costs around 231.62 Indian rupees. HEPAIN LOCK FLUSH 10u/10ml costs around 14 rupees/injection. The reasons for the treatment with HEPARIN vary as below. table 4

Table 5: Using UFH among different population

Different indications	Study Population	Dose Prescribed
Pulmonary Embolism	9	5000u s/c 8-12hrs
Pulmonary embolism; prophylaxis	26	5000 u Q8H
Venous thromboembolism	21	5000u IV bolus
Venous thromboembolism; prophylaxis	45	5000u subQ Q8H
Intravascular a coagulation	10	5000 u-10000 u every 4-6 hrs
ACS;ST Segment Elevation; Unstable angina	17	5000 u/hr IV
Thromboembolic disorder; prophylaxis	21	7500-10000 usubQ Q12H
Atrial fibrillation	9	4000u loading dose+ initial infusion of lOOOu
total	173	

Table 6: Use of Low Molecular Weight Heparin (Enoxaparin) Among Different Study Population

Different Indications	Study Population	Prescrib Ed Dose
Acute ST segment elevation MI	12	40 MG subQ every 12H
Post-operative DVT prophylaxis(cardiac, GI)	5	30mg subQ every 12h
DVT with or without PE	3	1mg/kg subQ every 12H
DVT, in patients with restricted mobility with acute illness	9	40 mg subQ every 12 H
Ischemia; prophylaxis	4	1mg/kg subQ every 12H
Post-operative DVT(ortho)	2	30 mg subQ every 12 H
Pulmonary embolism	6	0.5mg/kg IVbolus infusion/ 40 mg subQ every 12H
Total	41	

Treatment outcome has measured in related management of thrombosis in hospitalized patients, improvement in the risk of VTE, evaluating the tools for the prophylaxis are also being under kept. Treatment measures, prevalence rate of each of the conditions are also studied. Among the population, the apparently the outcome has measured as there was a huge limitation for securing the full data. table 5,6

Table 7: Treatment outcome measured

Indication for Therapy	Therapy They Received	No. of Study Population
Pe	Heparin/Lmwh	9
PE; Prophylaxis	Lmw	4
Vte	Ufh/Enoxaparin,	13
VTE;Prophylaxis	Enoxaparin	6
Intravascular Coagulation	Heparin	6
ACS; ST Segment Elevation;Unstable Angina	Enoxaparin/Heparin	4
DVT; Prophylaxis	Heparin	7
Atrial Fibrillation	Heparin	5
Total	54	

Among the 213 patients, only 54 cases the outcome has been assessed, most of the outcome source is being underlines as the measuring outcome has lied in difficulty. table 7

The pattern of use was based more on clinician's judgment and experience, and in few situations the usage pattern deviated from American College of Chest Physicians (ACCP) guidelines based on patient's requirements. During the study 173 patients were administered Heparin and 41 patients were administered Enoxaparin. Out of 213 patients 58 drug-drug interactions were found which was included of parental anticoagulants interaction. We also observed that in 176 cases PT and INR tests was performed and in 16 patients PT, INR and aPPT levels were increasing despite anticoagulant therapy, however in such patients the dose of anticoagulant drug administered was not further altered. Same thing was increasing in case of enoxaparin administration only in 2 cases. Taken together, the results presented here indicate that more attention needs to be paid to ensure a safe use of anticoagulants and diuretics, often used in elderly patients who experience for more ADR compared with children or younger adults. Targeting education and prevention actions on these two drug classes could help to reduce the incidence rate of ADR related hospitalization. Ultrasound data was not widely used, which limited our evaluation of the hemodynamic status of dissections. Stroke severity (i.e., NIHSS score) at presentation was not prospectively recorded, but found no association between antithrombotic choice and the ischemic symptoms at presentation or the presence of infarction on brain imaging. Traumatic CAD patients were also included in our study; their hospital course may have only allowed for AP treatment due to the risk of bleeding in the acute period. However, it is essential that a simple, inexpensive and widely approved test, like a PTT and INR, be available for clinical use, occasionally, in patients with severe hemorrhagic complications, recurrent thrombotic episodes or prior to percutaneous interventions and surgery. Prescribing drugs with generic name, avoiding irrational use

of drugs and polypharmacy, can help in reducing the cost of treatment and economic burden. Presence of multiple comorbidities and use of more parental and antimicrobial drugs are responsible for greater economic burden in expired than survived patients.

Conclusion

In this study appropriateness of prescribing different parenteral anti-coagulants has been studied. The study has been performed among UFH (heparin 5000IU) and Enoxaparin (40mg and 60mg). 213 patients have been included in the study. the ratios of different therapy and indications of anti-coagulation have been identified and categorized as specified. The guidelines for the appropriate use have been measured and being followed all during the study, all the 213 cases has evaluated under the guidelines, in which only 134 cases has adhered to the current guidelines that is only 68.77%. All the parenteral anti-coagulants have labeled as high alert medicines, as riskier than the indication specified. The risk of VTE being studied and identified the core for thromboprophylaxis, the material in which the actual thrombolysis needed and the actual indication of Anti-coagulation has carried out and being formulated as a conclusion of this study. in that population which essentially requires the therapy understood by the tests like D-dimer, Doppler ultrasonography and certain imaging techniques like Venography, CT venography. Only a few of the cases have undergone these techniques which is around 28 (16.99%), and those cases partially diagnosed as Deep Vein Thrombosis. Appropriate use of anticoagulant therapy and any deviation from the guidelines to a large extent also depends on patient characteristics and concomitant therapy patient is receiving. Repeat monitoring of the parameters helps to evaluate the safety of anticoagulant drug use. The need for dosage adjustments in different diagnostic situation or specific populations is very crucial. The therapy with parenteral anticoagulant drugs needs to be cost effective and reduce the complications associated with their use.

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