# Chemical Versus Mechanical and Chemical Venous Thromboembolism Prophylaxis in Neurocritically Ill Patients: A Cohort Study

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# Abstract

**Background:** Patients admitted with neurocritical illness are presumed to be at high risk for venothromboembolism (VTE). The administration of chemical and/or mechanical VTE prophylaxis is a common practice in critically ill patients. Recent data did not show a significant difference in the incidence of VTE between chemical compared to chemical and mechanical VTE prophylaxis in critically ill patients with limited data in neurocritically ill population. The objective of this study is to investigate the incidence of VTE between chemical alone compared to chemical and mechanical VTE prophylaxis in neurocritically ill patients. This was a retrospective cohort study at a tertiary teaching hospital. Data were obtained from electronic medical records for all patients admitted with neurocritical illness from 1/1/2016 to 1/12/2020. Patients were excluded if they did not receive VTE prophylaxis during admission or were younger than 18 YO. Major outcomes were symptomatic VTE based on clinical and radiological findings, intensive care unit (ICU) length of stay (LOS), and hospital LOS. Minor outcomes included severe or life-threatening bleeding based on GUSTO criteria, and mortality at 28-days.

**Results:** Two hundred and twelve patients were included in this study. Patients did not have any significant differences in their baseline characteristics. The incidence of VTE was not different between chemical only compared to chemical and mechanical VTE prophylaxis groups (19/166 (11.3%) vs 7/46 (15.2%); P=0.49. No difference between groups in their ICU LOS 6 [3 – 16.2] vs 6.5 [3 – 19]; P=0.52, nor their mortality (18/166 (10.7%) vs 3/46 (6.5%); P=0.38, respectively. Less bleeding events were seen in the chemical prophylaxis group compared to the combined VTE prophylaxis group (19/166 (11.3%) vs 12/46 (26.1%); P= 0.013.

**Conclusion:** Our findings observed no difference between the administration of chemical prophylaxis alone compared to combined VTE prophylaxis in neurocritically ill patients. More data are needed to confirm this finding with more robust methodology.


# Background:

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two clinical manifestations of venous thromboembolism (VTE), which is a common morbidity among patients with critical neurological illness (1,2). The rates of VTEs among different groups of neurological patients is reported to be between 1.2–31.6% (3-7). It continues to occur despite the prevalent use of both mechanical and chemical thromboprophylaxis (8). In a study conducted by Reiff et al, in patients with traumatic brain injury (TBI), the risk of DVT was increased by 3-4 folds even with the use of mechanical and chemical prophylaxis (9). When comparing neurocritically ill patients to non-neurocritically ill patients, the rates of VTE are estimated to be higher as a result of prolonged coma and paralysis (2).

Prevention of VTEs among hospitalized patients is a necessity to reduce morbidity and mortality, which may eventually decrease healthcare cost and improve patients' functional outcomes (10). Prospective studies reported that the current strategies for prophylaxis significantly reduced the risk of VTE when

compared to no prophylaxis in critically ill patients (2,11). Currently, mechanical, and chemical prophylactic strategies, either combined or not, are considered the standard of care to prevent VTEs among all hospitalized patients (2,11). Guidelines for VTE prophylaxis recommend using chemical prophylaxis over using mechanical prophylaxis strategies. Examples for commonly used chemical VTE prophylaxis are unfractionated heparin (UFH) or low-molecular weight heparin (LMWH), whereas gradual compression stockings (GCS) or intermittent pneumatic compression (IPC) are common examples of mechanical VTE prophylaxis (2). The efficacy of UFH or LMWH compared to placebo is well established with more than 50% reduction in deep vein thrombosis (DVT) occurrence rates among critically ill patients (12,13). The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial evaluated the use of IPC in immobile stroke patients to reduce the incidence of DVTs. The primary endpoint of DVT occurred in 8.5% in the IPC group and 12.1% in the other group without IPC resulting in an absolute risk reduction of 3.6% (95% CI 1.4–5.8%) (14).

The clinical practice guidelines for neurocritically ill patients generally recommend chemical VTE to be initiated within a range of 1-3 days from admission based on the patient diagnosis, if there are no contraindications. Most guidelines recommend using chemical and mechanical combination strategy compared to using chemical prophylaxis alone to reduce the risk of VTEs (2,14). The foundation of brain trauma in 2016 stated that evidence of level I and II is lacking, however, UFH or LMWH can be prescribed in addition to non-pharmacologic methods to prevent DVT as a level III recommendation. This comes at a cost of expanding intracranial hemorrhage. They also emphasized that only when the brain trauma is stable, pharmacologic prophylaxis can be utilized if the benefit outweighs the risk (15). The Neurocritical Care Society practice guidelines published in 2015 provided recommendations for various groups of neuorocritically ill patients. In patients with ischemic stroke, LMWH is recommended over UFH in combination with mechanical prophylaxis whereas there was no preference of which chemical agent to use in combination with mechanical in patients with intracranial hemorrhage (ICH). Additionally, in patients with aneurysmal subarachnoid hemorrhage (aSAH), only UFH was recommended alongside IPC. In patients with TBI, either LMWH or UFH can be used in addition to mechanical IPC within 24 hours of presentation (2). Nonetheless, a recent multinational randomized clinical trial (RCT) challenged this common practice in intensive care unit (ICU) patients. They found no difference in the incidence of DVT when adding IPC to chemical prophylaxis compared to chemical prophylaxis alone in a mixed ICU population with minimal representation for neurocritically ill patients. In our study we aim to investigate the incidence of VTEs associated with the use of chemical alone compared to chemical and mechanical prophylaxis of VTE in neurocritically ill patients only.

# Methods:

This is a retrospective cohort study that was conducted at King Abdulaziz Medical City, National Guard Health Affairs, which is a tertiary referral teaching hospital with dedicated neurocritical care unit in Riyadh, Saudi Arabia. Data was obtained from electronic medical records (BESTCare) for all patients admitted with neurocritical illness who were prescribed any chemical and/or any mechanical VTE prophylaxis for any of the following indications: ischemic stroke, spontaneous ICH, aSAH, TBI, and others

(such as status epilepticus, severe meningitis/encephalitis, brain tumors resections, myasthenia gravis crisis and severe diabetes insipidus) for at least 24 hours from 1/1/2016 to 1/12/2020. King Abdullah International Medical Research Center (KAIMRC) institutional review board (IRB) approved this study with IRB ethical approval number (SP20/446/R), along with waiver of the informed consent form based on the study design. Patients were excluded if they did not receive VTE prophylaxis of any kind during admission or were younger than 18 years of age. Patients who had VTE as an admission diagnosis, were diagnosed with VTE within 24 hours of admission, or who received full anticoagulation within 24 hours of hospital admission were also excluded. After primary screening, 791 patients were identified to be eligible for inclusion in the screened time period. We limited our data collection to only the first 249 patients according to their sequential medical record number from the extracted list by KAIMRC to reduce selection bias.

We screened for patients who were prescribed chemical VTE prophylaxis including UFH or enoxaparin (an example of LMWHs) during their ICU stay; however, only patients who received UFH or enoxaparin were included in the analysis. Additionally, we screened all patients for using mechanical VTE prophylaxis including IPC, and GCS. Data were stratified based on VTE prophylaxis modality to combined VTE prophylaxis group which is defined as using any chemical in addition to concomitant administration of any mechanical VTE prophylaxis strategy and chemical prophylaxis only group. Patients' demographic data included: age, gender, body mass index (BMI), serum creatinine (umol/L) upon ICU admission, creatinine clearance (CrCl) based on Cockcroft-Gault equation upon ICU admission, history of chronic kidney disease (CKD) and solid/hematological cancer based on lab values and chart documentation. The team collected all relevant chemical VTE prophylaxis information including agent, dose, frequency, time from admission to chemical prophylaxis medication order entry, switch between chemical agents, and interruption of VTE prophylaxis for more than five days. Data for patients who were switched to full anticoagulation and concomitant use of antiplatelets during hospitalization were also collected. Patients were stratified based on the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score. Data was stratified IMPROVE scoring system into moderate to high-risk group (score of $\geq 2$) or low risk (less than 2 out of 8). Major outcomes included symptomatic VTE based on clinical documentation and radiological findings (ultrasound findings or computed tomography when needed), ICU length of stay (LOS), and hospital LOS. Minor outcomes included severe or life-threatening bleeding based on the GUSTO criteria, and mortality at 28-days from admission date. Sample size calculations were not performed prior to conducting this study. Continuous data were analyzed using Student's t-test or Mann-Whitney U test. Chi-square and Fisher's exact tests were used to compare categorical data as appropriate. Binomial logistic regression was performed using STATA®. Statistical significance was defined as $p \leq 0.05$. All methods were performed in accordance with the relevant guidelines and regulations at our institution.

# Results:

After obtaining the data for 249 patients, we included 212 patients in the comparison analysis. Thirty-seven patients were excluded because they did not receive any chemical prophylaxis at any point during admission. No major differences observed in our baseline characteristics as shown in table-1.

**Table – 1. Baseline characteristics**

| Variable | Chemical VTE prophylaxis (N= 166) | Combined VTE prophylaxis (N=46) | p Value |
|---|---|---|---|
| Age, years | 68, [52 – 78] | 67, [53 – 75] | 0.795 |
| Gender (female) | 59, (35.2) | 17, (36.9) | 0.189 |
| Underwent surgical intervention during admission | 67, (40.1) | 26, (56.5) | 0.051 |
| Weight (kg) | 74 (15.5) | 76.7 (17.7) | 0.169 |
| BMI (kg/m$^2$) | 28.9, [23.5 – 31.1] | 29.1, [23.7 – 34.2] | 0.183 |
| History of cancer | 14, (8.3) | 1, (2.1) | 0.201 |
| Prior history of DVT/PE | 12, (7.2) | 2, (4.3) | 0.754 |
| Prior history of CVA | 36, (21.5) | 9, (19.5) | 0.755 |
| Indication for antithrombotic agents prior to admission | 73, (43.7) | 24, (52.1) | 0.323 |
| IMPROVE score ≥ 2 | 59, (35.3) | 17, (36.9) | 0.860 |
| Creatinine clearance upon admission based on CG | 73 (74.1) | 75 (76.7) | 0.244 |
| Baseline aPTT | 29.2 (6.0) | 26.9 (4.6) | 0.201 |
| Baseline PT | 12.7 (3.8) | 11.8 (2.3) | 0.125 |
| Reason for admission | | | |
| - Ischemic stroke | 73, (43.7) | 23, (50) | 0.467 |
| - ICH | 33, (19.7) | 10, (21.7) | 0.781 |
| - aSAH | 8, (4.7) | 4, (8.6) | 0.296 |
| - TBI | 18, (10.7) | 9, (19.5) | 0.137 |
| - Others | 34, (20.4) | 0, (0) | ---- |
| *Data expressed as n, (%) or mean (SD) or median [25th Q – 75th Q] as appropriate | | | |

Of the included patients, there was a shorter time to initiate chemical VTE prophylaxis in the chemical VTE prophylaxis compared to the combined VTE prophylaxis which was statistically significant (1 [1–3] Vs. 4 [2-5.2]; p<0.001). We observed higher percentage of UFH administration as a preferred chemical VTE prophylaxis for both groups as compared to enoxaparin. In-hospital concomitant use of antiplatelets and transition to full anticoagulation were similar between groups as shown in table-2. No statistical difference was found in patients who switched chemical agents between groups. Additional data regarding VTE prophylaxis regimen are shown in table-2.

**Table – 2. VTE prophylaxis regimen characteristics**

| Variable | Chemical VTE prophylaxis (N= 166) | Combined VTE prophylaxis (N=46) | p Value |
|---|---|---|---|
| **Time to initiation of chemical VTE prophylaxis** | 1, [1 – 3] | 4, [2 – 5.2] | <0.001 |
| **Unfractionated heparin** | 112, (67) | 36, (78.0) | 0.158 |
| **Enoxaparin** | 54, (32.5) | 10, (21.7) | 0.158 |
| **Switched from UFH to Enoxaparin or vice versa** | 26, (15.5) | 4, (8.7) | 0.230 |
| **VTE prophylaxis interruption for more than five days** | 20, (12) | 4, (8.7) | 0.510 |
| **Switched to full anticoagulation** | 26, (15.5) | 7, (15.2) | 0.941 |
| **In-hospital concomitant use of antiplatelets** | 88, (52.7) | 18, (39.1) | 0.095 |
| *Data expressed as n, (%) or median [25th Q – 75th Q] as appropriate | | | |

No major difference was found in our major outcomes between groups as shown in table-3. However, more severe or life-threatening bleeding was seen in the combination regimen group 19/166 (11.2%) Vs. 12/46 (26.1%); p < 0.05. A binomial regression analysis regression was used to identify predictors for post DVT prophylaxis VTE events in the overall cohort. Amongst the examined factors, previous administration of antithrombotic agents (antiplatelets or anticoagulants), DVT prophylaxis interruption and ICU stay for more than seven days were found to be strong predictors. All other factors were not statistically significant as shown in table-4.

**Table – 3. Study outcomes**

| Variable | Chemical VTE prophylaxis (N= 166) | Combined VTE prophylaxis (N=46) | p Value |
|---|---|---|---|
| Major outcomes | | | |
| **New onset symptomatic VTE** | 19, (11.3) | 7, (15.2) | 0.490 |
| **ICU LOS** | 6 [3 – 16.2] | 6.5 [3 – 19] | 0.528 |
| **Hospital LOS** | 25 [11 – 73.5] | 29.5 [13.5 – 52.5] | 0.638 |
| Minor outcomes | | | |
| **28-day mortality** | 18, (10.7) | 3, (6.5) | 0 .385 |
| **Severe or life threatening bleeding based on GUSTO** | 19, (11.3) | 12 (26.1) | 0.013 |
| *Data expressed as n, (%) or median [25th Q – 75th Q] as appropriate | | | |

**Table – 4. Predictors for VTE after initiating prophylaxis VTE regimens (N= 249)**

| Variable | Odds ratio | 95% Confidence interval | p Value |
|---|---|---|---|
| **Treatment with chemical and mechanical VTE prophylaxis** | 2.11 | 0.68 – 6.51 | 0.193 |
| **Age > 60 year-old** | 1.61 | 0.48 – 5.40 | 0438 |
| **Previous administration of antithrombotic agents** | 0.29 | 0.09 – 0.92 | 0.036 |
| **Prior surgical history** | 2.36 | 0.62 – 8.94 | 0.206 |
| **Prior neurosurgical history** | 0.73 | 0.14 – 3.68 | 0.709 |
| **Time to initiate chemical VTE prophylaxis** | 0.96 | 0.28 – 3.30 | 0.959 |
| **28-day mortality** | 3.88 | 1.22 – 12.31 | 0.021 |
| **ICU LOS > 7 days** | 7.08 | 1.83 – 27.44 | 0.005 |
| All data were analyzed using binomial regression model | | | |

# Discussion:

This retrospective study investigated the role of different VTE prophylaxis modalities on the incidence of symptomatic VTE in neurocritical ill patients and the associated incidence of major bleedings. We observed no difference in the incidence of VTE between the administration of chemical prophylaxis versus the combination of chemical and mechanical prophylaxis. Though, the use of chemical only

prophylaxis did result in a significantly lower risk of major bleedings. All other clinical outcomes of interest were not different between VTE prophylaxis strategies (i.e., ICU LOS, hospital LOS, and 28-day mortality).

There was no difference in baseline characteristics regarding the type of VTE prophylaxis in admitted patients with ischemic stroke between groups in our cohort. Patients admitted with ischemic stroke accounted for the majority of included patients with approximately 43.7% and 50%, in the chemical only and the combined prophylaxis group, respectively. Current guidelines recommend using chemical prophylaxis as soon as possible in acute ischemic stroke patients, except in patients with restricted mobility as the use of LMWH plus IPC is more preferred, mainly based on CLOTs 3 trial findings (2,16). These results are inconsistent with the results of the CLOTs 3 trial, which showed a 3.6% reduction in VTE with the use of IPC post-stroke (17). A fewer percentage of patients were admitted with the diagnosis of ICH accounted for 19.7% of the chemical prophylaxis group and 21.7% of the combination group in our cohort. Given the active bleeding status in this population, it is recommended to provide mechanical prophylaxis over chemical prophylaxis at the time of admission, except with stable hematomas where chemical prophylaxis could be administered after 48 hours of admission (2). In a large retrospective study, the utilization of chemical prophylaxis for ICH patients was very low, accounting for less than 20% of the total patients and <10% in the first two days of admission (18). The use of UFH was observed in 71.1% of the patients compared to enoxaparin which was used in 27.5%. This low compliance could have been caused by a lack of knowledge or safety concerns. Similarly, patients with an admission diagnosis of aSAH accounted for 4.7% of the chemical prophylaxis group and 8.6% of the combination group in our cohort. IPC is the recommended VTE strategy in this population and should be started immediately upon admission (2). UFH should be initiated as well unless in cases of unsecured ruptured aneurysms expected to undergo surgery (19). This may be extrapolated for patients undergoing endovascular treatment but data are not clear yet on this matter. In postoperative patients, UFH should be started within 24-hours as per guidelines recommendations. In a retrospective study investigating the timing of DVT in aSAH, the incidence of DVT peaked between day 5-9 of admission with a lower incidence of DVT in the group receiving heparin prophylaxis (19).

In patients with hemorrhagic stroke, early anticoagulation is associated with a significant reduction in PE, a non-significant reduction in DVT or death, and a non-significant increase in hematoma size (20). Moreover, TBI patients represented 10.7% of the chemical prophylaxis group compared to 19.5% of the combination group of the included patients. In this patient population, the use of IPC within 24 hours of presentation or 24 hours post craniotomy is recommended by the neurocritical society with reserving chemical prophylaxis for patients with TBI and ICH to be used within 24-48 hours, or 24 hours post craniotomy (2). In contrast, the American College of Chest Physicians (CHEST) guidelines recommend LMWH for major trauma patients unless contraindicated (21). The brain trauma foundation most recent guideline does not provide any strong recommendation for preference in VTE prophylaxis agent choice, dosing nor timing of administration (15). In addition, the recent clinical consensus from the American Association for the Surgery of Trauma (AAST) Critical Care Committee recommends initiating VTE prophylaxis within 24-72 hours depending on the stability of the intracranial and extracranial

hemorrhages (22). These recommendations may explain the higher percentage of our patients in the combination therapy as they may have been started on mechanical prophylaxis initially then combined with chemical prophylaxis later. Previous guidelines also emphasized on the superiority of LMWH over UFH with low quality evidence.

In a retrospective cohort study conducted by Sauro et al in Canada, the adherence of current practice guidelines and the effect on clinical outcomes were evaluated in patients admitted to 10 different neuro, medical and surgical ICUs. Among neurocritically ill patients, chemical prophylaxis, mechanical prophylaxis and no prophylaxis was provided to 60.9%, 46.9% and 12.2%, respectively. Only 56% of the days spent in ICU were adherent to the practice guidelines. Specifically, concordance to guidelines when prescribing pharmacologic prophylaxis was reported in 26.6% of ICU days, whereas it was up to 80% of ICU days in patients eligible for mechanical prophylaxis. The results of this study demonstrate the variations and uncertainty regarding the optimal practices for prevention of VTE in neurocritically ill patients (23).

In this study, we observed an increase in the utilization of UFH compared to enoxaparin despite having normal baseline renal function. This observation is mainly attributed to the pharmacokinetic advantages of UFH over LMWH, especially with patients who underwent neurosurgical interventions during their ICU admission. UFH is more reasonable when acute interruption of anticoagulation is needed for emergent surgery or active bleeding event. Also, anticoagulation reversal can be better controlled with UFH when compared to enoxaparin achieved (24,25). The incidence of symptomatic VTE post-acute stroke was reported to have range of 2-10%, while we observed slightly an increased incidence in our population despite having 65% being categorized as low thrombotic risk based on their IMPROVE scores of <2 (2,19). This minimal increase may be a result of the late re-initiation of anticoagulation in patients who had an indication. Approximately 50% of our included patients had an indication for antithrombotic agent prior to admission, however 15% only were transitioned eventually to full anticoagulation in both groups. Additionally, the concomitant use of antiplatelets was lower than expected in the combined VTE modality group, given difference the likelihood of these patients carrying higher risk of bleeding upon admission. This is possibly due to their higher percentage of having surgical interventions during ICU admission (40% vs 56%; p: 0.051).

This study includes some limitations. First, we randomly selected neurocritically ill patients who were admitted to our institution during the study window. Therefore, we may have missed some patients in our data collection. Second, we have combined all neurocritical injuries in our cohort. This may limit the application of our findings to a specific neurocritical injury due to our heterogeneity. Further studies with a specific focus on one injury may better reflect the impact of different VTE prophylaxis modalities. Third, we did not collect data on thrombolytic use in acute ischemic stroke patients. We have very limited patients who present to our institution within the appropriate window for administration of such therapy (25). Availability of such data may better help explain the increased incidence of bleeding in one group or the other. Fourth, UFH was used more than LMWH in our cohort which may have contributed to the similar efficacy between the two groups. In the PREVAIL trial, the use of LMWH was associated with a

reduction in VTE risk by 43% compared to UFH showing clear superiority in acute ischemic stroke patients (26). Lastly, we could not differentiate patients with a high or low risk of bleeding, as this would have only been achieved if better clinician documentation existed. However, up to our best knowledge there is no proven tool to predict or estimate the risk of bleeding in this patient population. More data will be needed to validate our findings in neurocritically ill patients.

# Conclusion:

The incidence of VTE was similar between neurocritical ill patients who received chemical versus chemical and mechanical VTE prophylaxis. More bleedings were observed in the chemical-only prophylaxis likely due to their increased risk of bleeding compared to the combined prophylaxis group. Further studies with a more robust design and targeted investigation of specific neurological injury are warranted to confirm the safety and efficacy of different VTE prophylaxis modalities in neurocritical ill patients.

# Abbreviations

DVT
Deep vein thrombosis
PE
Pulmonary embolism
VTE
Venous thromboembolism
TBI
traumatic brain injury
UFH
Unfractionated heparin
LMWH
Low molecular weight heparin
GCS
Gradual compression stockings
IPC
Intermittent pneumatic compression
ICH
Intracranial hemorrhage
SAH
subarachnoid hemorrhage
RCT
randomized clinical trial
CrCl

Creatinine clearance
CKD
Chronic kidney diseases
BMI
Body mass index
IMPROVE score
The International Medical Prevention Registry on Venous Thromboembolism score
ICU
Intensive care unit
LOS
length of stay

## Declarations

## Ethics approval and consent to participate

IRB approval for this study was granted by IRB of KAIMRC with study number (SP20/446/R)

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interest.

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This study is unfunded.

# Authors' Contributions

All authors participated equally in conceptualization, methodology, investigation, data collection, and data interpretation. All authors provided final approval of the version to be published. All authors revised it critically for important intellectual content and are accountable for all aspects of the work, ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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