Optimal Starting Dose of Warfarin for Treatment of Deep Vein Thrombosis in Nepalese Context, A Retrospective-Prospective Institutional Review

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ABSTRACT

Background

Deep vein thrombosis (DVT) requires an early establishment of effective anticoagulation in order to reduce harms and cost of concomitant treatments. Selection of the right warfarin dose at the start of treatment is important.

Objective

To know ideal starting dose of warfarin in adult with Deep Vein Thrombosis of our population.

Method

This is a retrospective-prospective single institution based analytical study including Deep Vein Thrombosis in adults from January 2015 to November 2017. On the first half (January 1, 2015 to July 31, 2016) of the study period, the cases were given 3mg of warfarin as initial dose (Group 1); while in the second half (August 1, 2016 to November 31, 2017) cases were given 5mg as the initial dose (Group 2). Two sequential International Normalisation Ratio (INR) within therapeutic range is considered as target attained.

Result

There were total of 63 patients (M:F=1:1.03) of which 85.7% (n=54) cases were acute deep vein thrombosis and 14.3% were chronic cases. Mean final dose of warfarin was 6.03 mg; where it was 6.50 mg in group 1 and 5.63 mg in group 2, p=0.11. Difference between final dose and starting dose it was found to be 3.5 mg in Group 1 while that was only 0.63 mg in Group 2 (p<0.01).

Conclusion

Lesser change in dose of warfarin from its initial starting dose (5 mg) was noticed in group 2. Warfarin 6 mg as ideal starting dose can be recommended but larger, multicentric and follow up studies are essential to substantiate the findings.

KEY WORDS

Deep vein thrombosis, International normalisation ratio, Warfarin

INTRODUCTION

All cases of venous thromboembolic (VTE) phenomenon shares common risk factors and pathophysiological characteristics of inflammation, hypercoagulability, and endothelial injury.[1] The commonest among them "deep vein thrombosis", possess a dreadful implication.

Wide variation is noted considering the annual incidenceof idiopathic VTE among adults of different race. It is found that among different races, incidence was highestamong African Americans (29/100000) and lowestamong Asian-PacificIslanders (6/100000) However there is paucity of data from our part of the world regarding the incidence of VTE.[2]

Treatment of DVT mainly focuses on preventing progression of thrombus, formation of new thrombus, and preventing dreadful complications like pulmonary embolism. Over the years various novel therapies have been developed and are being used in practice in the developed world. Warfarin has proved itself to be the anticoagulant of choice in the developing world.[3,4] However, owing to its narrow therapeutic window, maintaining a balance between 'reducing thrombotic events' without 'increasing risks of bleeding' has been a tiresome task.

Given the wide variation on dose response to warfarin, an optimal strategy to use warfarin on initial days of treatment still remains lacking.[5] Thus, management protocol differs in each individual case depending upon the institution where he/she presents. As balancing the need for effective anticoagulation is vital in treatment of DVT6and being short of data to direct the best approach to attain that balance in our context, we have set out to search for the most effective drug initiating strategy in DVT.

METHODS

This is a retrospective-prospective single institution based analytical study including all ultrasonologically diagnosed cases of DVT in adults with American society of Anesthesiologists (ASA) grade two or less than two from January 2015 to November 2017. Cases with malignancy, pregnant ladies and patients using warfarin for other indications were excluded from this study. Institutional approval was taken for the study. Informed consent was taken from each participant. On the first half (January 1, 2015 to July 31, 2016) of the study period, the cases were given 3mg of warfarin as initial dose (mentioned as Group 1 hereafter); while in the second half (August 1, 2016 to November 31, 2017) cases were given 5 mg as the initial dose (mentioned as Group 2 hereafter). Sequential International Normalised Ratio (INR) was considered after 24 and every 24 hours then after. Two sequential INR within therapeutic range (2 to 3) is considered as target attained. Until the appropriate INR was attained, along with warfarin, low molecular weight heparin (LMWH) is also given at appropriate dose. Clinical improvement and INR in therapeutic range are considered as criteria for discharge. Every case was followed up after 1 week for recanalisation status and maintenance of therapeutic INR.

RESULTS

During the study period there were 63 patients of whom 32 were female (50.8%) while 31 were male (49.2%). There were 29 patients (46%) in first half of our study period (Group 1) and 34 patients (54%) in the second half of our study period (Group 2). Mean age of patients included in the study was 48.52 years (S.D. 16.43, Range 15-89). In group 1,mean age was 51.93 years while that was 45.61 years in group 2, P=0.13. This study comprises 85.7% (n=54) cases of acute DVT in contrast to 14.3% of chronic cases. It was noted that left lower limb (37 patients, 58.7%) was more frequently involved than the right lower limb (26 patients, 41.3%). In accord to ultrasonographic results, 46% (n=29) of the patients had DVT involving upto common femoral vein, 42.9% (n=27) had DVT involving upto popliteal vein and remaining 11.1% (n=7) had their deep veins involved upto iliac vein (fig. 1).

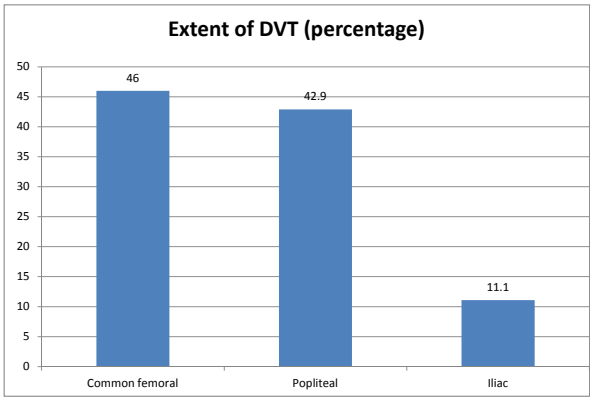

Figure 1. Extent of DVT

Mean final dose for all the cases was 6.03 mg (SD 2.17, Range 2 to 12.5). In group 1, mean final dose was 6.50 mg (SD 2.4, Range 2.5 to 12.5 mg) while in group 2, it was 5.63 mg (S.D. 1.87, Range 2 to 10 mg), p value = 0.11. In group 1, time taken to achieve therapeutic INR was 3.68 days while in group 2 it was 3.41 days (p=0.35). In relation to duration of stay, mean duration of stay in group 1 was 4.79 days (SD 1.49, Range 3 to 10 days) while in group 2 it was 4.50 days (SD 1.48, Range 2 to 9 days) with p value of 0.43. In computing the difference between final dose and starting dose, it was found to be 3.5 mg in Group 1 while that was only 0.63 mg in Group 2 ($p<0.01$). In the follow up phase we found 66.7% (n=42) had complete recanalisation, 30.2% (n=19) had partial recanalisation and 3.2% (n=2) had no recanalisation. Among the two patients who could not attain even partial recanalisation, one of them was bed ridden owing to spinal injury and the other one had history of intravenous drug abuse.

DISCUSSION

DVT is an important but fairly understated health issue. Incidence of deep vein thrombosis varies in different parts of the world. As of for today, there is paucity of data from our part of the globe regarding the incidence of DVT. However few literatures have emerged with the data that DVT is not a rarity in Asian patients nowadays.[7,8] In the issue of treatment, Warfarin has been the most commonly used anticoagulant in patients with DVT.[9] Over the time, it has proved itself to be an effective treatment as well.[10] However Warfarin has its own drawbacks. It needs close monitoring, especially at the beginning of treatment, owing to wide variation in dose response.[11] Monitoring of the dose response is done using an International Normalized Ratio (INR). In the background of narrow therapeutic range (INR 2 to 3); maintaining balance between the goal of preventing blood clots and risk of causing bleeding is a major challenge to be dealt with.[10]

In our study, male and female numbers were almost same which was similar to findings in other studies.[12] DVT was more common in left lower limb (58.7%) which is similar to findings in other studies. In a study done at North India, isolated left lower limb DVT was present in 65.8%.[13] Longer courses of left common iliac vein and proximity to pulsation of left external iliac artery causing some structural damage are known anatomic causes for more prevalence of DVT on left side.[14,15]

In our study, proximal extent of DVT has been found to be most common in common femoral vein (46%) followed by popliteal vein (42%). Similar findings were noted in a study done by Elias et al. where proximal DVT (iliac and femoral vein) was found in 55% out of all DVT and remaining 45% had DVT involving upto popliteal vein.[16] In our study mean warfarin dose for all the cases at the time of discharge was 6.03 mg. This is quite similar to the findings by Lastória et al. in which mean warfarin dose at the time of discharge was 5.3 mg and 7.3 mg in two groups of patients.[17] As per our INR monitoring protocol, minimum 4 days of stay was obligatory. Hence in our study, no significant difference was noted in both the groups considering mean duration to stay Group 1(4.79 days) and Group 2(4.5 days). Considering the therapeutic effect, complete recanalisation was noted in 66.7% cases in short term follow up (within a month). In a study done by Caprini et al. complete recanalisation has been found to occur in 70-80% of cases (slightly different in different DVT levels) at the follow up of 6 months.[18] Long term followup study is warranted in our patient population to delineate these findings.

CONCLUSION

There are some significant advantages in group with 5 mg warfarin as starting dose in comparison to group with 3 mg warfarin, notably lesser change in final dose to attain a therapeutic INR else both the group showed equivalent clinical results. And from this study, it can be stated that "preferential dose of Warfarin in DVT in our context can be concluded as 6 mg". But to recommend the dose as the standard, more studies in this regard is to be conducted in national level.

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