

## Original Research Article

# Current role of low molecular weight heparin in the treatment of acute ischemic stroke

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### ABSTRACT

**Background:** Nevertheless, several studies of LMWH in acute ischemic stroke have been neutral with regard to their primary outcomes, and it remains unclear whether these drugs should be used routinely or not. Our present trial endeavors to study the efficacy of LMWH (low and high dose dalteparin) in patients with progressive ischemic stroke in terms of morbidity and mortality as compared to control group and to compare it with AS+CLOP, with respect to these event rates, at the end of treatment.

**Methods:** Our study was performed on 38 patients of acute ischemic stroke admitted to LLR and associated Hospitals, G. S. V. M. Medical College, Kanpur and who were assigned randomly to any of the four treatment groups (0.4ml dalteparin, 0.8ml of dalteparin, 0 ml of placebo and aspirin +clopidogrel 150+75 mg). The standard error of proportion method and Chi square test was applied.

**Results:** 70% of patients in group I, 62.5% in Group II and 60% Group III presented with stroke in evolution at presentation as compared to only 30% in the placebo group. 75% of patients in group I, 66.66% in group II, 50% in Group III and 33.34% in group IV had a complete recovery. 25% of patients in Group-I, 33.34% in Group-II, 50% in Group III and 66.66% in Group-IV had an incomplete recovery.

**Conclusions:** There is no significant reduction in the mortality and morbidity amongst LMWH groups at the end of treatment and end of trial as compared to the AS+CLOP, or placebo group or even amongst the low and high dose LMWH groups.

**Keywords:** AS+CLOP, Ischemic stroke, Low and high dose dalteparin, Morbidity and mortality

### INTRODUCTION

Until recently, the management of stroke has involved largely supportive measures, but progress in our understanding of the mechanisms of stroke and resulting morbidity, combined with the development of newer therapies such as thrombolytic and low molecular weight heparins (LMWH) has led to the investigation of more active interventions.

Among these, only aspirin and possibly thrombolytic have been shown a beneficial effect on outcome. The International stroke trial 1 found that many drugs,

including glycerol, hem dilution drugs, and steroids, even though used routinely but there is no evidence from systematic reviews of randomized controlled trials (RCTs) that three agents improve outcome. Contradictory reports have appeared concerning the use of low molecular weight heparinoids (LMWHs) in acute ischemic stroke.

The use of LMWHs is recommended for this indication by several consensus conferences and experts, whereas others have concluded that there is no evidence to support the use of heparins (in general) in stroke. Compared with UFH, LMWHs have higher bioavailability, longer half-

life, reduced protein and dose-independent clearance. Hence, LMWHs produce a more predictable anticoagulant response such that they can be given subcutaneously once or twice daily without monitoring. LMWHs also have less antiplatelet activity and do not increase vascular permeability compared with UFH. As a result, LMWHs cause less bleeding than UFH. LMWHs also cause heparin-induced thrombocytopenia and osteoporosis.

Indeed, several trials in other areas of vascular medicine have shown that LMWHs are superior to ASP+CLOP. In their risk: benefit ratio. Nevertheless, several individual media-sized studies of LMWH in acute ischemic stroke have been neutral with regard to their primary outcomes, and it remains unclear whether these drugs should be used routinely.

Therefore, it was thought worthwhile to study the effect of low molecular weight heparin in the management of acute ischemic stroke in terms of long and short-term death and disability and to compare it with aspirin clopidogrel combination in terms of efficacy and safety.

## METHODS

The present study was conducted on the patients admitted to the medical wards of L.L.R. and associated Hospitals, G.S.V.M. Medical college, Kanpur after obtaining informed consent. Institutional ethical committee permission was also taken.

All patients of ischemic stroke of either sex without infective etiology and patients in whom symptoms of stroke had started during the previous 48hrs, especially cases with stroke in evolution were included in this study.

Patients aged over 80years, with transient neurological deficits, with history of recent major operation, known patients of bleeding diathesis, patients on anticoagulant therapy or valvular heart disease cases who were already on such a therapy and patients of bacterial endocarditis, with known hypersensitivity or any other adverse reaction to heparin, sustained hypertension with systolic blood pressure >180mmHg and diastolic blood pressure >120mmHg, neurological illness and C.T. Scan of brain showing intra cranial hemorrhage or space occupying mimicking symptoms of ischemic stroke were excluded.

A randomized single blind, placebo controlled trial comparing two dosage schedules of low molecular weight heparin (low and high dose) and Aspirin+ clopidogrel combination in the treatment of ischemic stroke was conducted. Detailed history of the patients

was taken, and clinical examination was done in all subjects of study group. Patients were randomly assigned to one of the four treatment modalities.

Group I (High dose LMW heparin group): It comprised of 10 patients who were treated by twice daily subcutaneous injection of 2500 anti XA IU of dalteparin in 0.4ml of solution,

Group II (High dose LMW heparin group): It comprised of 8 patients who were treated by twice daily subcutaneous injection of 2500 anti XA IU of dalteparin in 0.4ml of solution,

Group III (aspirin+clopidogrel combination group): It comprised of 10 patients who were treated by 150mg Aspirin+ 75mg clopidogrel combination per day,

Group IV (placebo Group): It comprised of 10 patients who received injection of placebo every 12hrs.

All the patients were followed to record any clinical improvement or complications. The primary, pre-specified study outcome after one month follow up was defined as complete recovery or incomplete recovery requiring help in performing activities of daily life. The secondary study outcome included death or other complications.

## Statistical analysis

Since the study design involved four groups of patients receiving different dosages of three active drugs (0.4ml,0.8ml of dalteparin, 0 ml of placebo and aspirin +clopidogrel 150+75mg) the standard error of proportion method and Chi square test for trend was used.

## RESULTS

The majority (63.15%) of patients were in the age group 51-70 years with a mean age of 60.5years. Stroke was more prevalent in men (73.68%) as compared to women (26.32%). 15 (39%) patients belonged to rural areas while 23 (61%) to urban areas. Most patients belonged to middle class (89.74%).

The overall prevalence of hypertension was 21.05%, smoking was 36.84%, NIDDM was 13.15 and hyperlipidemia was 21.05%. 84% of infarcts were less than 3.5cm at the time of presentation 92.10% of infarcts were in the middle cerebral artery. 70% of patients in group I, 75% in Group II and 60% in group III were conscious at the time of presentation as compared to 40% the placebo group.

**Table 1: Efficacy of low dose LMWH in treatment of acute ischemic stroke (LMWH v/s placebo) (after one month of follow-up).**

Events	Group I (low dose LMWH) n=10	Group iv (placebo) n=10	Significance (p<0.05)
Patients lost during follow-up	5	5	
Total no. of patients studied (n)	4	3	
Complete recovery	(3/4) 75%	(1/3) 33.34%	P>0.05
Incomplete recovery	(1/4) 25%	(2/3) 66.66%	P>0.05

In the low dose LMWH group 75% of patients had complete clinical recovery as compared to 33.34% in the placebo group. There was no significant difference in the proportion of patients who recovered completely among

the two groups. (P>0.05). 25% required help in their daily activities as compared to 66.66% in the placebo group. However, this difference in the event rates was not significant (P>0.05).

**Table 2: Comparative study of efficacy of LMWH with A+CLOP (LMWH v/AS+CLOP) (After one month of follow up).**

Events	Group I (low dose LMWH) n=10	Group iv (placebo) n=10	Significance (p<0.05)
Patients lost during follow-up	5	7	
Total no. of patients studied (n)	4	2	
Complete recovery	(3/4) 75%	(1/2) 50%	P>0.05*
Incomplete recovery	(1/4) 25%	(1/2) 50%	P>0.05*

75% of patients showed complete clinical recovery as compared to 50% in the AS+CLOP Group (P>0.5).

In the high dose LMWH group, 66.66% of the patients had complete clinical recovery as compared to 50% in the AS+CLOP Group (P>0.05).

**Table 3: Comparative study of efficacy of high dose LMWH with A+CLOP (LMWH v/AS+CLOP) (After one month of follow up).**

Events	Group II (low dose LMWH) n=8	Group III (placebo) n=10	Significance (p<0.05)
Patients lost during follow-up	4	7	
Total no. Of patients studied (n)	3	2	
Complete recovery	(2/3) 66.66%	(1/2) 50%	P>0.05
Incomplete recovery	(1/4) 33.34%	(1/2) 50%	P>0.05

**Table 4: Comparative study of efficacy of low dose LMWH with LMWH (LMWH v/AS+CLOP) (after one month of follow up).**

Events	Group I (low dose LMWH) n=10	Group II (high dose) n=8	Significance (p<0.05)
Patients lost during follow-up	5	4	
Total no. Of patients studied (n)	4	3	
Complete recovery	(3/4) 75%	(2/3) 50%	P>0.05
Incomplete recovery	(1/4) 25%	(1/3) 50%	P>0.05

75% of patient in low dose LMWH group showed complete clinical recovery as compared to 66.66% in the high dose LMWH group; while 25% of patients showed incomplete recovery as to 33.34% in the high LMWH ( $P>0.05$ ).

## DISCUSSION

After almost 3 decades of intensive research, LMWHs have established their niche as important class of antithrombotic compounds. Their better pharmacokinetic properties make them more powerful antithrombotic agents than AS+CLOP. With lower risk of hemorrhage i.e. they have a better risk: benefit ratio along with the advantage of easier administration of drug, LMWHs are used routinely by many physicians in patients with acute ischemic stroke, and it is pertinent to question this practice considering all available data from randomized controlled trials. Evidence from majority of completed trials of LMWHs in acute ischemic stroke patients suggest that they may reduce death and disability by small degree compared with control treatment. All trials have uniformly shown that LMWHs are useful in prevention and treatment of deep vein thrombosis and pulmonary embolism in acute ischemic stroke patients, which contribute significantly to the mortality and morbidity in these patients.

Patients with progressing stroke secondary to thromboembolism or those with atherothrombotic event may also benefit theoretically by preventing further embolism from occurring or exiting thrombus from propagating further, but reliable RCT evidence in these situations is lacking.

### Age

In our study the maximum percentage of patients (63.15%) were in the age group 51-70 years with a mean age of 60.5% years.

The risk of stroke doubled from 13.15% in age group 30-40 years (mean age 35 year) to 28.94% in age group 51-60 years (means age 55.5 years), primarily because of the increase in atherosclerotic and cardio embolic risk factors with advantage age.

Wolf PA et al and Brown RD et al studied the trends in stroke incidence, prevalence and survival and found that the risk of stroke doubles in each successive decade after 55 years of age.<sup>2,3</sup>

### Sex

Stroke was more prevalent in men (73.68%) as compared to women (26.32%) in our study. In an earlier study by Albers et al the age specific stroke incidence rates were also found to be higher for all age groups in men than in women.

### Hypertension

The overall prevalence of hypertension in our study was 21.05% in all age groups as compared to 36.5% as found in an international trial by Whisnant JB which tested the effectiveness of treatment of hypertension for stroke prevention.<sup>5</sup>

This difference in prevalence rates may be due to exclusion of patients above 80years of age, patients with previous stroke or with cardiogenic embolism who were on anticoagulant therapy from the present study.

### Smoking

The prevalence rate of smoking in our study was 36.84% which was the highest amongst all risk factors. Wolf PA et al in the Framingham study in 1978 reported the prevalence rate of 25% in these patients. This difference was due to lower socio economic and awareness levels among our study group.<sup>2</sup>

### Diabetes

The prevalence rate of NIDDM in ischemic stroke patients in our study was 13.15% as compared to 20% as reported by US preventive services task force 1996.<sup>6</sup>

### Hyperlipidemia

In our study the prevalence rate of hyperlipidemia with or without coronary heart disease in ischemic stroke patients was 21.05% Gorelick PB estimated the prevalence rate of hyperlipidemia to be 25 to 40% amongst different age groups.<sup>7</sup>

### Level of consciousness at presentation in different treatment groups and its prognostic significance

70% of patients in group I, 75% in group II and 60% in group III were fully conscious and oriented at presentation as compared to only 40% in the placebo group; while 30%, 25% and 40% were in the altered sensorium in the first 3 groups as compared to 60% in the placebo group. This was due to randomized allocation of patients in the different treatment groups.

Kay R et al observed that 83% of a patient in the low dose LMWH group and 78% in the high dose LMWH group were fully conscious whereas 18% and 24% respectively had an altered sensorium at presentation in these 2 groups.<sup>8</sup>

Our study demonstrates that the level of consciousness at the time of presentation was an important determinant that influenced the short-term prognosis in terms of mortality and morbidity. However, the results not being statistically significant appears to be due to small number of patients in our study.

Kay R et al also demonstrated that the patients level of consciousness at presentation had a significant predictive influence on the short and long-term prognosis of the patients with ischemic stroke ( $P>0.001$ ).<sup>8</sup>

#### ***Comparison of efficacy and complications between LMWH and placebo (after one month of follow up)***

##### *Case fatality*

In our study, there were no cases fatality in any of the treatment groups, while the meta-analysis of ten randomized controlled trials involving 2810 patients showed cases fatality rate of 14.3% as compared to 12.4% in the control group. This increase in the end of trial case fatality rates was not significant.

The reason for the differences in the cases fatalities in our study as compared to the meta-analysis was due to a short follow up of one month (as against 3-6 months of follow up in the international trials), small study sample size and exclusion of patients with previous stroke or cardio embolism who were on anticoagulation therapy.

##### *Complete recovery*

In the low dose LMWH group 75% of patients had complete clinical recovery, 66.66% in the high dose LMWH group as compared to 33.34% in the placebo group. These differences were not significant ( $P>0.05$ ).

Kay R et al in their randomized double bling, placebo controlled trial involving 312 patients.<sup>8</sup> compared the efficacy of low and high dose LMWH (nandroparin) with placebo group in reducing death or dependency at 3 and 6months after randomization. In this trial, after 3months of follow up, 23% of patients in low dose LMWH group, 21% in the high dose group and 16% placebo group had a complete clinical recovery whereas after 6 months the complete recovery rates were 26%, 29% and 20% respectively in the three groups.

The differences in the proportion of patients who recovered completely was not significant ( $P>0.05$ ).

##### *Incomplete recovery (disability)*

In our study 25% of the patients had an incomplete recovery in the low dose LMWH group, 33.34% in the high dose LMWH group and 66.66% in the placebo group ( $P>0.05$ ). Key R et al in their study of 312 patients found that after 3 months of follow up 46% of patients in the low dose group 41% in the high dose group and 52% in placebo group had an incomplete recovery and were disabled requiring help in their daily activities while after six months the corresponding rates were 36%, 32% and 48% respectively. However, these reduction in disability rates in the LMWH groups were not significant ( $P>0.05$ ).<sup>8</sup> The meta-analysis of 5 randomized controlled trials by Bath PMW 9 involving 2520 patients found that

the disability rates at the end of trial for varying periods of follow up (ranging from 1-6months) was 25.3% in LMWH group as against 25.9% in the control group. This reduction is disability rates in LMWH groups as compared to controlled group as compared to controlled group not significant.

#### ***Comparison of efficacy and complication between low and high doses of LMWH after one month of follow up***

##### *Case fatality*

In our study, there were no case fatality in any of the treatment groups. Kay R et al observed that 15% of patients in the low dose LMWH group and 12% in the high dose LMWH group died at the end of three months of follow up where as the fatality rates were 17% and 13% respectively after 6 months follow up ( $P>0.05$ ).<sup>8</sup>

##### *Complete recovery*

In our study, 75% of patients in group I and 66.66% in group II had a complete clinical recovery ( $P>0.05$ ).

Kay R et al observed that 23% of patients in low dose LMWH group and 21% in the high dose LMWH group had a complete clinical recovery after three months of follow up while the complete recovery rates were 26% and 29% in the two groups respectively, after 6 months ( $P>0.05$ ).<sup>8</sup>

##### *Incomplete recovery*

In our study 25% of patients in group I and 33.34% in group II had an incomplete recovery after one month of follow up ( $P>0.05$ ).

In the trial performed by Kay R et al the incomplete recovery rates after 3 months of follow up were 46% and 41% respectively in the low dose and high dose LMWH groups: whereas these events rates were 36% and 32% respectively in the two groups after 6 months of follow up ( $P>0.12$ ).<sup>8</sup> The therapy of patients with acute stroke (TOPAS) trial Observed that the proportion of patient with Barthel index  $\geq 90$  was 61.5% in the low dose LMWH and 56.3% in the high dose group after 3 months of follow up ( $P>0.05$ ).

#### ***Comparison of efficacy between LMWH and aspirin +clopidogrel***

The final analysis of our study shows that there is no significant reduction in the mortality and morbidity amongst LMWH groups at the end of treatment and end of trial as compared to the Aspirin+Clopidogrel or placebo group or even amongst the low and high dose LMWH groups. The incidence of recurrent stroke, extracranial or intracranial haemorrhagic complications between the treatment groups were non-significantly

increased in the Aspirin+Clopidogrel and placebo groups, as compared to the LMWH groups.

The result of our study is in accordance with the results of the majority of international trials that have studied the role of LMWH in acute ischemic stroke. These have also shown no additional benefit in the reduction of mortality, morbidity or recurrent stroke incidence with the use of LMWH as compared to the control or Aspirin+Clopidogrel group.

The only significant reduction was in the rate of deep vein thrombosis and pulmonary embolism in the LMWH group as compared to placebo. These events influence the mortality and morbidity rates in these patients thus significantly reducing the composite values of these rates at the end of trials.

A number of imbalances in prognostic factors created by randomization of patients in the different treatment group (level of consciousness at presentation, sub type and size of stroke at presentation) affected the final results in our study.

Apart from this the small study sample size, patients lost during second CT scanning and follow up and exclusion of patients with previous stroke or cardioembolism who were on anticoagulation therapy also affected the significance of different event rates in the final analysis.

Thus, sufficient questions remain about the use of LMWH in acute ischemic stroke that we suggest that additional, larger trials should be performed to determine the exact efficacy and risk associated stroke patients significantly reduces the incidence of deep vein thrombosis and pulmonary embolism and thus mortality and morbidity in these patients in the long term.

## CONCLUSION

There is no significant reduction in the mortality and morbidity amongst LMWH groups at the end of treatment and end of trial as compared to the AS+CLOP, or placebo

group or even amongst the low and high dose LMWH groups.

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