Original Research Article

Long-Term Safety, Efficacy, and Outcomes Following Treatment with Dabigatran as First-Line Treatment in Subjects with Cerebral Venous Sinus Thrombosis (CVST): A Clinical Study

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Abstract

Background: Dabigatran is a drug given orally having renal clearance primarily, and is equally efficient anticoagulant as Warfarin with the additive advantage of less bleeding risk compared to warfarin making it a promising anticoagulant with efficacy and safety in CVST subjects.
Aims: To assess the long-term safety, efficacy, and outcomes following treatment with Dabigatran as first-line treatment in subjects with Cerebral Venous Sinus Thrombosis (CVST).**Materials and Methods:** In 70 subjects with CVST, LMWH (Low Molecular Weight Heparin) was given for 5 days starting at the day of admission after confirmed diagnosis. The subjects were then started on 110 mg capsule of Dabigatran from day 3 for 3 months twice daily. The treatment outcomes were evaluated after 3 months using an MRI venogram. The collected data were subjected to statistical evaluation and the results were formulated.**Results:** Total deaths reported at 3 months were 7.46% (n=5) in subjects having GCS <8. 19.35% (n=12) of subjects survived after 3 months of Dabigatran use with a GCS score of <8 with small infarct, whereas, 80.64% (n=50) subjects with GCS >8 and either small lesion or non-haemorrhagic lesion also survived. Recanalization was seen in all 62 subjects at follow-up. **Conclusion:** The present study concludes that the recanalization in patients with CVST is quite early with the use of Dabigatran for 3 months after Cerebral venous sinus thrombosis event with very few adverse events.

Keywords: Cerebral venous sinus thrombosis, MRI venogram, treatment outcomes, anticoagulants, Dabigatran

Introduction

CVT (Cerebral venous thrombosis) is a stroke type occurring secondary to the thrombosis of cerebral veins and/or Dural sinuses. The occurrence of CVTs has been reported as a high occurrence in middle and low-income countries compared to high-income countries (1.3/lakh). Complete recovery following Cerebral venous thrombosis is seen in nearly 75% of the affected subjects, whereas approximately 5% of subjects die following CVT in the acute phase[1]. Recurrent VTEs (venous thrombotic events) are seen commonly in the survivors of acute CVTs after months of the event, commonly leading to pulmonary embolism by affecting Dural sinuses and cerebral veins, splanchnic veins, and/or veins of the limbs. CVST (Cerebral venous sinus thrombosis) occurs rarely and was earlier considered to be associated with very high mortality and morbidity rates. CVST is associated with varied clinical presentations, courses, and symptoms in different individuals affected by it. Prognosis of CVST has markedly increased lately owing to improved imaging modality in neurology, better awareness, early identification of symptoms,and advanced treatment modalities incorporating anticoagulants. Outcomes following CVST has also improved with more than 80 percent subjects reported having good outcome neurologically[2].Anticoagulants such as vitamin K antagonists and LMWH (Low Molecular Weight Heparin) are commonly used in subjects following CVT for different time intervals owing to thrombosis risk and preventing DVT (deep vein thrombosis). Pulmonary Embolism and Deep vein thrombosis now utilize Direct non–vitamin K oral anticoagulants shifting the focus from vitamin-k dependent anticoagulants[3]. One such Direct non–vitamin K oral anticoagulant is Dabigatran which has shown acceptable tolerability, safety, and efficacy in subjects with recurrent pulmonary embolism, DVT, and atrial fibrillation for stroke prevention. Dabigatran is a promising and effective agent with good prognosis and clinical outcomes in CVST subjects, that can be used in place of LMWH and Coumadin which are suggested by guidelines of the European Association of Neurosurgeons[4].

Dabigatran is a drug given orally having renal clearance primarily and is equally efficient anticoagulant as Warfarin with the additive advantage of less bleeding risk compared to warfarin making it a promising anticoagulant with efficacy and safety. An anti-drug for Dabigatran is Idarucizumab. It is used to prevent stroke in subjects with atrial defibrillation and thromboembolism subjects with CVST. However, the data available in CVST subjects is relatively scarce[5].Hence, the present study was conducted to assess the long-term safety, efficacy, and outcomes following treatment with

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Dabigatran as first-line treatment in subjects with Cerebral Venous Sinus Thrombosis (CVST).

Materials And Methods

The present study was conducted to assess the long-term safety, efficacy, and outcomes following

treatment with Dabigatran as first-line treatment in subjects with Cerebral Venous Sinus Thrombosis

(CVST). The study was carried out on patients resided in Chhattisgarh, India from January 2017 to March 2021 after taking clearance from the concerned Ethical Committee.

The study included a total of 70 subjects having both males and females within the age range of 18-60 years and the mean age of 38.6 years. The study subjects were recruited from the patients admitted to the Department of Neurosurgery secondary to CVST (Cerebral venous sinus thrombosis) having either venous infarct, haemorrhagic venous infarct, or without haemorrhage or infarct. After the final inclusion of the subjects, the study design was explained to the subjects/ their attendants (in case the subjects were not in the condition to understand). Informed consent was then taken from all the included subjects.

Following final inclusion, a complete neurological and physical examination was done to assess the GCS (Glasgow Coma Scale) scores. A detailed history was then taken for all the included subjects. The radiological examination included a CT scan head or MRI brain, and MRI venogram to reach a definitive diagnosis. Also, detailed medical history was noted for all study participants.

Among included 70 subjects, 32 subjects had venous infarct, 13 subjects had haemorrhagic venous infarct, and 25 subjects had no infarct or haemorrhage. After the initial examination, it was seen that 7 subjects had large haemorrhage with a volume of 30ml or more and GCS score of less than 8, and 15 subjects had a GCS score of less than 8 with small infarct/haemorrhage.

After diagnosis, the subjects were immediately started on LMWH (Low Molecular Weight Heparin) for 5 days. No steroid was given to any subject at any time. No need was there to monitor PT (Prothrombin Time) or INR (International Normalized Ratio). The subjects were then started on a 110 mg capsule of Dabigatran from day 3 for 3 months given twice daily.All 62 subjects were evaluated after 3 months to assess outcomes using an MRI venogram for recanalization. The collected data were subjected to statistical evaluation and the results were formulated.

Results

The present study was conducted to assess the long-term safety, efficacy, and outcomes following treatment with Dabigatran as first-line treatment in subjects with Cerebral Venous Sinus Thrombosis (CVST). The study included a total of 70 subjects having both males and females within the age range of 18-60 years and the mean age of 38.6 years. The demographic characteristics of the study subjects are listed in Table 1. There were 12.85% (n=9) males and 87.14% (n=61) females in the study. CVST was diagnosed using MRI venogram in all subjects. On diagnosing, venous infarct was seen in 45.71% (n=32) subjects, Hemorrhagic Venous Infarct in 18.57% (n=13) subjects, and non-hemorrhagic lesions in 35.71% (n=25) subjects. Volume of the lesions was 30 ml or more in 7.14% (n=5) subjects and was <30ml in 92.85% (n=65) subjects. Most commonly involved sinus was left lateral sinus in 50% (n=35) subjects followed by superior sagittal sinus in 40% (n=28) subjects, Right Lateral Sinus in 38.57% (n=270 subjects, and jugular vein in 32.85% (n=23) subjects. On examination and history recording, GCS score of <8 was seen in 24.28% (n=17) subjects, whereas, in 75.71% (n=53) subjects GCS score was >8 (8-14). The most common presenting symptom was headache in 77.14% (n=54) subjects, followed by seizures in 20% (n=14) subjects, Hemiparesis/monoparesis in 18.57% (n=13) subjects, and papillodema in 15.71% (n=11) subjects. Other less commonly reported symptoms were loss of vision, diplopia, and altered mental status. The commonly associated risk factors seen in the present study were use of oral contraceptives seen in 70% (n=49) subjects, BMI 25-30 in 24.28 (n=17) subjects, BMI >30 in 21.42% (n=15), Previous Thromboembolism history in 10% (n=7) subjects, genetic thrombophilia in 8.57% (n=6) subjects, Infection of Nose, Eye, ear in 7.14% (n=5) subjects, surgery and Puerperium in 5.71% (n=4) subjects. Other risks seen were Thromboembolism causing drugs, dehydration, and mechanical precipitants (Table 2).

Table 1: Demographic Characteristics of the Study subjects

Characteristics	%	N
Age Range (years)	18-60	
Mean age (years)	38.6	
Gender		
Males	12.85	9
Females	87.14	61
Diagnostic Modality		
CT head	0	0
MRI brain	0	0
MRI with Venogram	100	70
Lesions detected on Radio imaging		
Venous Infarct	45.71	32
Hemorrhagic Venous Infarct	18.57	13
No infarct/ Hemorrhage	35.71	25
The volume of detected lesions		
30 ml or more	7.14	5
Less than 30 ml	92.85	65
Involved Sinuses		
Cavernous sinus	2.85	2
Juglar Vein	32.85	23
Superior Sagittal Sinus	40	28
Straight sinus	12.85	9
Cerebellar Vein	0	0
Cortical Vein	17.14	12
Deep Venous System	12.85	9
Left Lateral Sinus	50	35
Right Lateral Sinus	38.57	27

Table 2: Disease-related variables and parameters in the Study subjects

Variables and Parameters	%	N
GCS Scores (Glasgow Coma Scores)		
<8	24.28	17
>8 (8-14)	75.71	53
Presenting Disease-Related Symptoms		
Headache	77.14	54
Seizure	20	14
Loss of Vision	11.42	8
Altered Mental Status	7.14	5
Diplopia	10	7
Hemiparesis/monoparesis	18.57	13
Papillodema	15.71	11
Disease-associated risks		
Surgery	5.71	4
Infection of Nose, Eye, ear	7.14	5
BMI 25-30	24.28	17
BMI more than 30	21.42	15
Oral Contraceptive use	70	49
Genetic Thrombophilia	8.57	6
Malignancy	0	0
Dehydration	2.85	2
Previous Thromboembolism history	10	7
Thromboembolism causing drugs	4.28	3
Puerperium	5.71	4
Inflammatory Bowel Disease	0	0
Precipitants (Mechanical)	2.85	2
Other Inflammatory Conditions	0	0

Adverse events with the use of Dabigatran in CVST subjects were also considered. Total adverse events were reported by 67.14% (n=47) subjects. Out of these total adverse events, serious events were reported by 14.28% (n=10) subjects, which included CVST worsening in 7 subjects, Urticaria, Major bleeding/ hematoma, Thrombocytopenia, and deranged liver profile in 1.42% (n=1) subject each, and epigastric discomfort in 2.85% (n=2) subjects. Other less severe adverse effects reported were headache by 15.71% (n=11) subjects, cough in 8.57% (n=6) subjects, abdominal pain and diarrhoea in 7.14% (n=5) subjects, and depression in 4.28% (n=3) study subjects (Table 3).

Table 3: Adverse Events Reported in the Study subjects

Adverse Events	%	N
Total Events	67.14	47
Serious Events	14.28	10
CVST worsening	10	7
Urticaria	1.42	1
Major bleeding/ hematoma	1.42	1
Thrombocytopenia	1.42	1
Epigastric discomfort	2.85	2
Deranged Liver Profile	1.42	1
Other reported adverse events		
Abdominal Pain	7.14	5
Cough	8.57	6
Diarrhea	7.14	5
Headache	15.71	11
Depression	4.28	3

The outcomes following Dabigatran use were evaluated after 3 months of the drug use. 3 subjects did not report to the follow-up leaving behind a total of 67 subjects at 3 months recall. Total deaths reported at 3 months were 7.46% (n=5). All death was seen in subjects having lesion volume of more than 30ml and GCS <8. 19.35% (n=12) of subjects survived after 3 months of Dabigatran use in CVST subjects where 19.35% (n=12) subjects had a GCS score of <8 with small infarct, whereas, 80.64% (n=50) subjects had GCS >8 with either small lesion or non-haemorrhagic lesion. Recanalization was seen in all 62 subjects at follow-up. Major venous thrombosis in form of pulmonary embolism was seen in 1.49% (n=1) subjects. Worsening of haemorrhage was shown in 1.49% (n=1) subjects., and minor bleeding in 2.98% (n=2) subjects (Table 4).

Table 4: Outcomes at 3 months recall following Dabigatran use in the Study subjects

Outcomes	%	N
Total Deaths	7.46	5
Major Venous Thrombosis	1.49	1
Splanchic vein thrombosis	-	-
Primary Embolism	1.49	1

DVT	-	-
Recurrent CVST	-	-
Recanalization	100	62
Minor bleeding	2.98	2
Major bleeding	1.49	1
Worsening of hemorrhage	1.49	1
New Hemorrhage	-	0
Major Outcomes		
Death (Vol. >30ml, GCS <8)	7.46	5
Survived	92.53	62
GCS <8 Small infarct	19.35	12
GCS>8	80.64	50

Discussion

The outcomes following Dabigatran use were evaluated after 3 months of the drug use. 3 subjects did not report to the follow-up leaving behind a total of 67 subjects at 3 months recall. Total deaths reported at 3 months were 7.46% (n=5). All death was seen in subjects having lesion volume of more than 30ml and GCS <8. 19.35% (n=12) of subjects survived after 3 months of Dabigatran use in CVST subjects where 19.35% (n=12) subjects had a GCS score of <8 with small infarct, whereas, 80.64% (n=50) subjects had GCS >8 with either small lesion or non-haemorrhagic lesion. Recanalization was seen in all 62 subjects at follow-up. Major venous thrombosis in form of pulmonary embolism was seen in 1.49% (n=1) subjects. Worsening of haemorrhage was shown in 1.49% (n=1) subjects., and minor bleeding in 2.98% (n=2) subjects. No recurrent CVST was seen in the present study. These findings were in agreement with the findings of Ferro JM et al[6] in 2017, Connolly SJ et al[7] in 2009, and Schulman S. et al[8] in 2009 where authors reported low recurrence, very low bleeding, and no major adverse event following Dabigatran use Following CVST.The study included a total of 70 subjects having both males and females within the age range of 18-45 years and the mean age of 28.6 years. There were 12.85% (n=9) males and 87.14% (n=61) females in the study. CVST was diagnosed using. On diagnosing, venous infarct was seen in 45.71% (n=32) subjects, Haemorrhagic Venous Infarct in 18.57% (n=13) subjects, and non-haemorrhagic lesions in 35.71% (n=25) subjects. Volume of the lesions was 30 ml or more in 7.14% (n=5) subjects and was <30ml in 92.85% (n=65) subjects. Most commonly involved sinus was left lateral sinus in 50% (n=35) subjects followed by superior sagittal sinus in 40% (n=28) subjects, Right Lateral Sinus in 38.57% (n=270 subjects, and jugular vein in 32.85% (n=23) subjects. These characteristics were comparable to the demographics used in the studies of Miranda B et al[9] in 2010 and Ntaios G et al[10] 2017.On examination and history recording, GCS score of <8 was seen in 24.28% (n=17) subjects, whereas, in 75.71% (n=53) subjects GCS score was >8 (8-14). The most common presenting symptom was headache in 77.14% (n=54) subjects, followed by seizures in 20% (n=14) subjects, Hemiparesis/monoparesis in 18.57% (n=13) subjects, and papilloedema in 15.71% (n=11) subjects. Other less commonly reported symptoms were loss of vision, diplopia, and altered mental status. The commonly associated risk factors seen in the present study were use of oral contraceptives seen in 70% (n=49) subjects, BMI 25-30 in 24.28 (n=17) subjects, BMI >30 in 21.42% (n=15), Previous Thromboembolism history in 10% (n=7) subjects, genetic thrombophilia in 8.57% (n=6) subjects, Infection of Nose, Eye, ear in 7.14% (n=5) subjects, surgery and Puerperium in 5.71% (n=4) subjects. Other risks seen were Thromboembolism causing drugs, dehydration, and mechanical precipitants. Oral contraceptives as a risk factor for cerebral venous thrombosis were also reported by Ibrahim, N. M. A et al[11] in 2018.Adverse events with the use of Dabigatran in CVST subjects were also considered. Total adverse events were reported by 67.14% (n=47) subjects. Out of these total adverse events, serious events were reported by 14.28% (n=10) subjects, which included CVST worsening in 7 subjects, Urticaria, Major bleeding/ hematoma, Thrombocytopenia, and deranged liver profile in 1.42% (n=1) subject each, and epigastric discomfort in 2.85% (n=2) subjects. Other less severe adverse effects reported were headache by 15.71% (n=11) subjects,cough in 8.57% (n=6) subjects,abdominal pain and diarrhoea in 7.14% (n=5) subjects, and depression in 4.28% (n=3) study subjects. These events were similar to the studies of Ferro JM et al[12] in 2019 and Schulman S et al[8] in 2009 where authors reported similar side effects as in the present study.

Conclusion

Within its limitations, the present study concludes that the recurrence risk of CVST is quite low with the use of Dabigatran, an oral anticoagulant for 3 months after a Cerebral venous sinus thrombosis event. However, the use of Dabigatran after CVST was linked to very few adverse events including major bleeding, new CVST, or worsening of existing Cerebral venous sinus thrombosis events. Hence, dabigatran is a safe anticoagulant that can be a potential candidate in preventing the recurrence of CVST. However, the present study had few limitations including smaller sample size, short monitoring period, use of the single drug with no comparing agent, and subjects after neurosurgery. Hence, more longitudinal studies with a larger sample size, longer monitoring period, comparative evaluation of various oral anticoagulants, and inclusion of comatose and post-surgical cases are required to reach a definitive conclusion

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