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Randomized Controlled Trial of Heparin in Puerperal Cerebral Venous / Sinus Thrombosis

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Abstract

Cerebral Venous / sinus Thrombosis (CVT) is an important cause of maternal mortality during the puerperium. Use of heparin has been debatable due to fear of hemorrhagic complications. Here, we report the results of the randomized control trial of heparin. Fifty-seven patients of puerperal CVT diagnosed clinically and radiologically were randomized into therapy group (29) and control group (28). After detailed clinical, radiological, hematological and biochemical investigations, therapy group received IV heparin 5000 units every 6 hourly to begin with and the dose was adjusted to keep the clotting time less than 7 minutes and partial thromboplastin time less than one and half times the normal. Both groups received anti convulsants and anti oedema measures, in addition to correction of anaemia. Heparin was tapered after 30th post partum day. Headache was reduced in the heparin group in 24-72 hours clearing in 7.10 days while in control group it was severe and continued for 2-3 weeks. Two patients died in the control group with one person having residual hemiparesis even after 6 months. There were no deaths in the therapy group and all were independent at 6th month. Though, there was an initial deterioration of clinical state in 2 patients of each group, on repeat CT examination in ten patients, there were no hemorrhagic complications in any.

Key words -

Anti-coagulant,
Cerebral sinus Thrombosis,
Heparin

Stroke, in the young individuals (less than 40 years) has been reported from many centers in India [1]. Cerebral Venous/Sinus Thrombosis (CVT) is an important cause of mortality due to Stroke, in women especially in the child

bearing age group [2], [3]. Puerperal CVT has been observed in a significant number of patients from Madras, Madurai, Chandigarh, Delhi and Bombay [3]. Puerperal CVT is the commonest form of CVT in our center [4]. Detailed studies at Bangalore and Madurai have revealed that there is hypercoagulable state in CVT with increase in fibrinogen levels, thereby Suggesting the role of heparin therapy in the management of puerperal CVT [3], [4].

Material and Methods

Consecutive cases of clinically suspected puerperal CVT were considered for the study. After excluding cases with hemorrhagic lesions by CT Scan, the remaining 57 patients with CVT who gave informed consent were included in this study.

Criteria for the diagnosis of CVT were:

1 Clinical - unexplained persistent headache in the puerperal period (within 30 days of delivery/abortion) with or without seizures, focal neurological deficits and alteration of consciousness.

2 Computerized tomographic scan (CT Scan) findings of:
- a Definite features of CVT - cord and delta signs
- b Suggestive features of CVT-ischemic infarction not conforming to arterial territory and bilateral infarctions with varying degree of edema.

3 In cases where CT Scan was normal or not suggestive of CVT, angio graphic evidence of venous/sinus thrombosis.

Exclusion criteria were

1 Symptoms preceding delivery/ abortion
2 CT scan showing hemorrhagic lesion(s)
3 Clear cut arterial infarction
4 Both CT and angio normal

All the 57 patients were evaluated with a detailed history and examination on a structured protocol. Investigations included haemoglobin, TLC, DLC, ESR, platelet counts, peripheral smear, fibrinogen, factor VIII, IX, bleeding and clotting time, prothrombin time, partial thromboplastin time, blood sugar, urea, creatinine, electrolytes, total cholesterol and triglycerides. Routine urine examination, culture and sensitivity of blood, urine and vaginal swab were carried out in all. All the patients were randomized into two groups (a) therapy and (b) control. After excluding bleeding tendency, peptic ulcer, bleeding piles and severe hypertension, patients in the group (a) were administered intravenous heparin 5,000 units 6th hourly which was monitored according to the partial thromboplastin time, prothrombin time, bleeding and clotting times. All patients received anti-edema measures, in the form of oral glycerol with or without IV mannitol. Anaemia was corrected with blood or packed cell transfusion in severe cases or oral iron therapy in milder cases. Heparin was continued up to 30th postpartum day or further if the patient was symptomatic in the form of headache. It was then tapered gradually over a period of 10-15 days. Patients were evaluated periodically and at the time of discharge for the evidence of residual symptoms or signs.

Results

Of the 57 patients, 29 were treated with heparin (treatment group) while the remaining served as control. Average age of patients in the two groups was 23.5 years (range 14-42 years) and 24.5 years (range 17-30 years) respectively. Mean duration between the delivery and the onset of treatment was similar in the two groups (20.7 days and 20.68 days), though the onset of symptoms following delivery was earlier in the therapy group (9.9 days compared to 13.7 days). The delivery was full term in 27 and 24 patients respectively. It was conducted at home in 17 patients in the therapy group and in 23 patients in the control group. In majority of subjects in both the groups (17 and 22) the delivery was conducted by a local dai. In the therapy group 28 deliveries were normal and in one CVT was noticed after an abortion. In the control group three patients developed CVT after abortion and in two the labor was induced/assisted by syntocinon infusion. The symptoms and signs did not differ between the two groups (Tables I and II). Headache was continuous with progressively increasing severity. Bladder disturbances were mainly retention or incontinence. The neurological state was stable for 24 hours in 17 persons of the therapy and 16 patients of the control group while it was progressively worsening in the rest. None was improving at the time of recruitment to the study.

Table I - Symptoms of CTV at presentation

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Table II - Signs of CTV during the illness

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Haemoglobin was less than 12 gms% in 27 and 26 patients in the therapy and the control group respectively (less than 6 gms% in 4 and 5 patients respectively). Blood culture was positive in 4 tnd 3 patients in each group respectively. Bleeding and clotting times were normal in all. Fibrinogen level, prothrombin time, partial thromboplastin time, factor VIII and factor IX values were similar in both the groups (Table III). The dose of heparin was reduced when clotting time went beyond 7 minutes or prothrombin time or PTT were more than 1.5 times the control value. The lowest dose of heparin given was 2500 units 6th hourly. Heparin therapy was continued up to the minimum of 30th postpartum day or till the patient became asymptomatic, when it was tapered gradually. The severity of headache reduced in the therapy group within 24 to 72 hours of starting heparin, subsiding completely in 7-10 days, while it persisted for a longer time in the control group (2 weeks or more). Two patients died in the control group while there was no death in the treated group (Table IV). Of the surviving patients at discharge two patients in each group had residual hemiparesis but at 6 months all but one in the control group had completely recovered.

Table III - Investigations

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Table IV - Outcome of CVT

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Discussion

Later part of pregnancy and early puerperium are associated with hypercoagulable states [5]. Platelet count and fibrinogen level are elevated in the third trimester of pregnancy. Platelet adhesive index increases in the postpartum period specially in the first ten days. Estonal et al [6] studied a number of coagulation parameters and found no differences between the CVT patients and non CVT puerperal patients [6]. Srinivasan reported elevated fibrinogen levels in 104 of 120 patients with puerperal CVT. Earlier study at NIMHANS revealed elevated levels of fibrinogen in patients with CVT (380.45 mg%) compared to the normal puerperal controls (302.7 mg%) and non pregnant non puerperal women of child bearing age (270 mg%) [3]. Similarly platelet abnormalities have been reported by Prakash et al [7] and Chopra and Prabhakar [8]. Stanfeldt [9] introduced heparin in the treatment of CVT in 1942. Krayenbuhl [10] reported the use of heparin in 17 patients with no adverse effects. Fairburn [11] reported total recovery with heparin in 2 patients of CVT due to oral contraceptive use and good results in one patient of puerperal CVT. Srinivasan in an uncontrolled study observed five deaths in 42 patients of puerperal CVT treated with heparin as compared to 21 of the 47 patients not receiving heparin [4]. However, it was not a randomized trial and information regarding the clinical data known to influence the outcome were not provided. Atkinson et al [12] and Bousser et al [13] also observed beneficial results in isolated cases of non puerperal CVT. However, some workers have expressed apprehension of hemorrhagic complications (ICH) [14], [15], [16]. Gettelfinger and Kokemen [17] observed development of CVT in two of the three patients on anticoagulant therapy and hence advocated use of anti edema measures alone in the management of CVT. The present randomized control trial indicates early arrest of progression and reduction of mortality as evidenced by the absence of deterioration and early reduction in the intensity of headache in heparin treated group. Similarly observations were made in another controlled trial of 20 patients with CVT by Einhaupl et al [28]. It is noteworthy that relatively low dosages of heparin were used in this study and no significant changes were observed in coagulation parameters during the course of treatment. Shulman [19] in his editorial emphasised the role of low dose heparin in the treatment of CVT and its relative safety as compared to high dose heparin therapy. He suggested that the low dose heparin does not alter the coagulation time, but reinforces the endogenous heparin on the endothelium thereby preventing adhesion of platelets [19]. In most of the earlier reports, heparin therapy was used in non-puerperal cases and involved conventional doses. We used low dose heparin in order to avoid hemorrhagic complications and thus did not encounter any complications as substantiated by the repeat CT scans in ten patients. This study however, excluded the cases with hemorrhagic infarctions and intracranial hematoma thereby avoiding a significant number of patients with puerperal CVT having poor prognosis. This is further substantiated by relatively low mortality of 2/57 (3.4%) compared to 25-30 per cent in series including all types of puerperal CVT. Shulman supported the value of low dose heparin in patients with intra-cerebral hemorrhage [18]. We suggest routine use of heparin in patients of CVT without hemorrhage and an attempt may be made to use low doses of heparin even in patients with hemorrhagic infarction due to CVT.

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