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Annual National Conference of
Indian Medical Association Academy of Medical Specialities

Organised by : IMA Bengal State Branch
Biswa Bangla Convention Centre • 1st & 2nd September, 2018

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AMSCON/KOL/2018/1 — 1st June, 2018, Kolkata

To,
All Branch Presidents / Secretaries
Indian Medical Association

Subject: AMSCON 2018

Dear Sir / Madam,

Season's Greetings!

As decided by IMA (HQs), IMA Bengal State Branch is going to host, **AMSCON 2018**, Annual Conference of IMA Academy of Medical Specialities on 1st & 2nd September at the State of Art, **BISWA BANGLA CONVENTION CENTRE**, New Town, Kolkata.

We promise to have a two days long, great **Academic Fiesta** in this Multispeciality Scientific Conference.

The prestigious **Convocation Ceremony** will be on **1st September at 4 pm** & you will witness a splendid **Inaugural Function at 5 pm** followed by a mind blowing **Cultural Evening**.

We ensure, you will remember the flavour of the **Fellowship Dinner** to be held on 1st September forever.

Kind presence of members of IMA and / or IMA AMS of your Branch is earnestly solicited to make this event a memorable one.

Request your members having Post Graduate Degree / Diploma or FCGP to become life members of IMA AMS & Fellows on 1st September.

Thanking you,

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Editor's Pen

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Hypertension and Cardiovascular Diseases in Pregnancy

Cardiovascular diseases (CVD) is the leading cause during Pregnancy occurring 33% of maternal death. There is also increasing evidence of significant link between complication of Pregnancy and CVD in later in life.

Pregnancy complications such as preeclampsia, gestational hypertension, preterm delivery and delay of an infant with IUGR provide mothers cardiovascular disease adaptability of physiological stress presents of CVD in pregnancy women posing a difficult clinical scenario in which the responsibility of the treating physician extend to the unborn faetus. Profound changes occur in the maternal circulation that have the potential to adversely affect maternal and faetal health especially in the presence of underlying heart disease.

Cardiovascular complications related either to hypertension in pregnancy or to establish cardiac disease either congenital or squired. Hypertension in pregnancy (PET) is a common serious complication to be looked for carefully and as a high risk pregnancy, chronic hypertension ie, pre-existing hypertension need to be evaluated with proper family history, obesity, multiparty or other disease known to be effect kidneys. Pre existing hypertension secondary to renal disease should be suspected when protinuria is disproportion act to the degree of hypertension specially when the patient is multifarious or presence of hypertension prior to 34 weeks.

Pregnant women presenting with PET had renal biopsy showing evidence of preexisting renal parenchyma or vascular disease. Women with diagnosis PET prior to 34 weeks shows 70% of pre-existing kidney disease on renal biopsy.

Advance diagnosis and treatment congenital disease in pregnancy have led to dramatically improved survival rates and consequently the predominant during pregnancy has shifted from Rheumatic to congenital heart disease. During pregnancy, total blood plasma volume increases by 50% however RBC increases only by 3%, ultimately resulting in a decrease hemoglobin and hematocrit value. The heart is able to accommodate increases in volume primarily because of decrease systemic vascular resistance. Cardiac artifact increases by 30 to 35% of which half of this increase in cardiac output occurs by 8 weeks of pregnancy profound alteration also occur in fibrinogen and factor VIII leading to increase chances of thromboembolic complications.

Congenital heart disease particularly Tetra logy of fallots, Isennenger syndrome, Edsteinanomaly are the diseases where serious complication of both mother and faetus may occurs where as aortic coarctation, ASD, VSD etc. are the diseases where complications are less.

Thus pregnancy with CHD or RHD should be taken care of in a well equipped specialized centre where medical professionals has to work as a team of obstretrian, cardiac consultant and good physician.

At last, diagnosis of hypertension during pregnancy is an utmost important where underlying reason of hypertension whether accrued or congenital, has to be diagnose.

Scenario of treatment of hypertension/cardiac disease has improved in modern medicine practice but yet to go long way in this particular segment to get result of minimum maternal and faetal mortality and morbidity.

Original Article

Fixation of subtrochanteric fractures : Comparative study of Dynamic condylar screw *versus* Proximal femoral nail

Zelio D'Mello[1], Lakimchand Ambapkar[2]

This prospective study was performed to compare the functional & anatomical results with two different implant fixation devices, in the management of Subtrochanteric femoral fractures in adults. Thirty patients were included in this study from June 2007 to June 2010. The proximal femoral nailed patient showed identical functional & anatomical results compared to patients fixed with dynamic condylar plating, but time to fracture union & full weight bearing was earlier in the PFN patient group.

[*J Indian Med Assoc* 2018; **116:** 10-3 & 20]

Key words **: Subtrochanteric fractures- Dynamic condylar screw/*versus* Proximal femoral nail.**

Subtrochanteric fractures of femur extend from lesser trochanter to isthmus of diaphysis. This segment of femur is subjected to axial loads of weight bearing and tremendous bending forces because of eccentric loading of femoral head. Compressive stresses in medical cortex are significantly higher than tensile stresses in lateral cortex. This asymmetrical loading pattern is important in determining the choice of internal fixation devices and understanding the causes and prevention of failure of these devices[1]. Despite marked improvements in implant design, surgical technique and patient care, subtrochanteric fractures continue to consume a substantial proportion of health care resources.

Subtrochanteric fractures comprises about 10 to 34% of hip fractures[2]. They have bimodal age distribution and different mechanisms of injury, in older patients they occur following low velocity trauma and in younger result from high energy motor vehicle accidents or fall from height.

Subtrochanteric fractures are complicated by malunion and delayed or nonunion. The factors responsible for these complications are high stress concentration, predominance of cortical bone and difficulties in getting biomechanically sound reduction because of comminution and intense concentration of deforming forces[3].

Many internal fixation devices have been recommended for use. Lack of single satisfactory implant has lead to series of evolution in design of a perfect implant. However these fractures were associated with high rates of nonunion and implant failure, regardless of the method of fixation. Only recently with better understanding of biology, reduction techniques and biomechanically improved implants these fractures can treated with consistent success.

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Materials and Methods

Our study consisted of 30 adult patients with subtrochanteric facture of femur, who were randomly treated with Proximal Femoral nail and Dynamic Condylar Screw in Goa Medical College and Hospital, Bambolim, Goa between June 2007 to June 2010. This study was carried out to testify the anatomical and functional outcomes of treatment with proximal femoral nail and dynamic condylar screw. All these 30 patients included in the study were followed up at regular intervals. Initially patients underwent necessary clinical and radiological evaluation and were admitted to the ward after splintage using appropriate size Thomas splint. Skeletal traction was then applied by passing stienmen pin through proximal tibia of the affected limb and kept till the surgery. All the patients were evaluated for associated medical problems and were referred to respective departments and necessary treatment was started. Associated injuries were evaluated and treated simultaneously. All patients were operated on elective basis. Fractures were classified according to Seinsheimer's and Russel & Taylor classification. Subtrochanteric fractures with intertrochanteric extension were included while pathological fractures were excluded from study.

All the cases included in our study were fresh fractures who underwent surgery at the earliest possible in our setup. The delay was due to associated injuries and medical conditions. Patients were operated at an average interval of 7 days from day of injury.

Technique :

Proximal femoral nailing :

Patient was placed in supine position on fracture table.

Affected limb was adducted by 10 to 15 degree and closed reduction of fracture was done by traction and gentle manipulation. Greater trochanter was exposed by a longitudinal incision 5 to 8 cm proximal to its tip. Entry point made slightly lateral to tip of trochanter and confirmed on C- arm image intensifier. Guidewire inserted and position confirmed on AP & lateral images. Canal was reamed with flexible reamers over the guide wire. Appropriate size nail with length determined preoperatively and with diameter 1 mm less than last reamer used was assembled to insertion handle and inserted manually into femoral opening. This step was done carefully without hammering by slight twisting movement of hands. Wherever satisfactory reduction was not possible open reduction was done.

Two self tapping 6.5 mm cannulated neck screws were inserted with help of aiming device tightly secured to the insertion handle and colour coded drill sleeve system after confirming correct positioning of guide wires on AP and lateral C-arm images. Inferior screw was placed first, superior screw was placed approximately 4 to 5 mm from superior cortical margin of femoral neck. Proximal screws were tightened after releasing traction to maximum compression at fracture site. Distal locking done with two 4.9 mm locking bolts by free hand technique using image intensifier.

Dynamic condylar screw :

With patient placed in supine position on fracture table, fracture was exposed by a 15 to 20 cm incision made along an straight imaginary line drawn from tip of trochanter to lateral femoral condyle. Guide wire inserted at an angle of 95 to anatomical axis of femur using angle guide roughly just below tip of greater trochanter and proximal aspect of osseous insertion of gluteus medius. After confirming the position on C-arm images an appropriate size Richards screw was inserted after reaming and tapping.

Fracture reduced by adjusting traction and manually using bone holders. Butterfly fragments were reduced and fixed with interfragments screws. After satisfactory reduction barrel of the plate was mounted on the Richards Screw and shaft of the plate fixed to distal fragment using 4.5mm cortical screws with minimum eight cortical purchase distal to fracture and atleast four cortical purchases in proximal fragment.

Posteromedial comminution was assessed, if necessary primary bone grafting done. Ipsilateral iliac crest was used for the purpose.

Postoperatively, patient's pulse, blood group, respiration and temperature were monitored. Injectable antibiotics were continued in the post operative period for 2 days. Analgesics were given as per patients compliance. Drain removal done by 48 hours & sutures removed on 12th postoperative day. Patients were encouraged to sit in the bed 24 hours after surgery. Quadriceps setting exercises were started in immediate post operative period. Patients were encouraged to walk with axillary crutches or walker with toe touch down depending on the pain tolerability and were discharged from the hospital when independent walking was possible. Patients were followed up every month till the fracture union and thereafter once in 3 months for 1 year. At every visit patients were assessed clinically regarding hip and knee function, walking ability, deformity and shortening. AP and lateral X ray of the involved hip with femur was done to assess fracture union.

Result of the Surgery :

Anatomical Result :

Anatomical result	Good	Poor
Shortening	<1cm	>1cm
Varus deformity	Absent	Present
Hip movement	Full range	Restricted
Knee movement	Full range	Restricted

Functional Results:

Functional assessment was done using Owestry hip scoring system (patient assessed score) which consisted of presence of hip pain, mobility and range of motion. Range of motion was measured in terms of ability to squat and sitting crossed legged. Following point system was used:

Hip pain :	
No pain	2 points
Occasional pain	1 point
Constant pain	0 point
Ambulatory status:	
Walking without aid	2 points
Walking with aid	1 point
Not able to walk	0 point
Range of motion :	
Able to squal	1 point
Unable to squal	0 point
Able to sit crossed leg	1 point
Unable to sit crossed leg	0 point
Interpretation :	
Excellent	6 points
Good	4 to 5
Fair	2 to 3
Poor	1

Observation and Results

The mean follow- up time was 18 months. All patients tolerated the operation well and adapted to rehabilitation program without any problem.

In our series maximum age was 70 years. Most of the patients were in the age group of 20 to 60 years, with mean age of 49.1 years. Males were affected more than females

and fractures were right sided in 22 patients. Out of 30 cases, 21 cases gave history of motor vehicular accidents, 03 cases gave history of fall height and remaining 6 cases gave history slip and fall.

Sinsheimer type 3B (36.66%) fractures were more common followed by type 3 A (20%) and according to Russel & Taylor type 2A (33.33%) were more common followed by 1A (30%) fractures.

Mean duration of surgery was 120 minutes for PFN and 90 minutes for DCS, with mean blood loss of 100ml for the former and 300ml for latter. Radiographic screening in DCS was used to pass a guide wire and was minimal as compared to PFN.

In PFN group, closed reduction was not possible in 2 cases and open reduction was attempted. One patient had iatrogenic fracture of the lateral cortex of the proximal segment which did not require any fixation but mobilization was delayed for 3 weeks. In all cases proximal and locking was possible. There were no incidences of jamming of nail and drill bit breakage.

In DCS group, one patient required primary bone grafting due to posteromedial comminution. Three had extensive blood loss more than 500 ml. On an average blood loss was approximately 300ml in most patients. No technical difficulties were encountered. The mean duration of hospital stay was 12.46 days while mean time for full weight bearing was 7.2 weeks in proximal femoral nailing and 14 weeks in Dynamic condylar plating. Average time required for radiologic fracture union was 14 weeks in PFN and 17.13 weeks in DCS.

Postoperative complications :

In DCS group, one patient had superficial skin infection at operative sight who required lavage and wound healed with regular dressing and appropriate antibiotics. One patient in PFN group, who required open reduction developed deep infection, lavage was given twice and antibiotic beads were put. However fracture healed without complications.

One patient had delayed union in DCS group who underwent secondary bone grafting. All cases operated with PFN united without bone grafting with no incidence of non union. Over all 90% of our cases had excellent to good results. No mortality was reported in our study. One patient in DCS group had nonunion with shortening who underwent revision ORIF with DCS and bone grafting. Another patient in DCS group had implant breakage following trauma, PFN was put along with bone grafting. Most of the patients enjoyed good range of motion at hip and knee except one in PFN group had knee stiffness and one had hip stiffness following iatrogenic breakage of lateral cortex while inserting nail. Only one patient in DCS group had hip stiffness.

Complications :

Complication	Number of cases	
	PFN	DCS
Hip Joint stiffness	01	01
Knee Joint stiffness	01	00
Delayed union	00	01
Non union	00	01
Shortening of >1cm	00	01
Malunion	00	00
Implant failure	00	01
Superficial infection	00	01
Deep infection	01	00
Functional Results :		
	PFN	DCS
Excellent	12	9
Good	1	3
Fair	1	1
Poor	1	2
Anatomical Results :		
	PFN	DCS
Good	13	11
Poor	2	4

Discussion

Management of subtrochantric fractures of femur poses a great challenge to orthopaedic surgeon. In adults these fractures are usually the result of high energy trauma and often comminuted at the medical cortex. In older patients the need for early mobilization and osteoporosis makes the selection of implant an important issue. Many clinical and biomechanical studies have analyzed the result of different implants. Treatment of subtrochanteric fractures of the proximal femur is still associated with some failure, the reason being: disregards for biomechanics, overestimation of the potential of new surgical techniques or new implants and poor adherence to established procedures[4]. High stress concentration that is subject to multiple deforming forces, slow healing time because of predominance of cortical bone, decreased vacularity[5], high incidence of complications reported after surgical treatment compels the surgeon to give a second thought regarding selection of the proper implant. The most common current modes of fixation are Blade plate systems, sliding screw systems and intramedullary devices. From the mechanical point of view, a combined intramedullary device inserted by mean of a minimally invasive procedure seems to be better, especially in elderly patients[6]. Closed reduction of the fracture preserves the fracture hematoma, an essential element in the consolidation process[7]. Intramedullary fixation allows the surgeon to minimize soft tissue dissection thereby reducing surgical trauma, blood loss, infection, and wound complications[8].

In 1996, AO/ASIF developed the proximal femoral nail as an intramedullary device for treatment of unstable per, intra- and subtrochanteric femoral fractures[9]. Careful surgical technique and modification of PFN can reduce high complication rates. Proximal femoral nail has all the advantages of an intramedullary device, such as decreasing the moment arm, can be inserted by closed technique, which retains the fracture hematoma an important consideration in fracture healing, decreases blood loss, infection, minimizes the soft tissue dissection and wound complications.

In an experimental study, Gotze *et al* (1998) compared the load ability of osteosynthesis of unstable per and subtrochanteric fractures and found that the PFN could bear the highest loads of all devices. Andrew J Pakut (2003) conducted a clinical study of treatment of subtrochanteric fractures of femur in 15 patients operated with DCS before 1999 and 11 operated with PFN after 1999. The mean age of patient was 70 years (31-90). Patients with intertrochanteric fractures and pathological fractures were excluded in study. The mean age of follow up was 16 months. All fractures united. There was no infection or implant cut out. In DCS group there was one malunion in varus and one late breakage of implant. In PFN group there was one malunion in internal rotation and three intraoperative fractures. Functional evaluation showed no significant difference in pain, range of movement or walking ability, but recovery was earlier in PFN group. In our study, mean age was 49.1 years and study included only subtrochantric fractures. There were two cases with postoperative infection one with PFN and other with DCS. In DCS group there was one case with nonunion and one case with late fracture with implant breakage. No case of malunion was reported. In PFN group we encountered one case with intraoperative fracture of lateral cortex. No cases of malunion was reported. Functional evalution showed significant difference in walking ability in form of early weight bearing in PFN group. Differences in pain and range of motion was similar in both the groups, but recovery was earlier in PFN.

Consecutive prospective randomized clinical study was conducted by Department of Orthopaedics surgery, Uppasal University Hospital, Uppasal, Suede of 203 patients admitted with subtrochanteric fractures of femur. Surgery was performed with Proximal femoral nailing and Dynamic condylar screw. Follow up visits occurred at 6 weeks, 4 weeks and 12 months. Functional outcome was measured by walking ability, rising up from chair, living conditions and complications. The ability to walk 15 meters at 6 weeks was significantly better in PFN group as compared with DCS group with P value of 0.04. The major complication rate (8% in PFN and 4% in DCS) did not differ statistically with P value of 0.50. Reoperations were more frequent in PFN group (9%) compared to DCS group (3%). Study concluded that there was no major difference in functional outcome or major complication between the treatment group. In our study of 30 patients functional outcome was measured by postoperative mobility, hip pain and patient assessed range of motion in terms of ability to squat and sit crossed leg. Anatomical outcome was assessed by presence of shortening, deformity, and hip and knee movements. No statistical significance was found in functional and anatomical outcomes with DCS and PFN with P values of 0.623 and 0.549 respectively. However union of fracture and ability of full weight bearing was statistically significant with P values of 0.042 and 0.0001. Complication rate was higher in DCS group and was the reoperations rate.

Major advantage of 95 DCS is its proximal extension, that makes it possible to insert two or more cortical screws through the plate into the calcar, which greatly strengthens its hold in proximal fragment and prevents varus and rotational deformities. However use of DCS is associated with blood loss due to extensive dissection, while chances of implant failure and delayed union or nonunion are more. Secondary procedure may be required in form of secondary bone grafting or revision ORIF with bone grafting. Although operative technique is easy the complications associated with DCS are many.

The modification of the PFN and careful surgical technique should reduce the complications associated with PFN. Locking the proximal fragment to nail has decreased the tendency to drift into varus and locking the distal fragment has prevented shortening and rotation. The locking of fragments provides exceptional rotational and axial stability which has permitted one to deal with all fracture patterns. Although technically challenging, PFN is an excellent minimally invasive device for stable and unstable subtrochanteric fractures of femur with excellent anatomical and functional outcomes and minimal complications in comparison with use of DCS.

Some of the disadvantages of P.F.N are:

(i) Steeper learning curve for the surgeon.

(ii) More technically demanding surgery.

(iii) Specialized instrumentation and larger inventory of implants.

(iv) Longer operative time.

(v) More exposure to radiation of image intensifier.

Conclusion

Subtrochanteric fractures are common in high velocity trauma. High stress concentration, slow healing time because of predominance of cortical bone and difficulties in getting biomechanically sound reduction because of usual medical communication, has led to evolution of various internal fixation devices. Inspite of it, the incidence of complications are high after surgical treatment. The potential advantages of the Proximal femoral nail over the 95 degrees Dynamic condylar screw with regards to mini-

(Continued on page 20)

Original Article

Indications and operative outcomes of acromioclavicular joint injuries fixed with bosworth screw

Anil J Nayak[1], Jayprakash V Modi[2], Zulfikar M Patel[3], Kirtan V Tankshali[4], Hriday P Acharya[5]

Acromioclavicular joint is a biomechanically complex joint, isolated injuries of which are rare. Complex classification system (Rockwood) and no universally approved guidelines for the treatment with the ever evolving surgical techniques pose further challenge for the treatment of the condition. We have in our current study, assessed operative outcomes of Bosworth screw fixation for AC joint injuries and the role of occupation in deciding treatment regimen and predict operative outcomes. This is a prospective cohort study of 11 patients having isolated AC joint injury classified as grade II or higher according to Rockwood classification treated with Bosworth screw fixation at high patient turnover tertiary care centre. AC joint injuries are more common in males and RTA accounts for the most of the injuries. There is significant difference in outcomes of operative fixation between high demanding and low demanding occupation as evaluated by constant shoulder score ($p<0.01$). Operative treatment in failed conservative treatment of type II/III injuries yields better constant score. The earlier the treatment, the earlier the vocational rehabilitation especially in high demanding occupation. Occupation should be considered in making treatment choice of AC joint injuries and not only type of injury. Bosworth technique of fixation is old but cost effective, easily reproducible, less time consuming technique with smaller learning curve and should be considered in all type V injuries and in patients with type II/III injuries involved in high demanding occupation.

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Key words **: AC joint injuries, Bosworth screw, High demanding Occupation, Rockwood classification.**

Acromioclavicular Joint is a plane synovial/ diarthrodial joint between acromion process of the scapula and lateral end of the clavicle bone[1]. The joint is important link between the appendicular skeleton (upper limb) and axial skeleton. Furthermore, joint is stabilized by structures like joint capsule, acromioclavicular ligament, deltotrapezial fascia, coracoclavicular ligaments (which play major role in weight transmission). Multiple ligaments acting on single joint make biomechanics of the joint more complex. Optimal joint functioning is desired for painfree upper limb function and normal day to day weight lifting activities. Injury to the joint is rare but remains an entity with complex classification system with no emphasis on role of occupation, no standard treatment protocol, no established guidelines for the choice of ideal surgical procedure. Advances described for the treatment options for these injuries, like anatomical coracoclavicular reconstruction (ACCR) or arthroscopic repair are more time consuming, not easily reproducible and require longer learning curves. Besides cost benefit analysis has also to be kept in mind as these newer procedures are costlier as compared to the conventional method. We have, in our present study, evaluated the role of occupation in decision making of treatment for these injuries especially Rockwood type 2 and 3 injuries (for which there still is no consensus regarding treatment recommendations) and assessed operative outcomes of Bosworth screw fixation for AC joint injuries.

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Materials and Methods

This is a prospective cohort study of the 11 Acromioclavicular joint injuries operated at a tertiary care centre between 1st January, 2014 and 31st May 2016 with Bosworth screw fixation. Patients with isolated injury of Rockwood type II to VI who were willing to get operated were included in our study. Patients of polytrauma having associated AC joint injury and patient giving negative consent for the surgery were excluded. Polytrauma patients were specifically excluded so as to remove any confounding factor affecting the treatment outcome of the procedure. Type I injury was excluded as standard treatment protocol of such injuries is conservative option only with skilful neglect. Though standard treatment protocol for type 2 injury is conservative treatment, we had patients with failed conservative treatment for these injuries and were included in our study.

As per our standard protocol, all the patients undervent radiographical investigations in the form of Anteroposterior, axillary radiograph of shoulder joint with clavicle, Zanca view of normal and affected side whenever possible in a single plate for better comparison. Patients were classified under high demanding and low demanding occupation depending upon the involvement of overhead activities and heavy weight lifting in day to day life. All the patients enrolled in our study were operated by Bosworth screw fixation[2,3] and followed upto minimum period of one year post-operatively. Above mentioned radiographic views were obtained at each visit with evaluation of constant score and outcomes analysed.

All the patients were operated under general anaesthesia in modified beach chair position by using cannulated cancellous screw of 4.0 mm size with washer. There was no added cost burden on patient or hospital system in terms of instrumentation as CCS screws along with washer and general surgical equipment are all that is required to perform the surgery and are readily available at our centre.

Observation and Analysis

All the 11 patients enrolled in our study were males with their age ranging from 22 to 55 years and average age being 34 years. The most common mode of trauma was road traffic accident in 7 out of 11 patients. Other modes being injury while playing sports (2/11) and fall down while doing manual labour (2/11). Only 6 out of 11 patients presented to us in acute setting ie, within 3 days of injury. The presentation time of other 5 patients ranged from 7 days to 90 days. The chief complaint at the time of presentation was pain or instability at the AC joint in 9/11 patients and 2 patients came to us for cosmetic purpose. 5 out of 11 patients were treated conservatively elsewhere prior to presenting to us. Distribution of patients according to Rockwood classification is shown in the table below[4]. No patient in our study had type IV/VI injury, indicating rarity of both types (Table 1).

Time to return to daily activities ranged from 30 to 50 days and time for vocational rehabilitation ranged from 1.5 months to 6 months. 10/11 patients achieved vocational rehabilitation in our study. Constant score at the end of one year follow-up ranged from 69 to 91. Major limitations noted in our study were reduced strength for abduction and restriction of movement at terminal abduction (>150 degrees). Implant impingement was observed in 2 out of 11 patients, persistent pain with restricted range of motion was noted in one patient and recurrence of cosmetic deformity was noted in one patient which occurred following implant removal due to impingement.

Table 1 — *Distribution of patients according to injury type*

Rockwood type	Number of patients
II	2
III	5
IV	-
V	4
VI	-

Discussions and Results

As observed in our study, AC joint injuries are more common in males (100% in our study) and in 3rd and 4th decade of life (9 patients). Most common mode of trauma was RTA (Road Traffic Accident) in our study (7/11). Sports related injury was found only in 2 patients which is contradictory to the various studies published in literature[6,9]. Clear mechanism of injury could not be established as majority of the RTA victims did not remember the event in the reproducible manner but majority of them had direct trauma to the joint or fall on outstretched hand. Among other modes of trauma, direct impact on AC joint (2 patients)-direct fall while performing heavy labour duties and excessive force on affected side's upper extremity- while playing sports (Kabaddi in both cases) accounted for equal incidences. There was no high risk occupation noted in our study which would predispose the patients to this type of injury.

Six patients presented to us in acute setting ie, within 3 days. The rest after atleast 7 days of injury, with range for presentation time being 7 to 90 days. The reason for late presentation was failure of conservative treatment to reduce pain and cosmetic deformity with relatively preserved range of motion. Even in the setting of acute trauma, the major presenting complain was pain or instability at the AC joint with 5/6 patients performing abduction of upto 90 degrees with pain only at terminal movements. 8/11 patients could reduce the joint manually with pressure and elevation of arm but complained of instability upon relieving the pressure/ inability to maintain reduction.

Out of 11, 2 patients had Rockwood type II injury. Both the patients were given conservative treatment trial previously for 8 weeks and persistent pain was the chief complaint at the time of admission. Rockwood type II injury has fair consensus regarding conservative treatment but we encountered these 2 patients who had failure of conservative treatment. Occupation of both the patients demanded routine overhead activities which might be the reason for the failure of conservative treatment. Five patients had Rockwood type III injury, out of which 3 patients were given conservative treatment trial previously elsewhere which had failed to relieve symptoms whereas 2 patients presented to us within 3 days of injury. None of the late presenters had SICK scapula syndrome[1]. Four patients had Rockwood type V injury, all of which presented to us within 3 days of injury and were fixed in the acute sitting. No patients of type IV or VI injuries presented to us during our study period, describing rarity of these types[7,9].

All the patients after necessary pre-operative workup, were operated with Bosworth screw fixation under General

Anaesthesia and in modified beach chair position. Average operative time was 25 minutes in our study. None of the patients required post-operative blood transfusion as there was minimal blood loss. Postoperatively Zanca views were obtained for bilateral AC joints and coracoclavicular distance of both the sides compared. All the patients had CC distance within 10% of the normal side. Average post-operative hospital stay was one day in our study. All the patients were guarded in shoulder arm immobilizer upto 1.5 months to allow for soft tissue healing and to avoid implant backout which is a known complication of this type of fixation. Wrist and finger mobilization were started on the same day and guarded passive mobilization at shoulder was started on post-operative day 15 at the time of stitch removal. Patients were followed upto one year post-operatively. Outcomes were analysed by using Constant shoulder score which includes subjective and objective criteria like pain, ADL (sleep, work, recreation), strength, ROM (Range of Motion). Constant scores ranged from 69 to 91 at the end of one year follow-up[5] (Figs 1& 2).

Major disability observed in our study was terminal restriction of abduction (>150 degrees) and inability to lift the heavy weight (>15kg). There was no correlation noted between type of injury and constant score. However, occupation had definite effect on outcome. Failure of conservative treatment was noted in patients who were involved in heavy weight lifting or overhead abduction activities i.e. "high demanding occupation". Occupation also had effect on vocational rehabilitation, with patients involved in high demanding occupation taking around 6 months for vocational rehabilitation as compared to low demanding occupation which on average required 2 months of time for vocational rehabilitation. Thus role of occupation in treatment and rehabilitation of these injuries need to be emphasized. Comparing constant scores of high demanding (74.8) with low demanding occupation (85.67), independent T test yielded t score of 4.68 with p value 0.0011 meaning thereby constant score was significantly lower in individuals involved in high demanding occupation as compared to low demanding occupation at final follow-up. High demanding occupation individuals with type II injury may be considered for operative treatment in the initial stage only as there also are high chances of failure with conservative management and operative treatment provides better vocational rehabilitation. 5/11 patients of our study presented after failed conservative treatment and 3 of them had type 2 injuries, 2 of them had type III. Except for type V injury, all the patients were involved in high demanding occupation and their shoulder score improved from average of 43.75 to 73.25 with the Bosworth technique as analysed at the one year follow-up. P values and significance is not commented due to only 4 patients but there clearly is improvement of scale 30 on average in constant scores. Thus earlier intervention should be offered even in type 2 injuries in high demanding individuals.

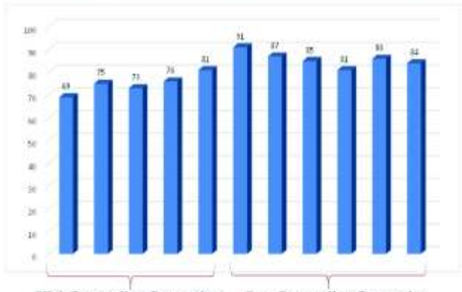

Fig 1 — Constant shoulder score follow-up at 1 year


Fig 2 — Pre and postoperative AP radiograph of AC joint injury

Complication of Implant impingement was observed in 2 patients which required implant removal at the end of one year.Recurrence of cosmetic deformity was observed in one patient after implant removal for impingement but patient had painfree and full ROM, so no further intervention was planned. One patient had persistent pain even at the end of one year with restricted ROM. The patient was manual labourer and did not follow standard physiotherapy protocol and started work at 45 days including painful overhead abduction with heavy weight carrying on head. Upon followup radiograph at one year, coracoclavicular distance was found to be 30% more than normal which might be the reason for persistent pain. The same patient could not achieve vocational rehabilitation for pre-injury occupation and had to change the ocuupation later on. Other than these 2 patients, no patients had increased coracoclavicular distance of more than 25% as compared to the normal side. There was no coracoid or clavicular fracture observed in our study[3,8,9].

Due to high patient load at our tertiary care centre,

(Continued on page 26)

Original Article

Prevalence of high risk HPV types in women referred to a colposcopy clinic in a public hospital, Chennai, South India

D M Christe[1], Saramini Jacob[2], Anitha Daniel[3]

To estimate the prevalence of high risk types of HPV infection in women attending colposcopy clinic in a public hospital in Chennai, South India. This was a cross sectional study. Consenting women who were attending the Gynecology Out Patient Department (OPD) and who were referred to the Colposcopy with high risk complaints were enrolled into the study. Cervical samples were taken for testing HPV types 16, 18, 31, 33, 35, 45, 52 and 58. There were a total of 55 women, aged between 24 to 60 years. High risk group women (n=12) were those women who were HIV Positive, women on steroid therapy and those who had Cervical Intraepithelial Neoplasia (CIN). 15 women (27%) were positive for HPV. Three women belonged to high risk group and five women had cancer cervix and the rest had chronic cervicitis. A total of 40 women were negative for HPV tests. Six women were HIV positive and two women were already treated for CIN2. Three women had CIN2 and One HIV positive woman had CIN3. HPV tests were negative in women with high grade lesions. All women with cancer tested positive for high risk HPV types. More studies should be done to evaluate the risk of various types of HPV in causing cancer.

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Key words **: High risk HPV types, colposcopy clinic, CIN, Cancer cervix**

Cervical cancer continues as a scourge to women worldwide, and still remains a major cause of mortality among women. The Human Papilloma Virus (HPV) has been proven as the causative agent, and causes cancer along with co factors. HPV is the most common sexually transmitted infection (STI). Over 100 types of HPV have been identified which affect humans and of these at least 40 types infect the genital mucosa. Taking into consideration their association with cancer, they have been grouped into high risk, intermediate risk and low risk groups.

Of the many different types of HPV, some can cause health problems including genital warts and cancers. HPV infection is the most important risk factor for cervical intraepithelial neoplasia and invasive cervical cancer[1].

There were an estimated 527,600 new cervical cancer cases and 265,700 deaths worldwide in 2012. It is the second most commonly diagnosed cancer and third leading cause of cancer death among females in less developed countries[2]. Cervical cancer is the second most common female cancer in women aged 15 to 44 years in the world[3]. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease[4]. In India the peak age for cervical cancer incidence is 55-59 years[5].

The persistence of HPV infection has been identified in almost all cervical cancers. The precancerous condition of cervix is called as cervical intraepithelial neoplasia (CIN). The natural history of HPV induced carcinogenesis has been proposed as initial infection with HPV of the cervical epithelium, usually unnoticed as it is asymptomatic in most women. More than 75% of all women are infected with HPV in their life time. The HPV infection causes changes in the cervical epithelium in a small group of less than 30% of infected women and can be detected by cytology. Though the infection is cleared spontaneously in most women, within one to three years, it has been observed that HPV infection persists in a small percentage of 10 to 20% of women and this persistence caused the abnormal changes in the cervical epithelium, which may become progressive and is termed as CIN. The initial low grade lesions affecting a third or less of the cervical epithelium slowly progress on to high grade lesions affecting more than half the thickness of the cervical epithelium and later on, by breaking the basement become invasive cancer.

HPV infection is typically asymptomatic to begin with[6]. The transmission occurs prior to any clinically detected expression of the virus. HPV infects the basal cells of the

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epithelium[7]. The virions assemble in the nucleus and are subsequently shed from keratinocytes. There is proliferation of all the epithelial layers except the basal epithelial layer. The virus has an incubation period of 3-4 months[8]. The strength of the HPV cervical cancer relationship is even greater than the association between smoking and lung cancer and other well established causal relationships in cancer[9]. Based on the epidemiologic classification the high-risk HPV types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. Low-risk types are 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP 6108[10]. HPV types 16, 18, 45 and 31 are considered to be the most important oncogenic types. Subtypes 16 and 18 are the causative agents of more than 50% of cervical pre-cancerous lesions, and more than 70% of cervical cancer cases[11].

Papanicoulou staining (Pap smear) is a common screening method for cervical cancer in India. Simple screening tests of visual inspection of cervix after application of acetic acid (VIA) and Lugol's iodine (VILI) are now most commonly used and cost effective. A clinical trial in rural India found that a single round of HPV testing reduced the number of cervical cancer deaths by about 50%[12]. PCR is now the gold standard test for HPV research. HPV DNA testing was both more sensitive and specific than Pap cytology and VIA[13].

The natural history of HPV infection has been more clearly defined with PCR. This methodology has overcome the problem of misclassification of HPV status that initially confused the scientific community regarding the role of HPV in cervical cancer[14].

The aim of this study was to find out the prevalence of high risk HPV types in women referred to colposcopy clinic in a tertiary care, public teaching hospital in South India.

Materials and Method

This was a cross sectional study. Women were referred to colposcopy clinic from Gynecology outpatient department (OPD) and from the wards. Referral to colposcopy clinic was for various complaints like abnormal vaginal discharge, women with high risk background such as HIV positive women, women on steroid therapy, women with family history of cancer cervix, symptomatic women hailing from areas with high incidence of cancer cervix, history of abnormal bleeding, abnormal appearance of cervix, abnormal pap smear reports and for colposcopic evaluation prior to gynecological surgical procedures[15-17].

Women were selected randomly and enrolled into the study after obtaining informed consent[16,18]. Routinely all wht women referred to the colposcopy clinic were examined and full colposcopic assessment of the anogenital area was done using 5% acetic acid (VIA). The observed colposcopic appearance was recorded for each participant. Punch biopsy was taken for histological examination for fifty two women with abnormalities detected under colposcope. Three women did not require cervical biopsy.

Cervical swab was obtained from women who were enrolled into the study and tested for HPV types 16, 18, 31, 33, 35, 45, 52 and 58. The samples were transported into the Department of Experimental Medicine, The Tamilnadu Dr MGR Medical University for further processing. DNA was extracted from the sample using AmpliGenei HPV Detection Kit. Polymerase Chain Reaction was performed with 21.6 µl HPV amplification mix with 0.4 µl of Genei Hotstart Taq polymerase and 3 µl of DNA was added into the tube. The reaction conditions were initial denaturation at 95ºC for 5 minutes for the first cycle and 94 ºC for 1 minute, 62ºC for 1 minute and 72ºC for 1 minute for 10 cycles and was followed by 94ºC for 45 seconds, 58ºC for 45 seconds and 72ºC for 45 seconds for 35 cycles and the extension was 72ºC for 5 minutes. The positive and negative controls were used along with each assay. The amplified products were run on 2% agarose gel electrophoresis and the positive bands were visualized on UV spectrophotometer. An amplification product of size between 230-270 base pair indicated infection with one or more of eight oncogenic HPV types. The HPV types tested were Type 16, 18, 31, 33, 35, 45, 52 and 58.

Discussions and Results

There were a total of 55 women who aged between 24 to 60 years. Nearly 47.7% of the women had no formal education and did not know to read or write. However 37% had primary education, 13.8% had secondary education and one woman held a degree qualification. Fifteen women had history of early marriage and child birth and history of coital activity of nine years, and more. Six women were referred from high incidence areas of cancer cervix. Fifteen women were referred for abnormal appearance of cervix, and nine women for abnormal vaginal discharge.

A high risk group was identified comprising of HIV positive women, women living with HIV positive spouse, women on steroid therapy and women with previous history of CIN (n=12). More than one risk factor was elicited in 60% of the women. One woman was on steroid therapy. Eight women were HIV positive and five of them were on antiretroviral therapy. One woman whose husband was HIV positive was tested negative for HIV and HPV but diagnosed with CIN1. Six HIV positive women tested negative for HPV, though two of them had high grade lesions in cervix and biopsy cervix showed CIN2 in one and CIN3 in the other. CIN 1 was reported in one HIV positive woman. Two women, who had been treated for CIN in the past, also tested negative for HPV and also cervical lesions.

A total of 15 (27%) women tested positive for HPV (Table 1) (Fig 1). A population study from Eastern India has showed the prevalence of HPV among women without cervical cancer to be 9.9%[19]. While HPV prevalence among cervical cancer patients in India is high as 91.7%[20].

In our study three (3/15) HPV positive women were belonged to high risk group and five women (5/15) had cancer cervix and the remaining seven women had chronic cervicitis.

Though seven women with an average age of 36.3 years, had high grade lesions of cervix, (CIN 2, n=4, CIN 3, n=3) only three women were positive for HPV. The average age of women with cancer was 42.2 years (n=5) and all were diagnosed with squamous cell carcinoma of cervix and tested positive for HPV. HPV positive tests were recorded in seven women with chronic cervicitis (average age was 37.2 years).

A total of 40 women were negative for HPV tests (Table2) (Fig 2). Six women were HIV positive and two women were already treated for CIN2. Three women had CIN2 and One HIV positive woman had CIN3 (Table 2)(Fig 2).

Table 1 — *HPV Positive Group*

Age in years	PAP smear	HPV test	Colposcopy diagnosis	HPE reports
35	LSIL	Pos	Cancer cervix	Squamous cell cancer
45	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
42	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
24	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
32	NSIL	Pos	High grade lesion	CIN2
40	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
35	CACX	Pos	Cancer cervix	Squamous cell cancer
38	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
44	NSIL	Pos	Cancer cervix	Squamous cell cancer
40	NSIL	Pos	High grade lesion	CIN3
58	BLEED	Pos	Cancer cervix	Squamous cell cancer
28	NSIL	Pos	Low grade lesion	Chronic cervicitis
HIGH RISK GROUP				
45	NSIL	Pos	Chronic cervicitis	Chronic cervicitis
39	----	Pos	Cancer cervix	Squamous cell cancer
35	LSIL	Pos	High grade lesion	CIN2

HPV tests were positive in 15 women. Five women had Cancer cervix, One woman had CIN1. Two women had CIN2 and seven women had chronic cervicitis. The last three women belonged to high risk group. Row one The woman was On steroid therapy for three years. Second and third row Both women were HIV positive and on ART.
NSIL - Negative for squamous intra epithelial lesion.
LSIL - Low Grade Squamous Intraepithelial lesion.
HSIL - High Grade Squamous Intra Epithelial Lesion.

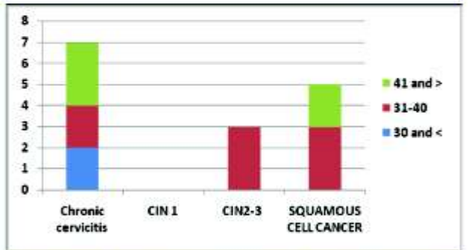

Fig 1— HPV positive group - diagnosis by cervical biopsy according to age group

HPV tests were positive in 15 women. The largest group of women who tested Positive for HPV were aged between 31 to 40 years. High grade CIN,was diagnosed in 37.5% and carcinoma of cervix was diagnosed in 37.5% of women in this age group.

Conclusion

All women with cancer tested positive for high risk HPV types. HPV tests were negative in women with high grade lesions, even in HIV positive women. More studies should be done to evaluate the risk of various types of HPV in causing cancer cervix, and precancerous lesions of cervix.

Table 2 — *HPV Negative Group*

No of women	Average age of women	HPE reports
27	41	chronic cervicitis
6	36.6	CIN1
2	40	CIN 2
2	34	CIN3

Forty women tested negative for HPV Tests.
Three women had normal study of cervix as diagnosed under Colposcope and did not require biopsy.
For twenty seven women, histopathological examination of biopsy tissue of cervix reported, chronic cervicitis and confirmed that there was no evidence of CIN.
HPE reports confirmed CIN in Ten women, with negative HPV tests. Six women had CIN 1, Two women had CIN2 and two women had CIN3.

Table 2A — *High Risk Group With HPV Negative Tests*

Age	Pap Smear	Colposcopy Diagnosis	HPV Result	High risk factor	HPE Report
42	NSIL	Chronic cervicitis	Neg	HIV +	CIN1
35	NSIL	Chronic cervicitis	Neg	Old CIN 2	Chronic cervicitis
39	NSIL	Chronic cervicitis	Neg	Old CIN	Chronic cervicitis
41	NSIL	Chronic cervicitis	Neg	HIV +	Chronic cervicitis
47	NSIL	Chronic cervicitis	Neg	HIV +	Chronic cervicitis
33	LSIL	Chronic cervicitis	Neg	HIV+spouse	CIN1
29	ASCUS	LSIL	Neg	HIV +	CIN3
24	NSIL	HSIL	Neg	HIV +	Chronic cervicitis
43	NSIL	Chronic cervicitis	Neg	HIV +	CIN2

HPV tests were negative in two HIV positive women with high grade lesions.

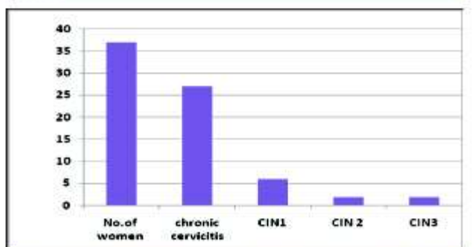

Fig 2 — HPV negative group - diagnosis by cervical biopsy

The average age of women grouped according to diagnosis by cervical biopsy ranged from 34 years to 41 years. The average age of all 37 women was 38 years.

Acknowledgement

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(Continued from page 13)

mal invasiveness because of closed technique and minimal soft tissue dissection, better biomechanical design to prevent implant failure and ability to bear more stress shows that this implant technique holds considerable promise in complex fractures. The earlier rehabilitation, less blood loss, less surgical trauma makes it the implant of choice in complex unstable subtrochanteric fractures.

With our sample study, we consider that PFN is an excellent implant for the treatment of subtrochanteric fractures of the proximal femur. The terms of successful outcome include a good understanding of fracture biomechanics, correct indication and exactly performed osteosynthesis.

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Observational Study

Efficacy and safety of fixed dose combination of drotaverine hydrochloride (80 mg) and mefenamic acid (250 mg) *versus* mefenamic acid (250mg) alone in treatment of primary dysmenorrhea : double-blind, randomised comparative study

J B Sharma[1], Alka Kriplani[2], Sunesh Kumar[3], K K Roy[4], Sona Dharmendra[5], Eshani Sharma[6], P Vanamail[7]

To compare the effect of combination of Mefenamic acid and Drotaverine hydrochloride with Mefenamic acid alone in primary dysmenorrhea. Out of 180 women with diagnosis of primary dysmenorrhea 87 women (Group A) were given combination of mefenamic acid 500mg with drotaverine 80 mg, while 93 women (Group B) were given Mefenamic acid 250 mg thrice a day during menstruation. Various pain intensity and relief scores were observed before and after treatment. The baseline characteristics and average pain score were similar. Post treatment pain intensity scores were significantly less in group A as compared to group B (p=0.001). The pain relief scores, patients satisfaction score and clinicians score were significantly higher in group A as compared to group B (p=0.001). Combination of mefenamic acid with drotaverine achieves significantly higher success in pain relief in primary dysmenorrhea as compared to mefenamic acid alone.

[*J Indian Med Assoc* 2018; **116:** 21-6]

Key words **: Primary dysmenorrhea, Mefenamic acid, Drotaverine, pain relief score, patient satisfaction score.**

Primary dysmenorrhea is a very common problem in young women. It is usually defined as cramping pain in the lower abdomen occurring at the onset of menstruation in the absence of any identifiable pelvic disease[1]. It is distinguished from secondary dysmenorrhea, which refers to painful menses resulting from pelvic pathology such as endometriosis. The prevalence rates reported for primary dysmenorrhea vary widely across studies due to the differences in measurement methods and are estimated to be between 40-50% with 30% needing medication and 15% being absent from work[2]. In India, the prevalence of dysmenorrhea has been estimated to be 87.87%[3], while in Malaysia it was 74.5%[4].

The symptoms of primary dysmenorrhea generally last for 2-3 days. The pain is most intense on the first or second day of the menstrual flow, or more precisely the first 24-36 hours, consistent with the time of maximal prostaglandin release into the menstrual fluid[1]. The Pain is suprapubic in location with radiation into the inner aspects of the thighs[1]. Dysmenorrheal pain is suprapubic and spasmodic, and associated with other symptoms like painful menstrual cramps, nausea, vomiting, diarrhoea, fatigue, dizziness and headache and is usually present during adolescence within 6 months to 1 year of menarche[1]. The consequences of untreated primary dysmenorrhea range from school absenteeism to disruption of relationships with family and friends[5,6]. The etiology of primary dysmenorrhea is not precisely understood, but most symptoms can be explained by the action of uterine prostaglandins, particularly $PGF2_{\alpha}$. There is increased endometrial secretion of prostaglandins $F2_{\alpha}$ from sloughed and disintegrating endometrial cell during the menstrual phase in women with primary dysmenorrhea[7].

$PGF2_{\alpha}$ stimulates myometrial contractions, ischemia and sensitization of nerve endings[1]. The clinical evidence for this theory is quite strong. Women who have more severe dysmenorrhea have higher levels of $PGF2_{\alpha}$ in their menstrual fluid[8]. These levels are highest during the first two days of menses, when symptoms peak. In addition, numerous studies have documented the impressive effi-

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cacy of NSAIDs, which act through prostaglandin synthetase inhibition[9,10].

A focused history and physical examination are usually sufficient to make the diagnosis of primary dysmenorrhea. The history reveals the typical cramping pain with menstruation, and the physical examination is completely normal. Secondary causes of dysmenorrhea must be excluded.

Treatment for primary dysmenorrhea aims to relieve pain or symptoms either by affecting the physiological mechanisms behind menstrual pain (such as prostaglandin production) or by relieving symptoms[11]. Most patients with primary dysmenorrhea show subjective improvement with NSAID treatment. These familiar drugs have a record of efficacy demonstrated by numerous studies over the past 15 years[1,9]. Cochrane Review (2003) also found NSAIDs effective for primary dysmenorrhea[12]. Oral contraceptives work by inhibiting ovulation and provide another effective and well-studied choice for therapy, especially in women desiring birth control[13]. Non-pharmacological treatments include diet, exercise and topical heat. For the approximately 10 percent who do not respond to these options, a host of alternatives exists, ranging from laparoscopic surgery to acupuncture, although with much less evidence to support their use. Mefenamic acid, an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) with demonstrated anti- inflammatory, analgesic and antipyretic activity in laboratory animals. Its mode of action is related to prostaglandin synthetase inhibition. It is widely used in gynecology to treat dysmenorrhea and menorrhagia and for pain relief for minor gynaecological surgeries[14,15]. An antispasmodic and a NSAID, mefenamic acid is believed to be an ideal combination for the treatment of conditions where pain is associated with spasm likely dysmenorrhea. Mefenamic acid inhibits prostaglandin synthesis and drotaverine acts as an antispasmodic. Drotaverine, a benzylisoquinoline derivative, has smooth muscle antispasmodic properties. It is a non-anticholinergic antispasmodic. It relieves smooth muscle spasm by increasing intracellular levels of cyclic-adenosine-monophosphate (cAMP), secondary to inhibition of phosphodiesterase[16-17]. Because of this antispasmodic action, it is widely used in biliary and renal colic, for augmentation of labor, dysmenorrhea and before instrumental diagnostic procedures[14-21]. Drotaverine as a smooth muscle relaxant reduces uterine contraction, which eventually improves uterine blood flow and hypoxia. Drotaverine is also free of the side-effects associated with the known anticholinergic anti-spasmodics like dicyclomine. Drotaverine is non-toxic, its side effects are very minimal and it can be administered even to children[21].

By virtue of two different mechanisms of action due to different active ingredients, a fixed dose combination of drotaverine hydrochloride with mefenamic acid would be expected to provide comprehensive and rapid relief from pain, spasm and/or inflammation in patients of primary dysmenorrhea and the combination of the two seems to be an attractive option. Thus, a study was undertaken to evaluate the effectiveness of fixed dose combination of NSAID (mefenamic acid) and antispasmodic (drotaverine hydrochloride) in women with primary dysmenorrhea as compared to mefenamic acid alone.

Materials and Methods

The present study was undertaken at the department of Obstetrics and Gynaecology department, in a tertiary referral centre, All India Institute of Medical Sciences, New Delhi after due approval of the ethical committee of the institute (Ref No IEC/NP-383/08-10-2014). The study was conducted from May 2015 to December 2016. The randomised controlled trial was registered with the CTRI number CTRI/2015/05/005796.

The sample size calculated with the help of biostatistician with 5% error and 90% power, was 140, with 25% loss to follow up, a sample size of 180 was taken. A total of 180 women aged 18-35 years with regular menstruation with complaints of primary dysmenorrhea and who were willing to participate in the study and were ready to come for follow up and signed written informed consent were enrolled in the study. The exclusion criteria were women (secondary dysmenorrhea), pregnancy, lactation, any medical disorder or on medication, premenstrual syndrome, infertility, with intrauterine device or oral contraceptive pill or patients not willing to participate in the study. Women fulfilling the criteria were randomised using computer generated randomisation number into two groups. Group A (87 women) were given a fixed dose combination of drotaverine hydrochloride (80mg) with mefenamic acid (250 mg) thrice a day starting on the first day of the menstrual cycle and continued for the whole menstrual cycle (for 5 days). Group B were given Mefenamic acid (250 mg) thrice a day starting on the first day of the menstrual cycle and continued for the whole menstrual cycle (for 5 days). The characteristics of women were noted in both the groups. Mean pain intensity score was calculated at the baseline using 11 point pain intensity numerical rating scale (PI-NRS) with 0 being no pain and 10 means worst pain. The 11 point intensity numerical rating scale was given after the start of the therapy at 15minutes, 30minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours (on phone). The mean pain relief score between the two groups was also recorded at the baseline and after the therapy. Patients were kept in outpatient department for first 2 hours during which time the pain score was recorded by the research fellow. The patient was then given a diary and taught to fill the pain intensity score and pain relief scores at 4, 8, 12, 24 and 48 hours at home. All patients were asked to come to hospital again between 5-10 days (mean 7th day) with the diary. The investigator assessed the patient self reported pain intensity and pain relief, medication compliance, concomitant medicines and any adverse reactions. At this time, 5 point patient satisfaction score and clinicians score (0=poor, 1= fair, 2=good, 3= very good, 4= excellent) were recorded for all the patients. Total area under pain relief score (TOPAR) was calculated at 2, 4 and 8 hours. Sum of pain intensity difference (SPID) was calculated at 2, 4 and 8 hours. Peak pain intensity difference was also calculated at 2, 4 and 8 hours. Pain relief was also calculated at 4 and 8 hours. Any adverse effects were noted in all the cases.

Statistical Analysis :

Statistical analyses were done based per protocol method in which patients lost to follow-up and those did not receive treatment were excluded from the analysis. Continuous data were subjected to Kolmogorov-Smirnov test to confirm whether the data follows normal distribution. Descriptive statistics such as mean, standard deviation (sd) and range values were calculated for normally distributed data. Comparisons of mean values of pain intensity score and pain relief scores between two groups were carried out using Student's t-independent test. Changes in pain intensity and pain relief scores from baseline to different follow-up times within the group were tested using Student's t-paired test. Further, repeated measures analysis of variance was carried out to correct the effect of drug while excluding the influence of base-line values. Spearman's rank correlation coefficient was computed between patients' satisfaction score and clinician's score. Frequencies of various adverse reactions by drug groups were compared using Chi-square/Fisher's Exact test as appropriate. For all statistical tests a two tailed probability of $P<0.05$ was considered for statistical significance. Statistical package for services solution (SPSS) IBM version 21.0 was used for data analysis.

Results :

Out of total of 180 women enrolled in the study, there were 87 women (48.3%) in group A, and 93 women (52.7%) in group B. The baseline characteristics of women in the two groups are shown in Table 1. Thus, the average age, body mass index (BMI), pain radiating to thigh, headache were similar in two groups. The average ±SD pain score at baseline was 5.55±0.49 in group A and 5.60±0.49 in group B and was not significantly different (p=0.496).

Table 2 shows comparison of mean pain intensity score between the two groups using 'T' tests before treatment, and at varying times (15 minutes, 30 minutes, 1 hour, 2 hour, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours) after treatment. Thus the pretreatment and 15 minutes post treatment mean pain intensity score in the two groups was similar. (p=0.274, p=0.167). However, the mean pain intensity score at 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 12 hours, 24 hours and 48 hours was significantly less in group A (drotaverine and mefenamic acid combination) as compared to group B (mefenamic acid alone) (p=0.001). Fig 1 gives diagrammatic representation of estimated marginal means of pain intensity using repeated measures of ANOVA model showing that pain intensity score was higher in group B as compared to group A.

Table 3 shows comparison of mean pain relief scores between the two groups using T test. Thus the mean relief score at 15 minutes in the two groups was similar (p=0.167). However, the mean pain relief score was significantly higher in group A as compared to group B at 30 minute, 1 hour, 2 hour, 4 hour, 8 hour, 12 hour, 24 hours and 48 hours (p=0.001). Fig 2 gives diagrammatic representation of estimated marginal mean of pain relief in the two groups showing that pain relief at 30 minutes and later was significantly higher in group A than in group B.

Table 4 shows comparison of mean values of face score difference, patient satisfaction score and clinicians score between the two groups using T test. Score was significantly higher in group A (4.25±0.45) as compared to group B (3.26±0.92) (p=0.001). Patients satisfaction score was also significantly higher in group A (2.62±0.58) as com-

Table 1 — *Comparison of base-line characteristics in terms of means/ percent values between the Groups*

Variables	Group A (n=87)	Group B (n=93)	P-value
Average Age±SD (years)	24.86±4.25	24.30±4.67	0.402*
Range values	18-35	13-35	
Average BMI±SD (Kg/m²)	20.97±1.38	20.86±1.38	0.592*
Range values	16.5-24.3	17.2-24.1	
Pain radiating thigh (n, %)	33 (37.9)	30 (32.3)	0.425$
Head ache (n, %)	17 (19.5)	13 (14)	0.317$
Average ± SD Pain score in the last six month	5.55±0.50	5.60±0.49	0.496*
Range values	5-6	5-6	

*- based on Student's t-independent test
$- based on Chi-square test

Table 2 — *Comparison of mean pain intensity scores between the groups at each time point using T-Test*

Time point	Group A (n=87)	Group B (n=93)	P-Value
Pre treatment	9.40±0.49	9.48±0.50	0.274
Post-treatment at 15 minutes	9.00±0.66	9.14±0.68	0.167
Post-treatment at 30 minutes	7.44±0.52	7.95±0.73	0.001
Post-treatment at 1 hour	6.47±0.52	6.87±0.63	0.001
Post-treatment at 2 hours	5.49±0.53	6.13±0.56	0.001
Post-treatment at 4 hours	4.58±0.52	5.55±0.50	0.001
Post-treatment at 8 hours	4.09±0.68	5.08±0.61	0.001
Post-treatment at 12 hours	3.24±0.63	4.11±0.58	0.001
Post-treatment at 24 hours	1.67±0.69	3.03±0.09	0.001
Post-treatment at 48 hours	0.72±0.68	1.31±0.97	0.001

Table 3— *Comparison of mean relief scores between the groups at each time point using T-Test*

Time point	Group A (n=87)	Group B (n=93)	P-Value
Post-treatment at 15 minutes	1.00±0.66	0.86±0.68	0.167
Post-treatment at 30 minutes	2.56±0.52	2.05±0.73	0.001
Post-treatment at 1 hour	3.53±0.52	3.13±0.63	0.001
Post-treatment at 2 hours	4.51±0.53	3.87±0.56	0.001
Post-treatment at 4 hours	5.43±0.52	4.45±0.50	0.001
Post-treatment at 8 hours	5.91±0.67	4.93±0.61	0.001
Post-treatment at 12 hours	6.76±0.63	5.89±0.58	0.001
Post-treatment at 24 hours	8.33±0.69	6.97±0.83	0.001
Post-treatment at 48 hours	9.28±0.68	8.69±0.97	0.001

Table 4 — *Comparison of mean values of face score difference (pre-final), patient's satisfaction score and clinician's score between the groups using T-Test*

Score Types	Group A (n=87)	Group B (n=93)	P-Value
Face score difference	4.25±0.65	3.26±0.92	0.001
Patient's satisfaction score	2.62±0.58	1.81±0.68	0.001
Clinician's score	2.71±0.53	1.73±0.65	0.001

Group A : Spearman's correlation coefficient between patient score and clinician's score = 0.289 (P=0.007).
Group B : Spearman's correlation coefficient between patient score and clinician's score = 0.376 (P=0.001).

pared to group B (1.81±0.68) (p=0.001). Similarly clinicians score was also significantly higher in group A (2.71± 0.53) as compared to group B (1.73±0.65) (p=0.001).

Table 5 shows comparison of efficacy parameters between the two groups. Thus the total area under pain relief (TOPAR) score at 2, 4 and 8 hours was significantly higher in group A (11.60±1.57, 17.02±1.86, 22.93±2.09) as compared to group B (9.91±2.03, 14.37±2.316, 19.29±2.479) (p=0.001).

Sum of pain intensity difference (PID) at 2, 4 and 8 hours was also higher within group A (9.21±2.59, 14.03±3.18, 19.34±3.71) than in group B (7.85±2.84, 11.78±3.378, 16.19±3.834) (p=0.001).

Peak pain intensity difference (peak PID) at 2, 4 and 8 hours was also significant higher in group A (3.91±0.757, 4.83±0.74, 5.36±0.79) as compared to group B (3.37±0.374, 3.95±0.682, 4.49±0.686) p=0.001.

Peak pain relief at 2, 4 and 8 hours was also significant

Table 5 — *Comparison of efficacy parameters between the two groups*

Efficacy parameters	Group A (N=87)		Group B (N=93)		P-Value
	Mean	SD	Mean	SD	
TOPAR-2hrs	11.60	1.573	9.91	2.031	0.001
TOPAR-4hrs	17.02	1.86	14.37	2.316	0.001
TOPAR-8hrs	22.93	2.09	19.29	2.479	0.001
SPID-2hrs	9.21	2.598	7.82	2.840	0.001
SPID-4hrs	14.03	3.18	11.78	3.378	0.001
SPID-8hrs	19.34	3.71	16.19	3.834	0.001
PEAK-PID/2hrs	3.91	0.757	3.37	0.734	0.001
PEAK-PID/4hrs	4.83	0.74	3.95	0.682	0.001
PEAK-PID/8hrs	5.36	0.79	4.49	0.686	0.001
PEAK-PR/2hrs	4.51	0.525	3.88	0.549	0.001
PEAK-PR/4hrs	5.43	0.52	4.46	0.501	0.001
PEAK-PR/8hrs	5.95	0.65	5.01	0.542	0.01

Fig 1 — Comparison of estimated Marginal Means using Repeated measures of ANOVA model

higher in group A (4.51±0.525, 5.43±0.52, 5.95±0.65) than in group B (3.88±0.549, 4.46±0.501, 5.01±0.542) (p=0.001).

Fig 3 gives diagrammatic representation of patients and clinicians response about the study drugs in two groups and shows results in group A as compared to group B.

Hence although mefenamic acid alone was also effective in controlling symptoms of dysmenorrhea, the addition of drotaverine to mefenamic acid improves the results in most cases. Hence combination of drotaverine and mefenamic acid was more effective in management of primary dysmenorrhea than mefenamic acid alone.

Discussion

Primary dysmenorrhea is defined as painful menstruation without any evident pathology for it[1]. Its prevalence varies from 40-50% with 15% rate of absenteeism from work or school[2,3]. There is increased abnormal uterine contractility due to increased menstrual endometrial secretion of menstrual prostaglandins F2? in women suffering from primary dysmenorrhea. Management includes pharmaco-

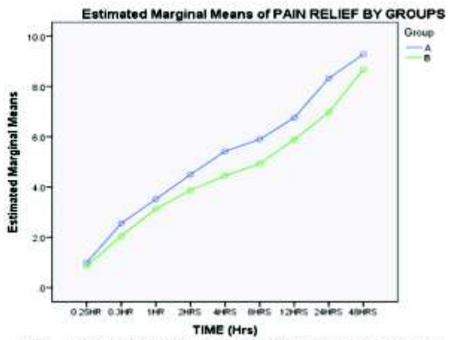

Fig 2 — Comparison of estimated Marginal Means using Repeated measures of ANOVA model

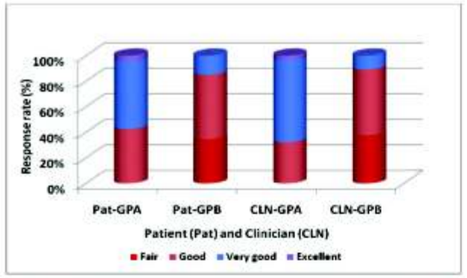

Fig 3 — Patients' and clinician's response about the study drugs

logical, non pharmacological and surgical methods. Most common treatment is use of non steroidal anti inflammatory drugs (NSAID) like mefenamic acid, aceclofenac, ibuprofen, naproxen given during menstruation. They act by inhibiting prostaglandin secretion which is the causative factor in primary dysmenorrhea[1,11,12]. Studies including Cochrane review have proven the efficacy of NSAID's in symptomatic relief in primary dysmenorrhea[10,12]. Drotaverine is an anti-spasmodic drug used for renal colic, abdominal colicy, pain, labour pains[16-21]. As there is spasmodic pain in primary dysmenorrhea, drotaverine should provide additional relief in its management when combined with mefenamic acid.

The results of the present study confirm that both mefenamic acid alone and combination of mefenamic acid and drotaverine hydrochloride are effective for pain relief in dysmenorrhea, but the combination therapy (mefenamic acid and drotaverine) was superior as compared to mefenamic acid alone. Thus the mean pain intensity score was significantly lower and mean pain relief score was significantly higher in group A (combination group) than in group B (mefenamic acid alone) (p=0.001).

The patient satisfaction score and clinicians score were significantly higher with combination therapy than mefenamic acid alone (p=0.001). The combination was also significantly superior to monotherapy in terms of total area under pain relief score (TOPAR 2, 4 and 8), (p=0.001), sum of pain intensity difference (2, 4 to 8 hours). (SPID 2, 4 to 8 hours) p=0.001, peak pain intensity difference (2, 4 to 8 hours) p=0.001 and peak pain relief at 2, 4 to 8 hours (PR 2, 4 to 8). Both treatments were well tolerated by all patients.

NSAIDs remain first choice of treatment for primary dysmenorrrhea with relief in as many as 80-85% of primary dysmenorrhea patients[1]. If relief is inadequate, combination oral contraceptive can be tried for upto 3 months[1]. If both NSAID and combined pill do not provide relief (only few cases), then diagnostic laparoscopy can be performed for finding any cause of secondary dysmenorrhea like endometriosis which doesn't respond to NSIAD's. The cause can also be treated at the same time by electrofulguration of endometriosis and adhesiolysis. Hysteroscopy and cervical dilation can be done along with laparoscopy which may help in widening the cervical canal promoting menstrual flow and thus reducing menstrual fluid prostaglandin contact with the myometrium. In addition, cervical dilation may induce partial disruption of paracervical innervation helping in pain relief.

In the present study, mefenamic acid, a prostaglandin inhibitor (NSAID's) exerted its anti-inflammatory activity by inhibition of prostaglandin synthesis and thus relieving pain of dysmenorrhea while drotaverine, an antispasmodic, produces rapid pain relief due to its antispasmodic effect. Mefenamic acid provides sustained analgesic effect in painful spasms of pelvic and abdominal origin. Thus the combination of mefenamic acid and drotaverine provides superior pain relief than mefenamic acid alone.

To conclude the combination of mefenamic acid and drotaverine provides superior and significantly higher pain relief for the medical management of primary dysmenorrhea than mefenamic acid. However, large multicentric randomized controlled trials are needed before recommendation of combination of drotaverine and mefenamic acid in the treatment of primary dysmenorrhea.

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The authors are thankful to Walter Bushnell Pvt Ltd. New Delhi for providing free drugs for this trial but they had no influence on the study or its results and were not shown the results. The authors are thankful to all the faculty, residents, nursing staff and patients for their help in this study.

Compliance with Ethical Requirements and Conflict of Interest

All procedures followed were in accordance with the Ethical Standard of the Responsible Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the patients. The study was conducted in department of Obstetrics and Gynaecology. The work was designed and performed after taking ethical clearance from the Institutional ethical committee. The study was funded by Walter Bushnell Pvt Ltd.

Registration number : CTRI Number: CTRI/2015/05/00579

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(Continued from page 16)

it was not possible to offer ACCR/ Arthroscopic reconstruction to all the patients. Our recommendation of operating type II injuries in high demanding occupation is based on small number of patients which requires larger multicentric studies to support the recommendation. Definition of High demanding occupation is based on 2 criteria of overhead abduction and heavy weight lifting which requires further validation. We recommend adding occupation to the classification system to help decide the treatment modality (Operative *versus* Conservative) and predict prognosis in a better way. But how much emphasis should be given to this occupation criteria needs to be standardized and for that larger demographic studies are required.

Conclusion

Acromioclavicular joint injuries are of rare occurrence and are common in males. Injury occurs mainly due to direct trauma to the joint caused by Road Traffic Accidents. Occupation has definite role in the prognosis of the injury and should be added in any classification system to recommend treatment modality.According to our study, Type II, III injuries in high demanding occupation and type V injuries should preferably be operated as it has better outcomes with earlier rehabilitation as compared to non-operative treatment. Bosworth technique is a highly cost effective, less time consuming method with excellent outcomes and can be used for any type of AC joint injuries.

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Review Article

Superiority of synthetic absorbable sutures over catgut suture in obstetric and gynecology surgeries — evidence based review

Pramod Kumar Sharma[1], Shashank Shekhar[2]

Some perineal trauma has been reported in more than 85% of women having a vaginal birth. In the UK and US, spontaneous tears requiring suturing are estimated to occur in at least one-third of women. Perineal trauma may result in long-term physical and psychological problems. Despite a high birth rate in India, maternal morbidity due to high rates of episiotomy are grossly underreported and needs to be addressed at different levels such as restricted use of episiotomy procedures, enhancing skill of health-care professionals and implementation of evidence-based approach for training on globally acceptable surgical procedures to minimize episiotomy-associated complications. This review summarizes evidences available to support use of synthetic absorbable sutures over catgut sutures for episiotomy.

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Key words **: Episiotomy, Sutures, Cat-gut sutures, Synthetic absorbable sutures.**

More than 85% of women having a vaginal birth suffer some perineal trauma. Spontaneous tears requiring suturing are estimated to occur in at least one third of women in the UK and US. Perineal trauma can lead to long-term physical and psychological problems[1]. Episiotomy, an incision to perineum is performed during the vaginal child birth to ease the process labour or delivery. The commonly reported complications of episiotomy are postoperative perineal pain, dyspareunia, hematoma, and possible infection.

The incidence of episiotomy is quite high in developed as well as in developing countries, particularly in primi gravidae. In United States, 30-35% women who gave birth vaginally had an episiotomy during the labour process[2]. Kettle C *et al*, reported that the incidence of perineal trauma in the UK was high in women (85%) who had a vaginal birth, out of which 60-70% required suturing[2].

Unfortunately, very little information is available about episiotomy rates in India. Sathiyasekaran *et al* has reported an episiotomy rate at 67% (95% CI 62.6-71.4). They also observed that the risk of episiotomy was 4.1 and 2.2 times higher when conducted in tertiary level institutions and secondary level institutions compared to primary level institutions respectively. The authors reported that Episiotomy rate was very high (91.8%) during delivery in private medical college hospitals as compared to secondary and primary level institutions. Adjusted odds ratio for episiotomy was 38 when doctors conducted delivery compared to trained birth attendants and 8.9 when delivery was conducted at private medical college hospitals compared to primary health centres[3].

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Saxena *et al* has reported around 71%episiotomy rate for vaginal deliveries at their institution[4], while Chhabra *et al*[5] found that overall episiotomy and vaginoperineal wound sepsis were the most common causes of postpartum admissions irrespective of the place of delivery. Home delivered women presented with unsutured infected perineal/vaginal tears whilehospital delivered ones hadinfected perineal, vaginal and cervical tears and infected episiotomies.

However, despite a high birth rate in India, maternal morbidity due to high rates of episiotomy is grossly underreported and needs to be addressed at different levels such as restricted use of episiotomy procedures, enhancing skill of doctors and nurses, and implementation of evidence based approach to train them on globally acceptable surgical procedures to minimize episiotomy associated complications.

In India, most of the surgeons/obstetricians/nurses are following the age old traditional way for episiotomy repair. Still, the plain catgut or chromic catgut sutures has remained the preferred choice for episiotomy, mainly due to their earlier experience of ease of use and local expert opinion and not because of evidences available.

Bharathi *et al* conducted a study to evaluate two different suture materials, namely, Vicryl Rapide and Chro-

mic Catgut for episiotomy repair, in relation to a short term maternal morbidity. The authors reported that compared to the chromic catgut group, the Vicryl Rapide group was associated with less pain (32.5% *versus* 57%) and a less need for analgesia (15.5% *versus* 0.5) at 3-5 days, along with a significant reduction in the wound indurations, uncomfortable stitches and wound dehiscence (4% *versus* 13.5%) and a better wound healing ($p<0.05$ significant) in the Vicryl Rapide group. Wound infections (3.5%) and wound resuturing (2%) were seen in the chromic catgut group but were absent in the Vicryl Rapide group[6].

This report summarizes the evidences available to support use of synthetic absorbable sutures over catgut sutures for episiotomy procedures.

Catgut Sutures – History and current worldwide regulatory status :

Initially used as strings for instruments such as violin, fiddle, harp in 15th century, catgut sutures which are made from sheep intestine (collagen in nature) enjoyed popularity for long time because of number of reasons, such as high and good tensile strength, ability to reduce rapid degradation, good absorbability and augmenting biological response for tissue regeneration[7].

The European Union (EU) has taken a drastic decision of banning catgut sutures due to concerns over transmission of bovine spongiform encephalopathy (TSE, mad-cow disease), although there is no clinical evidence suggesting or supporting an association between transmissible TSE and catgut sutures. In a report from the European Commission's Scientific Committee on Medicinal Products and Medical Devices (in September 1998) opined that, in the light of the bovine and ovine origin of the material, and the classification of intestines as tissues of medium infectivity, special conditions have to be met in order to manage the risks related to TSE[8]. Plain catgut has a life of only 3 to 7 days, but if treated or coated with chromic salts to form the chromic catgut, it has an increased life up to 20-40 days. Chromic salts enhance the cross linking of collagen and prevent its rapid degradation. Thus, chromic catgut derived from sheep intestinal submucosa combines desirable aspects like natural origin, smooth surface due to coating or chromicisation, good tensile strength and absorbability. Since catgut is a resorbable suture, the material decomposes in the tissue interfaces and may be replaced by regenerating tissues, which augments its biological acceptance[8,9].

It is documented that T cells are largely responsible for the rejection of tissue transplants or implants. They enlist the aid of macrophages in destroying foreign cells and stimulate B cells to increase the production of antibodies by cell cooperation leading to the rejection of the implant if it is not prepared from carefully selected polymers and conditions that are biocompatible. But biocompatibility of plain and chromic catgut is well established and in concordance they did not provoke any adverse reactions leading to rejection in vegetarians. However adverse reactions and extrusion of plain and chromic catgut sutures were observed in 'mutton eaters' only. This could be possibly explained as follows. Mutton or sheep meat could contain certain proteins that elicit an immune response in people who consume them. In these people, the body could have produced certain antibodies in response to the mutton protein antigens. The specific memory B cells and T cells remain in their body for a long time andare long lived lymphocytes primed by their first contact with antigens. On renewed contact with the same antigen, these memory T cells and B cells can produce a secondary immune response, which is more rapid, vigorous, with higher and longer antibody titer.

Conclusion and recommendation from European commission – scientific committee[8,9] :

(1) Availability of sufficient alternative products to catgut sutures, ie, synthetic absorbable sutures made from polymers such as polyglycolic acid, that provide equal, or even better, clinical performance than the catgut. Apart from possibilities of occurrence of TSE with the latter, there are apparently no other differences between these two types of sutures with respect to matters of safety.

(2) There are no clinical indications for the preferred use of catgut. Moreover, scientifically there is no further need for catgut sutures.

(3) Based on considerations of the bovine origin and the classification of intestines as tissues of medium infectivity, special conditions must be met to manage the risks related to TSE with catgut.

(4) Manufacturing guidelines are stringent for any continued production of catgut.

(5) Guidelines for risk management as there are no known inactivation processes that can be applied to catgut, risk management cannot be achieved by this method.

(6) Revised CE approval process (requirement of justification) for medical devices using animal tissue in situations where satisfactory alternative materials are available.

Following the developments in other European countries and discussion with UK Medical Devices Agency (MDA), catgut suture manufacturers stopped supplying these to the UK market. The MDA supported the move as acceptable alternative synthetic sutures were available, and stressed there was no evidence of any health risk associated with catgut sutures[9]. However, the catgut sutures are still available in other countries including United States.

But the use of synthetic absorbable sutures exceeded the catgut sutures in last couple of decades the cited reason was inconsistent properties of natural materials, fear of transmission of TSE, associated inflammatory response and availability of better clinical evidences for synthetic sutures[10].

Sutures available today are classified as permanent or absorbable, natural or synthetic, and multi-filament or monofilament. Multi-filament or braided sutures are easy to handle and have favourable knot-tying qualities. However, bacteria can enter the braided interstices and escape phagocytosis, potentially leading to suture infection, granulomas and sinuses. By contrast, monofilament sutures cause significantly fewer tissue reactions and glide easily through tissue. Their disadvantages include high retention of package shape, difficult handling, knot insecurity, and potentially cutting through tissue.

Absorbable Sutures : An overview

Absorbable sutures are characterized by the loss of most of their tensile strength within 60 days after placement. They should be absorbed with little or no tissue reaction at a predictable rate appropriate for the duration of the needed tissue support and are used primarily as buried sutures to close the dermis and subcutaneous tissue and to reduce wound tension. Absorbable sutures traditionally have not been recommended for skin closure, primarily due to unsightly railroad track formation. The only natural absorbable suture available is surgical gut or catgut sutures. Synthetic multi-filamentous materials include polyglycolic acid and polyglactin 910. Monofilamentous forms include polydioxanone, polytrimethylene carbonate, poliglecaprone, glycomer 631 and polyglytone. It is reported that original uncoated braided sutures from vicryl and one made of a homopolymer of glycolic acid) had rough surfaces and tendency to provoke inflammation and infection. To overcome this problem coated sutures like chromic catgut and dexon plus, with better tie down characteristics have replaced uncoated sutures.The use of absorbable material may be preferable because the sutures do not have to be removed, which saves the surgeon time and may lessen patient anxiety and discomfort.

Clinical evidences for synthetic absorbable sutures for episiotomy procedures :

The key parameters considered for reviewing the clinical database for synthetic absorbable sutures and catgut sutures are perineal pain, need for analgesia, wound dehiscence (impaired wound healing), dyspareunia, absorption profile (removal of suture material), local inflammatory response, infrction and physicochemical properties.

The meta-analysis on synthetic absorbable sutures in 'for primary repair of episiotomy and second degree tears' published in The Cochrane Library highlights the comparative clinical trials conducted with catgut sutures[11]. A total 11 trials with enrollment of 5072 women were considered in the review. Most of the parameters listed above were the comparative end points. The following section also highlights other studies which are not part of the Cochrane review.

(1) Pain — Postpartum pain is agonizing for a nursing mother, which has a great impact on the quality of life and on the nursing of the baby. Since Vicryl Rapide elicits less inflammatory tissue response than chromic catgut, it reduces the postpartum pain. Data from nine clinical trials involving 4017 women where pain was the primary outcome showed that fewer women in synthetic absorbable sutures group experienced less short-term pain compared to women in catgut suture group (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.76 to 0.90). Three trials also reported significantly less pain 10 days after delivery among women in synthetic absorbable group (RR 0.78, 95%CI 0.67 to 0.90, 2044 women). There was only one clinical trial which showed no difference between fast absorbing synthetic sutures and catgut sutures[11].

Other authors too showed that polyglactin 910 Rapide and polyglactin 910 is associated with either less pain, lesser short-term pain or mild pain compared to catgut sutures after episiotomy repair. In the early postpartum period, women in the polyglactin 910 Rapide group reported significantly lesser pain compared to other two groups ($P<0.05$) and by 30th day, all women in the same group were absolutely pain free in walking posture[12,13,14].

(2) Need for Analgesia — Analgesia use was measured as a secondary outcome in five clinical trials considered for Cochrane review. The women in the synthetic suture group had less number of analgesic use compared to catgut group (RR 0.71, 95%CI 0.59 to 0.87, five trials, 2820 women). Only one trial showed that the difference in analgesia use between groups was not statistically significant (RR 0.96, 95% CI 0.90 to 1.01)[11]. Kurian J *et al* also observed the similar findings in their study. At 7th day, 12% women in polyglactin 910 Rapide group required analgesics compared to 32% in polyglactine 910 and 50% in chromic catgut groups and by 42nd day, none of the women in polyglactin 910 Rapide required analgesics compared to 2% in polyglactin 910 and 4% in chromic catgut groups[12]. Similar observations were made by Shah *et al* where at analgesic requirement was slightly less in synthetic suture group compared to chromic catgut group[13]. while Bharathi *et al* reported that the difference in reduction in perineal pain between the two groups was statistically significant[6].

(3) Wound Dehiscence — Wound healing is a naturally occurring process. However, it depends on the types of the suture materials which are used, the presence or absence of an infection, etc. It also has an impact on the quality of life in the form of dyspareunia, incontinence of the bowel and bladder and pelvic floor dysfunction. While 15.7% of those with synthetic sutures had wound gaping, this applied to 25.5% of those with catgut sutures

(unweighted percentages). More women with catgut sutures required perineal re-suturing compared with those with synthetic sutures in the trials examining this outcome (RR 0.25, 95% CI 0.08 to 0.74, four trials, 1402 women)[11].

Shah *et al* have reported wound gaping were more in chromic catgut group where re-suturing was done in 1% of patients. However, wound healing process was good in synthetic suture group at day 20[13]. Sohail *et al* reported that 20% patients experienced mild pain on day 3 with chromic catgut, whereas as only 14% experienced mild pain with vicryl. None of the patients had dyspareunia after 3 months . The authors concluded that continuous suturing technique with either chromic catgut or vicryl is associated with less perineal pain and dyspareunia[14]. Dimitrov *et al* reported that patients with polyglycolic sutures showed better wound healing compared to catgut sutures. Additionally, noticeable scar was present in all women (replace patients with women) in catgut (42/42) versus 21/37 in polyglycolic sutures, out of which scar with granulation tissue (16/42 in catgut *versus* 3/37 in synthetic suture group) and wound gaping was also seen in 9/42 patients in catgut suture group versus none in synthetic suture group[15]. Bharathi *et al* reported that a wound discharge was observed in 3.5% of the cases and a wound infection was found in 4% of the cases in the Chromic Catgut group and they were observed in none of the cases in the Vicryl Rapide group[6].

Dyspareunia :

Ketcham *et al* showed that resumption of sexual activity was far better in synthetic sutures group (19/37) compared to catgut suture (1/42)[16]. The Cochrane review suggested that there was no significant difference in dyspareunia in patients with catgut or synthetic suturing[12]. The similar findings were observed by another group[15]. Bharathi et al reported that the uncomfortable stitches were less in the Vicryl Rapide group than in the Chromic Catgut group (24-48 hours 31.5% *versus* 48% , at 3-5 days 12.5% *versus* 27%), which was statistically significant ($p<0.05$) (24-48 hours 33% *versus* 40% , at 10th day 19% *versus* 26% with $p<0.001$). The lower rate of the uncomfortable stitches was related to the less tissue reaction of Vicryl Rapide and its rapid absorption[6].

(4) Removal of Suture Material — More women with standard synthetic sutures required the removal of unabsorbed suture material (RR 1.81, 95% CI 1.46 to 2.24, three trials, 2520 women)[12]. Kurian et al also reported similar findings in their study[12].

(5) Local inflammatory response — Pillai and Sharma have mentioned that catgut sutures elicit far more intense tissue reaction than synthetic absorbable sutures, because of their foreign protein structures. The local inflammatory response can be seen around the catgut sutures such as dense accumulation of macrophages, lymphocytes, and foreign body giant cells. After complete absorption, these are replaced by a dense mass of macrophages. The tissue reactions leading to exudates formation with tissue necrosis also reported with plain catgut sutures use[17]. In one retrospective study, it was observed the "rejection phenomenon" in patients sensitized to sheep protein mainly non vegetarians in whom catgut sutures were extruded from the wounds more often than vegetarians. Vicryl or prolene sutures were found to be not extruded in non-vegetarians[6]. Moreover a statistically significant reduction in the wound in duration was observed on the 3rd-5th days (7% *versus* 13.5%) in the same study[6].

(6) Infection — The infection rate in tissues containing the PGA suture was significantly less than the incidence of infection in tissue containing the gut sutures[17]. A wound discharge was observed by Bharathi *et al* in 3.5% of the cases and a wound infection was found in 4% of the cases in the Chromic Catgut group and they were observed in none of the cases in the Vicryl Rapide group. This was statistically significant with a p value of <0.05[8]. In one study, Leurox *et al*[18], reported that there was no infection at the site of the perineum repair in both the groups. In another study, Upton *et al*[19], reported that one woman in each group had an infection to the repair site.

(7) Physicochemical Properties — In one *in vitro* study, it was found that plain and chromic catgut disintegrated in pancreatic juice and pancreatic juice plus bile mixture. Polyglycolic acid and polyglactin 910 suture materials were vulnerable to pancreatic juice within 7 days. Polydioxanone retained most of its initial strength in pancreatic juice and bile. Polypropylene and silk retained 84% and 92% of their initial strength, respectively, showing polydioxanone was the strongest suture material in pancreatic juice[20,21]. An in vitro and in vivo evaluation of tensile strength in rat model showed that synthetic sutures proved to preserve its stability in all conditions but catgut lost its tensile strength in all medium. This in vitro study supports preferences of type of sutures in specific surgery[22].

The review article by Greenberg and Clark[23] summarizes the physical properties of various suture materials with respect to their use in obstetric and gynecologic surgery. The authors reported that there are currently 2 standards used to describe the size of suture material: the United States Pharmacopoeia (USP) and the European Pharmacopoeia (EP). The USP is more commonly listed. As expected, with all sutures increasing the size increases tensile strength. However, with both standards there is a marked reduction in the limits of the average minimum of knot-pulltensile strengths between collagen sutures and synthetic sutures for any given size.

The newer synthetic absorbable sutures have distinct advantages in obstetric and gynecological surgeries over the traditional natural collagen based catgut sutures[23].

Suture material is used in surgery to relieve healing tissues of disruptive forces. Because the degree of the for cevaries and the healing time needed for different wounds in different tissues varies, the sutures themselves should vary in their strength profiles. As noted above, minimum baseline suture tensile strengths are standardized by suture size and readily available from the USP. Yet, despite these minimum average standards, there is awide range of suture strengths among differing materials[23]. Each suture material has a recognized tensile strength which, for a given suture size, is most easily discussed as its failure or break load.This is the amount of weight in pounds or kilograms that is necessary to cause the suture to rupture. Typically, this measurement is presented in 2 forms, straight pull and knot pull, to reflect the reduction in any given suture's strength when it is knotted. In practical terms, the knot-pull tensile strength most accurately reflects a given smooth suture's in vivo tissue holding capacity. In a straight-pull tensile test, tension to rupture is applied at either end of a suture. A knot-pull tensile test is the same exceptth at a single knot has been tied in the middle of the strand[23].

All foreign bodies induce some degree of tissue reaction that impedes wound healing. The longer a suture material stays in the body, the more likely it is to serve as a nidus for undesirable tissue reactions that could delay and/or interfere with normal wound healing. Thus, the perfect suture material should retain adequate strength throughout the healing process and disappear afterward with minimal associated inflammatory reaction. Determining the balance between the added strength the suture provides to the tissues while they heal *versus* the negative effects of inflammation is central to choosing the proper sutures[23].

Thus in Sum, Level 1a and 1b evidence available for synthetic absorbable sutures over catgut sutures in perineal repair indicates a significant reduction in short terms pain with supportive data for reduction in long term pain, reduction in requirement of analgesic use, minimal local inflammatory reaction, relatively low incidence of re-suturing due to better wound healing and low incidence of wound gaping, higher incidence of removal of un-absorbed suture material and a lower infection rate. The other advantages of the synthetic sutures are their well-established superior biomechanical properties associated with good tensile strength, low tissue reactivity, easy to handle, low to high memory, predictable absorption and good knot security. Lastly, and more importantly, there are no exclusive indications for catgut sutures: their use is mainly driven by earlier experience and local expert opinion but not because the available evidences.

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Case Series

Cardiovascular Manifestations of Dengue Fever — Two Case Report and Review article

Kanak Kumar Mitra[1], Lipika Adhikari[2], Jyotirmay Pal[3], Uday Sankar Das[4], Palash Mondal[4], Tapobrata De[5]

Dengue is one of the most important viral diseases affecting human beings. The majority of symptomatic infections result in a relatively benign disease course. However, a small proportion of patients develop severe clinical manifestations due to platelet and endothelial dysfunction, immunological derangement with increased capillary permeability causing bleeding, hypovolaemic shock and cardiovascular collapse. Evidence is increasing that dengue can also cause myocardial impairment, arrhythmias and, occasionally, fulminant myocarditis. Here we are reporting two cases of Dengue fever presenting with Bradyarrhythmias (Atrioventricular Block) and another with myocarditis and heart failure. No antiviral agent is available till now and treatment remains supportive with judicious fluid replacement for patients with severe disease. Understanding of cardiovascular hemodyanamics in Dengue is important in the management specially during life threatening situation. In this Review Article we will outline the current understanding of the cardiovascular manifestations of dengue fever from the availalble literatures and conclude with a discussion of the possible therapeutic implication.

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Key words **: Dengue, Bradyarrhythmias.**

- **Myocarditis and Bradyarrhythmias are the common cardiological manifestations of Dengue**
- **Treatment is supportive**
- **IV fluid administration should be judicious**

Dengue is one of the most important mosquito–borne viral diseases in the world[1]. It is an acute febrile illness caused by any of the four serotypes (1,2,3 or 4) of a virus from the genus flavivirus, called Dengue virus. Cardinal clinical features of Dengue are fever, Rash, Arthralgia,myalgia, retroorbital pain, Hypovolemic shock or in extreme cases hemorrhagic shock. Cardiac involvement in Dengue is not very common. Cardiac manifestations in dengue virus infection can range from asymptomatic sinus bradycardia to life threatening myocarditis and Ventricular arrhythmias[2-5]. We are reporting 2 cases, reviewed the literature and discussed the implications of cardiac complications in dengue patients. A better understanding of cardiac complications will potentially improve the treatment of dengue illness by avoiding otherwise preventable morbidity and mortality in the affected patients.

Case Report

Case 1 :

A 11 year old boy was transferred to Cardiology Dept, RG Kar Mexical College & Hospital for evaluation of sinus bradycardia with history of fever for 5 days with myalgia without any form of bleeding manifestations. Neither the boy had any symptoms related to bradycardia (Vertigo, syncope or shortness of breath) nor he had any prior history of cardiac diseases. No family history of cardiac diseases was there. Upon arrival his temperature was 99.5°F , Pulse rate was 42/min with irregular volume, BP was 86/60 mm of Hg, RR was 24/min, Body weight was 23 Kg, multiple maculopapular rash appeared over right forearm on day[5] of fever which was mildly pruritic. There was no petechiae over skin or in the oral cavity, no tonsillar patch or tonsillar enlagement, no lymphadenopathy, B/L vesicular breath sound without any adventitious sound heard over chest, per abdominal examination was appeared to be normal. Hemoglobin was 13.8 gm/dl, TLC- 5400/dl with polymorphonuclear cells 64% Lymphocytes was 31%, Hematocrit was 38.95, Platelet count was 1.2 lakhs/ml. Urea 19mg/dl, creatinine 0.5 mg/dl, Cardiac Troponin T was WNL, His LFT came to be Normal. Chest xray found to have no abnormality. MP and MPDA were negative. Ns1 Ag was positive on day 5 of fever and IgM Dengue Ab was strongly positive on day 6 of fever by Capture ELISA Method. ECG showed Complete AV dissociation with T wave inversion in leads V1 to V5 (Fig 1). This ECG features persisted for 2 days then changed to 2:1 AV Block but again became CHB after 3 days and finally persistant 2:1 AV block remained with the heart rate of around 44 to 48/m and narrow QRS complex. The T inversion remained same as of his first ECG at the time of admission. Echo revealed mild mitral regurgitation without chamber enlargement and normal biventricular systolic function (LVEF-68%) and without other valvular involvement and pericardial effusion. So provisionally he was diagnosed as Dengue fever complicated with AV nodal Disease. We started Intravenous fluid with 0.9% normal saline at a rate of 4ml/kg/hour for hypotension, oral paracetamol on sos basis, Inj atropine o.5 mg Iv immediately followed by sos basis, injection ceftriaxone 500 mg twice a day IV was continued for 5 days (2 days after the patient became afebrile), during the whole admission period he was under close observation in ICCU. After 2 days his BP became 110/70 mm of Hg, so we stopped fluid therapy but his pulse rate remained around 48-50/min. Temporary pacing was not done as there was no symptoms related to bradyarrhythmia. We performed regularly platelet count & TLC which were never came down and Hematocrit which was never gone up. He was kept under observation for 12 days after he became afebrile but no warning features developed except his pulse rate was around 48-50/mim. Two weeks after discharge on follow up his BP was 110/70 mm of Hg and Pulse was irregular with average rate 68/min although ECG showed intermittent 2:1 AV block. Still we are following the patient at our OPD at regular basis.

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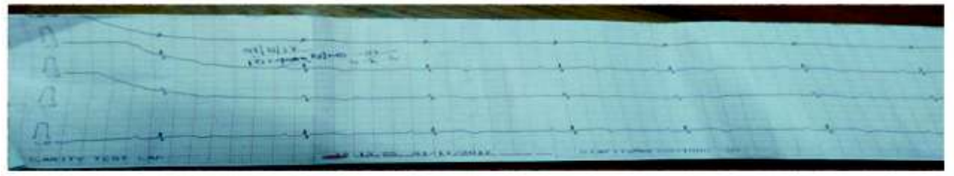

Fig 1 — Showing complete AV Dissociation

Case 2 :

21 years female admitted with fever for 4 days with left sided precordial chest pain which is independent of chest movements and posture. Fever was not associated with any cough, expectoration, dysuria, pain abdomen, rash, arthalgia or myalgia, headache, hemoptysis or any other form of bleeding manifestations. On admission her temperature was 100.4°F , Pulse rate- 100/min, BP- 100/70 mm of Hg, RR-20/min. No dry or wet purpura noted, chest / abdomen appeared to be normal, Cardiovascular Examination revealed pericardial rub. Routine blood- revealed Leucopenia (TLC-1740/ml with neutrophil 50%, Lymphocyte 40%) and Thrombocytopenia (Platelet -60,000/ml.) Electrolytes (Na+, K+), Urea, creatinine and LFT were normal. Cardiac Troponin T was positive (elevated). Dengue IgM Ab came to be positive on day 6 of fever. Chest X-ray showed- mild cardiomegaly with normal lung parenchyma. ECG on the day of admission was Normal (sinus tachycardia). Echo revealed- Dilated LV cavity (LVIDd-57mm,LVIDs-43mm), moderate Tricuspid regurgitation, mild Mitral regurgitation, depressed LV systolic function (LVEF = 35%) with chink of pericardial effusion. So provisionally she was diagnosed as Dengue fever with pancarditis with left ventricular systolic dysfunction. Day 2 of her admission she suddenly developed palpitation When her pulse rate was 150/m & BP was 96/60 mm of Hg, ECG done which revealed Non-sustained ventricular tachycardia (Fig 2), that was terminated by bolus injection of Amiodarone 150 mg IV followed by infusion over 24 hours. After 2-3 days she became afebrile, chest pain subsided after 5-7 days and no further episode of palpitation. Her Platelet count and TLC became normal. But echocardiographically her LV systolic function was as before (EF= 35-40%) but chamber size and mitral & tricuspid regurgitation were reduced to some extent (Figs 3-5). Now she is stable on Diuretics including spironolactone, beta blocker and ACE inhibitors. So finally she was diagnosed as Dengue fever with Left ventricular systolic dysfunction complicated with Ventricular Arrhythmias.

Review of Literature :

We searched PubMed database for articles published since 1975. Medical subject headings(MeSH) including dengue, myocarditis,

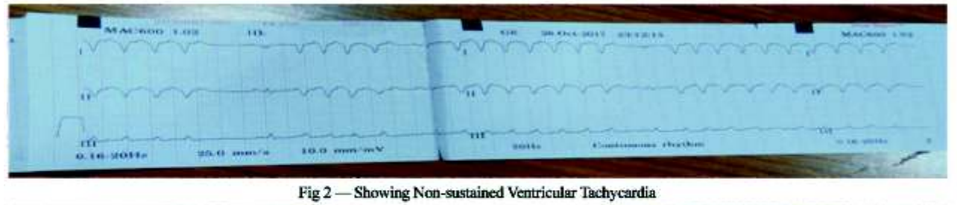

Fig 2 — Showing Non-sustained Ventricular Tachycardia

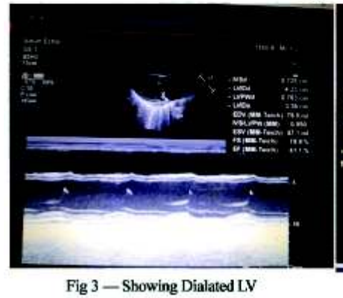

Fig 3 — Showing Dialated LV

Fig 4 — Showing Mitral Regurgitation

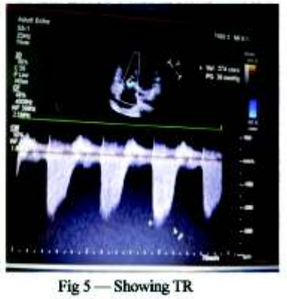

Fig 5 — Showing TR

pericarditis and arrhythmias were cross-referenced in the search which was supplemented with a secondary manual search.

Differing clinical severities were found, resulting from a wide spectrum of cardiac manifestations, which included self-limiting tachy–brady arrhythmia [9-19] and myocardial damage with decreased left ventricular ejection fraction, leading to hypotension and pulmonary edema[3,4,7,8,11,15,17]. Most of the affected patients were supportively treated for symptomatic relief[3,4,6,7,11,15,17,19]; some patients with left ventricle failure 1required parenteral inotropic agents (ie, dopamine and/ordobutamine) or vasopressor agents (Noradrenaline) for their cardiogenic shock. Although rare, fatal outcome was reported in dengue-affected patients with cardiac complications.

Discussion

The incidence and clinical manifestations of cardiac complications in Dengue illness varies considerably[2-8,9-19] from one series to another series. At one end of the clinical spectrum, patients are asymptomatic or have mild cardiac symptoms despite relative bradycardia, transient atrioventricular block or AV block which may persist upto 3 to 4 weeks and/or ventricular arrhythmia[3,4,7,8,11,15,17,19]. At the other severe end, patients may experience acute pulmonary edema and/or cardiogenic shock due to severe myocardial cell damage with left ventricular failure. Myocarditis can masquerade as acute myocardial infarction. The exact mechanism of the cardiac injury in dengue fever remains unknown, however it is proposed that the direct invasion of the cardiac myocyte by the virus and damage to the cardiac cells by the ongoing inflammatory damage are the major mechanism[20,21] of the cardiac manifestations. Dengue virus upon its entry in the body is taken up by the macrophages which causes activation of the T cells. These activated T cells cause release of various inflammatory cytokines, interleukins (IL1, IL2, IL6 etc), tumor necrosis factors (and activation of the complement pathway (C3a, C5a) and histamine[3]. This leads to the inflammation and necrosis of the endothelial cells leading to their dysfunction and plasma leakage. Leakage of the plasma in the interstitial space cause myocardial interstitial edema leading to impairment of myocardial function.

In our first case, the peculiar features was - the common conventional biochemical abnormalities ie, Thrombocytopenia, Leucopenia or raised hematocrit were absent, only cardiac involvement in the form of advanced AV nodal Block (2:1) and CHB were present. On the otherhand in our second case, in absence of Dengue hemorrhagic fever and Dengue shock syndrome (although there was thrombocytopenia and Leucopenia) there was Myocarditis in the form of Moderate to severe depressed LV systolic function with Malignant Ventricular arrhythmias (VT). So there was no correlation between the warning signs of Dengue fever (conventional features) and the cardiac manifestations in our two cases.

A recent report from Sri Lanka showed that 62.5% of 120 adults with dengue fever had an abnormal electrocardiogram[3]. These series suggest that cardiac complications in patients with dengue illness are not uncommon, and might have been under-diagnosed because most of the cases with cardiac complications are clinically mild and self-limited[2]. Our review shows that cardiac complications are not uncommon in dengue illness. Although it was self-limiting in our patient under supportive treatment, acute myocarditis in dengue may be clinically severe to such an extent that it has a fatal outcome[15,19]. Early recognition of myocardial involvement in dengue illness, prompt restoration of hemodynamic instability while avoiding fluid overload, and sparing unnecessary invasive management are important in treating dengue-affected patients with severe myocarditis.

Conclusion :

Cardiac manifestations of Dengue fever is not uncommon. Bradyarrhythmia and Heart failure due to Myocarditis are usual cardiac complications of Dengue, others being Ventricular tachycardia, Atrial fibrillation and valvular regurgitations. Low heart rate and hypotension may be due to cardiac involvement which should be evaluated by proper investigation like Electrocardiography and Echocardiography. Intravenous fluid administration to combat hypovolemic shock in Dengue should be monitored in presence of heart failure. Incidentally majority of bradyarrhythmias and heart failure as well as other cardiac manifestations resolve over time and don't require any active management.

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Special Supplement on CARDIOLOGY

Editorial

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Cardiology : The Emerging Perspective

Cardiology has come a long way since the days of our residency when Lasix, Lanoxin, oxygen and nitrates was the only drugs available to permuteor combine with and watchful expectancy of a recovery were the only option. Thereafter each decade has been revolutionised by advent of major epoch making drugs that has changed the horizon of pharmacotherapy in Cardiology leading to significant mortality benefits over and above immense relief from morbidity. The latest addition of Valsartan Sacubitril and PCSK9 inhibitors are to mention only a few. The same period has been blessed with advent and progress of interventions, both in coronary and structural heart disease again changing the concepts and outlook as to how Cardiac patients are to be treated.

However all said and one stumbling block has been penetration and percolation of these advancements to grass root level in the global society. We agree that all new therapies initially start with a price only to de-escalate, so that the benefit reaches the middle and lowerrung . However with all these, the penetration still remains abysmally low; and this is not a national phenomena but international. Therefore what should be the real approach to lessenthe disease burden in the society? Yes the old adage is self explanatory –"A stitch in time saves nine". So it is prevention that should take centre stage .

But the question comes "Are we really prepared "? In our opinion it is a "No".The reason is very simple – what mind doesn't know eyes doesn't see. Do we really have much data on even simple aspects like Lipid characteristics of Indians ? What should be the actual statin or fibrate dose for us? Is fibrate at all important in our subset of population ?Are our heart failure patients more resistant to ventricular arrhythmia than our western counterpart ? Questions galore but answer is in the negative as we are still really deficient in terms our own epidemiological data. Of course some laudable work has started. The CRRIS data, a segment of which is published in this edition, is one of its kind. ACS Registry from Kerala is again a unique database. Cardiological Society of India (CSI) is about to embark on ambitious ACS and ADHF Registry in four states of Eastern India. So the efforts have started . We hope this to flourish and we should nourish these work through our journals rather than extrapolating the data from the west and feel proud at learning it by heart. Once we have more data the preventive efforts that have already started with Cardiological Society of India leading from the front and playing a pioneering role in persuading government in particular and intelligentsia in general to promote prevention, will then be really complemented.

Original Article

Burden of cardiovascular problem and their risk factors among adolescent school children in Kolkata : an introspection

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The CRRIS Study Group on behalf of Cardiological Society of India, West Bengal branch.

This cross-sectional study was conducted among the adolescent school children of 9th grade (14-16 years) studying in 21 schools of Kolkata which were selected by using stratified random sampling based on school types and socio-economic status (SES). Total number of participants was 1651. Overall 21% reported known cardiac deaths among their first-degree relatives. Total 36 students (2.29%) were detected with cardiac murmurs. Almost a quarter (23.75%) of the participants were overweight and had abnormal blood pressure including both prehypertension and hypertension. Proportion with over-nutrition was more among the upper socio-economic group. Unhealthy eating practice and physical inactivity might have contributed to childhood over-weight and obesity. Early implementation of school-based awareness development programme regarding cardiovascular disease and appropriate lifestyle modification might be useful in delaying development of atherosclerosis in at-risk school-children.

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Key words **: Adolescent, Cross-sectional study, overweight, hypertension, socio-economic status.**

Cardiovascular diseases (CVDs) especially coronary artery diseases (CADs) contribute largely to mortality and morbidity worldwide with significant impact on health financing[1]. According to WHO estimates, globally almost 18 million deaths each year are attributed to CVDs, involving 31% of all deaths worldwide. The overall situation appeared more alarming in low and middle-income countries (LMIC) where CVDsremained responsible for 80% of deaths and 85% of disabilities[2,3]. Among CVDs, 75% of the global deaths and 82% of Disability Adjusted Life Years (DALYs) resulted from CADs in LMICs[4]. Moreover, among all ethnic groups, the highest prevalence of death from CADhas been reported among South East Asians and Indians were no exception[5].

In India, growing urbanization has resulted in better availability of amenities, economic stability and some improvement in the quality of life but as the ramification: junk food intake, physical inactivity, tobacco use etc. raised simultaneously leading to increase in the prevalence of the risk factors for the non-communicable diseases (NCDs) especially CVDs[6]. Based on available evidences, CVDs appears to be one of the principalcause of mortality and disability across the country and early age onset of CVD has been found to be associated with higher case fatality[7]. With epidemiological transition from communicable to non-communicable diseases, India experienced a loss of around 9 million productive life years due to CVDs in the dawn of this millennium with an estimatedloss of 18 million of the same by 2030[8]. Young and middle-aged individuals are likely to account for a sizable proportion among those lost life years[9].

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Higher mortality associated with early age of onset and the magnitude of lost life years warrant for precautionary measures since adolescence. Although, CVDs may be apparent from middle age, the arteriosclerosis process usually startsduring early adolescencewith gradual progression accelerated by exposures like smoking or other tobacco exposure, unhealthy dietary habits, physical inactivity, family history, obesity, hypertension and stress. As most of these self-inflicted risk factors are modifiable, so proper recognition, prevention and modification of the determinants of CVDs may reduce the future risk of CVDsby minimising the burden of risk factors during adolescence , the age when experimentations change into lifetime habits[10].

Apart from the CVDs which are detected mostly duringlate adulthood but enrooted since much earlier age with some modifiable risk factors, some other CVDs are usually detected prettyearly in life. World Heart Federation reported congenital heart disease and acquired heart disease or rheumatic heart disease as the most common CVDs among the young aged[11]. Prevalence of congenital heart disease has increased in an alarming rate globally, from less than 1 per 1,000 live births in 1930 up to 9 per 1,000 live births in the latest years. Thus almost 1.35 million live births among 150 live births worldwide are affected by congenital heart diseases[12]. In Asia the prevalence of Congenital Heart disease is 9.3 out of 1000 live births[13]. In the developing world, prevalence of the same approximately is 8 per 1000 live births. India also experiences a high burden of congenital heart diseases. It is estimated that Around 1,80,000 children are born with congenital heart disease every year in India[14]. On the other hand, about 2.4 million children aged between 5-14 years suffer from RHD globally. In Asia, the number of children suffering from RHD range approximately between 1.96 and 2.21 million. A recent study showed that mainly in urban areas in India prevalence of RHD among children varies from 0.2 -1.1/1000[15].

Dearth of information about the risk factors of CVD samong adolescentsin this part of the world, as well as insufficient data about CHDs and RHDs among the same population called for a study to estimate the burden of cardio vascular morbidity and associated risk factors among adolescent school-children of Kolkata, India.The effort had the potential for developing important insights that could contributeto the planningof interventions to reduce the future risk of CVDs among the adolescents.

Methodology :

Study design :

This cross-sectional study was conducted among the adolescent school children of 9th grade (14-16 years), studying in selected schools Kolkata during January to December, 2014.

Sampling :

Cluster random sampling was employed assuming school as cluster. To determine the sample size, the design effect was calculated to be 13.8, using a Rate of homogeneity (roh, presumed to be equal to the intra-cluster correlations) of 0.2 (according to the standard recommendation)[16-18], and an average cluster size of 75 (average number of students in the 9th grade/school). Using this and assuming a Type-I error of 0.05, assuming a non-response of 10%, 1755 students and their parents (preferably mother) were to be invited to have most conservative number of study subjects to be invited

Selection of schools :

At first, a comprehensive list of 426 schools in Kolkata metropolitan area was prepared. The schools were classified according to socio-economic status, higher/middle/low, as well as the types of student's enrolment i.e. boys only/girls only/ co-educational. Next, 21 schools were selected by using stratified random sampling based on school types and socio-economic status (SES) with probability proportion to size and by selecting at least two schools from each group. These 21 schools were invited with the help from the Department of School Education, Government of West Bengal. In 19 schools agreed to participate. To confirm the maximum attendance of the participants, time date and venue of the data collection were finalized and necessary formalities were completed. Written letters were sent to all students of the selected schools and their parents, preferably mother for the participation in the study.

Study population :

All the 9th grade students, present on the day of interview and accompanied by their guardians (preferably mother), were recruited for the study if agreed by signing written voluntary assent and their guardians if accorded by signing written informed consents. Students suffering from physical or mental illness that prevented them from normal communication were excluded from the study.

Data collection and variable definitions :

A structured, self-administered questionnaire was used for gathering information. The questionnaire was pre-tested for internal validation and consistency[19] in a sample of 160 students of the same grade appointed through random selection of school within the study area. Information related to age, sex, family income was collected. Based on the distribution of reported family income, relative socio-economic (SE) classes (lower/middle/higher) were constructed. Data regarding family history of cardiovascular morbidities among first degree relative of the participants, individual ailments including fatigue and shortness of breath over the last six months were recorded along with frequency of visit to a doctor in last one year. Reported physical ailments were categorised based on its intensity

of occurrence (occurring at rest, with regular activities and with more than regular activities). Participants also asked about any specific history of cardiovascular morbidity, surgery and regular medicine intake. All the students were clinically examined by cardiologists for detection of cardiac murmurs or other abnormal cardiac signs (if any). Individual height and weight were measured and using them, body mass index (BMI) was calculated based on standard formula and categorised as per WHO guideline for BMI for age to normal weight, overweight and obese[20]. Blood pressure (BP) was measured in two separate occasions, half an hour apart with appropriate cuff size by an electronic BP recording machine. Based on average systolic BP (SBP) and diastolic BP (DBP) students were categorised as non-hypertensive, prehypertensive and hypertensive based on age specific percentile cut off of SBP and DBP values.

Statistical analysis :

Data was entered in Microsoft excel software with the help of a predesigned codebook. Logical data cleaning and recoding employed. Variables were described with mean (numerical variable) or proportions (categorical variables) with associated 95% confidence interval (CI). Stratified analysis performed across gender and SE groups. Significant differences between stratum specific values were assessed based on the non-overlapping of CI values of a variable between two different strata.For all statistical analysis SAS 9.3.2 was used.

Result :

Among the participants (n=1651),almost half of the girls (n= 427, 57.86%, 95%CI=54.29-61.43) and two-third of the boys[n=585, 66.10%(62.98-69.23)] were from middle SE status. Lower SE group was relatively less represented among girl students [n= 106, 14.36%(11.83-16.90)] compared to the boys (n=170, 19.21%(16.61-21.81)]. However, proportion of upperSE class appeared significantly more among the girls [n_{girls}=205, 27.78% (24.54-31.02) *versus* n_{boys}=130, 14.69% (12.35-17.03)].

Overall 21% [n=230, 21.12%(18.69-23.55)] reported known cardiac deaths among their first-degree relatives. History of heart attack affecting any first-degree male relative before the age of 55 years [n=135, 11.56%(9.72-13.39)] and female relative before her age of 65 years [n= 111, 9.66%(7.95-11.37)] were also noted.

For the treatment of any ailment, majority[n= 1169, 70.89% (68.70-73.09)] visited a doctor twice or less over the last one year. However, around 7% [n=108, 6.55% (5.35-7.74) reported visiting a doctor once or more in a month. Similar proportion reported about fatigue on rest (n= 101, 6.14% (4.98-7.30)]. Altogether almost 10% of the students had shortness of breath at rest [n=55, 3.34% (2.47-4.21)] or with some routine activities [n= 110, 6.68% (5.47-7.89)]. Almost a quarter of the participants were overweight [n= 389, 23.75% (21.69-25.81)] and had abnormal blood pressure including both prehypertension [n =245, 15.01%(13.28-16.75)]and hypertension [n = 207, 12.68%(11.07-14.30)]. Girls (n=766) had higher systolic [GirlsSBP 107.44(106.64-108.23) *versus* BoysSBP 103.12(102.31-103.93)] and diastolic blood pressure [GirlsDBP 71.09(70.55-71.63) *versus* Boys DBP 68.47(67.91-69.03)] as opposed to boys.

History of cardiovascular ailments [n= 49, 3.05%(2.21-3.89)], cardiovascular surgery [n= 4, 0.25%(0.01-0.49)] and regular intake of some cardiac medication (n= 46, 2.87% (2.05-3.69)] were observed in few students. Total 36 students were detected with cardiac murmurs [2.29% (1.55-3.03)]. Involvement of mitral valve was maximum [n= 14, 0.89%(0.43-1.35)] followed by murmurs originating from pulmonary valve [n= 10, 0.64%(0.24-1.03)].

The distribution of cardiovascular risk factors in the population across gender appeared more or less similar in stratified analysis. Although among the study participants proportion of overweight was more among the boys, whereas proportion with abnormal blood pressure was more among the girls.

Stratified analysis across the SE groups indicated a pattern of declining family risk of cardiovascular ailments from lower to higher socioeconomic status. Death due to cardiac reason among first degree relatives appeared significantly more among the lower [n= 54, 32.93%(25.66-40.20)] and middle [n= 150, 23.73%(20.41-27.06)]SE group compared to the upper SE class (n= 23, 8.49%(5.15-11.83)].

Similarly,proportionof first-degree male and female relative with heart attack before 55th / 65th birthdaywas more in the lower [$n_{male\ relative}$= 29, 16.86%(11.21-22.51) and $n_{female\ relative}$= 29, 17.79%(11.86-23.72)] and middle [$n_{male\ relative}$= 88, 12.79%(10.29-15.29) and $n_{female\ relative}$= 74, 10.96%(8.60-13.33)] SE class compared to the upper SE group [$n_{male\ relative}$ = 15, 5.26%(2.66-7.87) and $n_{female\ relative}$= 8, 2.78%(0.87-4.69)]. Proportion with over nutrition was more among the upper SE group [$n_{overweight}$= 89, 26.57%(21.81-31.32) and n_{obese}= 29, 8.66%(5.63-11.68)] compared to lower SE class [$n_{overweight}$= 41, 14.96%(10.71-19.21) and n_{obese}= 9, 3.28%(1.16-5.41)]. More prehypertensive individuals were found to belong to upper SE class [n= 75, 22.39%(17.90-26.87)]as opposed to those from lower SE class (n= 33, 12.04%(8.17-15.92)].

Discussion :

The study demonstrated the prevalence of modifiable and non-modifiable risk factors of CVDs among the adolescent school children. Early identification of the population at risk and effective intervention at early age might

help in controlling the potential upsurge of CVDsduring late adulthood.

Worldwide, early age obesity emerged as major health problem inviting high risk of CVDs in adulthood. Prior evidence from Lithuaniareported around 12% overweight and 2% obesity among the adolescent 21. Finding from Saudi Arabia reportedeven higherprevalence of overweight and obesity among the both male (20.6%) and female (29.4%) adolescent[22]. Another study held in Delhi among the adolescents school children aged 4-17 years, reported that overall prevalence of obesity was 6%[10]. Alike other studies, the current investigation also revealed considerably high prevalence of overweight and obesity among adolescent school-students of Kolkata. Unlike previous findings[21], in the present study, adolescent girls appeared to have higher average bodyweight, although they did not differ significantly in their nutritional status. Effective intervention in the form of lifestyle modification and motivation for bringing sustainable changes in dietary habits of adolescents might help in curbing the potential future risk down.

Alike obesity hypertension is also emerged as major public health problem of the world[23]. Increasing prevalence of hypertension among the adolescents being observed worldwide[24]. A study conducted in Londrina among the children and adolescents reported 11.8% of the study population with high blood pressure[1]. Around 6% of the male and 4% of the female adolescents were estimated as hypertensive in a study in Saudi Arabia[22]. Estimates from India reported around 9% hypertension among boys and 7% among girls[10]. Present studywas in line with the previous findings and reported even more alarming situation. Unlike before, both the systolic and diastolic pressures were more among the girls[21]. Although proportion of hypertensives did not vary in between different SE classes, but the findings of having significantly more prehypertensive among upper SE class perhaps indicated towards the negative effect of socio-economic affluence on the lifestyle of the adolescents belonging to those families.

According to World Heart Federation Report, if both the parents of an individual had experienced heart disease before the age of 55 then the risk of developing cardiovascular disease would ascend to 50% compared to the rest of the population. Also if a first degree male relative of an individual had suffered a heart attack before the age of 55 or a first degree female relative of an individual was affected by the same then that individual was found to be at a higher risk of being affected by heart disease[25]. A study conducted in Kerala showed 2.9% participants had positive family history of CVD[26]. Another study organized in Delhi exhibited that one-fifth of the study participants had family history of CVD[10]. Compatible with earlier findings, this present study also reported sizable proportion of participants with first degree male and female relatives who had a heart attack at an early age. Findings of having more adverse family cardiac events in lower SE groups could be seen as proxy of evidences showing more CVD events in lower SE class[27]. Prior identification of these students at risk and effective targeted intervention may reduce the burden of CVDs.

Alike any observational study, the findings from the study should be extrapolated beyond the study sample with caution. Being of self-reported nature the information always had the potential for recall and social desirability issues. Residual confounding could be another potential limitation. Despite these shortcomings, it appears that the current research could generate interesting and useful insights in to the cardiovascular risk factors and their distribution among urban adults.

Conclusions :

Non-modifiable risk factors like positive Family history of CVD found in a good magnitude among the participants. Singling out the participants at risk at the early stage and generating awareness among them would be worthwhile. Unhealthy eating practice and physical inactivity might have contributed to childhood overweight and obesity. Lifestyle modification and implementation of the CVD related awareness in practice might be advantageous in delaying the arteriosclerosis process at the early stage among the at-risk population. In addition, school based screening of existing cardiac abnormalities would help in early identification of morbidities among the adolescent and specific intervention for them.

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Review Article

Heart Failure with Preserved Ejection Fraction (HFpEF)

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It has been estimated that Heart Failure with Preserved Ejection Fraction (HFpEF) may account for over 60% of patients hospitalized for HF. Key haemodynamic alterations in HFpEF include subtle systolic dysfunction (depicted by despite reduced average LV global longitudinal strain despite a preserved LVEF), pulmonary hypertension, right ventricular dysfunction, chronotropic incompetence. Diagnosis of HFpEF is established by typical signs and symptoms of HF, LVEF>50%, elevated natriuretic peptides and characteristic echocardiographic features of cardiac structural and functional alteration (eg increased LV mass index, LA volume index, E/E' ratio). Treatment mainly comprises of relief of congestion with diuretics, control of blood pressure and tachycardia. Exercise training has a significant role to play in symptomatic improvement. Disease modifying therapies like RAAS blockers, Mineralocorticoid Receptor Antagonists etc. have proved to be futile in HFpEF. Several emerging therapeutic modalities including device therapy are now being studied.

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It has been projectedthat underlying HFpEFmay account forup to 65% of patients hospitalised for HF. Although diagnostic accuracy is limited in patients with more than one contributors fortheir dyspnoea, the overall prevalence of HFpEF has been estimated as being between 1.1 and 3% of the whole population, with much higher percentage of patients having subclinical diastolic dysfunction[2]. Inpatients over the age of 65 years, the prevalence ranges from 3.1 to 5.5%[3]. The Trivandrum HF Registry (THER) reported a prevalence of 26% for HFpEF in a patient population whose mean age was 61.2 years[4]. In another study from AIIMS comprising of rural population in Northern India, overall prevalence of heart failure was 1.2/1000 and two-thirds had HFpEF and all of them had uncontrolled hypertension[5].

The increase in HFpEF prevalence reflects the changing demographic of the general population, including increasing longevity, obesity and diabetes and the persistent presence of poorly controlled hypertension Table 2)[6]. Each of these factors is known to affect myocardial and vascular stiffness, pulmonary systolic pressure and left ventricular diastolic dysfunction[1]. Communitystudies of healthy volunteers demonstrate that derangements in diastolic function are more common than in systolic function, and progress at a greater rate[7]. Non-cardiac comorbidities such as chronic kidney disease, anaemia, malignancy and thyroid dysfunction quite frequent common in HFpEF; chronic kidney disease in particular may play a dual role in that it contributes to extracardiac volume overload and the development of the cardiorenalsyndrome[8,9]. Obesity is a predictor for HFpEF but not for HFrEF, and the adverse cardiac remodelling and biochemical abnormalities linked with the metabolic syndrome predispose to the development of increased myocardial stiffness and diastolic dysfunction[10,11]. The total influence of comorbidities on myocardial dysfunction and functional capacity is higher in patients with HFpEF than in those with HFrEF[10]. Largescale studies are in progress to target this mechanism[12].

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Preamble to Understanding of Hemodynamic Abnormalities in Heart Failure :

Architectural arrangement of LV myocardial fibres comprises of endo and epicardialfibres and mid-myocardial circumferential fibres. Shortening of longitudinal fibres in systole causes displacement of the LV basal plane towards more stationery apex and contraction of circumferential fibres causes inward deformation of the LV cavity. LV ejection fraction (LVEF) refers to contribution by both longitudinal and circumferential fibres without distinguishing between relative contributions of the two. However, in many cardiac pathologies, longitudinal muscles fibre shortening is impaired prior to any impairment of circumferential muscle fibre shortening and infact, in this initial period, circumferential function can even to a certain extent compensate for the impaired longitudinal function. This accounts for situations where despite a normal or even increased LVEF, subclinical LV dysfunction caused by deranged longitudinal function sets the breakdrop of "Heart Failure with Preserved Ejection Fraction" (HEpEF). Assessment of myocardial deformation in

different planes can now be studied by several echocardiographic methods eg, tissue doppler imaging and more recent two and three dimensional speckle-tracking echocardiography which can provide data on myocardial deformation by measuring strain and strain rate. Strain and strain rate is less load-dependent than LVEF and provides earlier insight into myocardial dysfunction than LVEF. When there is an ultimate impairment of circumferential deformation with disease progression, an impairment of LVEF occurs, inducing the transition from HFpEF to HFrEF (Heart Failure with reduced Ejection Fraction).

Cardiac Factors in HFpEF

Haemodynamics :

Significantly, it has been shown that HFpEF patients – despite the measured LVEF in the normal or near-normal range,– have subtlesystolic dysfunction at rest as demonstrated by reduced LV strain at echocardiographic imaging, andthis dysfunction has prognostic relevance[13,14]. Moreover, it has been suggested thatcontractile dysfunction may contribute to inadequate myocardial response to exertion, leadingto the appearance and exacerbation of HF symptoms[15,16]. Indeed, a recent study in HFpEF subjects examined cardiac systolic reserve during exercise and found that positive contractilityresponse was depressed[17]. Hence, the exercise test may unravel mild deficits in systolicfunction in HFpEF.

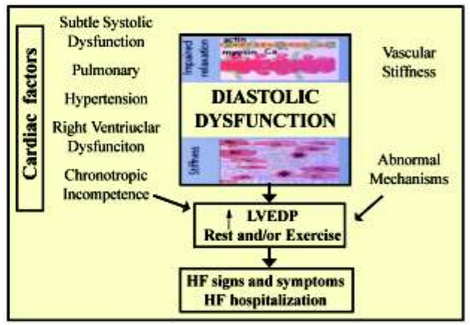
There is a high prevalence of pulmonary hypertension (PH) in HFpEF[18]. A study has shown that pulmonary artery systolic pressure (PASP) rises along with pulmonary artery capillary wedge pressure (PAWP) in patients with both hypertension and HFpEF[19]. However, PASP remains higher in HFpEF, even when adjusting for PAWP, suggesting a pre-capillary component to PH on top of pulmonary venous hypertension.

An invasive haemodynamic study has recently shown that RV dysfunction is common inHFpEF and is contributed by both RV contractile impairment and afterload mismatch from PH[20]. It has also been demonstrated that patients with HFpEF exhibit impaired RV reserve during exercise that is associated with high filling pressures and inadequate cardiac output responses[21]. These findings emphasizes the co-existence of biventricular dysfunction in HFpEF haemodynamics.

Chronotropic incompetence represents another important facet of HFpEF, which hasbeen described in approximately 30 % of patients[22,23,24]. Chronotropic incompetence may help to partially explain why most patients with HFpEF complain of symptoms predominantly during physical exertion. Since the rise in plasma catecholamine with exercise is similar in HFpEF and healthy controls, it has been proposed that chronotropic incompetence may be linked to deficits in beta-adrenergic stimulation[22]. In addition, autonomic dysfunction may be a contributing factor, as heart rate recovery is abnormal and baroreflex sensitivity is attenuated in HFpEF[23].

Cardiac function is determinedby the net balance between afterload and preload[25]. Central aortic stiffness, increasing systolic load andnegatively directedventricular–vascular coupling, may accelerate HF development in at-risk patients. Aortic stiffness increases with age,ventricular systolic stiffening also increases, and this coupled ventricular–vascular stiffeningis a hallmark of HFpEF[26,27]. This restricts LV systolic reserve, augments the cardiac energy demands required to enhance cardiac output, and plays a key role in arterial pressure liability accompanying small changes in LV preload[28].

Schematic Representation of HFpEF Haemodynamics :



HFpEF has remained a diagnostic challenge with variable definitions over the past decade, culminating in the development of a stricter definition in the recently published European Society of Cardiology guidelines (Table 1)[29]. The diagnosis of HFpEF can be somewhatdifficult to make, and often occurs after significant much delay and consideration of alternative diagnoses for dyspnoea. For most patients, recognition of the typical features of HFpEF on resting echocardiography with the clinical syndrome of HF aids the diagnosis, and where the diagnosis remains unclear stresstesting should be considered. An approach to diagnosing HFpEF is given in the Flowchart (Table 2).

Treatment :

The heterogeneity of thepatient population, the wide range of clinical phenotype and short-comings with a clear definition around HFpEF have led to largely negative clinical trials and a paucity of effective treatment options. Despite these limitations, acareful application of the trial outcomes together with a mechanistic understanding have led to basic principles for the treatment of the patient with HFpEF, as listed in Table 3[30].

Table 1 — *Diagnostic Criteria for HFPEF*[28]

- Presence of symptoms and signs typical of heart failure
  - ✓ note that signs are not always evident in patients with HFpEF, as filling pressures may only increase with exercise, the JVP may not be elevated at rest
  - ✓ typical signs and symptoms include breathlessness, reduced exercise tolerance, fatigue and ankle swelling; features such as a displaced apex beat and third heart sound are absent
- A preserved ejection fraction (LVEF ≥ 50%)
  - ✓ previous studies have included patients with LVEF ≥ 40%
  - ✓ new guidelines suggest a grey zone between LVEF 40 and 50%
- Elevated levels of natriuretic peptides#
  - ✓ BNP level ≥35 pg/mL
  - ✓ NT-proBNP level ≥125 pg/mL
- Objective evidence of other cardiac structural or functional alteration
  - ✓ either left ventricular hypertrophy (increased left ventricular mass index) or left atrial enlargement
  - ✓ diastolic dysfunction on echo (increased E/e' or decreased e') or cardiac catheterization (increased LVEFP or PCWP, particularly with exercise)

[Abbreviatrions: BNP=brain natriuretic peptide; HFpEF=heart failure with preserved ejection fraction; JVP=jugular venous pressure; LVEFP=left ventricular end diastolic pressure; LVEF=left ventricular ejection fraction; NT=N-terminal; PCWP= pulmonary capillary wedge pressure]

Adapted from the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart failure[1].

Non-pharmacological Therapy Approaches in HFpEF :

Exercise : In the Ex-DHF pilot trial[31], 64 patients with HFpEF were treated either according to the current recommendations or were exposed to an additional dedicated training programme. After 3 months, patients in the intervention group exhibited an improved peak VO_2 and improved physical fitness. This was associated with an improvement of both diastolic and atrial function. These finding were corroborated by a recent meta-analysis by Pandey*et al*[32].

Diet : In a very small study, 3 weeks of treatment with a salt-restricted DASH diet improved diastolic function, arterial stiffness, and ventricular-arterial coupling in 13 subjects with HFpEF[33]. Further, a 20-week caloric restriction diet was feasible in obese HFpEF patients, and improved symptom burden, peak oxygen consumption, and quality of life. Quantitatively, the improvement in quality of life was greater with diet than exercise. The combination of diet with endurance exercise training appeared supplementary[34].

However, much larger studies are required before making firm clinical recommendations.

Management of Comorbid Conditions :

It has been suggested that the root cause of myocardial, vascular and peripheral dysfunctionin patients with HFpEF may be precipitated by the pro-inflammatory milieu created by the presence of multiple comorbid conditions[10,35,36]. Increasing numbers of comorbidities correlate with higher frequency of hospital admissions, and patients with HFpEF have higher rates of noncardiac comorbidities compared with those with HFrEF[37]. Patients with HFpEF who have diabetes have greater left ventricular wall thickness and reduced physical function compared with those withHFpEF without diabetes[38]. Patients with COPD have a worse prognosis in HFpEF than see with HFrEF[39].

Fluid Retention :

In HFrEF, fluid retention can be treated with diuretics. Mechanistically, patients with HFrEF and HFpEF differ regarding changes in total blood volume (TBV). TBV expansion in HFpEF is mainly characterized by a red cell mass deficit, indicating that true anaemia (ie, haemoglobin concentration <12 mg/d) and a compensatory plasma volume expansion reflects the qualitative changes of TBV in most of the decompensated HFpEF patients[40]. Loop diuretics, thiazide and thiazide-like drugs are necessary to overcome TBV expansion and congestion in both forms of HF[41]. Differences among loop diuretics for the treatment of HFpEF could be of great potential interest, since smaller studies have suggested that torasemide, in contrast to furosemide, may have additional positive effects on collagen metabolism by inhibition of procollagen type I (PIP)[42]. The Hong Kong Diastolic Heart Failure Study[43] showed that the quality of life can be improved by a monotherapy with diuretics, and this effects was amplified when ACEi was added . Thus, diuretics appear indispensable for the improvement of symptom relief. According to the report of a small study, adding the vasopressin antagonist tolvaptan can be effective in severe cases accompanied by hyponatraemia[44]. However, an excessive preload reduction by diuretics can lead to an under-filling of the left ventricle and therefore, to a reduction of stroke volume and cardiac output. This can be a specific a problem in HFpEF patients with pronounced left ventricular hypertrophy and small ventricles.

Atrial Contraction :

Patients withHFpEFtolerateatrial fibrillationpoorly, especially when ventricular heart rate is high. Cessation of the atrial contraction diminishes the left ventricular fill-

Table 2 — *An approach to diagnosis of heart failure with preserved ejection fraction*

Patient presents with exertional dyspnoea

- Take history and perform physical examination
- Measure natriuretic peptides
- Exclude other causes (pulmonary disease, Ischaemic heart diseases, anaemia, physical deconditioning)
- Assess risk factor profile (advanced age, hypertension, raised BMI)

Clinical diagnosis of heart failure made when following diagnostic criteria met:

- Presence of typical symptoms and signs of heart failure (including breathlessness, reduced exercise tolerance, fatigue and ankle swelling) features such as a displaced apex beat and third heart sound may be absent in heart failure
- Elevated natriuretic peptides (BNP > 35 pg/ml or NT-proBNP ≥125pg/mL).
- Other causes excluded (pulmonary disease, Ischaemic heart disease, anaemia. Physical deconditioning)

Perform transthoracic echocardiography (resting)

The following features on resting echocardiography are consistent with a diagnosis of HFpEF (not all need be present) :

- Raised pulmonary pressures (TR jet velocity> 2.8 m/s)
- Left atriai enlargement (left atriai volume index >34 mL/M²)
- Reised E/e' ratio (≥13)*
- Increased wall thickness (LV mass index >115 g/m² for men: >95 g/m² for women)

Consider exercise study in consultation with cardiologist to confirm impaired diastolic performance and elevated filling pressures

- Exercise right heart catheterisation – the gold standard measurement of haemodynamics, but not available in all centres
- Stress echocardiography- noninvasive, but relles on good image quality and the presence of tricuspid regurgitation

*Abbreviations : BMI = body mass index: BNP = brain natriuretic peptide: HFpEF= heart failure with preserved ejection fraction: LV= left ventricle: NT=N-terminal : TR=tricuspid regurgitant: *E/e' measured on tissue Doppler echocardiography.*

ing and along with that, decreases cardiac output[45]. Hence, restoration of sinus rhythm including ablation strategies and pharmacologic interventions including class I, II or III antiarrhythmic drugs may improve clinical symptoms. If this is not possible, ventricular heart rate should be lowered using beta-blockers or heart rate lowering calcium antagonists[46]. Theoretically, late sodium current-inhibitors like ranolazine or eleclazine may exhibit ancillary antiarrythmic effects and may be considered in HFpEF patients with angina symptoms to maintain sinus rhythm.

ACE Inhibitors and Angiotensin Receptor Blockers :

ACE inhibition has become a pharmacological mainstay in the treatment of patients with low ejection fraction HF (ie, HFrEF), significantly reducing morbidity and mortality and also favorablyaltering ventricular remodelling[47,48]. Neurohormonal activation is evident across the spectrum of HF, irrespective of ejection fraction; however, one study of perindoprial in HFpEFhas shown benefits on HF hospitalisation with ACE inhibitor therapy within the first year, but did not achieve its primaryendpoint[49]. Two large trials have examined the role of angiotensin receptor blockade in patients with HFpEF. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), a large trial of more than 4000 patients with HFpEF, with clinical characteristics typical of HFpEF, showed no impact of irbesartan on death, hospitalisation or quality of life[50]. CHARM-Preserved (Candesartan in Heart Failure – Assessment of Mortality and Morbidity; in patients with LVEF higher than 40%) demonstrated a modest impact of candesartan on hospitalization in an HFpEF, although it is important to note the less stringent entry criteria in thistrial, including inclusion of patients with an ejection fraction down to 40%[51].

Aldosterone Blockade :

Aldosterone has a major role in myocardial collagen formation, suggesting arole for spironolactone in the treatment of patients with HFpEF. Early trials demonstrated a reduction in left ventricularfilling pressures, culminating in the international TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial), which enrolled 3445 patients[52]. Although the study was neutral regarding mortality and hospitalisation, post hoc analysisdemonstrated significant regional variation in outcomes between patients enrolled in Russia/Georgia and those from the Americas, with the latter group demonstrating a significant reduction in cardiovascular death and hospitalization for HF[53]. In support of these findings, asmaller randomised study of 131 patients with HFpEF demonstrated improvements in exercise capacity and echocardiographic parameters of diastolic function after taking spironolactone for sixmonths.

These findings support future trials with aldosterone antagonists. However, it is important to remember that impaired renal function and hyperkalaemia were more common in patients taking spironolactone, particularly in the patients who gained most benefit, and that renal function and biochemistry must be carefully monitored for patients on these agents.

Table 3 — *Principles of Management in Patients with HFPEF*

(A) Avoid tachycardia — Use digoxin or beta-blockers in patients with atrial fibrillation

(B) Control Blood Pressure — ACE inhibitors, angiotensin receptor blockers and mineralocoticoid receptor antagonists may be of greatest benefit due to the physiological benefits seen in HFREF; further studies are required

(C) Treat Comorbid conditions — Optimise cardiac and non-cardiac conditions (commonly atrial fibrillation, pulmonary disease, anaemia and obesity)

(D) Relieve congestion with diuretics — Juducious use of loop diuretic with careful monitoring of renal function

(E) Encourage Exercise Training — Improves exercise capacity and physical function

[Abbreviations: ACE=angiotensin converting enzyme; HFpEF= heart failure with preserved ejection fraction]

Heart Rate Modification :

Diastole is shortened during tachycardia, and a reduction in heart rate would be presumed to improve symptoms in patients with HFpEF. Trials of beta blockers have been negative in this regard, probably due to the presence of chronotropic incompetence in certain patients with HFpEF[54,55]. Trials of heart rate modification with ivabradine, an If-channel blocker with effects on heart rate but not blood pressure, have shown early positive results, but not consistently across all studies[56,57].

Other Pharmacotherapy :

Pulmonary hypertension secondary to elevated left ventricular pressures is a key component in the pathophysiology of HFpEF, however trials of sildenafil, soluble guanylate cyclase inhibitors and isosorbidemononitrate have been neutral[58,59,60]. Neprilysin inhibition, recently demonstrated to reduce mortality with startling success in patients with HFrEF, is under investigation in patients with HFpEF. In the ongoing PARAGON trial[61,62].

Device Therapy :

The management of patients with HFrEF has become noteworthy for the beneficial combined effects of pharmacotherapy and device therapy, including implantable cardiac defibrillators and cardiac resynchronization therapy demonstrating remarkable impacts on morbidity and mortality[63]. In patients with HFpEF, the fundamental physiological target is the elevated left atrial pressure. To offset left atrial pressure, an interatrial shunt can be inserted percutaneously, with recent trial results suggesting significant improvements in quality of life and functional capacity[64]. Beyond this approach, large trials targeted to offset chronotropic incompetence and improve dyssynchrony with atrial pacing, with larger trials are yet to be completed[65].

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Review Article

Lipoprotein(a) : always relevant for Indians

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Lipoprotein(a) [Lp(a)] comprises of an LDL-like particle consisting of apoB which is covalently bound by a disulfide bond to apolipoprotein(a) (apo[a]). Role of Lp(a) in promoting cardiovascular disease (CVD) is well-proven. Apo(a) predisposes to atherosclerosis through its three prong actions : proinflammatory, proatherogenc and prothrombotic. The "residual risk" following adequate lowering of LDL with statins is predominantly attributable to elevated Lp(a). This particularly explains the high prevalence of atherosclerotic CVD amongst Asian Indians because as many as 40% of Indian population has elevated Lp(a). Niacin and PCSK9 inhibitors are only agents with any appreciable effect on Lp(a) lowering. The newest emerging therapy in lowering Lp(a) is a group of agents called Antisense Oligonucleotides (ASO). It remains to be seen whether lowering genetically elevated Lp(a) can reduce CVD risk.

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Key words **: Apolipoprotein(a), Antisense Oligonucleotides CADI study, Genetic predisposition.**

Cardiovascular disease(CVD) includes myocardial infarction (MI) or coronary artery disease (CAD), stroke and peripheral vascular disease and is a major cause of mortality in developed as well as developing countries including India. Deaths due to CVD in India was estimated to have doubled in the 30 years from 1985 to 2015[1]. When it comes to the subject of prevention of cardiovascular disease (CVD), most preventive strategies have targeted the established modifiable risk factors like smoking, dyslipidemias, diabetes, hypertension and obesity. Unfortunately, however, people continue to suffer from these diseases. It seems that inspite of therapeutic advances, some risk factors continue to elude us and these may be responsible for the additional CVD risk. Of all the lipid disorders currently held responsible for CVD risk, elevated lipoprotein(a) (Lp[a]) is usually the most commonly overlooked one. Role of Lp(a) in promoting CVD and calcific aortic valve stenosis(CAVS) has been consistently proven and now presents to us a unique opportunity to modify CVD risk by targeting the same with novel therapeutic modalities.

Lipoprotein(a): Structure and Metabolism:

Lp(a) along with very low-density lipoprotein(VLDL), intermediate-density lipoprotein(IDL) and low-density lipoprotein(LDL) all contain apolipoprotein B-100 (apoB) and it is now apparent that apoB containing lipoproteins are maximally responsible for CVD risk. Lp(a) consists of an LDL-like particle consisting of apoB which is bound covalently by a disulfide bond to apolipoprotein(a) (apo[a]), the pathognomonic constituent of Lp(a)[2]. The apo(a) gene is located on the telomeric region of chromosome 6 (6q26-27)[3] and was found to have evolved from the plasminogen gene, a fact which might have pathophysiological implications as mentioned later. The plasminogen molecule consists of 5 kringles (KI to KV) and a protease domain. Only 2 out of these, the KIV and KV are present in apo(a) along with an inactive protease domain. Absence of KI to KIII has led to loss of plasmin activity and KIV has expanded into 10 subtypes(KIV_{1-10}) due to further mutation. A variable number of KIV copies are present (1 copy each of KIV1 and KIV_{3-10} and 1 to >40 copies of KIV_2).

Another unique feature of apo(a) protein is the extensive variation in size, with >40 different isoforms, and thus, >40 different sizes of Lp(a) particles. Other circulating proteins usually have a single defined mass. Size of the isoform is dictated by the number of KIV_2 repeats. Individuals may carry 2 different isoforms with greater contribution to the total Lp(a) level being from the smaller sized isoform. The size of the isoform correlates inversely with plasma Lp(a) levels as the smaller isoform can be produced in larger molar quantities than the larger form in the same amount of time.Apo(a) differs from apoB as it does not contain any lipid domains and instead, is hydrophilic in nature and has a propensity to bind to lysine moieties of the denuded and exposed vascular endothelium. This action is similar to that of plasminogen and hence might lead to a competitive inhibition of fibrinolytic activity in-vivo.

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Apo(a) is synthesized exclusively in the liver but the exact site of assembly of the molecule is not known. During assembly, the apo(a) docks onto an LDL molecule and there is formation of a disulfide bond between the KIV-9 of apo(a) and apoB of LDL. The LDL component was found to have been newly synthesized rather than being derived from a VLDL precursor. The apo(a) component is larger than apoB and is attached near the LDL receptor (LDLR) binding site of the apoB, thereby hindering clearance of the LP(a) molecule through the LDLR. That the LDLR does not play any major role in Lp(a) metabolism is also evident from the fact that statins, which upregulate LDLR, do not lower Lp(a), whereas proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors increase LDLR numbers, yet reduce Lp(a). The mechanisms by which Lp(a) metabolism occurs are still unclear. The kidney, scavenger receptor B1 and plasminogen receptors, and proteolytic cleavage of apo(a) may play a role but conclusive data is lacking[4,5].

Lp(a) as a Mediator of Atherosclerosis :

Apo(a) predisposes to atherosclerosis through three mechanisms:proinflammatory, proatherogenic and prothrombotic (Fig 1).The oxidized phospholipid (OxPL) component of apo(a) is proinflammatory in nature. Patients with elevated Lp(a) levels were found to have increased arterial inflammation detected by raised levels of 18-fluorodeoxyglucose in the carotids and the aorta[6]. In addition there is increased production of proinflammatory cytokines from the macrophages in these vessels, along with enhanced ability to penetrate the endothelial layer[7]. Some trials have even showed that elevated levels of OxPL on apoB-containing particles(OxPL-apoB) are similar or superior to Lp(a) in predicting CVD and CAVS[8]. These proinflammatory effects are diminished when a specific antibody is used to inactivate OxPL, thus firmly establishing its role in the pathogenesis of the proinflammatory state. Release of interleukin-8[9] and monocyte chemoattractant protein-1(MCP-1)[10], two inflammatory mediators, is also stimulated by OxPL. In fact the MCP-1 molecule is present on the Lp(a) and facilitates its entry into the vessel wall. Lysine-binding sites are also present on apo(a) which bind to denuded endothelium. Thus, entry of apo(a) into subintimal spaces via these mechanisms and its accumulation also promotes inflammation.

The enhanced binding to endothelial cells(EC)is also due to upregulation of adhesion molecules like intercellular adhesion molecule-1(ICAM-1)[11], vascular cell adhesion molecule-1(VCAM-1), E-selectin, endothelin-1[12,13], and I-309[14]. Enhanced EC binding along with increased proliferation of smooth muscle cells and formation of foam cells are some of the characteristics of Lp(a) that impart the proatherogenic effect. Lp(a) also inhibits plasminogen activation by competitive inhibition of binding to lysine rich vascular endothelium and thereby decreases fibrinolytic activity, which is the major prothrombotic effect. However, it must be kept in mind that except in individuals with very high Lp(a) levels, plasminogen levels are usually much greater than Lp(a) levels and hence the potential role of competitive inhibition of plasminogen activity is questionable.Other proposed prothrombotic mechanisms include decreased tissue plasminogen activator[15], decreased fibrin degradation, increased platelet responsiveness and increased plasminogen activator inhibitor-1[16] (PAI-1) expression.

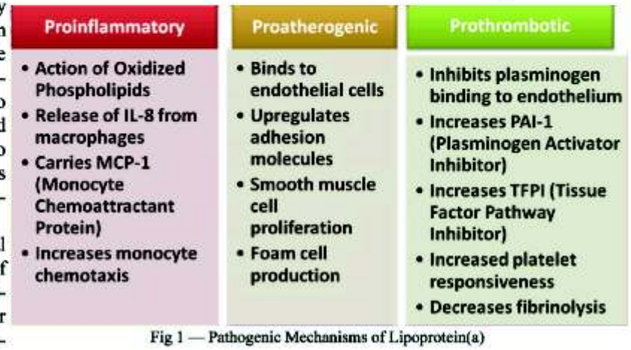


Fig 1 — Pathogenic Mechanisms of Lipoprotein(a)

How is Lp(a) Different from LDL?

Synthesis of Lp(a) requires attachment of an apo(a) particle to the apoB of an LDL particle. The apo(a) component is larger than apoB and is bound near the LDL receptor (LDLR) binding site of apoB. Thereby it interferes with the clearance of the Lp(a) molecule through the LDLR. Lp(a) thus has a longer plasma half-life than LDL. Lp(a) also carries a greater atherogenic risk than LDL, because not only does it contain all the proatherogenic characteristics of LDL, but also those of apo(a)[17]. Circulating Lp(a) levels are predominantly genetically determined (LPA gene), and there is only minor, if any, influence of diet and environmental factors[18]. Almost 90% of circulating Lp(a) levels are quantitatively related to the LPA gene locus and plasma levels are more-or-less constant throughout a person's lifetime. Thus it is proposed that Lp(a) level should be estimated only once and no subsequent testing is needed. This is in contrast to the changes in levels of LDL which must be regularly monitored and therapies modified accordingly.

Earlier it was assumed that controlling LDL-C levels

eliminates the risk due to elevated Lp(a) levels. As a result, on finding elevated Lp(a), clinicians would start treating the LDL-C rather than the Lp(a). Recent trials like the JUPITER trial (Justification for the Use of Statins in Prevention: an Interventional Trial Evaluating Rosuvastatin) have shown that Lp(a) remains a risk factor even in patients in whom an LDL-C level <70 mg/dl has been achieved thereby revealing the flaw in the above-mentioned approach[19]. In the IMPROVE-IT trial (Improved Reductionof Outcomes: Vytorin Efficacy International Trial), a combination of simvastatin and ezetimibe added to CAD patients was able to reduce LDL-C to a mean level of 54mg/dl but the subsequent major adverse cardiovascular event(MACE) rate was still 32.7%[20]. This "residual risk" of CVD in statin treated patients is suggested to be due to elevated Lp(a), which plays a major role independent of the LDL-C action.

When and in Whom to Measure Lp(a) Levels?

Before instituting lipid-lowering therapy, the aim of the clinician is to classify a patient into either a high risk or a low risk group. In the Bruneck study, it was observed that addition of Lp(a) to established risk scores (like Framingham or Reynolds) helped in reclassifying almost 40% of intermediate risk individuals into either high risk or low risk categories[21]. Although the impact of withholding therapy in a low risk patient is not well established, the potential benefit of starting statins is definitely high in patients newly upgraded to the high risk group. In the 2016 European Society of Cardiology(ESC) and European Atherosclerosis Society(EAS) guidelines, Lp(a) estimation is suggested in selected individuals with high risk, or a family history of premature CVD and also for reclassification in those with borderline risk[22]. As Lp(a) levels do not vary over a lifetime, it is rational to add Lp(a) measurement to the lipid panel when a person's lipids are measured for the first time with no need for further testing irrespective of change in diet or therapy.Traditionally Lp(a) levels < 30 mg/dl were suggested as optimal and associated with negligible CVD risk, but current EAS recommendations delineate Lp(a) levels <50 mg/dl as optimal.

Existing and Emerging Therapies for Lp(a) Reduction :

Earlier statins were thought to exert no effect on Lp(a), the metabolism of which is independent of LDLR. Now, however, there is data to suggest that statins raise Lp(a) levels by 10-20% although the mechanisms by which it does so is unclear. In a recent study, comparison in patients pre- and post-statin therapy showed an increase in Lp(a) levels by 11% and in OxPL-apoB levels by 24% in the post-statin group[23]. Thus, failure of statin therapy might suggest that the patient has most of his harmful cholesterol in the form of Lp(a) rather than LDL-C.

Unfortunately there are no approved medications which are specifically targeted at lowering Lp(a) levels and there has been a remarkable lack of randomized trials of Lp(a) lowering till now. Niacin and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors like aliorocumab and evolocumab are the only agents with any recognized efficacy in lowering Lp(a), with estrogen also being used in a limited population. Niacin reduced Lp(a) levels by around 39%in patients with high baseline levels (>50 mg/dl) in the AIM-HIGH study[24] but no reduction in event rate was seen. In the same trial, cholesterol ester transfer protein (CETP) inhibitors like anacetrapib, evacetrapib showed a 20-30% reduction in Lp(a) levels but again without any clinical benefit. The inference that was drawn from these findings was that potential benefit of Lp(a) lowering will not become evident unless >50% reductions in mean levels is achieved.Another existing option is the use of apheresis for reducing Lp(a) and clinical benefit has been observed in some cases[25]. Lp(a) levels >60 mg/dl are used as cutoff for reimbursement of lipoprotein apheresis in Germany and the United Kingdom.

The newest emerging therapy in lowering Lp(a) is a group of agents known as Antisense Oligonucleotides (ASO) (Fig 2). Mipomersen is a prototype ASO targeting apoB mRNA that was shown to lower Lp(a) and OxPL-apoB in trials on transgenic mice[26] and these findings were subsequently confirmed in several randomized trials[27]. ASOs are injected subcutaneously and accumulate in the liver where they bind to the target mRNA to form a double-stranded unit. Ribonuclease H1 cleaves the sense strand to prevent protein synthesis but releases the antisense strand in an intact form which can then attach to additional mRNAs. Mipomersen only inhibited apoB production and thereby Lp(a) synthesis whereas apo(a) continued to be secreted as free molecules into the circulation. Similarly, trials involving ASOs specific to apo(a) have also been initiated and have seen promising results with reduction in apo(a) production by almost 80%[28].

Clinical Evidence Supporting Lp(a) as a Major Promoter of Cvd And Cavs in the Community — The International Scenario:

Throughout the world, over the last decade, epidemiological studies carried out in individuals without any prior CVD have comprehensively proved that elevated Lp(a) levels are associated with a greater risk of myocardial infarction, stroke and peripheral arterial disease[29-31]. In the Cardiogram Plus 4CD Consortium, studies carried out in coronary artery disease(CAD) patients identified several genetic

loci associated with increased susceptibility for CAD. Among these, the LPA locus was determined to have the strongest association, thus proving the role of LPA gene as one of the strongest monogenetic risk factors for CAD[32]. This, in turn, has paved the way for introducing specific therapies targeting Lp(a) for lowering CVD risk[33].

Similar evidence is also available in support of Lp(a) being the only monogenetic risk factor for aortic valve calcification and CAVS[34]. The ASTRONOMER Trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) studied patients with pre-existing mild-to-moderate aortic stenosis and showed that the individuals with elevated Lp(a) and OxPL-apoB had a faster progression rate and an earlier need for aortic valve replacement[35]. Further, younger patients were found to progress more rapidly and had the highest need for valve replacement, a fact that can be explained if we consider the genetically mediated Lp(a) to be the major determinant. Recently, an enzyme called autotaxin was also found to play an important role in CAVS[36]. Autotaxin helps in breakdown of lysophosphatidylcholine to lysophospatidic acid, an inflammatory mediator, and elevated autotaxin activity was found to be associated with raised levels of Lp(a) and OxPL-apoB. Thus, in summary, we can hypothesize that Lp(a) transfers autotaxin as well as OxPL into the substance of aortic valve leaflets and promotes inflammation and calcification[37].

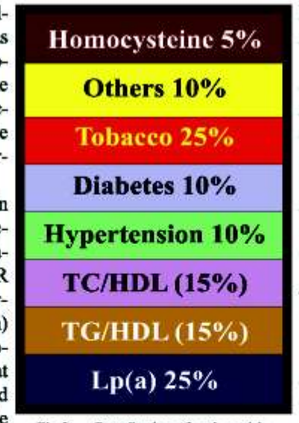


Fig 3 — Contribution of various risk factors for CAD amongst Indian

(1) Antisense oligonucleotide binds to the mRNA.
(2) This double, stranded region can inhibit the production of protein by two mechanisms
- Stopping the ribosome from reading the message
- Leading to the destruction of the mRNA by an enzyme already in the cells called RNAse H.

Fig 2 — Mechanism of Action of Antisense Oligonucleolide

Current Status of Lp(a) In India :

According to recent studies more than 60% of CAD in Indians is unexplainable by the conventional risk factors[38]. Failure of established preventive strategies in reducing the risk of CVD in the Indian population ushered in renewed efforts to identify newer modifiable risk factors including Lipoprotein(a) and homocysteine etc[39]. The role of Lp(a) in pathogenesis and progression of atherosclerosis and coronary artery disease(CAD) specifically in the Indian population has been established by several recent studies[40,41]. Presence of related risk factors also enhance the association between Lp(a) and CVD[42,43]. A study in North Indian CAD patients found elevated levels of Lp(a) and raised Lp(a)/HDL-C ratio to be valuable predictive markers[44].

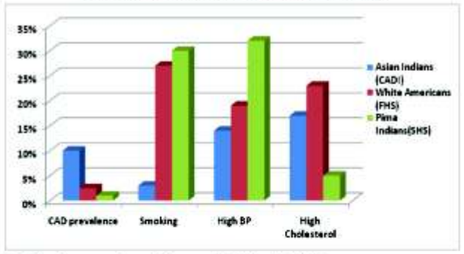
The high rate of CAD in Asian Indians is due to a combination of nature (genetic predisposition) and nurture (life style factors). The "nature" component is predominantly contributed by elevated level of Lp(a) which has a prevalence of more than 40% amongst the Indian population and accounts for 25% of all deaths due to CAD (Fig.3).

Special Relevance of Lp(a) in Indians All Over the World :

In the Coronary Artery Disease in Asian Indian(CADI) study, the prevalence of CAD in Indians residing in the United States of America(USA) was found to be four-fold higher compared to Caucasian population and six-fold higher than the Chinese Americans of the same age group[46]. This was in spite of the fact that almost half of the Indian population in the study had vegetarian dietary habits, a factor that is considered to be protective against CAD.This phenomenon of high CAD rates appears to hold truefor all inhabitants of the Indian subcontinent and immigrants from these countries to various regions of the world. Studies in countries other than USA also found a higher CAD incidence in Indian immigrants compared to those of other ethnic origins. It appears now ,that Indians as a race, have a higher predisposition to CAD and this is characterized by three important features: extreme prematurity, marked severity and relatively low prevalence of conventional risk factors.

Indians are prone to develop CAD five to ten years earlier than other populations and risk of occurrence of first MI before the age of 40 years is five-to-ten times higher as well. The severity of disease is also greater in Indians as detected by coronary angiography. Extensive multi-vessel disease is seen in a majority of individuals and sometimes even in non-smoking premenopausal women. Surprisingly, the high rates of CAD in Indians was accompanied by a low rate of conventional risk factors (Fig 3). Among the population studied in the CADI study, only 3% were smokers, 3% were obese, and 14% had high blood pressure. The corresponding percentages in White Americans were 27%, 31% and 19%[47]. Studies on Pima Indians in the US also showed similarly low CAD risk despite high prevalence of conventional risk factors[48]. With the help of further research, this disproportionately high incidence and severity has now been attributed to a genetic predisposition due to elevated Lp(a) levels[49].The CADI study found significantly raised Lp(a) levels (>30 mg/dl) in 25% of Indians settled in the US compared to 17% of Whites and

Table 1 — *Prevalence of CAD and its risk factors in Indian immigrants in comparison with other populations in the US*



CADI : Coronary Artery Disease in Indians Study[46]
FHS : Framingham Heart Study[47]
SHS : Strong Heart Study[48]

8% of Hispanics. A strong correlation between Lp(a) levels and severity of CAD in Indians was alsoreported by Shaukat *et al*[50]. Furthermore, as adult levels of Lp(a) are reached early in life, its effects start earlier than other risk factors and this may explain its role in premature-onset CAD in Indians.

In addition to being an independent risk factor, Lp(a) has its effects multiplied by elevated levels of other lipoproteins. The pathological effects of Lp(a) become much more pronounced in Indians due to co-existence of the well-known lipid triad (high triglycerides, high LDL, and low HDL). This unique pattern of dyslipidemia or lipid tetrad (elevated Lp(a) in combination with the lipid triad) is a common finding in Indians and is rarely encountered in other populations. In contrast, in the African Americans, the harmful effects of high Lp(a) is partially neutralized by low LDL, triglyceride and high HDL[51].

Conclusions :

It is clear that the excess burden of CVD in Indians cannot be explained by the conventional risk factors.Hence, it is unlikely that conventional approaches to prevention and treatment will be sufficient for the Indian population. About one in four Indians has elevated Lp(a) levels and Lp(a) is now considered to be responsible in a major part for the genetic predisposition of Indians to CAD. As already mentioned, Lp(a) is fully expressed in the first few years of life. Thus, identification of risk and prevention of CAD in Indians can begin at an early age. Several potent and efficacious therapies targeting Lp(a) are currently in development and once they are introduced, further data will become available to test the hypothesis that reduction of genetically elevated Lp(a) can reduce CVD risk. In conclusion, it can be said thatLp(a) as a risk factor for CVD will always be relevant throughout the world and more so in the Indian population.

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Case Report

Rare case of familial restrictive cardiomyopathy : a case report

Abhishek Roy[1], Debabrata Roy[2], S Kumar[3]

Familial restrictive cardiomyopathy is an extremely rare disease affecting the heart. The exact incidence and genetic associations are not well delineated. It generally presents with a restrictive filling pattern on echocardiography with normal or near normal systolic function. We present the case of a 29 year old male who had features of biventricular failure. Echocardiography, cardiac MRI and catheterisation data confirmed the diagnosis of restrictive cardiomyopathy. Other investigations ruled out secondary causes of a restrictive physiology and the strong family history clinched the diagnosis in favour of a familial restrictive cardiomyopathy. Familial restrictive cardiomyopathy heralds a grave prognosis. A heart transplant appears to be the only modality of therapy which offers long term sustained resolution of symptoms. Our patient is currently waiting for the availability of a suitable donor for a heart transplant.

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Key words **: Cardiomyopathy, restrictive, familial, RCM.**

As per the definition of the AmericanHeart Association (AHA), "Primary restrictive non-hypertrophied cardiomyopathy is a rare form of heart muscledisease and a cause of heartfailure that is characterized by normal or decreased volume of bothventricles associated with biatrial enlargement, normal LV wall thickness and AV valves, impaired ventricular fillingwith restrictive physiology, and normal (or near normal) systolic function"[1]. However in a series of 94 patients, Ammash *et al* reported systolic dysfunction in 16%[2]. Data about the exact burden of restrictive cardiomyopathy (RCM) is largely unavailable.However, an epidemiologic survey carried out in Japanese hospitalsnationwide, estimated a prevalence of 0.2 per 100,000 inhabitants[3].

RCM can be classified as primary/idiopathic or acquired[4]. What is common to primary/idiopathic or acquired RCM though,is the restrictive ventricular physiology. However, the causes of this disorder are widely heterogeneous.Distinguishing primary/idiopathic RCM from other diseasesmanifesting secondarily as restrictive ventricular physiology is especially important as it influences subsequent therapy and long-term prognosis. We describe here a rare case of familial idiopathic RCM presenting with biventricular systolic dysfunction.

Case Report

A 29 year old non-diabetic, non-hypertensive male presented with complaints of insidious onset, steadily progressive exertional dyspnoea for the past four months which had worsened over the past six days. He had a history of palpitations at a young age for which he was put on metoprolol 50 mg. His father had a sudden cardiac death at the age of 25-26 years of age and his younger sister had recently succumbed to a massive ischaemic stroke at the age of 25 years (Fig 3A).

Physical examination revealed bilateral pitting pedal oedema, raised jugular venous pressure with a positive Kussmaul's sign, a heart rate of 100/minute, blood pressure of 92/60 mm of Hg and respiratory rate of 28/minute. His cardiac apex was in the left 5th intercostal space on the left mid-clavicular line, a left ventricular S3 was heard and there were fine crepitations at both the lung bases. Hepatomegaly with mild ascites was also noted.

Routine blood panels were unremarkable except for raised liver enzymes and a deranged INR. Chest skiagram was reflective of pulmonary congestion (Fig 1A). There was evidence of marked biatrial enlargement on the electrocardiogram (Fig 1B) and echocardiography corroborated the same (Fig 2B). A restrictive ventricular inflow pattern (Fig 2C) along with generalised wall hypokinesia and a compromised left ventricular systolic function was detected. Average Global longitudinal strain was -4.5 % and right ventricular systolic function was also reduced (Fig 2A).

A diagnosis of RCMwith biventricular failure was made. Cardiac catheterisation confirmed the diagnosis with characteristic square root sign and elevated right atrial and right ventricular pressures. A search for potential causes of his conditiondid not turn up any evidence in favour of secondary causes of restrictive physiology such as amyloidosis, haemochromatosis, sarcoidosis or eosinophilic myocarditis. Cardiac MRI suggested the possibility of cardiac amyloidosis owing to relative apical sparing on late gadolinium enhancement (Fig 2D). However, in view of no other supportive evidence for amyloidosis, a diagnosis of idiopathic RCM was considered significantly more likely. Further elaboration of the strong family history also yieldedan echocardiographic image of his recently deceased younger sister, which showed prominent biatrial enlargement (Fig 3B). Based on all the clinical, biochemical and imaging evidence, a final diagnosis of familial idiopathic RCM was made.

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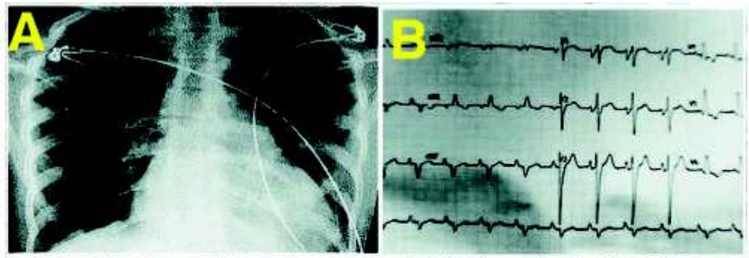

Fig 1 — Chest skiagram and electrocardiogram of patient. (A) Chest skiagram showed evidence of pulmonary congestion. (B) Electrocardiogram revealed marked biatrial hypertrophy and repolarisation abnormalities

He was treated with standard heart failure therapy upon which his condition showed some improvement. Currently he has been put on the heart transplant registry and is awaiting a suitable donor.

Discussion

Initial discovery of a familial form of RCM was in 1998[5]. Genetic counselling, family history, and evaluation of clinical reportsof family members are part of the clinical genetic workup for patientsdiagnosed with RCM[6]. Familial RCM demonstrates autosomaldominantinheritance in the majority of cases. However, even an extensive search of the medical literature did not turn up any reference of familial restrictive cardiomyopathy in the Indian sub-continent. To the best of our knowledge, our patient represents the first reported case of familial restrictive cardiomyopathy from India.

The family history of our patient was significant for sudden cardiac death of his father at a young age of 25-26 years, presumably due to a fatal arrhythmia. His sister's ischemic stroke was likely cardioembolic in origin. Biatrial enlargement seen in her echocardiographic image suggests that she might have been suffering from the same restrictive physiology that her brother currently suffers from. However, the unavailability of information about a full diagnostic and imaging work up prevents us from confirming that assumption about his sister with absolute certainty. Fortunately, the young children of our patient and his deceased sister are yet to be substantially affected by the disease process as their current echocardiographic and doppler studies are essentially normal. They will be closely followed up through successive years.

The TNNI3 gene that encodes the thin filament troponin I is the most commondisease gene responsible for RCM[7]. Mutations in thetroponin T2 gene (TNNT2) are less common in RCM and may alsocause HCM and DCM[8]. Other sarcomeric genes involved in RCMinclude ACTC1, MYL3, MYH7, TTN, TPM1, MYL3, and MYL2[9-13]. Recent reports have described mutations in Z-disc protein-encodinggenes, including

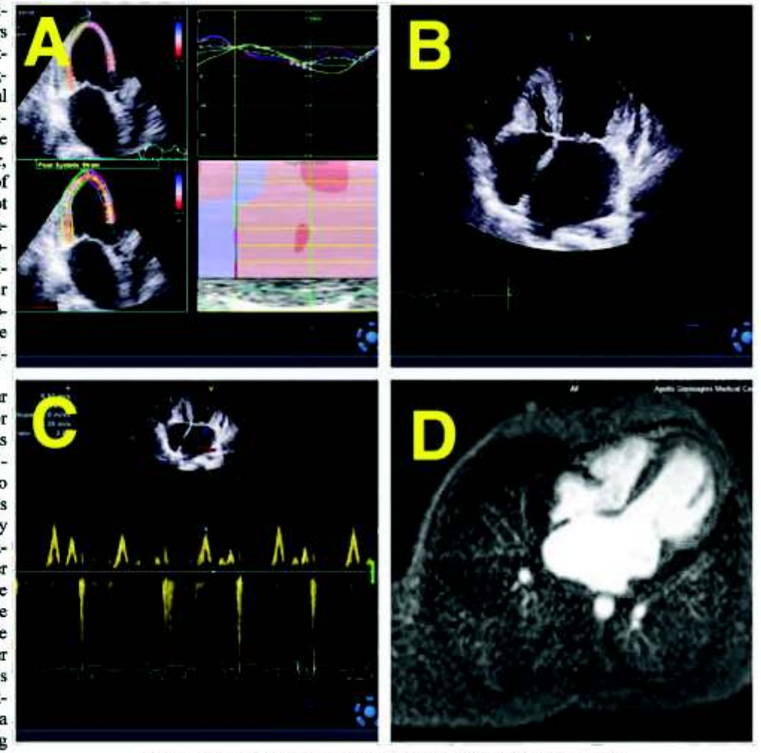

Fig 2 — Systolic dysfunction with average global longitudinal strain = -4.5%.
(B) Massive biatrial enlargement. (C) Restrictive ventricular physiology with E/e' = 2.0. (D) Cardiac MRI showed a lack of late gadolinium enhancement in the apical region, thus favouring cardiac amyloidosis over familial RCM.

MYPN, FLNC, and BAG3, in patients with RCM[14-17]. Pending genetic testing data for our patient and his family, accurate characterisation of the culprit genes responsible for his RCM will not be possible. Also, information from an endomyocardial biopsy will be sought during subsequent follow-up of our patient. The absence of such data is acknowledged as a limitation of this report.

Interestingly, our patient did not have any evidence of skeletal myopathy at presentation. Certain series have found a progressive non-wasting skeletal myopathy in individuals who survived into the 5th decade.18Whether the same holds true for our patient remains to be seen in the due course of time. In the interim period, he is being prepared for a heart transplantation, which is by far the most definitive long-term treatment for this condition.

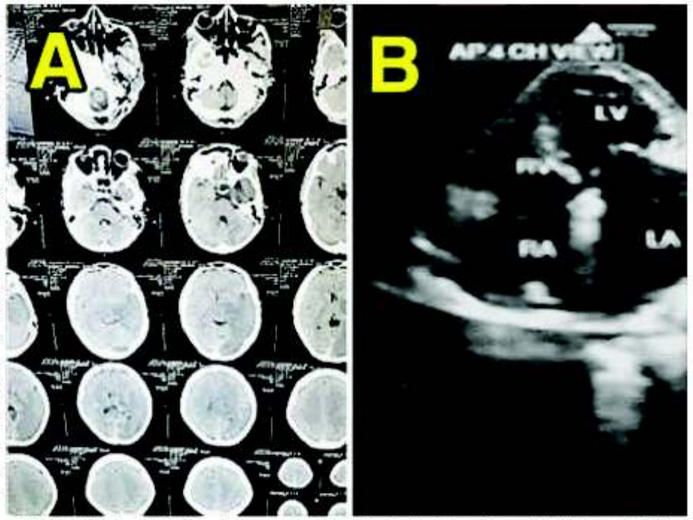

Fig 3 — Sister's available imaging reports. (A) CT brain showing left parieto-occipital infarct. (B) Still echocardiographic image showing biatrial enlargement

Conclusion

Familial idiopathic RCM is an exceedingly rare clinical entity. Given the grave prognosis that it portends, cardiac transplantation often turns out to be the only long-term therapeutic option[2]. The challenge lies in identifying such patients early, optimising their treatment protocols and proactively screening the entire family for evidence of latent cardiac compromise.

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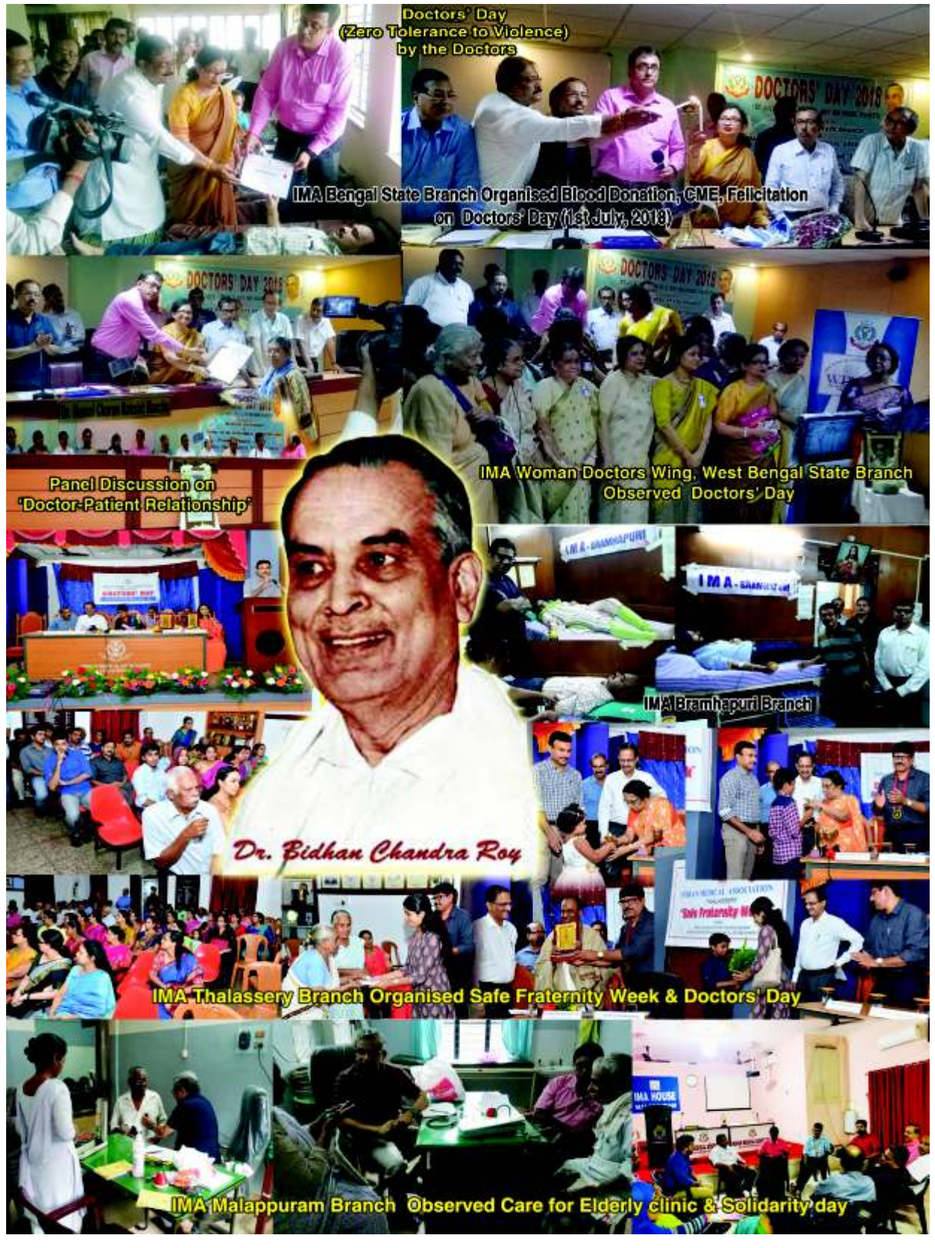
Activities Report



Activities Report

IMA Assansol Branch Observed 76th Foundation Day Conference & World Health Day on 7th April, 2018 at Assansol IMA House

IMA Bramhapuri branch organised a CME Topic : "Facial nerve palsy....- an overview".

IMA Pattambi Branch organised full day CME, Release of IMA logo & Doctor's Emblem

IMA Vatakara Branch Organised World Environment Day, Elder Abuse Awareness Class & Condolence Meeting

IMA Tellicherry Branch Organised World Environment Day, Health Awareness Class, CME, Medical Camp, International Day Against Drug Abuse and Illicit Trafficking conducting an awareness class

IMA Trivandrum Branch Organised Medical Camp, International Seminar on Medical Ethics Redefined 2018 & WIMA (SOUTH ZONE CONFERENCE 2018) at YWCA Hall, Trivandrum

IMA Desinganad Branch conducted multispecialty medical camp and Cancer Screening awareness program on World Women's Day

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