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Original articles should not normally exceed 2000 words and should not have more than six tables or illustrations; they should normally report original research. Case reports should preferably by limited to 600 words, with one table or illustration, and not more than five references. Clinical case histories and brief or negative research findings may be included among them. Letters should not exceed 400 words, and must be signed by each author.

Articles on the organization, operation and planning of medical care should be limited to 1500 words, with not more than four tables or figures.

Each manuscript component should begin on a new page, in this sequence; Title page; abstract and key words; text; acknowledgements; references; tables (each table complete with title and footnotes on a separate page); legends for illustrations. Pages should be numbered.

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The title page should have (1) the title of the article, which should be concise but informative; (2) initial(s) and surname of each author below; (3) at the foot of the page, the initials and name(s) again, with the highest academic degrees (not more than two degrees and or diplomas) of each author, and the designation and department of each, ranged alongside.

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Appropriate scientific nomenclature giving both genus and species should be italicised (underlined in typescript), with an initial capital and abbreviation for the genus only, after a full spelling at the first mention, thus: *Mycobacterium Tuberculosis*, the *Myco, tuberculosis*, Drugs should be given their approved names, not their proprietary names.
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As far as practicable, marking of lines and letters should be avoided; if absolutely necessary, separate sets of marked and unmarked prints should be drawn with black India ink on the white background. Original artwork, X-ray films, ECG tracing, etc. should be photographed and enlarged on glossypaper, identity of patients should be masked. The magnification of photomicrographs should be stated (e.g. x 200). All illustrations should accompany the manuscript with suitable legends, numbered and marked on the back with the author's name and article title.
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The author must obtain permission for reproduction of illustrations previously published.

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Editorial

In Search of an Ideal Thrombolytic Agent

In 1933, Dr. William Tillett discovered streptokinase (SK) through sheer chance when he observed that streptococci agglutinated plasma not serum. In 1958, Fletcher first reported the use of thrombolytic therapy for management of AMI. The GISSI and ISIS trials firmly established the efficacy of intravenous SK in management of patients with AMI. Subsequent search for ideal thrombolytic agent led to emergence of second and third generation thrombolytics, namely alteplase (t-PA), reteplase (rPA) and tenecteplase (TNK) amongst others. Table below shows a comparison of common fibrinolytic agents:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Streptokinase (SK)</th>
<th>Ateplase (tPA)</th>
<th>Reteplase (rPA)</th>
<th>TNK t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1.5 MU in 30-60 min.</td>
<td>Upto 100 mg in 90 min.</td>
<td>10 Ux2 (30 min.) apart each over 2 minutes</td>
<td>30-50 mg (based on weight)</td>
</tr>
<tr>
<td>Bolus administration</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antigenic (Allergic reactions)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Systemic fibrinogen depletion</td>
<td>Marked</td>
<td>Mild</td>
<td>Moderate</td>
<td>Minimal</td>
</tr>
<tr>
<td>90 min. patency rate (%)</td>
<td>≦ 50</td>
<td>≦ 75</td>
<td>≦ 75</td>
<td>≦ 75</td>
</tr>
<tr>
<td>TIMI grade 3 flow (%)</td>
<td>32</td>
<td>54</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>Cost per dose (US $)</td>
<td>568</td>
<td>2,750</td>
<td>2,750</td>
<td>2,750 for 50 mg</td>
</tr>
</tbody>
</table>

An article in this issue of the journal by J. Nawaz et al compares use of thrombolytics in Ramakrishna Mission Seva Pratishthan. In this study of 245 patients with ST-elevation myocardial infarction, success rate of Rateplase has been reported as highest at 91.66% and success rates of Tenecteplase have been reported as comparable to that of streptokinase (80.76%...
vs, 72.75%). However, profile of patients in each group in terms of age, sex, time of presentation after onset of chest pain, co-morbid conditions etc. have not been described. Assessment of success without multivariate analysis of these factors is not acceptable on scientific ground. Same logic applies to assessment of bleeding complications.

However, major international trials with TNK-tPA and rPA do not report major differences in terms of success (vide table) and complications although direct comparisons have not been made. The ideal thrombolytic agent still continue to elude us. Future research might see development of optimal thrombolytic strategy with ability of maximal reperfusion and with minimal bleeding and re-occlusion complications. Awaiting such breakthrough, at present time patients presenting within 4 hours of symptom onset to non-pCI centres (where delay to invasive strategy is expected), speed of reperfusion of infarct vessel is of paramount importance and bolus fibrinolytic agent (ie. TNK-tPA or rPA) is to be preferred.

For those presenting between 4 hours and 12 hours after onset of chest discomfort, speed of reperfusion of the infarct vessel is of lesser importance and SK and accelerated t-PA are equivalent options given the difference in costs; Infact in patients with low mortality risk but an increased risk of intracerebral haemorrhage (ICH) SK is probably preferable to t-PA.

References:


Dr. Soumitra Kumar, MD, DM, Prof. & Head, Dept. of Cardiology, RKMSP, VIMS
A Study on Patient with ST Elevation Myocardial Infarction and Use of Thrombolytics in Ramakrishna Mission Seva Pratishthan

Dr. J. Nawaz¹, Dr. J. Chakraborty², Dr. P. Mukherjee³

Abstract:
Introduction:
STEMI is a medical emergency caused by acute occlusion of coronary arteries. Mortality is directly related to total ischemia time. Treatment include rapid recognition, diagnosis and prompt reperfusion therapy by different thrombolytic agents (Streptokinase, Tenecteplase / Reteplase). Cost effectiveness is to be concerned.

Aims:
To note the prevalence of STEMI among the patients admitted with chest pain in ICU of RKMS and effects of of different thrombolytic drugs.

Methods:
The study group in this Retrospective observational study included patients admitted with chest pain in our ICU during the period June 2013 to June 2015 out of which data of STEMI patients who were thrombolysed were retrieved from medical record section and collected data was analysed.

Results:
245 patients admitted with chest pain in ICU of RKMS during the period of June 2013 to June 2015 out of which 76.73% (188/245) patients had ACS. Among 188 ACS patients 43.61% (82/188) patients had STEMI. Out of 82 STEMI patients 67 patients were eligible for thrombolysis and thrombolysed with different thrombolytic agents as per affordability of the patient party not of the discretion of the physician. Out of 67 thrombolysed patients 91.04% (61/67) were male, 8.95% (6/67) were female, 47.76% (32/67) patients came during night time (8pm-8am), 25.37% (17/67) patients came during morning time (8am-2pm), 26.86% (18/67) patients came during evening time (2pm-8pm), 29 patients had been thrombolysed with tenecteplase out of which successful thrombolysis was 82.75% (24/29) failure was 17.25% (5/29), cerebral bleeding was 6.89% (2/29), noncerebral bleeding was 3.44% (1/29), 12 patients had been thrombolysed with reteplase out of which successful thrombolysis was 91.66% (11/12), failure was 8.33% (1/12), cerebral bleeding was 0% (0/12), noncerebral bleeding was 8.33% (1/12), 26 patients had been thrombolysed with streptokinase out of which successful thrombolysis was 80.76% (21/26), failure was 19.23% (5/26), cerebral bleeding was 0% (0/26), noncerebral bleeding was 3.84% (1/26).

Conclusion:
Prevalence of STEMI patients was 43.61% among ACS patients. Success rate of thrombolysis is highest with Reteplase (91.66%). Success rate of with Streptokinase was comparable with Tenecteplase (80.76% Vs 82.75%) with much less bleeding complication.

Key words: STEMI, Thrombolysis, Reperfusion

Introduction:
ST elevation myocardial infarction (STEMI) is

¹MD (Med), PGT, Dept. of Medicine; ²MD, Prof. & HOD, Dept. of Medicine; ³DNB, Asst. Prof., Dept. of Medicine
an medical emergency caused by acute total occlusion of an epicardial coronary artery.
Mortality is directly related to total ischemia time. So keys to treatment of STEMI include rapid recognition and diagnosis, coordinated mobilization of health care resources and prompt repurfusion therapy. Repurfusion can be done by different thrombolytic agents like lower cost Streptokinase, much higher cost Tenecteplase/ Reteplasr. For a resource limited set up it is necessary to know the distribution of time of admission of STEMI patients and cost effective thrombolytic agent.

Aims:
This study was done to note the prevalence of ST elevation MI (STEMI) among the patients admitted with chest pain and distribution of time of admission of STEMI patients in our ICU in last two years. We want to study the use of different thrombolytic drugs, their success rate, failure rate and complication rate.

Methods:
In this Retrospective observational study, patients admitted with chest pain in our ICU during the period of June 2013 to June 2015 written in admission register book were taken as study group, out of which data of STEMI patients who were thrombolysed with different thrombolytic agents were retrieved from medical record section and collected data was analysed.

ECG Criteria for STEMI:
New ST elevation at J-point > 0.1mV in two contiguous leads other than leads V2-V3, where the cut points are
- = 0.2mV for men above 40 years
- = 0.25mV for men below 40 years
- = 0.15mV for women

Thrombolysis was done with those STEMI patients who came within 12 hrs of ischemic symptoms by different thrombolytic agents as per affordability of the patient party not of the discretion of the treating physicians.

ECG criteria for successful thrombolysis:
Resolution of ST segment elevation > 70% within 90 min after thrombolysis was considered as successful thrombolysis in this study.

Results:
Total no of patients admitted with chest pain in our ICU during the period of June 2013 to June 2015 were 245, out of which 76.73% (188/245) patients had acute coronary syndrome (ACS). Among 188 ACS patients 23.40% (44/188) patients had unstable angina (UA), 32.97% (62/188) patients had non ST elevation MI (NSTEMI) and 43.61% (82/188) patients had ST elevation MI (STEMI). Out of 82 STEMI patients 67 patients were eligible for thrombolysis. They were thrombolysed with different thrombolytic agents as per affordability of the patient party not of the discretion of the physician. Out of 67 thrombolysed patients 91.04% (61/67) were male, 8.95% (6/67) were female, 47.76% (32/67) patients came during night shift (8pm-8am), 25.37% (17/67) patients came during morning shift (8am-2pm), 26.86% (18/67) patients came during evening shift (2pm-8pm), 29 patients had been thrombolysed with tenecteplase out of which successful thrombolysis was 82.75% (24/29) failure was 17.25% (5/29), cerebral bleeding was 6.89% (2/29), noncerebral bleeding was 3.44% (1/29), 12 patients had been thrombolysed with reteplase out of which successful thrombolysis was 91.66% (11/12), failure was 8.33% (1/12), cerebral bleeding was 0% (0/12), noncerebral
bleeding was 8.33% (1/12), 26 patients had been thrombolysed with streptokinase out of which successful thrombolysis was 80.76% (21/26), failure was 19.23% (5/26), cerebral bleeding was 0% (0/26), noncerebral bleeding was 3.84% (1/26).

<table>
<thead>
<tr>
<th>Types of chest pain</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiac chest pain</td>
<td>57</td>
<td>23.27</td>
</tr>
<tr>
<td>Cardiac chest pain (ACS)</td>
<td>188</td>
<td>76.73</td>
</tr>
<tr>
<td>Total chest pain</td>
<td>245</td>
<td>100</td>
</tr>
</tbody>
</table>

Table : 1 Distribution of patients according to types of chest pain  

<table>
<thead>
<tr>
<th>Types of ACS</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA</td>
<td>44</td>
<td>23.4</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>62</td>
<td>32.97</td>
</tr>
<tr>
<td>STEMI</td>
<td>82</td>
<td>43.61</td>
</tr>
<tr>
<td>Total ACS</td>
<td>188</td>
<td>100</td>
</tr>
</tbody>
</table>

Table : 2 Distribution of patients according to types of Acute Coronary Syndrome (ACS)

Admission time of thrombolysed STEMI patient

Figure : 1 Distribution of time of admission of thrombolysed STEMI patients
Figure : 2 Distribution of thrombolysed STEMI patients according to sex

Figure : 3 Comparison of different thrombolytic agents in respect to success rate, failure rate, cerebral hemorrhage, non-cerebral hemorrhage
Discussion:

Prevalence of STEMI patients was 43.61% among ACS patients. Success rate of thrombolysis is highest with Reteplase and it was 91.66%. Success rate of thrombolysis with Streptokinase was comparable with that of Tenecteplase (80.76% Vs 82.75%) with much less bleeding complications. Cerebral hemorrhage was highest with Tenecteplase which was 6.89%. Among the thrombolysed STEMI patients prevalence of male was much higher than that of female (91.04% Vs 8.95%), most of the STEMI patients came during night time (47.76%).

Initial trials of streptokinase performed in 1980s showed a pronounced mortality benefit\cite{1,2}. The GUSTO-I trial showed a slight mortality benefit (14%) with Alteplase infused over 90 minutes compared with streptokinase at the cost of two extra strokes per 1000 patients randomized\cite{3}. In subsequent studies showed Reteplase and Tenecteplase were equivalent to accelerated Alteplase\cite{4}.

One study had been conducted in south India by Ranakishore Pelluri and others and they showed in terms of efficacy the Reteplase (93.33%) was good as compared to Streptokinase (86.77%) & Tenecteplase (80.00%), the p-value was <0.001\cite{5}.

References:

1. GISSI. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;397-402.
Study of Effect of Weight Reduction on Vitamin D Status in Obese and Overweight Subjects — A Pilot Study

Dr. Jayanta Chakraborty1, Dr. Semanti Chakraborty2, Dr. Rita Chakraborty3, Dr. Dinabandhu Naga4

Abstract:
Vitamin D deficiency-insufficiency is paradoxical in sunny India. More so in Bengal where majority of people consume fatty fishes. In the present study which is preliminary report of a larger population study weight reduction causes increase of Vitamin D from baseline level to a maximum of 9.51 ng/ml.

Introduction:
Vitamin D deficiency is in epidemic proportions worldwide. In one of our previous study vitamin D deficiency-insufficiency were 100% in type 2 diabetic subjects.[1]

In USA in a recent study the overall prevalence rate of vitamin D deficiency was 41.6%, with the highest rate seen in blacks (82.1%), followed by Hispanics (69.2%).[2]. This vitamin D deficiency is steadily increasing over decades in USA. In a report of Mayo clinic proceedings in 2006 - Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States”[3].

In Saudi Arabia vitamin D deficiency was also substantial 78.1% in females and 72.4% in males.[4]

In Pakistan when the studied population was premenopausal women it was 91.50%.[5]

So this global deficiency is sustained despite diverse food habit and varying exposure to the Sun.

There must be other causal relationship of this malady, besides the above two which have been widely addressed without any benefit.

The present study, which is an encouraging preliminary report of a larger study, gives a plausible insight into the problem.

Methods:
The present study is an excerpt of the parent study of vitamin D deficiency in India its cause and remedy. In an intervention of life style modification and weight reduction among 200 subjects randomized from an endocrinology clinic. The pilot study included 10 subjects. The target was weight reduction of minimum one kilogram (kg) over six months run over period. Maximum weight reduction permitted ten kilograms. 25 hydroxy Vitamin D (Vitamin D) was assessed initially and after six months. After three months those who did not lose weight, were treated with orlistat.

Results:
Among 10 subjects, only 6 subjects lost weight to target of 1kg or more. Minimum weight loss was 1kg and maximum was 10kg. Mean weight loss was 5.5kg. Minimum initial vitamin D was 11.04 ng/ml and maximum was 24.30 ng/ml. Mean increase of vitamin D was 6.26 ng/ml.

1Prof. & HOD of Medicine and Endocrinologist RKMS, VIMS
2Post Graduate Trainee, Dept. of Medicine RKMS, VIMS.
3Visiting Paediatrician, Dept. of Paediatrics RKMS, VIMS.
4Post Graduate Trainee, Dept. of Medicine RKMS, VIMS
Among these 6 subjects who succeeded to lose weight. Vitamin D rose from 3.30 ng/ml to a maximum of 9.51 ng/ml, through weight loss without any vitamin D supplementation through diet or drugs.

**Discussion:**

The pandemic of vitamin D deficiency worldwide is a major global health concern. Not deficiency but sufficiency of diet and consequent obesity and metabolic syndrome is the principal causative factor. In another study we found that vitamin D deficiency is directly related to increased body mass index.[6] Obesity and metabolic syndrome causes inadequate active Vitamin D available to body, which we have discussed in details in another publication. So life style modification and reduction of body weight to ideal body weight is an important intervention for this Global epidemic.

**Conclusion:**

Body weight reduction in overweight and obese subjects normalizes vitamin D status, without requirement for vitamin D supplementation.

**References:**


Comparison of Myocardial Tissue Doppler and Conventional Vessel Doppler in Predicting Perinatal Outcomes in Babies with Intrauterine Growth Restriction

Dr. Barnali Basu¹, Dr. A. Das², Dr. B. Choudhury³

Abstract:

Introduction:
Myocardial Tissue Doppler in echocardiography is a new and upcoming technique being claimed to detect adverse outcomes in babies with intrauterine growth restriction and hence can act as a useful tool in their management. We undertake this study to see whether it is a better technique than Vessel Doppler which is used conventionally for this purpose.

Objectives:
The objective of the study was to compare conventional vessel Doppler and Myocardial tissue Doppler in predicting adverse outcomes in babies with intrauterine growth restriction.

Design:
It was a prospective case control study.

Population:
Patients in the third trimester of pregnancy.

Methods:
Fetal cardiac function was evaluated with the help of Myocardial Tissue Doppler in IUGR babies and correlated with vessel Doppler findings and neonatal outcomes.

Main Outcome Measures:
Right and Left Ventricular and Interventricular septal E’, A, E'/A’ and Myocardial performance index (MPI’).

Results:
There were sixty two IUGR babies in the study. Twenty seven among them had abnormal vessel Doppler. They were found to have both significantly reduced Right Ventricular late diastolic velocity and Myocardial performance Index (p-0.05,p-0.019). The rest thirty five did not show any significant difference in their Myocardial tissue Doppler parameters. In eleven babies with abnormal vessel Doppler and adverse neonatal outcomes, right ventricular MPI’ was found to be significantly lower. However, the variable had a poor sensitivity (40%) in detecting fetuses at risk for poor neonatal outcomes. Also the Myocardial tissue Doppler variables were also found to be significantly abnormal in nineteen (40%) of the forty seven babies with normal perinatal outcomes. Conventional vessel Doppler, on the other hand, was normal in only four of the fifteen babies with abnormal perinatal outcomes but normal in all babies with normal outcomes.

Conclusion:
Myocardial tissue Doppler shows subtle right sided cardiac dysfunction in IUGR babies with adverse perinatal outcomes. It is however not a sensitive indicator of adverse perinatal outcome in IUGR babies in comparison to Conventional vessel Doppler.

Keywords:
Cardiac dysfunction, IUGR, Myocardial tissue Doppler.

Introduction:
Intrauterine growth restriction (IUGR) affects about 3-5 % fetuses in India. It mainly occurs due to uteroplacental insufficiency. If present for prolonged periods, the chronic hypoxia can lead to abnormal manifestations in various fetal

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organ systems with continued adaptive mechanisms that tend to get decompensated with time leading to adverse outcomes in the baby. Several studies have proved the effect of the pathological process of placental dysfunction in IUGR on the fetal heart\(^1\,^2\,^3\,^4\,^5\). Fetal cardiac function is complex and depends on myocardial contractility as well as on extra-cardiac factors such as developmental maturation, loading conditions and fetal disease. With progressive prolonged hypoxia there is deterioration with impaired cardiac filling and drop in cardiac function.

Myocardial tissue Doppler ultrasonography is a technique that allows measurement of myocardial velocimetry in systole and diastole without the limitations of conventional Doppler which is influenced by cardiac rate and afterload conditions. As this technique involves assessment of tissue function, if used correctly it can provide us with valuable information regarding the functioning of fetal myocardium as it has done in case of adults and children. As the cardiovascular changes in IUGR with progressive deterioration of intracardiac perfusion and consequent function tend to occur sometime before the signs of fetal distress appear on biophysical tests, the technique can detect cardiac dysfunction and may prove to be of valuable help in deciding on the management of fetuses with growth restriction. From the studies done so far, tissue Doppler looks like a promising tool for the detection of IUGR babies at risk for adverse outcomes\(^6\,^7\,^8\).

Conventionally Doppler ultrasound assessment of flow patterns and velocities in a number of fetal vessels particularly the umbilical artery is has been the test of choice in the management of IUGR babies. They often act as an important adjunct to fetal biometry in identifying the IUGR fetus at risk of numerous complications. IUGR has been postulated to develop from changes in the placental circulation different from the ones seen in normal babies resulting in reduced oxygen and blood supply to the fetus. These changes in the placental circulation soon lead to redistribution of the entire fetal circulation reflected as changes in the Doppler flow in the major vessels of the fetal circulation. Progressive Doppler studies have been found to have predictive values for fetal growth restriction\(^9\,^10\,^11\). The most widely used Doppler studies for this purpose are those conducted on Umbilical arteries, middle cerebral arteries and ductus venosus.

A number of studies have come up recently questioning the usefulness of Doppler in IUGR fetuses and whether the absence of any Doppler changes can indeed be reliably taken as a sign of absence of any fetal decompensation and future neonatal morbidity\(^12\,^13\,^14\). This is more so in fetuses >34 weeks where despite normal Doppler findings, a sizeable proportion of SGA fetuses were found to have perinatal complications requiring intervention. Hence there is always a search for better studies than conventional vessel Doppler to detect dysfunction in babies with IUGR so that intervention can be taken in time for them balancing the complications of prematurity. We undertook this study to see if Myocardial tissue Doppler is a better investigative test than conventional vessel Doppler in the prediction of adverse outcomes in babies with intrauterine growth restriction.

**Materials and Methods :**

The study was a prospective observational study, carried out between August 2011-August 2013, in the Department of Obstetrics and Gynaecology, Kasturba Hospital, Manipal.
Patients in the third trimester of pregnancy who were identified as having IUGR were taken for the study. Written and informed consent was obtained from all patients. IUGR was diagnosed through ultrasound examination using the Haddock’s formula to calculate the estimated fetal weight and plotting of charts. The fetuses whose growth curve were below the 10th percentile or showed a fall in the expected growth curve were taken for the study. The growth curves were plotted with standardized custom made charts used in the hospital for the diagnosis and management of fetal growth restriction. Exclusion criteria were patients with multiple gestation and fetuses with cardiac anomalies.

Fetal echocardiography was done along with myocardial tissue Doppler in all these patients with help of Vivid GE machine. Sampling was done at the level of the basal part of the left ventricular free wall, right ventricular wall and interventricular septum.

The variables of tissue Doppler taken for all the three areas were:

- **E’** - the mean peak value of three early diastolic waves,
- **A’** - the mean value of three late diastolic or atrial filling waves,
- **E’/A’** - The ratio between the two.

**Myocardial performance index (MPI’)** - Calculated by the formula ICT’+IRT’/ET’ where:

- **ICT’** stands for isovolumetric contraction time,
- **ET’** stands for ejection time and
- **IRT’** for isovolumetric relaxation time.

Conventional Vessel Doppler examination was done for all of these patients. The vessels imaged were:

1) Umbilical Artery, 2) Middle cerebral Artery, 3) Ductus Venousus.

Variables looked for were: Pulsatility index: Systolic end diastolic peak velocity/time averaged maximum velocity (PI), Resistance index: Systolic end diastolic peak velocity/systolic peak velocity (RI), Systolic to diastolic ratio: Systolic peak velocity/diastolic peak velocity. (S/D ratio)

**Peak Systolic velocity**: Mean of three values of maximum systolic velocity in the middle cerebral artery.

**Cerebroplacental ratio (CP ratio)**: Ratio of pulsatility index of Middle cerebral artery with that of umbilical artery. A value of more than 1 defined as adequate cerebral blood flow. The variables of the measurements made closest to delivery were taken.

All patients were followed up to 7 days post-delivery. Adverse neonatal outcomes were taken as: NICU admission for > 5 days, hypoglycemia, respiratory distress syndrome, presence of cardiomegaly, neonatal seizures and mortality. The variables obtained by myocardial tissue Doppler were compared those obtained by conventional Vessel Doppler. Comparison of the two tests was made between babies with normal and adverse outcomes. Statistical analysis was done with the help of SPSS software.

**Results**:

Among the patients attending the antenatal OPD, sixty-two patients with IUGR could be taken for the study (Table 1). Among them, twenty-seven had abnormal vessel Doppler (defined as raised umbilical artery indices, absent or reversed end diastolic flow) while thirty-five had normal vessel Doppler (Table 2). Myocardial tissue Doppler was performed on all these patients and its efficacy in detecting cardiac dysfunction compared with that of conventional vessel Doppler.

The Myocardial tissue Doppler parameters of the two groups of IUGR with normal and abnormal vessel Doppler were compared using the independent t-test (Table 3). The tissue Doppler parameters were lesser in the IUGR babies with abnormal vessel Doppler than the

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16
ones with normal. None of them were however statistically significant. This indicates that Myocardial tissue Doppler is not able to differentiate between the babies requiring more particular attention as defined by conventional Vessel Doppler.

All patients were followed up to 7 days post-delivery to look for neonatal outcome. The babies were looked for the development of any complications like: NICU admission for > 5 days, Hypoglycemia, Hyperbilirubinemia, Need for ventilator, Respiratory distress syndrome, Presence of cardiomegaly, Need for ionotropes, Necrotizing enterocolitis, Neonatal seizures, Mortality.

Twenty six IUGR babies required prolonged NICU admission however only fifteen had severe complications of respiratory distress requiring ventilator care. Among these nine were found to be asphyxiated at birth, five of them acidotic. Other adverse neonatal outcomes like hypoglycemia and cardiomegaly were not found to be in sufficient number among the IUGR babies. Three of the IUGR babies died, one of pulmonary hemorrhage and another of cardiac failure. In the case of the 3\textsuperscript{rd} baby, in view of poor prognosis the mother refused any intervention leading to intrauterine death. On comparing the Myocardial tissue Doppler parameters between the babies with adverse and normal outcomes, only the right ventricle Myocardial performance index was found to be significantly lesser in babies who developed severe morbidity (Table 4). This probably indicates the presence of right ventricular dysfunction in IUGR babies who develop adverse neonatal outcomes.

The two babies who died also developed cardiac failure and they were also found to have abnormal Myocardial tissue Doppler variables for the right ventricle.

Hence, among all the Myocardial tissue Doppler variables, the right ventricular tissue Doppler variables are significantly affected and could act as markers of cardiac dysfunction or adverse neonatal outcome in IUGR.

As there is no defined cutoff as yet for fetuses for these parameters, the sensitivity of these variables in predicting adverse outcomes was assessed with Correlation curves.

On preparing a correlation curve of Right MPI' with neonatal outcomes, a negative correlation of was found (Figure 1). Lower the MPI', worse is the outcome of the baby. However the sensitivity as per the curve obtained is only 40% at a cutoff value of 0.65. Hence this value is likely to miss a lot of patients with adverse neonatal outcomes.

![ROC Curve](image)

**Diagonal segments are produced by ties**
(Values in percentage as MPI' is a ratio)

**Fig 1:** Sensitivity curve of Right Ventricular Myocardial performance Index in predicting adverse neonatal outcomes:
As there are no fixed cutoffs for Myocardial tissue Doppler, the ones obtained by this curve was used for comparison with conventional vessel Doppler.

Among the Twenty seven babies with IUGR and abnormal vessel Doppler, nineteen had values less than the defined cutoff values as per the sensitivity curve. Out of these, eleven babies had adverse neonatal outcomes.

When the same cutoffs for Myocardial Tissue Doppler were applied to IUGR babies with normal outcomes, there were still significant numbers of babies with abnormal values (Table 5). Conventional Vessel Doppler in comparison to myocardial tissue Doppler had less false positives as well as negatives showing both more sensitivity and specificity than the latter. Statistically significant difference between babies with adverse and normal outcomes with the Doppler values were found with Conventional Vessel Doppler (Table 6) which is thus more sensitive in predicting adverse neonatal outcomes than Myocardial Tissue Doppler.

Discussion :

It was a prospective observational study conducted to compare the efficacy of conventional Vessel Doppler and Myocardial Tissue Doppler in detecting adverse perinatal outcome in IUGR. Sixty two IUGR patients were taken for the study. Dating forms an important consideration in the diagnosis of IUGR. In our data, most of the patients had excellent or good dating, so it can be reliably said that no patient was falsely categorized.

Myocardial tissue Doppler was used for the study which uses the high amplitude and low frequency signals generated by the myocardial tissue while movement during the cardiac cycle giving an impartial view of the actual functioning of the different ventricles of the heart without being biased by the load conditions. This can enable us to identify if there is actual cardiac dysfunction or just altered functioning as a compensation to tide over unfavorable circulatory changes. All measurements were made on the same machine and were carried out by the same trained person. Hence the chances of interobserver variations and the problems of expertise and knowledge were nullified.

Vessel Doppler making use of flow patterns in the fetal circulation to look for abnormalities in circulation has been used for a long time to assess the uteroplacental insufficiency seen in intrauterine growth restriction. The major vessels used for this purpose are the umbilical artery, middle cerebral artery and the ductusvenosus. The changes of uteroplacental insufficiency and the resultant compensatory mechanisms in the fetal circulation are reflected in the different indices of these vessels. These are followed by changes in the non-stress test and biophysical profile which can lead to fetal death if not acted timely. Hence Vessel Doppler can act as indicator of adverse neonatal outcome.

In the present study 35 IUGR babies were found to have normal vessel Doppler. Four of these had adverse neonatal outcomes. The 27 babies with abnormal vessel Doppler on the other hand showed significant reduction in Right ventricle MPI’. This essentially shows that all abnormalities of Myocardial tissue Doppler seen in IUGR are only confined to the ones with abnormal Vessel Doppler. Hence conventional Vessel Doppler is as efficacious in detecting the babies with cardiac dysfunction.

In fetal life it is the right side of the heart which plays the dominant role in the circulation of
blood. As a result this is the area to be more in requirement of oxygen and nutrients and also more susceptible for hypoxia and ischemia. This therefore explains the observation of right sided parameters to be abnormal with IUGR. Despite indicating the presence of cardiac dysfunction in IUGR babies, the Myocardial tissue Doppler parameters fared poorly in sensitivity and specificity in predicting the babies with increased chances of developing adverse neonatal outcomes. On account of its still being in the research phase, cutoff levels as to what is defined as abnormal tissue Doppler are not present. To enable looking for the level above which adverse neonatal outcome could be predicted, ROC curves were prepared for assessing the sensitivity of Tissue Doppler in predicting adverse neonatal outcomes. Using the cutoff as obtained by these curves to define normal and abnormal tissue Doppler, not only do the curves in themselves show a poor sensitivity of 40% only for Right ventricle MPI', but also these values tag lot of IUGR babies with normal outcomes as having abnormal tissue Doppler.

Undoubtedly, the babies with serious adverse outcomes seen in our study were all found to have abnormal Myocardial tissue Doppler values, but these were also detected as easily by vessel Doppler. On the other hand Myocardial tissue Doppler showed an unacceptable number of abnormal values both in IUGR babies with normal outcome and normal vessel Doppler. Myocardial Tissue Doppler has hence high numbers of false positives and low sensitivity in babies with IUGR.

There were as many as 15 babies with adverse neonatal outcomes of mainly respiratory distress and birth asphyxia. Comparable number of babies in this group had both abnormal Myocardial and conventional vessel Doppler. The babies with adverse neonatal outcomes also conformed to the findings of IUGR babies with abnormal vessel Doppler in having lower right ventricle MPI' in comparison to IUGR babies with normal outcomes. This shows good reliability of the technique in predicting adverse perinatal outcome in IUGR babies. Of note however is the presence of a number of IUGR babies with normal neonatal outcome who still had abnormal Myocardial tissue Doppler. The Right ventricular MPI' has been found to have low sensitivity on statistical analysis in this study and this could be a reflection of the same.

There have been a lot of studies[12,13,14] questioning the effectiveness of Conventional vessel Doppler with some finding abnormal myocardial tissue Doppler variables in patients with normal vessel Doppler[15]. However there has been hardly any study that looks at the neonatal outcomes of the babies taken up. In our study, even though the babies with serious adverse outcomes seen in our study like mortality, cardiomegaly, acidosis and birth asphyxia were all found to have abnormal Myocardial tissue Doppler values, these were also detected as easily by vessel Doppler. On the other hand Myocardial tissue Doppler showed an unacceptable number of abnormal values both in babies with normal outcome and normal vessel Doppler. This makes the Myocardial tissue Doppler a poor predictor for adverse neonatal outcomes as well as poor indicator in deciding the time of delivery in IUGR babies which is a critical decision. The present study was undertaken to see if the upcoming technique of Myocardial tissue Doppler which already has proved its mettle in
adults and children could be applied successfully in fetuses as well. But trying to correlate this investigation with conventional vessel Doppler and has not yielded very good results. The conventional vessel Doppler still remains the test to be carried out when faced with the dilemma of whether to deliver or observe when faced with the problem of IUGR in a patient.

Even though Myocardial tissue Doppler had a low sensitivity in predicting adverse perinatal outcome, it did indicate cardiac dysfunction in IUGR. Further research is needed with a larger sample size to further determine its usefulness.

**Conclusion:**
We conclude that Myocardial tissue Doppler shows right ventricular dysfunction in IUGR. Myocardial tissue Doppler is however not a sensitive indicator of adverse perinatal outcome in IUGR babies. Hence it is only a research tool and not useful in the clinical management of IUGR babies where conventional vessel Doppler is more useful.

**Limitations:**
As the babies were not followed up for a long period of time it is not known whether the abnormal tissue Doppler values found in the babies with normal vessel Doppler are indicative of cardiac dysfunction in future life. Also Troponin T levels of these babies were not checked and hence it cannot be confirmed if the abnormal values were incidental findings or subtle cardiac dysfunction. More research is needed in this regard.

**Acknowledgements:**
The authors would like to thank Dr. Lavanya Rai, Dr. Pratap Kumar and Dr. Muralidhar V. Pai for their valuable help and guidance in conducting this study.

**Conflict of Interest:**
The authors wish to report no conflict of interest over this study.

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**Table 1. Demographic Characteristics of the Patients (N-62):**

<table>
<thead>
<tr>
<th></th>
<th>n-62</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
<td>28.10</td>
<td>4.74</td>
</tr>
<tr>
<td>Gestational age in weeks</td>
<td></td>
<td>33.1</td>
<td>0.41</td>
</tr>
<tr>
<td>Parity</td>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>primi</td>
<td>33</td>
<td>53.2%</td>
<td></td>
</tr>
<tr>
<td>Multiple abortions</td>
<td>9</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>multi</td>
<td>20</td>
<td>32.3%</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>17</td>
<td>27.4%</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>45</td>
<td>72.6%</td>
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</tr>
</tbody>
</table>
### Table 2: Comparison of Vessel Doppler Parameters Among the IUGR Babies:

<table>
<thead>
<tr>
<th></th>
<th>Abnormal Doppler (N-27)</th>
<th>Normal Doppler (N-35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>UA PI</td>
<td>1.100</td>
<td>0.615</td>
<td>0.87</td>
</tr>
<tr>
<td>UA RI</td>
<td>0.64</td>
<td>0.22</td>
<td>0.61</td>
</tr>
<tr>
<td>UA S/D</td>
<td>3.16</td>
<td>1.33</td>
<td>2.28</td>
</tr>
<tr>
<td>MCA PSV</td>
<td>53.8</td>
<td>17.6</td>
<td>51.4</td>
</tr>
<tr>
<td>MCA PI</td>
<td>1.58</td>
<td>0.41</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Test used: Independent t test, p value <0.05 considered significant

### Table 3: Myocardial Tissue Doppler Parameters Among IUGR Fetuses with Normal and Abnormal Vessel Doppler:

<table>
<thead>
<tr>
<th></th>
<th>Abnormal Doppler (N-27)</th>
<th>Normal Doppler (N-35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>IV-E’</td>
<td>0.037</td>
<td>0.009</td>
<td>0.039</td>
</tr>
<tr>
<td>IV-A’</td>
<td>0.0481</td>
<td>0.13</td>
<td>0.486</td>
</tr>
<tr>
<td>IV-E'/A’</td>
<td>0.79</td>
<td>0.37</td>
<td>0.84</td>
</tr>
<tr>
<td>IV-MPI’</td>
<td>0.60</td>
<td>0.10</td>
<td>0.63</td>
</tr>
<tr>
<td>LV-E’</td>
<td>0.05</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>LV-A’</td>
<td>0.068</td>
<td>0.02</td>
<td>0.061</td>
</tr>
<tr>
<td>LV-E'/A’</td>
<td>0.76</td>
<td>0.37</td>
<td>0.92</td>
</tr>
<tr>
<td>LV-MPI’</td>
<td>0.62</td>
<td>0.17</td>
<td>0.64</td>
</tr>
<tr>
<td>RV-E’</td>
<td>0.06</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>RV-A’</td>
<td>0.09</td>
<td>0.02</td>
<td>0.094</td>
</tr>
<tr>
<td>RV-E'/A’</td>
<td>0.64</td>
<td>0.15</td>
<td>0.62</td>
</tr>
<tr>
<td>RV-MPI’</td>
<td>0.58</td>
<td>0.14</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Test used: Independent t test, p value <0.05 considered significant. E’, A’ in m/sec, E’/A’ and MPI’ are ratios
Table 4: Myocardial Tissue Parameters Among IUGR Babies Who Developed Morbidities:

<table>
<thead>
<tr>
<th></th>
<th>IUGR(62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morbidity(N-15)</td>
<td>Normal Outcome (N-47)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>IV-E’</td>
<td>0.04</td>
<td>0.0078</td>
</tr>
<tr>
<td>IV-A’</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>IV-E'/A'</td>
<td>0.81</td>
<td>0.33</td>
</tr>
<tr>
<td>IV-MPI'</td>
<td>0.61</td>
<td>0.10</td>
</tr>
<tr>
<td>LV-E’</td>
<td>0.05</td>
<td>0.017</td>
</tr>
<tr>
<td>LV-A’</td>
<td>0.066</td>
<td>0.023</td>
</tr>
<tr>
<td>LV-E'/A'</td>
<td>0.80</td>
<td>0.36</td>
</tr>
<tr>
<td>LV-MPI'</td>
<td>0.628</td>
<td>0.17</td>
</tr>
<tr>
<td>RV-E’</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>RV-A’</td>
<td>0.09</td>
<td>0.017</td>
</tr>
<tr>
<td>RV-E'/A'</td>
<td>0.63</td>
<td>0.15</td>
</tr>
<tr>
<td>RV-MPI'</td>
<td>0.59</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Test used: Independent t test, p value <0.05 considered significant. E’, A’ in m/sec, E’/A’ and MPI’ are ratios. Values in m/sec

Table 5: Efficacy of Myocardial Tissue Doppler in Detecting IUGR Babies with Adverse Neonatal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Abnormal Myocardial Tissue Doppler</th>
<th>Normal Myocardial Tissue Doppler</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR babies with morbidity(15)</td>
<td>12</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>IUGR babies with normal outcome(47)</td>
<td>28</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Test used: Chi Square test, p Value <0.05 considered significant
Table 6: Efficacy of Conventional Vessel Doppler in Detecting IUGR Babies with Adverse Neonatal Outcomes

<table>
<thead>
<tr>
<th>Abnormal Vessel Doppler</th>
<th>Normal Vessel Doppler</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR babies with morbidity(15)</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>IUGR babies with normal outcome(47)</td>
<td>4</td>
<td>43</td>
</tr>
</tbody>
</table>

Test used: Chi Square test, p Value <0.05 considered significant

References:


Comparison of Post Dural Puncture Headache with 25 g Quincke and Whitacre Spinal Needles in Obstetrics Patients

Dr. Ruchi Shah (Sarkar)¹, Dr. Tulsi Nag²

Abstract:

Background- Spinal neuraxial block produces intense analgesia and excellent skeletal muscle relaxation to facilitate surgical exposure. It requires a small amount of drug that produces minimum systemic pharmacological effect on mother and fetus. It also avoids the complications of general anaesthesia. Hence it is the preferred mode of anaesthesia for caesarean section delivery. Although it has various advantages, it is associated with some disadvantages like hypotension and Post Dural Puncture Headache (PDPH).

Material and Methods:

On the basis of this fact, present study was performed in Kamla Raja Hospital, G.R.M.C, Gwalior on 120 pregnant women of ASA grade I and II aged between 18 to 40 years posted elective Lower Uterine Caesarean Section. All patients were equally divided in two groups, Group I and Group II and included in a prospective, randomized, double blind study. With all aseptic precautions subarachanoid block was performed with 25 G Quincke spinal needle in Group I and 25 G Whitacre spinal needle in Group II. In the post-operative period all patients were interviewed daily till discharge about headache in details. The occurrence of other adverse effects were also interrogated. Intra-operative haemodynamic parameters were also observed and compared between two groups. The incidence of PDPH between the two groups was compared using Pearson Chi Square Test.

Results:

In Group I, eight patients suffered from PDPH whereas only one patient had PDPH in Group II, showing that, the difference between the incidence of PDPH in two groups was statistically significant p=0.03. Needle tip design and modification can result in significant decrease in the incidence of PDPH. The incidence of PDPH in Group I and II was 13.34% and 1.67% respectively and the difference was statistically significant (p<0.05). Quincke spinal needle have a beveled tip with cutting edges which cuts through the dura whereas Whitacre spinal needle has a pencil point tip with the needle hole on the side of the shaft, which spreads the dural fibres. Hence, the CSF leakage is less in patients where dural fibres are spread compared to patients where fibres are cut and a permanent opening results, subsequently loss of CSF decreases buoyant support of brain in erect posture causing sagging of brain causing traction on pain sensitive intracranial structures.

Conclusion:

The observations of this study reveals that, the incidence of PDPH with 25 G Whitacre spinal needle was significantly less as compared to 25 G Quincke spinal needle in patients undergoing elective Lower Uterine Caesarean Section.

Keywords:

Spinal anaesthesia, Caesarean delivery, Post Dural Puncture Headache, Whitacre and Quincke spinal needles.

¹,² Dept. of Anaesthesia, RKMSP, VIMS
Introduction:

Spinal neuraxial block results sympathetic blockade, sensory analgesia or anaesthesia and motor blockade.

Spinal anaesthesia requires a small mass of drug, virtually devoid of systemic pharmacological effect, to produce profound, reproducible sensory analgesia. It also produces excellent skeletal muscle relaxation that facilitates surgical exposure.\(^1\)

The end point of Cerebrospinal Fluid (CSF) return is well-defined, making spinal anaesthetic technique easy.

Spinal anaesthesia has rapid onset, and produces dense neural block. Because small dose is used, there is little risk of local anaesthetic toxicity and minimum transfer of drug to the fetus. It has minimum risk of aspiration of gastric contents and is devoid of complications of General anaesthesia. For all these advantages spinal block is preferred anaesthetic technique for Caesarean delivery.\(^2\)

The disadvantages of this technique include:
- Hypotension
- Post Dural Puncture Headache (PDPH).

On August 15, 1898, August Bier and his assistant used Quincke method of entering intrathecal space and injected 5 to 15 mg of cocaine to produce spinal anaesthesia. Side effects they observed were nausea, vomiting, dizziness and headache which he proposed were due to escape of cerebrospinal fluid from dural sac.\(^3\)

Further studies found that PDPH is more common in female, pregnant patients. Factors influencing incidence of PDPH includes —

- Age - more frequent in younger.
- Needle size - larger bore > smaller bore

Needle bevel - less when the needle bevel is placed in the long axis.

Needle categories - more with those that cut the dura (Quincke) and less with those which split the dura with a conical tip (Whitacre).

Number of dural puncture - more with multiple puncture.

PDPH is not exclusively related to spinal anaesthesia but also may occur after diagnostic and therapeutic lumbar puncture.

In PDPH, headache is mild or absent when the patient is supine. Head elevation leads to severe fronto-occipital headache. Occasionally nausea, vomiting, tinnitus, and diplopia are also present. Proposed theory is loss of CSF through meningeal needle hole leading to decreased buoyant support of brain. In upright position brain sags putting traction on pain sensitive structures.

The PDPH was treated conservatively initially with bed rest, hydration and paracetamol 15 mg/kg orally four times daily. If the PDPH persisted longer than 24 hours with the same severity, the decision to perform epidural blood patch was taken by a consultant anaesthesiologist and neurosurgeon.

On the basis of these facts we have chosen Caesarean section under spinal anaesthesia for our study.

Aims and Objectives:

1. To compare the incidence of PDPH in obstetrics patients under subarachnoid block using 25 G Quincke or 25 G Whitacre spinal needles.
2. Intra-operative haemodynamic monitoring.
3. To note the complications other than PDPH.
Material and Method:

The present study was carried out in the department of Anaesthesiology, in Kamla Raja Hospital and Jaya Arogya Group of hospitals of G. R. Medical College, Gwalior, after approval from institutional ethical and scientific committee. The study was done in 120 pregnant patients of ASA grade I and II aged between 18-40 years scheduled for elective lower segment caesarean section under subarachnoid block. Informed written consent was obtained from each patient during the pre-operative visit.

Exclusion Criteria-unwilling patients, fetal distress, any incidence of local sepsis, spinal deformity, severe co-morbidities and haemodynamic instability.

Patients were randomly divided into two equal groups and blinded by sealed envelope technique. Group I- patients in whom subarachanoid block (SAB) was done with 25 G Quincke spinal needle.

Group II- patients in whom SAB was done with 25 G Whitacre spinal needle.

Equipment used -
(a) 25 Quincke spinal needle – it is the standard needle with a medium cutting bevel and orifice at the needle tip.
(b) 25 G Whitacre spinal needle- it has diamond shaped tip with the orifice up to 0.5 mm from the needle tip.

A detailed history, physical examination and routine investigations were done. Patients were kept fasting for 6 hours for solid food and 2 hours for clear liquid prior to spinal anaesthesia. Premedication was done using injection Glycopyrrolate 0.2 mg i.m 30 minutes before operation. On arrival to operating room a baseline pulse rate, NIBP, ECG and SpO2 were recorded. An intra-venous (18 G) cannulation was inserted on non-dominant hand. All patients were administered injection Ranitidine 50 mg i.v and injection Metaclopramide 10 mg i.v, 15 minutes before giving SAB. Preloading was done with Ringer lactate 10 ml/kg body weight over 10 minutes.

A midline lumbar puncture between L3-4 or L4-5 intervertebral space was done in left lateral position with either type of needles following

![Figure-1](image)

Showing (a) Quincke spinal needle and (b) Whitacre spinal needle
strict asepsis. The spinal needle was introduced with the bevel parallel to the dural fibers. Upon entering the subarachanoid space as evidenced by clear, free flowing CSF the needle was rotated anticlockwise to direct the ejection orifice cephalad. Following lumbar puncture; local anaesthetic solution, 0.5% Bupivacaine heavy 2.5 ml (12.5 mg) was injected over 90 seconds.

Figure-2

No sedation was given to any patient intraoperatively. Oxygen (5L/min) y by face-mask was given until delivery of the baby. Fluid therapy was maintained with lactated Ringers solution (10ml/kg/hr). Sensory level was assessed with cold water swab and pin-prick along mid-clavicular line. Motor block was assessed by using Bromage’s scale:-

Bromage’s scale:–

1-Free movement of legs and feet.
2-Just able to flex knees with free movement of feet.
3-Unable to flex knees; but with free movement of feet.
4-Unable to move legs or feet.

Intra-operatively, heart rate, SpO2, Respiratory Rate and NIBP were evaluated at every 2 minutes for the first 20 minutes after spinal block and then every 5 minutes subsequently until the end of surgery. All episodes of hypotension, bradycardia, nausea and vomiting, shivering, somnolence and respiratory depression were observed and attended.
Post operatively all patients were interviewed daily till discharge about presence of headache. If the patient complained of headache, the details of headache regarding site, intensity with change of position (supine/erect) and any other associated symptoms like nausea, vomiting, fever, or neck rigidity. All observations were made to elicit whether the headache was PDPH or not. Post Dural Puncture Headache was confirmed if it fulfilled the following criteria:

1. Occipital or frontal in location.
2. Exacerbation of the symptoms while sitting, standing or walking.
3. Relieved or decreased on assumption of supine or prone position.

Data Analysis:
Number of patients with PDPH, the mean number of attempts to achieve lumbar puncture and accompanying symptoms like nausea, vomiting, hypotension, bradycardia and shivering in each group were noted and expressed as percentage. Demographic data like age, height, weight were expressed as mean± two standard deviation. Comparison of demographic data between the two groups was done using Student's unpaired two-tailed t-test or equivalent non-parametric tests as appropriate. The incidence of PDPH between the two groups was also compared by using Pearson Chi Square Test. A P value of less than 0.05 was considered statistically significant.

Result:

Table - 1
Demographic Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=60)</th>
<th>Group II (n=60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>25.12 ± 4.07</td>
<td>24.44 ± 3.37</td>
<td>0.32(NS)</td>
</tr>
<tr>
<td>Weight (in kg)</td>
<td>54.83 ± 8</td>
<td>52.72 ± 7.55</td>
<td>0.14(NS)</td>
</tr>
<tr>
<td>Height (in cm)</td>
<td>149.83 ± 14.77</td>
<td>145.63 ± 13.98</td>
<td>0.11(NS)</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation.

This Table shows that the demographic data like age, weight and height of patients in two groups were almost comparable and the difference between the two groups was not statistically significant(p>0.05).
### Table-2

**Intra-operative Haemodynamic Parameters**

<table>
<thead>
<tr>
<th>Time (min) (after SAB)</th>
<th>Pulse rate (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>Mean (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td>P value</td>
</tr>
<tr>
<td>Baseline (before SAB)</td>
<td>84±13.78</td>
<td>79±11.87</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>83±19.59</td>
<td>77±15.76</td>
<td>0.43 (NS)</td>
</tr>
<tr>
<td>5</td>
<td>81±20.17</td>
<td>78±14.52</td>
<td>0.71 (NS)</td>
</tr>
<tr>
<td>10</td>
<td>77±19.08</td>
<td>78±15.18</td>
<td>1 (NS)</td>
</tr>
<tr>
<td>20</td>
<td>78±17.95</td>
<td>76±15.22</td>
<td>0.47 (NS)</td>
</tr>
</tbody>
</table>

All values are expressed in mean ± standard deviation

This Table shows the intra-operative haemodynamic parameters in both the Groups. The values were almost comparable between the two groups and the difference was statistically insignificant (p>0.05).

### Table-3

**Post Dural Puncture Headache**

<table>
<thead>
<tr>
<th>Incidence</th>
<th>n</th>
<th>(%)</th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>8</td>
<td>(13.34)</td>
<td>1</td>
<td></td>
<td>1.67</td>
</tr>
<tr>
<td>Day 4</td>
<td>6</td>
<td></td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>2</td>
<td></td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>2</td>
<td></td>
<td>3.34</td>
<td>1</td>
<td>1.67</td>
</tr>
<tr>
<td>Frontal</td>
<td>6</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throbbing</td>
<td>6</td>
<td></td>
<td>10</td>
<td></td>
<td>1.67</td>
</tr>
<tr>
<td>Dull ache</td>
<td>2</td>
<td></td>
<td>3.34</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Duration (Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>3.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

29
All values are expressed as mean ± standard deviation.

This Table shows the incidence of PDPH in both the groups. The incidence was more in group I (13.34%) as compared to group II (1.67%) only. The difference between the incidence was statistically significant (p value is 0.03).

In all the patients of both the groups the intra-operative SpO2 was maintained within normal limits (96-99%).

Discussion:

Spinal anaesthesia has rapid onset, and produces dense neural block. Because small dose is used, there is little risk of local anaesthetic toxicity and minimum transfer of drug to the fetus. It has minimum risk of aspiration of gastric contents and is devoid of complications of General anaesthesia. For all these advantages spinal block is preferred anaesthetic technique for Caesarean delivery.[2] The disadvantages of this technique includes-Hypotension and Post Dural Puncture Headache (PDPH).

PDPH is more common in female, pregnant patients. Factors influencing incidence of PDPH includes-

- Age-more frequent in younger.
- Needle size-larger bore>smaller bore.
- Needle bevel-less when the needle bevel is placed in the long axis.
- Needle categories-more with those that cut the dura (Quincke) and less with those which split the dura with a conical tip (Whitacre).
- Number of dural puncture-more with multiple puncture.

On this basis, we have chosen Caesarean section under spinal anaesthesia for our study.

The age of patients in the present study ranged from 18 to 40 years. Mean (±SD) age of patients in Group I and Group II were 25.2±4.07 years and 24.4±3.37 years respectively. Mean (±SD) age of patients were almost identical in both the groups and the difference was statistically insignificant (p>0.05) [Table-1].

The weight of the patients in this study ranged from 40 to 72 kg and the mean weight was comparable in both groups and the difference was statistically insignificant, as in Group I & Group II mean (+) were 54.8±8 kg and 52.7±7.55 kg respectively (p>0.05) [Table 1].

The height of patients in the present study ranged between 124 cm and 175 cm. Mean (+SD) height of patients in Group I was 149.83+14.77 & in Group II was 145.63+13.98 and the difference was statistically insignificant (p>0.05)[Table 1].

The intra-operative haemodynamic parameters like pulse rate, systolic blood pressure, diastolic blood pressure, mean blood pressure and oxygen saturation were noted at regular intervals in both the groups. All the readings were comparable between the groups and the differences were statistically insignificant (p>0.05) [Table 2].

Multiple attempts of lumbar puncture are an independent predisposing factor for PDPH. So cases requiring more than three attempts were not included in the study and have been mentioned as exclusion criteria. Lumbar puncture was achieved in the first attempt in 96.66% cases in Group I and in 96.66% cases in GroupII. 3.34% patients in Group I and 3.34% patients in Group II required second attempt. There is no statistically significant difference regarding the number of attempts of lumbar puncture in the two study groups (p > 0.05).

Table 3 shows the number and percentage of
patients who experienced POSTDURAL PUNCTURE HEADACHE. The main objective of this study was to find the difference, if any, in the incidences of PDPH between the two groups I and II. In Group I 8 out of 60 patients i.e., 13.34% patients had PDPH. In Group II 1 out of 60 patients i.e, 1.67% patients had PDPH. Chi square test was applied to find out whether this difference in incidence of PDPH between the two groups is statistically significant and it was found out to be STATISTICALLY SIGNIFICANT. (p value is 0.03 i.e p<0.05) [Table 3].

A cutting type of needle inserted through the dural wall tears off a number of fibers in the wall and a permanent opening in it is ensured. The anatomical feature of dura is such that longitudinal dispersion of its fibres plus a copious interspersion of elastic fibers keeps the rent open once the dural fibres are cut.

Carrie[4] suggested the use of a pencil point lumbar puncture needle and the tip of the pencil point needles (25G Whitacre).

Hwang J J et al.[6] in their study with caesarean section patients under SAB, using 25G Whitacre and 25G and 26G Quincke needles, found that though not statistically significant, the 25G Whitacre caused a lower incidence and less severity of PDPH compared to 25G, 26G Quincke needle.

Shutt Le et al[7], in their study with Caesarean section under SAB, using 26 G Quincke and 25G Whitacre needles, found that PDPH was more in Whitacre (4%) compared to Quincke (1%).

Tabedar[9], using 25 G Quincke and 26 G Whitacre spinal needles found that PDPH was more in Quincke (8%) as compared to Whitacre (2.2%).

Bano F et al[10], studied on pregnant women undergoing L.U.C.S under SAB, using 25 G Quincke and 25 G Whitacre needles also found, more incidence of PDPH in Quincke (4%) as compared to Whitacre (0.75%).

Buettner J et al[11], in their study of non-obstetric patients undergoing lower extremity surgery under spinal anaesthesia, by using 25G Quincke and 25G Whitacre needles, found that the use of a Whitacre needle results in significantly less PDPH compared to a standard Quincke spinal needle of the same size.

The usual onset of PDPH is on day 3 after subarachnoid block. In our study, out of eight patients of group I who developed PDPH, six patients had its onset on day 4 and only two had
its onset on day 5 whereas in group II, the only patient who developed PDPH had its onset on day 5 which is comparable to the study conducted by Flaaten et al[12].

Six patients of group I had headache which was frontal in location (10%) whereas two patients in group I (3.34%) and one patient in group II had occipital headache (1.67%). The headache was throbbing in nature in 6 patients and dull-ache in 2 patients of group I whereas only one patient of group II had headache of dull ache quality.

The duration of headache was 3 days in six patients and 1 day in two patients of group I whereas in group II the only patient had headache for 2 days. [Table 3] These findings are similar to study conducted by Ripul Oberoi, K, Kaul et al[13].

The patients who experienced headache were asked about accompanying symptoms like nausea, vomiting, dizziness, blurred vision, and tinnitus. In Group I, 2 patients (3.34%) experienced nausea, vomiting and dizziness, in Group II, only 1 patient (1.67%) had nausea and vomiting. There was no case of blurred vision and tinnitus. These findings are similar to study conducted by Ripul Oberoi, K, Kaul et al[13].

Summary:
Subarachnoid block is a safe, economical and reliable technique devoid of complications of general anaesthesia but is often associated with most distressing complication like post-dural puncture headache (PDPH). Of the various factors related to PDPH such as age of the patient, gender, direction of the bevel of the needle, number of attempts at dural puncture, needle size and needle tip design, the needle tip modification can result in significant decrease in the incidence of PDPH.

In this study, 120 obstetric patients of ASA grade I & II undergoing elective caesarean section under subarachnoid block, aged between 18 to 40 years. All patients were equally divided into group I and II, based on the use of Quincke and Whitacre spinal needles respectively and were included in a prospective, randomized, double blind study.

Aim of the study was to compare the difference, if any, in the incidence of PDPH between these two groups of patients.

By using a closed envelope method, the patients were divided into two groups. The patients who received 25G Quincke needle were placed in group I (n = 60) and those who received Whitacre needle for subarachnoid block were placed in group II (n = 60). Postoperatively all patients in the study group were interviewed daily for seven consecutive days by an anesthesiologist unaware of the type of needle used and were questioned for the presence of headache and any other accompanying symptoms such as nausea, vomiting, blurred vision and tinnitus. The incidence of headache fulfilling the criteria of PDPH was recorded. The data was analyzed using statistical tests to find out whether the difference in incidence of PDPH between the two groups was statistically significant or not. The incidence of accompanying symptoms like nausea, vomiting, blurred vision and tinnitus were noted.

Demographic data like age, height and weight were comparable between the two groups and the differences not statistically significant. Intra-operative haemodynamic data were almost similar in both the groups and the differences between the groups were found to be statistically
The incidence of PDPH between the groups I and II was 13.34% and 1.67% respectively and the differences between the groups was found to be statistically significant (P value of 0.03). The incidence of nausea and vomiting were not clinically or statistically significant. There was no case of blurred vision or tinnitus.

Hence to conclude, the incidence of PDPH is less in patients in whom 25 G Whitacre spinal needle was used as compared to 25 G Quincke spinal needle for Sub-arachanoid Block in patients undergoing elective Lower Uterine Caesarean Section. Further studies should be performed to establish this fact.

References:

10. Bano et al. complication of 25 gauge Quincke and Whitacre needle for post dural puncture headache in obstetrics patients, department of anaesthesiology and surgical ICU. DOW University of health sciences and civil Hospital, Karachi; p.647-50.

It is well recognised that there is an increased incidence of rheumatological disorders in diabetes. Crispin[1] classified these disorders into four types: those that were a consequence of complications; those that were a result of metabolic consequences of diabetes; syndromes that shared pathogenesis with microvascular complications; and associations of diabetes. Research in the field is hampered by poor characterisation of subjects and lack of uniformity in definitions. Perhaps as a consequence, there is a wide reported variation in the incidence of various rheumatological complications. For example, a study from Jordan on 1000 type 2 diabetes patients found limited joint mobility (LJM) in 63% of patients[2] while a study from Kolkata on 100 patients found an incidence of only 29 %[3]. A study on type 1 diabetes patients, comprising the follow up of the DCCT trial cohort, the EDIC group of 1217 subjects, looked at cheiroarthropathy and functional disability after an average of 24 years of follow up[4]. Cheiroarthropathy was present 64 % of subjects in the erstwhile intensive group and 68% in the erstwhile conventional group (non significant). The affected subjects were significantly more likely to have functional disability as well.

The association of diabetes and rheumatological disease has its underpinning in the nature of collagen itself. Collagen fibers tend to form an increased number of crosslinks when exposed to oxidative stress and hyperglycemia. The reactive carbonyl group of a sugar attaches to a nucleophilic amino group of an amino acid to form complex series of molecules. This is the basis of the Maillard Reaction, first described in 1912. In vivo, this reaction is best studied with the help of a pentose sugar, pentosidine which forms an arginine – lysine crosslink. The resulting compounds exhibit autofluorescence between wavelengths of 420 and 600 nm, a fortuitous finding which allows the process to be studied in exposed tissues like skin. Hyperglycemia induced collagen crosslinkages have widespread and deleterious consequences in long lasting collagen tissues. These include the arterial wall, periarticular soft tissue and the lens of the eye. The products of the Maillard Reaction are collectively called advanced glycation end products or AGE. These products make the tissues more stiff, and in the case of joints, limit their movement, causing disability.

Various pharmaceutical methods to avoid the deleterious effects of AGE have been tried. For example, aminoguanidine to inhibit AGE formation and ligands to block the AGE receptor. None of these approaches have yielded desired results. Poor glycemic control and long duration of diabetes correlate well with the incidence and severity of musculoskeletal disorders, while on the other hand patients with good control of their diabetes are likely to have fewer musculoskeletal problems. A few of the commonest disorders will be discussed in the following paragraphs.

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Dr. Sudip Chatterjee
MD (Cal) MNAMS (Endocrinology) FRCP (Lond) FACP, Prof., Dept. of Medicine, RKMSP, VIMS
Adhesive capsulitis of the shoulder is a painful and usually self limiting disorder where external rotation and abduction are principally affected. The joint volume is reduced due to thickening of the capsule and its adherence to the head of the humerus. Non diabetic associations include stroke, myocardial infarction and shoulder trauma. Patients with diabetes are affected at a younger age, and the condition takes longer to resolve. The condition is self limiting. Management consists of gentle stretching, analgesics and in severe cases, intra articular corticosteroids and manipulation under anesthesia.

Diabetic cheiroarthropathy has been used synonymously with limited joint mobility (LJM) by most authors. However a study on the EDIC cohort used the term LJM to include carpal tunnel syndrome, tenosynovitis and Duputreyn’s contracture[4]. LJM has a strong association with microvascular complications.

In the carpal tunnel syndrome (CTS) the median nerve is compressed as it passes through the fibro osseous carpal tunnel. Sensory symptoms usually occur first with tingling and numbness of the first to 4th digits especially at night. This is followed by motor symptoms with weakness of the thenar muscles. Initial treatment is with rest, splints and gabapentin. Invasive treatments include local corticosteroid injection and surgical decompression. Electrophysiological criteria for diagnosis in Indian subjects have been formulated[5]. Using electrophysiologic criteria the author found asymptomatic CTS in 58.2 % of a series of 62 unselected type 2 diabetes patients (unpublished data).

Duputreyn’s contracture typically affects the third and fourth digits of patients with diabetes as opposed to a predilection for the fifth digit in non diabetic patients. Treatment depends on disease severity. Tenosynovitis of the flexor tendons of the fingers typically responds to local corticosteroid infiltration.

Diffuse idiopathic skeletal hyperostosis (DISH) is a non inflammatory disease of the spine primarily involving calcification of the anterior longitudinal ligament at the level of the thoracic spine. The condition has been associated with diabetes and with several components of the metabolic syndrome. There is ossification of the points of attachment of tendons and muscles to bone and may occur anywhere in the body. As the condition is often asymptomatic, prevalence of the condition varies widely[6].

Type 1 and type 2 diabetes are both associated with attenuation of bone trabecular architecture, poor osteoblast function, accelerated bone resorption leading to poor quality of bone. Although earlier studies showed increased bone mineral density in type 2 diabetes, current data show that patients (and animals) with both types of diabetes have similar bone defects. Also glycation of collagen leads to formation of AGE in the bone matrix which decreases its mechanical strength[7]. Osteoarthritis appears to be more common in patients with diabetes. In vitro evidence comes from cultured knee cartilage harvested during knee replacement surgery. Cartilage from diabetes patients showed a higher responsiveness to inflammation induced by interleukin 1b[8].

In type 1 diabetes there is an increased incidence of rheumatoid disease[9]. Also, there are type 1 DM patients with no arthropathy who are positive for anti CCP antibodies (author’s unpublished data). Hydroxychloroquine and sulfasalazine, often used in RA, have been shown to increase insulin sensitivity in non diabetic subjects[10] and several studies are underway to explore this
finding and turn it to clinical benefit. A large series from Jaipur looked at 5632 patients with type 2 DM and found musculoskeletal manifestations in 57.01% of them. The commonest conditions were adhesive capsulitis, carpal tunnel syndrome, LJM with a slightly higher incidence in type 1 DM patients.[11]

**Summary:**

It is evident from the literature that musculoskeletal disorders are common in patients with diabetes, and these problems diminish their quality of life. At the same time it is an area which has received less attention than other co-morbidities of diabetes. One of the reasons for this is that the conditions are poorly defined leading to lack of agreement among investigators. Also there is lack of recognition of the fact that these disorders are more common in diabetes. Specialists in the subject should actively seek out and treat musculoskeletal problems in their patients. Also a common nomenclature and classification needs to evolve.

This article is based on a article written by the author and published in RSSDI Update 2015, edited by Dr. Sarita Bajaj and published by Jaypee Brothers Medical Publishers (P) Ltd, New Delhi. This is with the kind permission of the Editor and Publishers.

**Reference:**

Long Term Glaucoma Therapy: A Cost Intensive Socio Economic Burden

Dr. Bhaskar Mukherjee¹, Dr. Malini Majumdar²

Glaucoma:
It is a multifactorial optic neuropathy in which there is a characteristic loss of retinal ganglion cells and atrophy of optic nerve leading to irreversible loss of visual field.¹ Glaucoma is a chronic disease for which lifelong control of intraocular pressure (IOP) is mandatory. The primary treatment for glaucoma is medical, as surgeries have a risk of failure and complications. Medicines are thought to be safer, however patients often need >1 medications to reach the "target" IOP, which may increase the possibility of side effects, as well as long-term costs. In developed countries, the cost of glaucoma therapy is largely borne by government schemes or medical insurance companies while there are very few studies on the cost of glaucoma therapy in developing countries.²

Glaucoma - The Indian Scenario:
Glaucoma is the second leading cause of blindness in India and the country has been predicted to host nearly 20% of the world population by 2020. It was estimated that 12 million Indians will be affected by 2010 and 16 million by 2020. The reported prevalence of primary open angle glaucoma (POAG) is 0.41-3.51%.

Management of Glaucoma in India:
Many of the newer diagnostic modalities for early diagnosis and monitoring progression of glaucoma are available in the country. The spectrum of antiglaucoma medications is available. Yet, more than 90% of the glaucoma remains undiagnosed contrary to 40-60% in developed countries. Less than one fifth of those with glaucoma in the Aravind Comprehensive Eye Survey (ACES) had been previously diagnosed as having the disease despite an eye examination in the past. In Chennai Glaucoma Study, a significant number (40%) diagnosed as POAG actually had primary angle closure glaucoma (PACG). Most ophthalmologist in India (70%) are located in urban areas and cater to only 23% of its population. A large percentage of blindness in our country stems from the population living in the rural areas where medical facilities are not easily available. Nearly 35% of the Indian population falls below the international poverty line and medications are still not affordable considering the life long need. In ACES, 42% of glaucoma patients reported one or more problems in using the medications. This makes glaucoma a cost-intensive disease, with a low socioeconomic status having a negative impact.³ Apart from illiteracy and lack of awareness, two factors which may disrupt the ability to adhere to the treatment for glaucoma are cognitive impairment and depressive symptoms, common in older patients with glaucoma.⁴ Studies done on prevalence of glaucoma have reported a high proportion of undiagnosed patients. Late diagnosis is related to increased risk of glaucoma.

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associated with visual disability. Lack of awareness and non-availability of appropriate screening procedures are among the major reasons for non-diagnosis or late diagnosis of glaucoma leading to increase in cost of glaucoma management.[5]

**Glaucoma Therapy and Cost Analysis**[6]:
Studies provide strong evidence that high IOP plays an important role in the neuropathy of POAG. It has been demonstrated that the reduction in the level of IOP lessens the risk of visual field progression in open angle glaucoma. Treatment strategies of glaucoma aims at lowering IOP, which helps to prevent optic nerve damage and glaucoma related blindness. Pharmacotherapy is usually the first line of treatment for elevated IOP and open-angle glaucoma. Major drug classes for medical treatment of POAG include alpha-agonists (brimonidine), beta-blockers (timolol, betaxolol, levobunalol), topical carbonic anhydrase inhibitors (dorzolamide, brinzolamide), oral carbonic anhydrase inhibitors (acetazolamide), miotic agents (pilocarpine), prostaglandin (PG) analogs (travoprost, latanoprost), prostamides (bimatoprost), and sympathomimetic drugs (epinephrine, dipivefrine). The ophthalmologist have a wide range of choices for management of glaucoma, in terms of cost, efficacy and adverse effects. There is an increased demand from society and health care payers that clinical medicine in particular when aimed at treatment of chronic life-long disease should justify its cost. Taking into consideration, the broadening gap between therapeutic possibilities and resources available, the choices have to be made by prioritizing (rationing) all treatment strategies. Economic evaluation of glaucoma therapy needs to be targeted at assessment of efficiency, that is, health effects weighed against the sacrifices incurred for attaining them.

**Cost analysis**:
Cost of particular anti-glaucoma medications per day per eye
\[
\text{Cost per bottle} = \frac{\text{Cost of particular anti-glaucoma medications per bottle}}{\text{No. of drops required per day per eye} \times \text{Number of drops per bottle}}
\]

Cost of anti glaucoma medication for 4 weeks per eye = Cost per day per eye \times 28
Cost/year/eye = Cost/day/eye \times 365.

**Range of cost of various anti glaucoma drugs in India.**[7]

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Drug Description</th>
<th>Range of price(Rs/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Timolol 0.5%</td>
<td>13.50-89</td>
</tr>
<tr>
<td>2.</td>
<td>Betoxalol 0.5%</td>
<td>29.50-33.95</td>
</tr>
<tr>
<td>3.</td>
<td>Levobunalol</td>
<td>62-67</td>
</tr>
<tr>
<td>4.</td>
<td>Pilocarpine 2%</td>
<td>12-42</td>
</tr>
<tr>
<td>5.</td>
<td>Brimonidine 0.15%</td>
<td>100.25-300</td>
</tr>
<tr>
<td>6.</td>
<td>Latoprost 0.005%</td>
<td>229-1142</td>
</tr>
<tr>
<td>7.</td>
<td>Bimatroprost 0.3mg/ml</td>
<td>250-1348</td>
</tr>
<tr>
<td>8.</td>
<td>Dorzolamide</td>
<td>195-202</td>
</tr>
<tr>
<td>9.</td>
<td>Dorzolamide + Timolol</td>
<td>204-208</td>
</tr>
<tr>
<td>10.</td>
<td>Bimatropost+Timolol</td>
<td>167-280</td>
</tr>
<tr>
<td>11.</td>
<td>Brimonidine+Timolol</td>
<td>150-178</td>
</tr>
<tr>
<td>12.</td>
<td>Travoprost</td>
<td>553-756</td>
</tr>
</tbody>
</table>
Timolol may be started as an initial treatment in poorer patients, when not contraindicated, as it is extremely cost-effective and prostaglandin analogues may be reserved as an alternative or as add-on therapy for patients not achieving “target” IOP with timolol. Pilocarpine, which is a cheap, effective and comfortable alternative, should be utilized especially in cases of angle closure glaucoma. It should be available in developing countries. The availability of quality controlled generic drugs may make a significant impact to the cost of medical therapy. As most patients were on more than one drug, drug combinations may be considered, both from an economic and quality of life aspect, after evaluating the efficacy of each component. Besides, all glaucoma investigations, such as the perimetry, imaging and diurnal phasing costs around Rs 900/- in private hospitals and that of tonometry which is included in consultation charges is in average Rs 400/- in any metropolitan city. Hence, the total cost would rise significantly if the cost of these essential investigations at least twice a year is included. Glaucoma surgery (Trabeculectomy) costs around 5000/- to 7000/- in any private hospital. Thus, there is need for proper follow up guidelines, which should be drafted for these patients to avoid unnecessary OPD visits at short intervals, thereby increasing the cost of treatment.

**Conclusion 3:**

As awareness about glaucoma can lead to early detection, a very important step in preventing glaucoma-related blindness, similarly educating masses with proper implementation of health communication principles, will offer a promise of improving awareness. Studies have shown that there exists a relationship between education level & awareness of disease. This has a direct influence on disease process and thereby long term cost burden of glaucoma treatment. Furthermore, there is a need to identify interventions that reinforce people’s attitude above the perceived level of awareness about glaucoma and to devise strategies that can influence behavior to the risk of blindness from glaucoma.

Economic evaluation of glaucoma therapy needs to be targeted at assessment of efficiency, that is health effects weighed against the cost incurred for attaining them. The deciding criterion should be cost effectiveness of treatment strategy rather than efficiency or cost alone.

Implementation of glaucoma screening programs for all patients over 40 years presenting to the hospital would help detect glaucoma early, which would decrease cost in the long term. Primary surgery could be considered for the low socio-economic group and also for drug non compliant patients. A successful trabeculectomy operation remains viable atleast for 20 years, thereby reducing the long term cost for glaucoma management. The socioeconomic impact of medical therapy in glaucoma is considerable, and treatment should be individualized to suit the educational and socio economic aspect of each patient. Economic burden of travelling and loss of livelihood due to the frequent follow ups at the hospital has to be taken into consideration. This can be minimized by introduction of teleophthalmology facilities in peripheral areas. Introduction of quality controlled generic drugs, and use of cheaper alternatives such as timolol and pilocarpine in suitable candidates may address the cost issue for some patients. Periodic training of ophthalmologists at district hospitals in the management and follow up of glaucoma patients will be helpful.
References


6. Natt NK, Gupta A, Singh G, Singh T. A pharcoeconomic analysis to determine the relative cost-effectiveness of bimatoprost 0.03% eye drops and brimonidine 0.2% eyedrops in patients of primary open-angle glaucoma/ocular hypertension. *Indian J Ophthalmol.* 62:1136-1140.

Introduction:
For several years now, the pharmacological manipulation of hormone levels has been used very successfully in the treatment of estrogen-dependent disease processes such as uterine leiomyomas, breast cancer, and endometriosis. As a part of this continued approach, aromatase inhibitors (AIs) have been introduced for the treatment of breast cancer, and more recently, endometriosis. AIs have also been used as agents for ovulation induction (OI).

Aromatase Enzyme:
Aromatase, a cytochrome P450 complex encoded by a single gene, is widely expressed in tissues such as brain, breast, placenta, ovary, testes, endometrium, skin, bone and fat. It catalyzes three consecutive hydroxylation reactions converting C19 androgens to aromatic C18 estrogens. Upon receiving electrons from NADPH-cytochrome P450 reductase, aromatase converts androstenedione and testosterone to estrone (E1) and estradiol (E2), respectively. The aromatization of androgen is the terminal and rate-limiting step in estrogen synthesis. Thus, for tissues that express this enzyme, conversion of circulating androgens from an adrenal or ovarian source will significantly increase the in-situ estrogen concentrations and provide these tissues with a proliferative advantage. Pathologically, an abnormal overexpression of aromatase in breast tissue plays an important role in breast cancer development.[1-9] Inhibition of aromatase is a new strategy for reducing growth-stimulatory effects of estrogen in breast cancer by decreasing circulating levels of estrogen.

Aromatase Inhibitors: Classification and Properties:
The effective aromatase inhibitors (AIs) developed as therapeutic agents are commonly described as first-, second-, and third-generation inhibitors according to the order of their clinical development.

The first-generation inhibitor refers to the non-steroidal inhibitor aminoglutethimide (AG), which was the first AI to be studied in patients,[10] but the reports of adrenal insufficiency led to withdrawal from clinical use. AG is less specific and inhibits other CYP450 enzymes involved in cortisol and aldosterone biosynthesis, which results in toxicity. Its efficacy in inhibiting aromatase activity stimulated the development of various new inhibitors during the 1980s and 1990s.

The second-generation inhibitors include the imidazole derivative fadrozole[11] and steroid analogue formestane (4-hydroxyandrostenedione).[12,13] Fadrozole is more selective and potent than AG, but it still has inhibitory effects on aldosterone, progesterone, and corticosterone biosynthesis. Formestane was the first selective AI to be used clinically and was
effective and well tolerated.[14] However, the fact of its requirement of intramuscular administration limited its clinical use.

The third-generation inhibitors, developed in the early 1990s, including two triazole derivatives anastrozole[15] and letrozole[16] and one steroid analogue exemestane[17] are widely used as the first-line drugs in the endocrine treatment of hormone-dependent breast cancer in postmenopausal women.

Anastrozole, letrozole and exemestane are administered orally with 1 mg, 2.5 mg, and 25 mg once daily, respectively. Compared to the first- and second-generation inhibitors, the third-generation inhibitors produce greater clinical benefit with near-complete specificity at clinical use. These AIs were also better tolerated than tamoxifen and were associated with lower incidences of endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flashes.[18,19] In addition, the incidence of contralateral breast cancer occurrence was found to be significantly lower in the AI group than the tamoxifen group.[18,20,21] However, the long-term effects of these drugs on skeletal problems, cardiovascular disease, and Alzheimer’s disease need to be carefully followed up.

Anastrozole and letrozole are non-steroidal derivatives that have the triazole functional which interacts with the heme prosthetic group of aromatase, and they act as competitive inhibitors with respect to the androgen substrates. Exemestane is a steroidal and mechanism-based inhibitor that is catalytically converted into a chemically reactive species, leading to irreversible inactivation of aromatase. All three AIs appear to have similar clinical efficacy despite these differences in pharmacological properties.

Clinical Uses of Aromatase Inhibitors in Gynecological Practice:

1. Breast Cancer:

In postmenopausal women, AIs were first introduced for the treatment of advanced breast cancer. Although these drugs did not increase overall survival, they appeared to be similar or better than megestrol acetate when objective responses were the end-point.[22]

The early success of these studies led to clinical trials of AIs in breast cancer patients with resectable, estrogen positive tumors. The largest of these trials compared anastrozole with tamoxifen, alone or in combination, as adjuvant treatment in women with early breast cancer following surgical resection. The study results demonstrated a small but significantly improved 3-year disease free-survival in postmenopausal women with invasive, operable breast cancer who received anastrozole alone compared with tamoxifen (89.4% versus 87.4%, hazard ratio 0.83 [95% confidence interval, 0.71–0.96]).[18]

Subsequently, many trials have been initiated to examine the role of AIs in other breast cancer clinical scenarios including its role as a sequential therapy following tamoxifen, in the treatment of ductal carcinoma in-situ, and in the prevention of breast cancer in high-risk patients.[23] Although data from these trials are still incomplete, it can be postulated that AIs will play a significant role in the therapy of estrogen receptor-positive breast cancer.

AIs have also been used as a treatment modality for premenopausal women with early breast cancer who have chemotherapy-induced amenorrhea. This off-label use should be prescribed with caution because case series have described the resumption of ovarian function.
following initiation of an AI regimen.\textsuperscript{[24,25]} To identify women who experience a return of ovarian function, serial monitoring of estradiol and gonadotropin levels to may be indicated.\textsuperscript{[24]}

Adverse effects of AIs
The short- and long-term adverse effects of AIs in postmenopausal women are related to the lack of estrogen at aromatase-targeted tissue sites and include: hot flashes, vaginal dryness, arthralgias, decreased bone mineral density and an increased fracture rate.\textsuperscript{[26]} It is currently recommended that bone mineral density (BMD) screening be repeated annually in all patients receiving AI adjuvant therapy, and bisphosphonate therapy should be initiated when T scores are -2.5 or lower.\textsuperscript{[27]} To reduce the risk of osteoporosis in high-risk patients, bisphosphonates may be co-administered to patients during long-term treatment with AIs.

2. Endometriosis:
Endometriosis, defined as the presence of endometrial tissue outside of the uterine cavity (ectopic endometrium), affects 10\% of women of reproductive age and as many as 50\% of women with chronic pelvic pain or infertility. The principal symptoms are chronic pelvic pain, dysmenorrhea, deep dyspareunia, infertility, and urinary and cyclic bowel alterations. The pathogenesis of endometriosis is complex and multifactorial and despite being one of the most studied diseases in gynecology, its etiology has yet to be clarified. Currently, a combination of theories that include an impaired immunologic response, a genetic predisposition, and an inflammatory component provide possible explanations as to the cause of the disease.

An overexpression of the aromatase enzyme, the main responsible factor for estrogen synthesis in ectopic endometrium, has been demonstrated in endometrial tissue.\textsuperscript{[28]} Aromatase catalyzes the conversion of the steroidal precursors to estrogen, which stimulates the expression of the enzyme COX-2. The estrogens produced in the endometrial tissue through aromatase promote the growth and invasion of endometrial lesion and favour the onset of pain and prostaglandin-mediated inflammation.\textsuperscript{[29]} This local production of estrogen may explain the progression of endometriosis during therapy with gonadotropin-releasing hormone analogues (GnRH-a) that act only at the level of the ovarian production of estrogen.\textsuperscript{[30]} AIs on the contrary, lead to a reduction of extra-ovarian estrogen concentration.\textsuperscript{[31]} The estrogen plasma levels in women taking 1–5 mg of letrozole or anastrozole daily are reduced by 97–99\%.\textsuperscript{[32]}

By reducing the production of extra-ovarian estrogens, AIs stimulate an increased secretion of FSH from pituitary gland, promoting an increased ovarian production of estrogens and follicular recruitment. When used in premenopausal women, it is important to associate drugs that lead to a down-regulation of ovarian activity, such as progestins, GnRH-a, or oral contraceptives, in order to counteract the potential formation of follicular cysts.\textsuperscript{[32,33,34]} The combination of conventional therapy and AIs determines the block of the production of estrogens both in ovarian and extra-ovarian endometriotic foci, reducing the painful symptoms. They have been used in a pilot study evaluating 12 women with recto-vaginal endometriosis, who had pelvic pain resistant to conventional treatments: after 6 months of treatment with letrozole (2.5mg/day), norethisterone acetate (2.5mg/day), calcium citrate, and vitamin D, there has been a significant
reduction in abdominal-pelvic pain and the disappearance of endometriotic lesions at second-look surgery.\cite{35} A subsequent study, from the same group, showed that the association of letrozole with norethisterone acetate provides pelvic pain control more effectively than norethisterone acetate alone.\cite{36} Pelvic pain, however, tends to recur after discontinuation of treatment, just as after the discontinuation of GnRH-a.\cite{37}

3. Ovulation Induction:

In premenopausal women, AIs reduce hypothalamic-pituitary estrogen feedback that leads to increased gonadotropin-releasing hormone (GnRH) secretion, concomitant elevations in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and increased follicular development. The gonadotropin-stimulating action of letrozole has been used off-label in the treatment of patients with ovulatory dysfunction, such as polycystic ovary syndrome (PCOS), and for increasing the number of ovarian follicles recruited for ovulation in women who are already ovulatory.\cite{38,39}

In a meta-analysis of four published trials, including 662 women with PCOS, pregnancy rates were similar between women treated with clomiphene citrate and women treated with letrozole (relative risk, 1.02; 95% confidence interval, 0.83–1.26).\cite{40} Some have raised concerns about this off-label use because letrozole may disrupt the normal aromatase activity in tissues during early fetal development and can be potentially teratogenic if administered inadvertently during early pregnancy. However, a large study of 911 newborns conceived using letrozole for ovulation induction (OI) showed no difference in rates of congenital malformations.\cite{41} In addition, the half-life of letrozole (approximately 30 – 60 hours) is much shorter than that of clomiphene citrate (5 – 7 days) and, thus, should be effectively cleared from the body by the time of embryo implantation, likely preventing a teratogenic effect when used in OI. The possible advantages of letrozole over clomiphene citrate include reduced multiple pregnancies, lower estradiol levels, and an absence of anti-estrogenic adverse effect on the endometrium. However, there is no evidence currently to prove that letrozole is more effective than clomiphene citrate for OI. However, letrozole may have a role in the treatment of clomiphene-resistant patients.\cite{42,43}

Conclusion:

Aromatase inhibitors (AIs) have definitely gained importance in modern gynecological practice as an effective therapeutic adjuvant for early-stage and late-stage breast cancer. Their role in chemoprevention of breast cancer in high-risk patients remains to be defined. Adverse effects of AIs in postmenopausal women are due to the estrogen lowering action at the target tissues and include hot flashes, vaginal dryness, arthralgias and decreased bone mineral density. Several studies have positively indicated a molecular basis for treating endometriosis with AIs. AIs with conventional therapy as oral contraceptive pills, progestins, or gonadotropin-releasing hormone analogues have been used to control endometriosis-associated pain and pain recurrence in premenopausal women, particularly those with pain due to recto-vaginal endometriosis refractory to other medical or surgical treatment. AIs have shown promise in the treatment of postmenopausal endometriosis as first-line treatment, when surgery is contraindicated, or as second-line treatment in the case of postoperative recurrence. In the
reproductive-aged women, AIs stimulate gonadotropin secretion and increase follicular activity, proving a strong challenger to the time-tested clomiphene citrate as an ovulation induction agent in patients with polycystic ovary syndrome and in cases of unexplained infertility. Data from recent retrospective and prospective studies support the safety of AIs for ovulation induction.

Acknowledgements:
The authors gracefully acknowledge and record their gratitude to the ACOG Committee Opinion No. 412, August 2008 (reaffirmed in 2014), and to Dr. Gabriella Zito et al (Hindawi Publishing Corporation, BioMed Research International, Volume 2014, Article ID 191967) for reproduction of information in the above-mentioned review article.

References:


Preoperative Blood Transfusion in Paediatric Patients
Dr. Tulsi Nag¹, Dr. Kasturi Hussain Banerjee²

Abstract:
Paediatric patients undergoing surgical procedures commonly require some volume of blood or blood component replacement in perioperative period. Those undergoing major surgery with substantial blood loss should be evaluated preoperatively. Preoperative Correction of anaemia may be done considering the age, plasma volume status, clinical condition and co morbidities. Maximum allowable blood loss (MABL) for surgery must be calculated and appropriate quantity of blood and blood components should be arranged. Intra operative monitoring of blood loss should be done and volume of transfusion should be assessed considering the volume status and trigger threshold for transfusion.
Early haemostasis should be achieved by judicious administration of red blood cells, blood components and pharmacological agents.

Key Words:
Paediatric patients, Perioperative transfusion, Blood loss, Anaemia.

Introduction:
Perioperative blood management refers to perioperative blood transfusion and adjuvant therapies. Perioperative blood transfusion addresses the preoperative, intraoperative and postoperative administration of blood and blood components. Adjuvant therapies refer to drugs and techniques used to reduce or prevent blood loss and need for allogenic blood transfusion.

Guidelines for Blood Transfusion and Adjuvant Therapy.

Preoperative Evaluation:
It identifies the cause for blood transfusion or adjuvant therapy by:
1. Reviewing previous medical records.
2. Conducting a patient or family interview.
3. Reviewing laboratory test results.
4. Ordering additional laboratory tests when indicated

Review of previous medical records and interview of patient or family help to elicit:
H/O previous blood transfusion, drug induced Coagulopathy, Congenital Coagulopathy, thromboembolic events and risk factors for organ ischaemia.

Review of laboratory tests exhibits haemoglobin level, Haematocrit and coagulation profile. Additional tests are ordered based on medical condition like anaemia, Coagulopathy. Physical examination is done to detect pallor, petechiae and ecchymosis.

Preoperative evaluation is performed well in advance to allow time for patient preparation.

Preadmission Patient Preparation:
It includes:
- Treatment of anaemia

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² Consultant Anaesthesiology, Medica Super Speciality Hospital, Kolkata
Discontinuation of anticoagulants and antiplatelets.

Preadmission autologous blood collection

Anaemia is treated with erythropoietin and/or iron to improve haemoglobin levels. Iron is administered to treat patients with iron deficiency anaemia.

Discontinuation of anticoagulation therapy is done before surgery with transition to a shorter acting drug like low molecular weight heparin. Antiplatelet agent like clopidogrel needs discontinuation well in advance of surgery except for patients having percutaneous Coronary intervention. The risk of thrombosis versus the risk of bleeding should be considered during altering anticoagulation status.

Availability of blood component should be assured when significant blood loss or transfusion is expected.

Preoperative autologous donation (PAD) offsets the risk of allogenic blood transfusion. PAD targets specific surgical blood procedures where excessive blood loss is expected. Compensatory erythropoiesis occurs during the Course of PAD. RBC production increases with increasing interval from last donation to surgery and this interval should be maximized. Treatment with erythropoietin during PAD increases the amount of blood collected and decreases allogenic blood transfusion. Erythropoietin is used to increase haematocrit preoperatively either alone or as an adjunct to PAD.

Pre-procedural Patient Preparation:

Strategies for reducing intraoperative allogenic blood transfusion consists of:

- Blood management protocols
- Reversal of anticoagulation
- Prophylactic anti fibrinolytics for excessive blood loss.

Acute normovolaemic haemodilution (ANH)

Multimodal protocols consist of predetermined “bundle” of interventions to reduce blood loss and transfusion requirements.

Algorithms are intended to identify decision points or pathways during procedure.

Haemoglobin criteria of less than 8g/dL and haematocrit value of less than 25% are typically reported as restrictive transfusion. In restrictive transfusion strategies, fewer blood cell transfusion are required.

Massive transfusions are implemented in cases of life threatening haemorrhage after trauma and/or during a procedure to minimize adverse effects of hypovolaemia and dilutional Coagulopathy. This requires availability of large amount of allogenic blood & blood products. Often transfusion of fresh frozen plasma (FFP) and platelets in a ratio of 1:1 is prescribed with transfusion of red cells. Studies indicate that the ratio of FFP to cells is higher after the implementation of massive transfusion.

For urgent reversal of anticoagulation from warfarin preprocedural administration of prothrombin complex concentrates (PCCS) and FFP is indicated and reduces INR.

Vitamin k is administered for non-urgent reversal from warfarin. Antifibrinolytics are used as prophylaxis for excessive blood loss. They reduce allogenic blood transfusion during surgical procedures with excessive bleeding. Preoperative and intraoperative administration of ε-aminocaproic acid is effective in reducing total perioperative blood loss, the number of patients transfused and the volume of blood transfused. There are less blood loss and low
RBC transfusion requirement when prophylactic e-aminocaproic acid is administered for excessive bleeding during surgery.

Preoperative and intraoperative administration of **tranexamic acid** effectively reduces perioperative blood loss, the number of patients transfused and the volume of blood products transfused.

A acute normovolaemic haemodilution (ANH) is effective in reducing the volume of allogenic blood transfusion and number of patients transfused with allogenic blood for major surgeries. Combined ANH with intraoperative RBC recovery is more effective in reducing volume of allogenic blood transfusion than ANH alone in patients with high risk of excessive bleeding.

**Interventions for Intraoperative and Postoperative Management of Blood Loss:**

These include:

- Allogenic RBC transfusion
- Reinfusion of recovered RBC
- Treatment of excessive bleeding
- Intraoperative and postoperative monitoring.

Transfusion of allogenic RBC transfusion should consider the age of stored RBC and leukocyte reduction in it. ASA members disagree regarding the administration of blood without considering the duration of storage. They also strongly agree that to reduce complications associated with allogenic blood transfusion, leukocyte reduced blood should be used.

Intraoperative RBC recovery is effective in reducing the volume of allogenic blood transfused. Postoperative RBC recovery and reinfusion reduces the frequency of allogenic blood transfusion in patients undergoing major surgeries. Treatment of intraoperative and postoperative excessive bleeding is done by transfusion of platelets, FFP, Cryoprecipitate and pharmacological treatment. Coagulation tests are obtained before transfusion of FFP.

In patients with excessive bleeding fibrinogen level should be assessed before administration of cryoprecipitate.

Pharmacological treatment of excessive bleeding is done using:

- Desmopressin which effectively reduces the amount of postoperative blood loss.
- Antifibrinolytes such as €-aminocaproic acid and tranexamic acid.
- Topical haemostatics like fibrin glue and thrombin get which effectively reduce blood loss and time to haemostasis.
- Uses of PCCs are considered in patients with excessive bleeding and increased INR.

- When traditional options for treating excessive bleeding due to Coagulopathy have been exhausted, administration of recombinant activated factor VII is considered.

- Fibrinogen concentrate is considered for treatment of excessive bleeding due to hypotibrinogenemia.

Intraoperative and postoperative monitoring is done for:

- Blood loss
- Vital organ perfusion
- Anaemia
- Coagulopathy
- Adverse effects of transfusion.

Blood loss is monitored periodically by visual assessment of surgical field including extent of
blood present, presence of micro vascular bleeding, surgical sponges, clot size and shape and volume of blood in suction canister.

Perfusion of vital organs is monitored by standard ASA monitorings. Additional monitoring include:

- Echocardiography
- Renal monitoring
- Cerebral monitoring

Anaemia is monitored by estimation of haemoglobin and haematocrit levels based on estimated blood loss and clinical signs. Monitoring of Coagulopathy involves standard coagulation tests and platelet count. Additional monitoring includes tests of platelet function and viscoelastic assay (Thromboelastogram).

Adverse effects are assessed by periodic checking for:

1) Signs of ABO incompatibility such as:
   - Hyperthermia
   - Haemoglobinuria
   - Micro vascular bleeding

2) Signs of transfusion related lung injury such as fever, dyspnea of hypoxia.

3) Transfusion associated circulatory overload characterized by:
   - Hypoxia, respiratory distress and increased peak airway pressure.

4) Signs of bacterial contamination as:
   - Hyperthermia
   - Hypotension

5) Signs of allergic reactions like urticaria.

6) Signs of citrate toxicity such as hypocalcaemia.

Before initiating therapy for transfusion reactions, blood transfusion should be stopped and appropriate diagnostic testing should be ordered.

**Transfusion in Paediatric Patients**

The current guidelines for paediatric blood transfusion in adults, keeping a higher transfusion threshold for children as haemoglobin levels are usually lower in normal children. Though transfusion guidelines for children and adolescents are similar to adults, neonates have special needs.

**Guidelines of Paediatric Haemotherapy Committee of American Association of Blood Bank**

The committee considers that:

- Blood components should be the neonates’ own ABO and RHD group or an compatible ABO and RHD group.
- For all paediatric patients blood donated from first degree relatives should be indicated.
- Gamma irradiated cellular products are used for preterm infants in many Countries.
- Frozen cellular products such as FFP and antihaemophylic factors do not need irradiation.
- All cellular blood products except granulocyte concentrates should be leukocyte depleted by gamma irradiation.

RBC transfusion is primarily indicated to increase oxygen carrying capacity along with control of haemorrhage and restoration of tissue perfusion.

Before RBC transfusion the MABL should be estimated to avoid over transfusion.

The MABL is estimated as follows:

\[
\text{MABL} = \frac{\text{EBVX} (\text{HO} - \text{HI})}{\text{HO}}
\]

EBV = estimated blood volume
HO = initial or starting Haematocrit.
H1 = Lowest acceptable or target Haematocrit.
The MABL indicates the volume of red packed cells to be transfused according to desired haematocrit. Blood volume is estimated according to age.

### Estimated Circulatory Volume Based on Age of Children:

<table>
<thead>
<tr>
<th>AGE</th>
<th>BLOOD VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm newborn</td>
<td>90ml/kg</td>
</tr>
<tr>
<td>Term newborn to 3 months of age</td>
<td>80-90ml/kg</td>
</tr>
<tr>
<td>Over 3 months of age</td>
<td>70-80ml/kg</td>
</tr>
<tr>
<td>Over 2 months of age</td>
<td>70ml/kg</td>
</tr>
</tbody>
</table>

### Normal Haemoglobin Concentration and Haematocrit Values Based on Age of Children:

<table>
<thead>
<tr>
<th>Age</th>
<th>Haemoglobin(g/dl)</th>
<th>Haematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>18.5</td>
<td>56</td>
</tr>
<tr>
<td>3-6 months</td>
<td>11.5</td>
<td>35</td>
</tr>
<tr>
<td>6 months-2 years</td>
<td>12.0</td>
<td>36</td>
</tr>
<tr>
<td>2-6 years</td>
<td>12.5</td>
<td>37</td>
</tr>
<tr>
<td>6-12 years</td>
<td>13.5</td>
<td>40</td>
</tr>
</tbody>
</table>

For blood transfusion, paediatric patients are divided between younger and older than 4 months on physiological basis.

Preterm and low birth weight infants along with infants younger than 4 months need special consideration of their immature haemostatic and immune systems with limited capacities to tolerate thermal and metabolic alterations from transfusion.

Before ordering RBC transfusion the desired haemoglobin level should be assessed to estimate the required transfusion volume. Special care is taken to minimize the multiple units and maximize the use of each unit.

### Transfusion Threshold for Infants Under 4 Months

<table>
<thead>
<tr>
<th>Causes</th>
<th>Haemoglobin Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia in first 24 hours of life</td>
<td>12g/dl</td>
</tr>
<tr>
<td>Cummulative blood loss in 1 week in neonates requiring ICU</td>
<td>10% of blood volume</td>
</tr>
<tr>
<td>Neonates receiving ICU care</td>
<td>12g/dl</td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>10% of blood volume</td>
</tr>
<tr>
<td>Chronic O2 dependency</td>
<td>11g/dl</td>
</tr>
<tr>
<td>Late anaemia in stable child.</td>
<td>7g/dl</td>
</tr>
</tbody>
</table>
Guidelines for RBC Transfusion in Infants Under 4 Months:
- Haematocrit less than 20% with low reticulocyte count.
- Haematocrit less than 30% in an infant on:
  a. 30% hood oxygen, oxygen via nasal mask, CPAP or IMV with a mean airway pressure less than 6cm H2O and with
  b. Signs of tachycardia or tachypnoea (Tachycardia-HR more than 180 beats/min for 24 hours. Tachypnoea-RP more than 80 breaths/min)
  c. Signs of apnoea or bradycardia. (A pnoea-more than 6 episodes in 12hrs. or 2 episodes in 24hrs. requiring bag-mask ventilation while receiving xanthenes)
  d. Low weight gain (gain of less than 10g/day observed over 4 days while receiving more than 100kcal/kg/day)
    - Haematocrit less than 35% in an infant on:
      a. More than 35% hood oxygen.
      b. CPAP or IMV with a mean airway pressure between 6-8cmH2O.
      - Haematocrit less than 45% in an infant:
        a. With congenital heart disease
        b. On ECMO.

Guidelines for RBC Transfusion in Children and Adolescents:
- Acute blood loss more than 25% of blood volume.
- Haemoglobin level below 8g/dl in perioperative period and below 13g/dl associated with cardiopulmonary disease.
- Symptomatic chromic anaemia or bone marrow failure.
- Severe chronic anaemia with haemoglobin level less than 7g/dl.
- Hypovolaemia not responding to other treatment.
- Preparative haemoglobin less than 12g/dl with severe cardiopulmonary disease.
- Post operative anaemia with haemoglobin less than 10g/dl

RBC transfusions though life saving is associated with complications like:
- Transfusion transmitted infection
- Haemodynamic instability
- Intravenous volume overload
- Acute haemolysis
- Transfusion related acute lung injury
- Various Immunological consequences.

Therefore RBC transfusion should only be given when true benefits are likely.

Indications for Transfusion:
For over 40 years transfusion was indicated to maintain haemoglobin concentration above 10g/dl and haematocrit level above 30%. Over past 10 years paediatric physician became more restrictive in use of RBC.

In anaemic children, the only indication for RBC is to prevent or reverse tissue hypoxia due to inadequate circulating RBC mass.

A child’s haemoglobin value though important should not be the sole deciding factor when considering RBC transfusion. Decision to transfusion must be based on an assessment of risk of anaemia versus the risk of transfusion. In addition to assessment of child’s duration of anaemia must be taken into account. The extent of trauma and surgery with probability of blood loss and co-existing conditions should also be considered.
Acute anaemia usually needs immediate medical attention. Treatment depends on severity and underlying cause.

As per restrictive criteria, in healthy children a transfusion haemoglobin threshold of 7 g/dl is appropriate. In presence of cardiac disease it may be safe to maintain haemoglobin level above 9 g/dl.

**Haemoglobin Threshold for RBC Transfusion in Paediatric Age Group.**

**In infants less than 4 months:**

Haemoglobin threshold for RBC transfusion is less than:

- a. 7g/dl in a stable infant with late anaemia
- b. 8g/dl for symptomatic anaemia
- c. 10g/dl for major surgery
- d. 10g/dl in infant with moderate cardio-pulmonary disease.
- e. 13g/dl in infant with severe cardio-pulmonary disease.

**In children:**

The threshold for RBC transfusion is

- a. Haemoglobin level less than
- 1. 7g/dl for symptomatic anaemia and
- 2. 9g/dL in presence of cardio-pulmonary disease
- b. Acute blood loss more than 30% of blood volume.

In practice diagnosis of presence and degree of blood loss is quite difficult in healthy young children who can sustain a large hemorrhage with few external signs of cardiovascular compromise such as:

- Hypotension
- Cold extremities
- Weak peripheral pulse
- Decreased capillary filling time

During active bleeding transfusion is appropriate to maintain haemoglobin above 7g/dL. In critically ill children with anaemia, transfusion is effective to control symptoms of anaemia if haemoglobin level falls below 7g/dL, with an aim to maintain haemoglobin between 7-9 g/dL. A packed RBC product comprises the sedimented or centrifuged RBC from one unit of single donor whole blood and is the component of choice for replacement therapy during RBC loss from surgery or trauma.

As transfusion of allogenic cellular blood products is associated with deleterious effects from presence of residual leukocytes, these should be reduced. Specialized leak filtration or pheresis collection devices achieve a reduction of leukocyte count more than $10^4$ fold, in final blood products.

Routine leukoreduction of RBC to less than $5 \times 10^6$ leukocytes/unit reduces the incidence of febrile, non-hemolytic reactions and alloimmunization to human histocompatibility antigens in transfusion dependent children. It is also effective in preventing CMV transfusion in neonates.

The long term use of leukoreduced RBCs in children and neonates’ undergoing surgery for malignancy is evidence supported. The use of CMV seronegative leukoreduced products is recommended in:

- Children undergoing haemopoietic stem cell transplants.
- Infants of CMV-seronegative mothers
- Children with immune-deficiencies.

Washing of RBC is indicated only in the event...
of allergic or anaphylactic transfusion reactions to allogenic plasma proteins. Washing a unit of RBC with sterile normal saline removes all plasma proteins, electrolytes and antibodies. As the extracellular K⁺ concentration increases with duration of RBC storage, small infants may require saline washed RBC if fresh RBCs are not available for rapid or large transfusion (more than 20ml/kg) such as during exchange transfusion or ECMO procedures.

Transfusion over 25ml/kg or more than one volume of RBC in 24 hours need careful attention for:
- Cardiovascular instability
- Dilutional Coagulopathy
- Metabolic and thermal disturbances.
- In massive transfusion citrate binds to ionized ca++ causing hypocalcaemia.

Rapid RBC transfusion containing high concentration of extracellular K⁺, results cardiac disturbances in small children. Hypothermia is a concern when rapid transfusion is needed.

Varieties of additive solution have evolved with well developed storage systems improving safety and effectiveness of RBC transfusion. Small stored in an extended storage preservative solution with haematocrit of 55-60%. RBC components centrifuged before transfusion have improved volume and RBC mass attaining a uniformly packed RBC concentrates with haematocrit of 80-90%.

**Considerations in Neonates:**

Anaemia in infants may be physiological or non-physiological.

A physiological drop in haemoglobin occurs during the first several weeks or months of life. In healthy term infants the lowest value rarely falls below 9g/dL. This occurs at the age of 10-12 weeks, remains stable for several weeks and then increases progressively. It is asymptomatic and does not require transfusion. The decline in haemoglobin is more pronounced and occur earlier in premature infants.

In sick preterm infants anaemia of prematurity can be exacerbated by non-physiological anaemia, the most common of which is blood loss related to repeat laboratory testing. The optimum haemoglobin for neonates facing major surgery is not established but it seems reasonable to maintain haemoglobin above 10g/dL, because of limited ability of neonate’s heart, lungs and vasculature to compensate for anaemia.

Anaemia is defined as the reduction in RBC mass or haemoglobin concentration that results in decreased oxygen carrying capacity. Infants with chronic anaemia are well compensated having only tachycardia. In acute anaemia the heart responds to tissue hypoxia by increasing cardiac output which is matched by decreased systemic vascular resistance and decreased blood viscosity without increase in blood pressure.

In neonates cardiac output depends on heart rate rather than stoke volume. Hence tachycardia if prolonged may compromise cardiac output. Increased oxygen extraction from anaemic blood by tissues produces increased concentration of deoxyaemoglobin in RBC, stimulating production of 2, 3 DPG which shifts oxygen dissociation curve to right decreasing affinity of oxygen for haemoglobin resulting better oxygen delivery to tissues.

In case of more gradual onset, the blood volume, size of vascular bed and rate of production of
RBC increase, resulting mild to moderate anaemia, without significant symptoms. Severe anaemia is detrimental to sick children causing shock and haemodynamic compromise.

**Need for Intraoperative Transfusion Depends on:**
- Rapidity and amount of blood loss
- Assessment of blood volume
- Preoperative Haematocrit
- Medical conditions like cardiopulmonary disease.
- Nature of surgery
- Risk benefit ratio of transfusion.

**Intraoperative Monitoring Based on Expected Blood Loss:**

<table>
<thead>
<tr>
<th>Expected Blood Loss</th>
<th>Monitoring / Action Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30% of circulating blood volume</td>
<td>Routine monitoring.</td>
</tr>
<tr>
<td>30-50% of circulating blood volume</td>
<td>Additional urine output monitoring, two venous line done.</td>
</tr>
<tr>
<td>50-100% of circulating blood volume</td>
<td>Additional Central venous lines, Arterial line, rapid transfusion equipments.</td>
</tr>
<tr>
<td>Massive blood transfusion expected</td>
<td>Arterial blood gases, Metabolic and Coagulation monitoring, Hypothermia prevented, in addition to above monitoring.</td>
</tr>
</tbody>
</table>

**Conclusion:**
The current guidelines for paediatric blood transfusion are mainly based on available information regarding transfusion in adults, except that the transfusion thresholds are kept higher in children.

Though guidelines are similar to adults in children and adolescents, neonates have special needs. Additional information are needed to better define the guidelines for children.

Transfusion decision in children should be based on child’s physical status, associated co-morbidities, presence of bleeding, risks of anaemia versus transfusion and not only on haemoglobin level.

Before RBC transfusion MABL should be estimated to know the volume of red packed cells to be transfused, avoiding over transfusion. During active bleeding transfusion is appropriate to maintain haemoglobin above 7g/dL. Restrictive strategy For RBC transfusion with haemoglobin less that 7g/dL is equally effective as liberal transfusion strategy with haemoglobin less than 10g/dL.

A symptomatic transfusion strategy is as effective as or superior to haemoglobin based transfusion strategy. Despite significant improvement in blood testing and handling, there remains infections or non-infections risks associated with allogenic blood transfusion. Incidence of adverse effects is greater in children specially infants with long term repercussion.

Antifibrinolytics are used as prophylaxis for
excessive blood loss and to reduce allogenic blood transfusion in children undergoing procedures with excessive blood loss.

Acute normovolaemic haemodilution is effective in reducing the volume of allogenic blood transfusion and member of children transfused with allogenic blood during procedures associated with excessive bleeding.

Blood conservation modalities can be used safely in paediatric patients.

Paediatric transfusion medicine is evolving and intense research into manufacture of red cells are ongoing of promising.

References:


Abstract:
Uterine anomalies are present in 1 to 10% of the unselected population and presents with various gynaecological obstetric and even renal problems. Although the reproductive outcome of women with unicornuate uterus is poor, a successful pregnancy is possible. We report a case of a 29 years old women having a successful pregnancy after 7 spontaneous abortions.

Keywords: Congenital Mullerian malformations, Congenital uterine anomalies, Recurrent Pregnancy Loss

Introduction:
Uterine anomalies are present in 1 to 10% of the unselected population, 2 to 8% of infertile women and 5 to 30% of women with a history of miscarriages.

A unicornuate uterus is a type II AFS classification with unilateral hypoplasia or agenesis that can be further subclassified into communicating, non communicating, no cavity and no horn.

It accounts for 2.5 to 3% of all Mullerian Anomalies, and presents at different stages of life starting with dysmenorrhoea, hematometra, endometriosis. It causes infertility due to abnormal genital tract, recurrent pregnancy loss due to faulty implantation, ectopic pregnancy. Obstetric outcome in case of unicornuate uterus is also poor as it causes intra uterine growth restrictions, malpresentations, preterm delivery, stillborn, uterine rupture. These can be explained by mechanical factors (decreased and distorted uterine space), and reduced blood flow (absent or abnormal uterine artery). The reproductive performance of women with unicornuate uterus is poor, with a live birth rate of only 29.2%, prematurity rate of 44%, and an ectopic pregnancy rate of 4%. Moreover, women with this anomaly, present rates of 24.3% first trimester abortion, 9.7% second trimester abortion and 10.5% intrauterine fetal demise.

Associated Renal anomalies like renal agenesis, Horseshoe kidney and pelvic kidney may be present in 44% of cases. (In the presence of obstructed horn)

We present a case report of a successful pregnancy in a P0+7 woman with unicornuate uterus.

Case Presentation:
A 30 years old G8P0+7 visited our antenatal OPD for the first time at 13 weeks period of gestation with an USG report that showed a single live fetus with good decidual reaction, and gestational age corresponding to that of last menstrual period, the pregnancy was in the Left horn of the uterus.

Detailed history was elicited and routine antenatal investigations were done. Serial obstetric ultrasounds were done at 2nd and 3rd trimester and revealed no gross anomaly of the fetus, cervical length of around 4 cm. and normal
growth pattern with a breech presentation. She was admitted at 35 weeks 6 days period of gestation for monitoring when she was given a course of steroid to ensure fetal maturity. An USG at 36 weeks POG was done to see the growth pattern and liquor volume of the fetus, and an elective Caesarean Section was planned at 37 weeks period of gestation.

She delivered a healthy male baby of 2.8 kg birth weight, APGAR score 9/10 at 1 and 5 mins of birth with no structural anomaly.

**Past History:**

The patient had pain during menstruation from her menarche but did not seek medical help. She was married at 18 years of age after which she conceived for the first time within 8 months of regular intercourse, but she had a spontaneous complete abortion at 8 weeks period of gestation. The second pregnancy also had the same course (i.e., first trimester abortion).

Then she went for medical help where a battery of tests was done and she was diagnosed to have a unicornuate uterus.

Her USG (2D, TVS) could not pick up any gross anomaly.

**Laparoscopic dye test result:**

- Unicornuate uterus
- Well developed left horn
- Presence of left tube and ovary
- Ill developed right horn
- Mid portion of the right fallopian tube was absent
- Right ovary was visualised.

**Figure 3. Unicornuate uterus after delivery of the baby showing the non communicating cavities.**

**Figure 1. The gravid uterus prior to uterine incision. Note - rt fallopian tube is absent.**

**Figure 2. Well developed left horn with tube and ovary.**
USG KUB found no abnormality.

**Menstrual history**
- Menarche 14 years
- Cycle –regular 28 days
- Duration-4 to 5 days
- Associated with pain lower abdomen

**Family history**
- Nothing significant

**Obstetric history**

<table>
<thead>
<tr>
<th>Month, Year</th>
<th>Type of abortion</th>
<th>Period of gestation</th>
<th>?D&amp;E needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb, 2004</td>
<td>spontaneous</td>
<td>8 wks</td>
<td>No</td>
</tr>
<tr>
<td>Jan, 2005</td>
<td>spontaneous</td>
<td>8 wks</td>
<td>No</td>
</tr>
<tr>
<td>Jan, 2008</td>
<td>spontaneous</td>
<td>10 wks</td>
<td>Yes</td>
</tr>
<tr>
<td>Nov, 2009</td>
<td>spontaneous</td>
<td>12 wks</td>
<td>No</td>
</tr>
<tr>
<td>Oct, 2010</td>
<td>spontaneous</td>
<td>8 wks</td>
<td>Yes</td>
</tr>
<tr>
<td>Feb, 2012</td>
<td>spontaneous</td>
<td>14 wks</td>
<td>Yes</td>
</tr>
<tr>
<td>June, 2013</td>
<td>spontaneous</td>
<td>12 wks</td>
<td>No</td>
</tr>
</tbody>
</table>

**Past Medical History**
- Nothing significant

**Discussion:**

Women with unicornuate uterus have an increased incidence of gynecologic and obstetric problems and tend to present, at menarche or later in their life, with symptoms such as dysmenorrhea and chronic pelvic pain, infertility, recurrent pregnancy loss, etc.

The primary investigation to these problems is therefore an USG of pelvis. Nevertheless ultrasound diagnosis can be missed, particularly in inexperienced hands.

A unicornuate uterus is often associated with ectopic pregnancies and with rupture of the rudimentary horn and, although it is unclear whether or not to remove the rudimentary horn before conception or early in pregnancy, its resection may improve the obstetrical outcome.

Patients with a unicornuate uterus present a higher risk of obstetrical complications, such as first trimester abortion, second trimester abortion, intrauterine growth restriction, preterm delivery and intrauterine fetal demise, and only a few obstetrical risks can be reduced by a particular pregnancy follow up and specific interventions.

As for the risk of preterm labor, there are no consistent data that any intervention can delay delivery in women for longer than 24 to 48 hours once they present a preterm labor. For this reason, much attention has been focused on preventive strategies rather than on intervention strategies. Although several strategies have been proposed, the prevention of preterm birth has been largely unsuccessful. [6]

The utility of ultrasound cervix length measurement for assessing the risk of preterm birth has been well documented, with an accepted cut off value for cervix length of <25mm before the 24th week of gestational age.

The predictive value of a negative test is high (92%); this implies that pregnant women who
do not have a shortened cervix can be reassured, and unnecessary therapeutic measures can be avoided.

By contrast, cervical cerclage is the best treatment for women with a short cervix (<25mm), and particularly for women with a history of prior midtrimester pregnancy losses due to cervical insufficiency. Therefore, in our case report, a cervical cerclage was considered unnecessary. Whether progesterone acts by attenuating further cervical shortening is not clear yet.

Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role.

Nevertheless, the optimal management approach cannot be clearly stated. Further large observational and prospective studies are essential to investigate the treatments needed during pregnancies in this uterine anomaly.

Referrences:
Fertility Preservation in A Young Woman with Gestational Trophoblastic Neoplasia

Prof. Sudip Saha, Dr. Biswajit Ghosh, Dr. Poushali Sanyal, Dr. Bidisha Roychoudhury

Abstract:
A patient with Gestational Trophoblastic Neoplasia (GTN) was treated by means of MTX-FA. Changes in serum β-HCG levels and changes in USG findings were checked after regular intervals. Finally patient responded after 12 cycles of chemotherapy with 3 consecutive negative values of serum β-HCG.

This is a case report of invasive mole in a 19 year old female with possibility to preserve reproductive health. GTN developed 3 months after spontaneous abortion in 8th week gestation. 3 months after abortion and 1 month after GTN confirmed she started on her chemotherapy cycles with MTX-FA.

Keywords: GTN, HCG, MTX-FA

Introduction:
Malignant GTN can develop as invasive mole, choriocarcinoma, PSTT. Ovarian theca lutein cysts usually follow malignant GTN. Reproductive organs can be severely damaged in malignant GTN. Early diagnosis and treatment according to accepted protocols could preserve reproductive health in malignant GTN. Serum β-HCG is of great value for early diagnosis and checking the effects of treatment.

Case Report:
A 19 year old female presented to a GP in the periphery around Jan’14 with history of amenorrhoea for 2 months with complaints of expulsion of products and pain abdomen. Her UPT was positive and USG reports showed incomplete abortion. She underwent D & E. During that time her Hb was 9.2 and blood group B+ve with TC, DC-WNL. Around end of Feb’14 she again presented with complaints of vomiting and no periods following D & E, her UPT was positive. USG (5/3/14) showed early intrauterine pregnancy of 5 weeks gestation with no cardiac activity. She was admitted in the periphery from 9/3/14 to 12/3/14 with complaints of low back pain. On examination she was pale with tenderness all over her abdomen. On bimanual pelvic examination the uterus was soft and bulky with suspected pelvic mass. Her sonography on 15/3/14 showed bulky uterus with no definite GSac with few cystic areas in myometrial and endometrial cavities with gestational trophoblastic disease which was confirmed with another scan few days later. Thus she was planned for D & E with endometrial biopsy in which endometrial biopsy showed only decidua like changes of the endometrium; serum β-HCG value was around 201841.65 mIU/ml. On 30/3/14 she complained of pain abdomen and on examination there was a pelvic lump. Thus she was advised for a CT scan of pelvis in which the report came out to be Intramural invasive mole. At that time her complete haemogram, liver, renal parameters, coagulation profiles all were within normal limits and serum β-HCG value (8/4/14) was 724133.17 mIU/ml.

With these reports she was admitted in our hospital and advised complete metastatic work up for Gestational Trophoblastic disease.
up including serum biochemistry, chest x-ray, CT brain, which did not reveal any evidence of metastasis. Radiotherapy department was consulted and she was planned for chemotherapy with Methotrexate and Leucovorin. She received her first dose on 11/4/14 and at interval of 15 days she received total 6 cycles at our hospital. During this time her \( \beta \)-HCG was on 6/5/14-5879.78, on 4/6/14-74.67, on 5/7/14-15.98 mIU/ml respectively.

She was under follow up outside at Burdwan Medical College till October’14 with regular monitoring of her blood counts, liver and renal parameters. In September’14 her USG on 6/9/14 showed ? residual secondary in the myometrium with right ovarian lutein cyst; serum \( \beta \)-HCG 2.1mIU/ml. She received another 5 cycles of chemotherapy with Methotrexate and Leucovorin, the last dose of which was around 14/10/14 at Burdwan medical college. During this time all her metastatic work ups were within normal limits.

She received the 12\textsuperscript{th} cycle of chemotherapy on 29/10/14 at our hospital and then finally on 28/11/14 her USG whole abdomen showed marginally bulky uterus with bilateral bulky ovaries. Serum \( \beta \)-HCG values in the next consecutive 3 months were within normal limits. Patient is still under follow up of radiotherapy and Gynae department in our hospital; presently on OCP having regular periods ; waiting to plan her future pregnancy eagerly.

\textbf{Results :}

This patient had long cycle of chemotherapy (12 cycles). USG confirmation of response to chemotherapy was of great help. In this patient the reproductive health could be preserved thankfully since she was so young. The treatment of this progressive malignant GTN was successful.
Discussion:
Serum β-HCG is the most relevant parameter in GTN detection as well as in checking the efficacy of administered therapy[1,2]. Successful treatment of malignant GTN does not mean that reproductive health can always be preserved. Chemotherapy plus hysterectomy is sometimes the method of choice in advanced malignant GTN treatment[1,2,3,4]. Malignant GTN does not have specific sonographic pictures and it is not easy to detect specific changes in uterine structure. Massive tissue destruction, hypervascularisation, low R.I., ovarian theca luteal cysts could be characteristic USG findings for GTN. According to recommendations CRCOG[5,6] USG is of limited value in detection of partial mole and malignant GTN[5,6].

Conclusion:
Progressive changes in uterine structure could be of great help in therapy decisions along with changes of serum β-HCG levels. Treatment can be longlasting with good prognosis but it needs good collaboration between gynecologist, radiologist, radiotherapist and patient including all kinds of support.

References:
Abstract:
The term cicatricial alopecia refers to the destruction of the hair follicles and their replacement with scar tissue, and permanent hair loss. It may be due to many diseases. Here we report two cases of cicatricial alopecia associated with two very rare diseases. The first case is Kyrle’s disease in a 10-yr-old male patient presenting with hyperkeratotic, dome-shaped papules resolving with atrophic scars over both upper and lower extremities, face and scalp. The second case is epidermolysis bullosa pruriginosa in a 21-year-old male patient who presented with albopapuloid and prurigo like lesions over body with scarring alopecia since five years of age.

Key words:
Cicatricial alopecia, Epidermolysis bullosa pruriginosa, Kyrle’s disease.

Introduction:
Kyrle in 1916 described a dermatosis which he named “hyperkeratosis follicularis et parafollicularis in cutem penetrans”[1]. Clinically Kyrle’s disease is characterized by hyperkeratotic para-follicular or follicular papules, with central cone-shaped plug which can be removed easily, usually involving the extensor surface of extremities. The cause of disease is not known, but it may be associated with diabetes, chronic renal failure and hepatic dysfunction[2],[3]. Epidermolysis bullosa pruriginosa (EBP) presents either at birth with mild acral blistering and erosions, or during infancy or childhood. It is characterized by extremely pruritic, lichenified or nodular lesions predominantly over legs, milia formation and albopapuloid lesions on the trunk. Most cases are sporadic; however, both autosomal recessive and dominant inheritances are recognized [4].

Case reports:
Case - 1
A 10-year-old male patient presented to our outpatient department with the chief complaint of raised multiple skin lesions over both upper and lower extremities, face and scalp for last 1 year. Some of the elevated lesions healed with scarring. The patient was otherwise in good health and was taking no medications. There was no family history of similar disease.

Examination demonstrated multiple, hyperkeratotic, dome-shaped, umbilicated papules with a diameter of 2 to 4 mm with central keratinous plug over his arms, hands, legs [Figure 1], face and scalp. In addition to hyperkeratotic lesions, cicatricial alopecia was present over the scalp [Figure 2]. Examination of the nails and mucosa showed no abnormality. Systemic examination was unremarkable.

On investigation, complete hemogram, fasting and post prandial blood sugar, serum urea and creatinine and routine urine analysis were

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Two biopsies were taken, one from extremity and another from scalp. Histology showed a hyperplastic epidermis, and multiple epidermal invaginations containing parakeratotic scale with basophilic debris [Figure 3]. Elastosis perforans serpiginosa was ruled out by the absence of thickened elastic fibres around epidermal invaginations, confirmed by the Von Gieson stain. Reactive perforating collagenosis was not considered due to the lack of degenerated collagen at the base of the perforation and negative Masson-trichrome stain. In perforating folliculitis, the epidermal invagination is seen in relation to a vellus hair, but that was absent in our case. The case was diagnosed as Kyrle’s disease involving scalp along with the other body sites. Patient was given oral isotretin at 1mg/kg/day along with topical retinoic acid (0.025% cream), and was asked to come for follow-up, but there was insignificant improvement.

Case - 2
A 21-year-old male patient presented to our outpatient department with the complaint of hyperkeratotic, dome-shaped papules with central keratinous plug over both legs.

Figure 1. Hyperkeratotic, dome-shaped papules with central keratinous plug over both legs.

Figure 2. Multiple patches of cicatricial alopecia over scalp.

Figure 3. Histopathology of skin lesion. (H&E, X10). Cornified plug with focal parakeratosis in an epidermal invagination containing basophilic debris.

Case - 2
A 21-year-old male patient presented to our outpatient department with the complaint of
blisters since the age of five years all over body. The blisters first appeared on the scalp, then progressed to involve back, chest, arms, thighs and legs, and then healed with pruritic papules or with scars. Prior to his visit to us, he had been treated for the skin disease with different modalities, including topical and systemic steroids, with no long-lasting benefit. No family members of the patient had any similar skin disease. Cutaneous examination demonstrated whitish papules (the so-called albopapuloid lesions) as well as prurigo-like lesions over back and chest. There were pruriginous papules in linear distribution over both the shins [Figure 4]. Multiple patches of scarring alopecia with crusted scaly plaques were seen over the scalp [Figure 5]. Mucosa, nail, palms and soles were free from any lesion and the teeth were normal. Systemic examination was unremarkable. Routine blood and urine examination were within normal limits. Histology from a lesion on the back showed sub-epidermal separation with mixed inflammatory cell infiltrate in upper dermis. Histology from scalp lesion showed sub-epidermal separation [Figure 6]. We diagnosed it as a case of epidermolysis bullosa pruriginosa on the basis of long history, albopapuloid lesions, pruritus, and histopathological finding of dermo-epidermal separation. Patient was given topical tacrolimus ointment and lotion (0.03%) for body and scalp lesions respectively. Patient had come for follow-up after 1 month; there was significant improvement in itching and body lesions [Figure 7]. Progression of the lichenified plaques and erosions was arrested and in some areas lichenified plaques were reduced.
Discussion:

Kyrle’s disease is one of the perforating dermatoses and a rare chronic disorder of unknown aetiology. The primary event is claimed to be a disturbance of epidermal keratinization characterized by the formation of dyskeratotic foci and acceleration of the process of keratinization\(^5\).

Kyrle’s disease has two distinct forms: an inherited form that presents in childhood and an acquired form that usually develops in adulthood, more commonly in women between 30 and 50 years of age associated with some underlying systemic disorder\(^6\). Topical retinoic acid may reduce the number of lesions. Other treatments which may help include oral isotretinoin, methotrexate, emollient creams, and high-dose vitamin A\(^7\).

EBP is a type of dystrophic epidermolysis bullosa (EB) described by McGrath et al in 1994\(^8\). In the one original series of eight cases reported by McGrath, three had family history of similar skin disease, with two showing an autosomal dominant and the other an autosomal recessive pattern of inheritance\(^8\). In our cases there was no family history of similar complaints indicating a sporadic case.

Ultrastructurally, there is a blister formation below the level of the lamina densa, and quantitative or qualitative changes in anchoring fibrils at the dermoepidermal junction. Reduction in anchoring fibril numbers is found in lesional, perilesional and non-lesional skin of patients with EB pruriginosa\(^9\). However, we could not perform electron microscopy in our case as we do not have facility for the same.

Treatment with topical tacrolimus has been reported to reduce the pruritus and progression of disease\(^10\).

In dystrophic epidermolysis bullosa, scalp is sometimes involved, leading to scarring alopecia, but as the disease is so rare, it is a very rare cause of scarring alopecia. In Kyrle’s disease involvement of scalp is very uncommon. We described the cases here, as among the various causes of cicatrical alopecia, these diseases are very rare.

In the literature, case reports of Kyrle’s disease and EB pruriginosa has been described. Here, these cases are of considerable clinical importance because of involvement of the scalp.
References:


Macular Amyloidosis Associated with Chronic Lichen Planus

Dr. Heena Parmar¹, Dr. Leelavathy Thiyagarajan², Dr. Jayanta Kr. Das³, Dr. Asok Gangopadhyay⁴

Abstract:
Macular amyloidosis represents a common variant of primary localized cutaneous amyloidosis, the later being characterized by deposition of a proteinaceous substance composed of one of a family of biochemically unrelated proteins in previously apparently normal skin. Lichen planus is an interface dermatitis where apoptotic keratinocytes may be present in the dermis. Here we describe a patient with macular amyloidosis associated with chronic lichen planus. The case is being reported because of rarity of the association.

Introduction:
Amyloidosis is a generic term that signifies the abnormal extracellular tissue deposition of one of a family of biochemically unrelated proteins that share certain characteristic staining properties, including apple-green birefringence of congo-red stained preparations viewed under polarising light[1]. Clinically macular amyloidosis presents as poorly delineated hyperpigmented patches of grayish-brown macules with a rippled pattern, associated with deposition of amyloid material in the papillary dermis[2]. The close proximity of the amyloid deposits to the lower epidermis in macular and lichen amyloidosis suggests that the epidermis plays a major role in its pathogenesis[3]. Amyloid deposits in macular amyloidosis bind to anti-keratin antibodies and contain sulphydryl groups, pointing to altered keratin as a source for the deposits. Lichen planus is an immunologically mediated disease that is characterized by violaceous, flat-topped polygonal papules. The exact etiology of lichen planus remains unknown. Recent studies have shown that lichen planus represents a cell mediated immune response to an induced antigenic change in the epidermal cells in a genetically predisposed individual[4]. T cells, both CD4+ and CD8+, accumulate in the dermis, while CD8+T cells infiltrate the epidermis. Histologically macular amyloidosis is characterized by deposition of amyloid in the form of small multifaceted amorphous globules, similar in size to the hyaline bodies found in lichen planus.

Case report:
A 57-year-old male patient with severely pruritic lesions involving his lower legs and hands for 12 years presented to our out-patient department. It clinically was typical hypertrophic lichen planus. He had been treated with different modalities, including topical and intralesional steroids. He remained disease-free for some time but then the disease recurred. At the time of presentation he had the chief complaint of a new eruption involving his legs, thighs, and arms. Thorough history-taking revealed that the patient had been suffering from diabetes mellitus, asthma and hypertension. There was no family history of similar skin disease.

Cutaneous examination demonstrated hyperkeratotic, violaceous, two to four cm

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⁴MD (Dermatology & Venereology), Prof. & Head, Dept. of Dermatology, RKMSR, VIMS
Fig 1. Hypertrophic, violaceous lesions of lichen planus on left leg.

Fig 2. Hyperpigmented macules of macular amyloidosis on right thigh.

Fig 3. Macular amyloidosis: eosinophilic, hyaline amyloid deposits with pigmentary incontinence in papillary dermis. (H&E, 40X)

Fig 4. Macular amyloidosis: homogeneous, globular amyloid deposits in papillary dermis. (Congo-red stain, 40X)

Fig 5. Lichen planus: epidermal hyperkeratosis, acanthosis, and hydropic degeneration of basal cell layer with lymphocytic cell infiltration. (H&E, 10X)
irregular plaques and nodules presented over both the shins and the ankle joints [fig1]. In addition, there were hyperpigmented macules arranged in a rippled pattern over his legs, thighs, and arms [fig2].

On investigation, complete haemogram and thyroid function test were normal. A biopsy specimen of the hyperpigmented macule on thigh revealed normal epidermis and the presence of round, homogeneous, eosinophilic material in the superficial papillary dermis, with a sparse superficial perivascular lymphocytic infiltrate [fig3]. Congo-red stain was consistent with the presence of scanty amount of amyloid [fig4]. A diagnosis of macular amyloidosis was made. A biopsy specimen of the hyperkeratotic nodule on left leg revealed acanthosis, hypergranulosis, papillomatosis, patchy lymphocytic infiltrate along the upper dermis and dermoepidermal junction, along with hydropic degeneration of the basal cell layer at places [fig5]. A diagnosis of hypertrophic lichen planus was made. The patient was initially given topical steroid and oral antihistamines, but he did not improve. He was put on colchicines 0.5 mg two times daily for two months with regular follow-up, but he did not respond. Finally intralesional steroid was given for hypertrophic lichen planus, and there was some temporary relief from itching, with some of the hypertrophic lesions subsiding considerable.

Discussion:
Chronic irritation to the skin resulting in excessive production of degenerate keratins, and their subsequent conversion into amyloid deposits has been described to be an etiologic factor of primary cutaneous amyloidosis[5]. The concept of focal epidermal damage and filamentous degeneration of keratinocytes, followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis, perhaps with a contribution from the dermal-epidermal junction has been proposed, and widely accepted[6]. If the apoptosis theory is true, any damage to the keratinocyte, beyond the ability of the phagocytic cell to remove the abnormal keratins, should be able to cause amyloid deposits. Immunohistochemical staining of amyloid deposits with anti-keratin antibodies has been investigated in several studies. Apaydin et al carried out immunohistochemical investigation on cytokeratins in amyloid deposits in formalin fixed and paraffin-embedded tissue specimens from subjects with macular and lichen amyloidosis to clarify the role of epidermal cells in the pathogenesis of these diseases[7]. Hashimoto et al proposed that degenerate keratins from apoptotic keratinocytes are transformed into amyloid by dermal macrophages and fibroblasts but exact mechanism of the conversion of the alpha tertiary structure of normal tonofilament into the beta-pleated sheet configuration of amyloid remain unknown.[8]

In our case, the patient had chronic lichen planus on both legs before macular amyloidosis developed. Theoretically chronic excessive production of cytoid bodies and disruption of basement membrane can allow degenerated keratins to be processed by macrophages into amyloid filaments later. It is possible that in this case chronic lichen planus produced enough damage at the dermoepidermal junction to induce macular amyloidosis.

There have been reports of response of cutaneous amyloidosis to topical DMSO therapy in some[9] but not all. Role of oral colchicines in primary localized cutaneous amyloidosis has been
described\textsuperscript{[10]}. Colchicine probably blocks the release of lysosomal enzymes within the degenerated epidermal cells thereby preventing conversion of tonofilaments into amyloid.

We have described this patient manifesting both macular amyloidosis and hypertrophic lichen planus, both for the rarity of such case reports, and for the probable aetiological connection between the two. The association, while it may be merely coincidental, raises the interesting possibility that amyloidosis is related to the chronic trauma to the skin, either from chronic pruritus or interface dermatitis.

References :

Acanthosis Nigricans

Dr. Jayanta Chakrabarty1, Dr. Debdatta Kar2

Acanthosis nigricans is a fairly common skin pigmentation disorder. The most notable sign of acanthosis nigricans is dark patches of skin with a thick, velvety texture. These patches may appear on the armpits, groin, neck, elbows, knees, knuckles, or skin folds. Lips, palms and soles of the feet may also be affected.

Pathophysiology:

Acanthosis nigricans is caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation.

In the benign form of acanthosis, the factor is insulin or insulin like growth factors that incites epidermal cell proliferation. Other mediators include tyrosine kinase receptors (epidermal growth factor receptors or fibroblast growth factor receptor).

In Familial and syndromic forms of acanthosis, many syndromes share common features like obesity and hyperinsulinaemia. They may be due to insulin resistance syndromes (like type 1 DM, leprechaunism, Rabson-Mendenhall syndrome) or may be due to fibroblast growth factor defects like Beare Stevenson syndrome (FGFR 2), Crouzon syndrome (FGFR 3).

In malignant acanthosis nigricans, the stimulating factor is hypothesized to be a factor secreted by either the tumor or substance secreted in response to the tumor.

Incidence:

Acanthosis nigricans is more common in people with darker skin complexions, with a prevalence of about 13.3% in african-americans, as compared to 1% in whites. Incidence is equal in men and women.

Causes:

Several types of acanthosis nigricans have been described.

1Prof. & Head, Dept. of Medicine, RKMSP, VIMS
2MD PGT, Dept. of Medicine, RKMSP, VIMS
1. Familial (as an autosomal dominant trait).
2. Obesity associated – Also k/a pseudo acanthosis nigricans, is the most common type. The dermatosis is weight dependant and lesions may regress completely with weight reduction. Insulin resistance is often present in such patients.
3. Syndromic AN- Acanthosis nigricans can be associated with numerous syndromes. Type A syndrome, also termed as hyperandrogenemia, insulin resistance, and acanthosis nigricans (HAIR-AN syndrome) often occurs in young women (especially black). It is often a/w PCOS phenotype, with high levels of plasma testosterone.

Type B usually occurs in women who have uncontrolled diabetes mellitus, ovarian hyperandrogenism, or autoimmune diseases like SLE, scleroderma, sjogrens, or hashimoto thyroiditis.

Other syndromes include acromegaly, alstrom telangiectasia, barter syndrome, Laurence-moon-bardet, phenylketonuria, stein-leventhal syndrome, Werner syndrome, Wilson’s disease and many others.

4. Acral acanthotic anomaly - More common in dark skinned individuals. Hyperkeratotic skin lesions are present on the dorsal surfaces of hands and feet, with knuckle hyperpigmentation most prominent.

5. Unilateral acanthosis nigricans, or nevoid acanthosis, is inherited as an autosomal dominant trait. Lesions are unilateral and become evident infancy, childhood or adulthood.

6. Generalised acanthosis-has been reported in paediatric patients with no underlying systemic abnormality.

7. Malignant acanthosis nigricans -The most reported cancer associated with acanthosis nigricans is adenocarcinoma of GI origin. Other malignancies include pancreatic cancer, esophageal cancer, bladder carcinoma, hepatocellular carcinoma, non-hodgkin’s lymphoma, rectal cancer, testicular cancer, bile-duct cancer and others.

In 25-50% of malignant AN, oral cavity is involved. The tongue and lips are most commonly affected, with elongation of filliform papillae on dorsal and lateral surfaces of tongue. Regression of AN has been seen with treatment of underlying malignancy, and reappearance has suggest with metastases.

8. Drug induced acanthosis-Use of insulin, nicotinic acid, systemic corticosteroids, pituitary extracts and diethylstilbestrol may induce AN. Nicotinic acid use has been found to have the highest association. OCP has been found to cause acanthosis.

9. Mixed type acanthosis nigricans - When an individual with a pre-existing obesity associated acanthosis develops malignant AN.

**Differential Diagnosis :**

Neck lesions of pellagra may often resemble acanthosis nigricans.

Addison disease may present with hyperpigmentation in axillary folds or neck region.

Hemochromatosis may present with similar clinical features.

**Workup :**

In vast majority of cases with obesity and/or insulin resistance, screening for diabetes should be done. Plasma insulin level should be looked for, which will be high in those with insulin resistance. High insulin levels may be the first
indicator of such metabolic abnormality in younger patients who do not have overt diabetes mellitus.

In middle aged or elderly patients with extensive skin lesions, a workup for internal malignancy is indicated.

**Management:**

Goal of therapy is to correct the underlying disease process.

Correction of hyperinsulinaemia and weight reduction may lead to resolution of dermatoses. Treatment of the skin lesions is for cosmetic reasons only.

These include keratolytics (eg. tropical tretinoin 0.05%, ammonium lactate 12% cream or a combination of the two).

Oral agents like isotretinoin, metformin and dietary fish oils have shown some benefit. HAIR-AN syndrome may be treated with metformin and OCP.

Dermaabrasion and laser therapy may be used to reduce the bulk of the lesion.

In case of malignant AN, surgical removal of tumor is the mainstay of treatment. Cyproheptadine may inhibit release of tumor products. Psoralen and UVA (PUVA) has been beneficial in case of paraneoplastic acanthosis nigricans.
Spot the Diagnosis and What will be the Management?

Courtesy by:
Dr. Debasish Maji
Dept. of Medicine, RKMSP, VIMS
Spot the Diagnosis

Photo - 1

Photo - 2

Courtesy by:
Dr. Bhaskar Mukherjee
Consultant Ophthalmologist
Dr. Nihar Munsi Eye Foundation
The editorial board of the Journal of the Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, expresses deep sorrow at the passing away of

DR. RAMENDRA NATH BASU,
former head of the Department of Ophthalmology on 24th December 2015, and it shares the burden of sorrow with the bereaved family and offers heart-felt condolences.

The members of the board remembers with respectful gratitude the dedicated and selfless service of DR. R. N. Basu to this Pratishthan during his association with it starting on 01-11-1962 when he first joined as a Non-Resident Ophthalmologist in the Department of Ophthalmology. Later, from 01-01-1965, he was appointed as an Hony. Dy. Visiting Surgeon and continued upto 31-03-1973.

From 01-04-1973, he was appointed as Visiting Surgeon and became Head of the Dept. from 01-04-1980. He continued both the posts upto 31-12-1993. From 01-01-1994, he was associated with this Pratishthan as an Hony. Consultant of the Dept. and continued upto 31-12-2007.

The members whole-heartedly prays to the Almighty for the eternal peace of the departed soul.
Spot the Diagnosis and What will be the Management?

Answer for Page No. 77:
Diagnosis: Lingual Thyroid
Management: Lifelong Thyroid Suppression with L-Thyroxine Sodium

Spot the Diagnosis

Answer for Page No. 78:

Photo - 1: Diagnosis-OSSN (Ocular Surface Squamous neoplasia)
Photo - 2: Fundus photo of eye showing Roth’s Spot found in severe anaemia or leukemia.