Amrita Journal of Medicine

Retinal Toxicity with Hydroxychloroquine

Treatment of Neuropathic Pain

Lung Cancer and Smoking

Hand Deformities in Rheumatoid Arthritis
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Research Misconduct

Manu Raj

The primary objective of medical research publication is propagation and dissemination of medical knowledge with the good intention of improving health of the global population. Numerous instances of individuals and institutions subverting the ethos of medical research and committing fraud are regularly being reported by international media. Majority of these fraudulent actions are committed for personal or financial gain making this crime absolutely deplorable for a profession that is considered to be sacred. The prevalence of research misconduct is unknown thanks to the lack of a standardized definition. A recent meta-analysis by Fanelli reported that 2% of the scientists admitted to committing a serious misconduct (falsification or fabrication of data) at least once during their career and one in three admitted to committing other questionable research practices. The reporting of numerous cases in international and national media prompts us to believe that the problem is rather serious than earlier beliefs. Arguably, this problem has the potential to inflict serious harm to innocent patients worldwide.

The taxonomy of research misconduct proposed by Evans has a long list of condemnable activities. The noxious trilogy of Fabrication, falsification and plagiarism tops the list in terms of lethality. Together, these three are indeed threatening the very existence of our faith in published medical literature. Fabrication is invention of data or cases and has been reported even from major clinical trials. Falsification is wilful distortion of data and is assumed to be widely prevalent especially in the early stages of a research career. Plagiarism is the act of copying of ideas, data or words without proper attribution and is akin to stealing.

There is an urgent need to address the grave problem of research misconduct and to take preventive measures in the right direction. Current as well as future medical researchers should be educated about the existence of research misconduct as well as the seriousness of its repercussions. Medical journals are required to up the ante and conduct proper surveillance to clean the system and detoxify the published literature from research misconduct by all possible means. An honest attempt in this direction has the potential to save millions of lives who are at risk of falling prey to defective treatment options based on fraudulent research findings.

REFERENCES

2. Evans S. How common is it? Royal college of physicians of Edinburgh. Joint Consensus Conference on Misconduct in Biomedical Research Suppl. 7. 2000;30(1)
Screening Tools for Assessment of Early Changes of Retinal Toxicity in Patients on Hydroxychloroquine Therapy

Shilpa Sasidharan, Meenakshi Y Dhar, Anuradha S Rao

ABSTRACT

Background: Chloroquine (CQ) and hydroxychloroquine (HCQ) are used for the treatment of malaria and now more commonly for the treatment of inflammatory diseases. It is critical to detect early toxicity to limit the extent of visual loss as retinal damage from these medications is irreversible. In early HCQ retinopathy, patients are often asymptomatic although later patients develop a bull’s eye maculopathy, characterised by a ring of RPE depigmentation in the macula sparing the fovea, accompanied by paracentral and central scotomas. End stage HCQ toxicity leads to widespread RPE and retinal atrophy with loss of central vision, peripheral vision and night vision.

Aim: To evaluate and compare the value of spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) with Humphrey Visual Fields (VF) as screening tools to detect early changes of HCQ induced retinal toxicity and to identify factors predisposing to it.

Materials and Method: 60 patients (120 eyes) on HCQ for ≥ 1 year for various rheumatologic disorders were enrolled in the study. All subjects underwent a systemic and ocular examination including visual acuity, slit lamp examination, IOP measurement, colour vision and fundus examination. Visual field examination with 10-2 full threshold programme, inner retinal thickness measurement (ganglion cell analysis) with HD 5 line scan at the macula using cirrus SD-OCT and FAF imaging was also performed.

Results: 60 patients were included [male:female;13:47] in the study. Mean age was 41 years. Median duration of HCQ usage was 24 months and average maintenance dose was 200-400 mg/ day. Anterior segment examination and VF were normal in all patients. Inner retinal thinning was seen in 6 patients on SD-OCT(GCC analysis). Mean Inner retinal thickness in each quadrant at the macula was significantly reduced in the study group compared to normal population (p<0.01). 1 of the 6 patients who had abnormality on SD-OCT showed abnormality on FAF.

Conclusion: Inner retinal thinning on SD-OCT was observed in the absence of fundus and VF changes. As early toxic signs were more frequent on SD-OCT, FAF can be used as a reliable indicator of early retinopathy but not as early as when ganglion cell abnormalities begin to occur as seen in SD-OCT. Age, duration of HCQ intake, daily dosage and body mass index may have a role in the development of retinal toxicity but the appearance of toxicity features in patients within the low risk group indicate other factors such as genetic predisposition, ethnicity, that may have a contributory role.

INTRODUCTION

Chloroquine(CQ) and hydroxychloroquine(HCQ) are used to treat malaria and inflammatory diseases, like rheumatoid arthritis and lupus. Both belong to the quinolone family and share similar clinical indications and side effects, including retinal toxicity. The hallmark of HCQ toxicity is bilateral pigmentary retinopathy. In early HCQ retinopathy, patients are asymptomatic despite having subtle paracentral scotomas. Later in the disease, patients develop a bull’s eye maculopathy with loss of central, peripheral and night vision in severe disease. Retinal toxicity progresses after cessation of HCQ, making early screening inevitable to limit potential visual loss. Although HFA 10 -2 is routinely recommended for the diagnosis, it still does not form a standard measure to detect early damage. AAO has incorporated new advances in technology such as SD-OCT, multifocal ERG (mERG) and FAF that compliment 10-2 HFA in detection of early HCQ toxicity. The aim of this study is to assess these modalities (SD OCT and FAF) and find out the their usefulness in early detection of HCQ toxicity.

Materials and Methods

60 patients on HCQ for ≥1 year duration for various rheumatologic disorders (group 1) and 60 visually normal age matched volunteers (group 2) were enrolled in the study. Both eyes of patients were studied. Exclusion criteria included eyes with concomitant diseases - optic nerve diseases/anomalies, known retinal diseases, uveitis, glaucoma or glaucoma suspects. Patients with ocular hypertension or with IOP>20mmHg,high refractive error (> +/- 6D sphere or +/- 3D cylinder), any previous intraocular/ refractive surgery and media opacity that precluded a high quality OCT examination were not included. Renal failure and liver dysfunction patients were also excluded. Control group had no HCQ exposure.

Data collection included age, gender, duration and dosage of drug intake, current BMI status, ocular symptoms if any. All subjects underwent a thorough systemic evaluation and a detailed ophthalmic examination including visual acuity, slit lamp examination, intraocular pressure measurement, colour vision test using Ishihara chart and fundus evaluation.
RESULTS

60 patients were included in the study. There were more women (n=47) than men (n=13). Mean age was 41 years. One third of the patients were from the age group of 45-55 years, and more than three fourth of the patients were between ages of 25-55 years. Median duration of HCQ usage was 24 months and average maintenance dose was 200-400 mg/day. All these 60 patients were included in Group I. All these were selected keeping in mind the inclusion & exclusion criteria outlined earlier. Group II included 60 age matched controls.

Anterior segment examination and VF 10-2 was normal in these patients of Group I & Group II. Inner retinal thinning was seen in 6 patients on SD-OCT (GCC analysis) in Group I. Mean inner retinal thickness in each quadrant at the macula was significantly reduced in the study group compared to normal population (p<0.01) [Table 1].

The details of the patients with GCC thinning is out-

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<tr>
<th>Quadrant</th>
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<th>n</th>
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<td>Average Inner retinal layer thickness</td>
<td>Groups 1</td>
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<td>79.9</td>
<td>4.46</td>
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<td>Groups 2</td>
<td>60</td>
<td>83.61</td>
<td>3.87</td>
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Table 1: Mean ganglion cell thickness in the superior, nasal, inferior and temporal quadrants at macula in group 1 and group 2.
A higher Dosage/Kg body weight alone probably did not have a direct correlation with toxicity on SD-OCT as all the 6 patients had a dosage of <6.5mg/Kg body weight. 5 of the 6 patients with thinning had taken HCQ for less than 5 years, hence duration in itself is not a predictor for toxicity alone. Higher age group are supposed to be more susceptible to HCQ toxicity- 1 out of our 6 patients above 60 years on HCQ showed GCC thinning. [Table 3]

4 Patients with higher BMI (>25) had GCC thinning, while only 2 patients with GCC thinning had BMI <25 [Table 4].
Statistical analysis was performed using IBM SPSS statistics 20.0. One sample Kolmogorov – Smirnov test was used for checking the normality of data. Means of continuous parameters between groups were compared using Student’s Independent Samples t-test. For finding the association with the categorical variables, Pearson Chi-square test with Yates Continuity correction was performed. To compare the value of the two tests (SD-OCT and FAF) with VF, 2 sample z test for proportions was used. p value ≤0.05 was considered statistically significant.

**DISCUSSION**

The mechanism of action of HCQ is unknown. It concentrates in liver, spleen, kidney, heart, lungs, brain and retina. Approximately 50% of unchanged drug is excreted in urine. Urinary elimination is slow and persists for months/years after discontinuation. Retinal toxicity is its most serious side effect. Symptoms include blurred vision, photophobia, and photopsias. Ophthalmoscopy reveal granular pigmented alterations in the form of bull’s eye maculopathy with a surrounding circle of RPE atrophy sparing the fovea. The toxicity risk increases to 1% after 5-7 years of cumulative dose of 1000 grams of HCQ. Multifocal ERG, SD-OCT and FAF are the new objective tests for early detection of toxicity of HCQ. mfERG is probably most sensitive, but, it is not available in all centers. Its cost factor and requirement for patient cooperation makes it difficult to be performed as a routine screening tool. Hence, in our study SD-OCT and FAF have been used (easily available and more feasible than mfERG).

Some, recent studies also show that there is no relation between therapy duration and OCT parameters. Patients take HCQ for many years without problems whereas few patients develop retinal changes at very low cumulative doses.

Effectiveness of VF testing depends on patient cooperation and certain macular changes in early toxicity may not be associated with VF defects. 10-2 pattern is more sensitive than other VF programmes in detecting early retinopathy, as large test patterns (24-2 or 30-2) do not have sufficient number of central targets for effective screening. As described by C. Andersan et al in his study on patients with HCQ toxicity, any subtle decrease on VF within 2-6 degrees from center was considered significant and even mildly decreased thresholds (4-8db) was recognized as positive when there was a contiguous pattern of a paracentral/partial ring. Easterbrook reported 10-2 red test to be 91% sensitive with a low specificity of 57% but 10-2 white test to have lower sensitivity of 78% but a better specificity of 84% for detection of retinal toxicity. In our study, 10-2 white full threshold testing in all patients were normal.

FAF imaging technology utilizes the properties of fluorophores (lipofuscin) which accumulates in conditions of high photoreceptor outer segment metabolism and dysfunctional RPE. In our study, one patient (both eyes) had a pericentral ring of increased fluorescence. This was in correspondence to the finding in Ulrich et al’s study using FAF imaging for early detection of retinal alterations in long term HCQ patients. They found that it can be reliably used to detect early RPE alterations in HCQ retinopathy. These abnormalities begin with a fine pericentral ring of increased FAF that appears to broaden, first mottled and later on as general loss of pigment epithelium, with absence of FAF in advanced cases. Fovea becomes involved with complete loss of RPE in severe cases.

On SD-OCT, our 6 patients showed significant thinning of perifoveal inner retinal layer, especially the inner plexiform and ganglion cell layer without of any clinically evident toxic changes in the current study. Inner retinal thickness in each quadrant at the macula was significantly reduced in the study group compared to normal population (p<0.01). This is in agreement with the previous studies, which demonstrated significant thinning of inner retinal layers in the absence of clinical fundus changes in patients on HCQ for < 5 years. However, alteration of the photoreceptor IS-OS junction and thinning of the outer nuclear layer was reported with OCT by Padilla et al and Kimberly et al in patients on long term treatment (> 5 years). None of the patients in this study had IS-OS junction disruption on HD 5 line macula scanning.

Literature shows that most severe damage occurs at the parafoveal vascular network region and retinopathy starts with the distribution of a drug via the retinal vessels first affecting the retinal ganglion cells. Findings in this study also confirms the same as there was inner retinal thinning(ganglion cell loss) in 6 patients with one of the six patients having increased perifoveal fluorescence on FAF. It is to be noted that two of six patients who showed retinal structural abnormalities were taking HCQ for < 2 years. HCQ accumulates in the ganglion cells throughout the retina however significant SD-OCT changes were detected in the perifoveal area where ganglion cells are most populated.

The observations in our study show, a correlation between age group > 60 years, HCQ intake > 6 years, obesity and higher incidence of toxicity. But the fact that these retinal toxic changes were evident even in the low risk group indicates that there are factors other than the above risk factors that have a role in predisposing patients to HCQ retinal toxicity. Shroyer et al in his study reported that mutation of the ABR gene associated with Stargardt disease may predispose to the development of retinal toxicity on HCQ exposure. Further studies are warranted to find out other factors that contribute to the development of retinal toxicity in HCQ patients and also, if ethnicity has a contributory role.
CONCLUSION

SD-OCT and FAF give an early indication of HCQ toxicity as structural changes may precede clinically detectable functional abnormalities. Inner retinal thinning of the parafoveal and perifoveal areas was seen on SD-OCT. It may be an early indicator of HCQ induced retinal toxicity even in patients on HCQ for < 2 years duration. As abnormalities on SD-OCT were more frequent than that obtained on FAF imaging, it indicates that although FAF can detect early RPE alterations in HCQ retinopathy, these changes are not evident as early as when the ganglion cell damage begins to occur as demonstrated by SD-OCT. As none of these tests can be used as an autonomous indicator of early toxicity, a combination of these tests can be performed on an annual basis after the baseline investigation to detect structural and functional changes early enough so that irreversible retinal damage is avoided. Thus, in the absence of multifocal ERG which is costly and less readily available, ophthalmologists can use the ganglion cell protocol on spectral domain OCT and autofluorescence as a screening tool, in addition to 10-2 protocol on HFA to detect early changes of Chloroquine retinal toxicity.

For retinal toxicity development, risk factors such as age, duration of intake, daily dosage and BMI have a role but the appearance of toxicity features in low risk patients indicate other factors such as genetic predisposition and ethnicity, that may have a contributory role. Limitations of this study are: sample size is not large enough to comment on relative sensitivity and specificity of each test over the other and impact of rheumatological disorders itself on retinal structures cannot be ruled out.

REFERENCES

A Prospective Comparative Study on the Outcome of Treatment with Gabapentin and Oxcarbazepine in Patients with Neuropathic Pain Due to Lumbosacral Radiculopathy

Vidya G, Surendran K, George Joseph N, Ravi Sankaran, Krishnan Radhakrishna Pillai

ABSTRACT
Background: Clinical research has demonstrated that antiepileptic drugs can be effective in the treatment of neuropathic pain. Gabapentin is often regarded as first-line therapy for post herpetic neuralgia and painful diabetic neuropathy. It was hypothesized that oxcarbazepine can provide significant analgesia and may be effective in treating neuropathic pain refractory to other antiepileptic drugs such as gabapentin.

Aims: To compare the effects of gabapentin and oxcarbazepine in relation to mean reduction in severity of pain, reduction in functional disability, improvement of neurological deficits and occurrence of adverse effects of treatment in patients with lumbosacral radiculopathy.

Materials and Methods: This study included seventy patients diagnosed with lumbosacral radiculopathy by clinical assessment. Thirty five patients each were included in group I (gabapentin) and group II (oxcarbazepine) and followed up for 6 months. The outcome of treatment was evaluated using visual analogue scale (VAS) and Oswestry disability index (ODI).

Statistical Analysis: The Student’s t test, Mann Whitney U test, Wilcoxon signed rank test, Paired t-test and Chi-square test were applied to examine variable differences. The level of statistical significance was chosen to be p<0.05.

Results: A significant reduction in pain intensity (mean VAS scores) was found as early as 2 weeks and continued to improve throughout the study period. There was significant reduction in mean ODI scores from baseline in both the groups at 8 weeks. There was no statistically significant difference between the two groups in any of these parameters. Though most of the side effects experienced were mild to moderate, two patients experienced severe adverse effects like drowsiness and hypersensitivity.

Conclusion: Monotherapy with Gabapentin or Oxcarbazepine was found to be effective in treatment of neuropathic pain due to lumbosacral radiculopathy. Like its efficacy, the safety profile and adverse effects of both drugs were comparable.

Key words: Lumbosacral radiculopathy, neuropathic pain, gabapentin, oxcarbazepine, Oswestry disability index.

INTRODUCTION
Neuropathic pain, defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system is a common clinical situation and often refractory to treatment. Till recently, not many clinical trials have demonstrated significant efficacy of treatment with medications for lumbosacral radiculopathy, which is probably the most common type of neuropathic pain. It results from nerve root impingement and inflammation that has progressed enough to cause neurologic symptoms and/or signs in the areas supplied by the affected nerve root(s). Disc herniation and foraminal stenosis due to spondylotic degeneration are the most common etiologies of lumbosacral radiculopathy.

Gabapentin is an analogue of the neurotransmitter gamma aminobutyric acid (GABA) with anticonvulsant and analgesic properties and is widely used to treat neuropathic pain. The exact mechanism of action is unknown, but the therapeutic action on neuropathic pain is thought to involve voltage gated N-type calcium ion channels. Gabapentin is thought to bind to the alpha-2-delta subunit of voltage dependent calcium channel in the CNS. Oxcarbazepine is the 10-keto analogue of carbamazepine which has a distinct pharmacokinetic profile which is used as an antiepileptic drug and also in several neuropathic pain conditions like trigeminal neuralgia and painful diabetic neuropathy. The effectiveness of oxcarbazepine in treating neuropathic pain is probably due to a dual mechanism: the inhibition of sustained, high frequency, repetitive firing of voltage-gated sodium channels combined with inhibition of high-voltage P/Q and N-type calcium channels.

Gabapentin and pregabalin are often regarded as first-line therapy for post herpetic neuralgia and painful diabetic neuropathy, whereas carbamazepine and oxcarbazepine are used as first line therapy for trigeminal neuralgia. In our study, we aimed to compare the efficacy and safety of two antiepileptic drugs with analgesic action namely gabapentin and oxcarbazepine with respect to reduction in pain and functional disability in a group of patients with lumbosacral radiculopathy.

Materials and Methods
This study was conducted in the Department of Physical Medicine and Rehabilitation of Amrita Institute of Medical Sciences and Research Centre, Kochi, between December 2013 and June 2015. The study was conduct-
ed as per the approval and guidelines of the ethical committee of AIMS - School of Medicine and with the informed, written consent of the participants. Patients with lumbosacral radiculopathy were eligible for the study.

Patients aged 20-75 yrs with neuropathic pain attributed to lumbosacral radiculopathy in the form of low back pain radiating to lower limbs characterized as burning or aching pain, allodynia or hyperalgesia, with at least one objective sign of motor or sensory deficit or reflex change were included in the study.

Patients were excluded from participation for any of the following reasons-

- History of traumatic nerve injury
- Presence of severe cardiac, hepatic or renal co-morbidities.
- If on corticosteroids for radiculopathy or any other disease.
- History of spinal surgery in previous 6 months
- Pregnancy and lactation

The demographic data was obtained for each patient at the first visit to the outpatient clinic of our department. Also an elaborate history on the presenting complaints including the duration of back pain and radicular pain, sensory, motor or sphincter complaints, personal history, past medical and surgical history, and associated comorbidities was taken. The intensity of the low back and leg pain was quantified using the visual analogue pain scale (VAS), where the score ranges from 0 (no pain) to 10 (the worst pain). A detailed clinical examination including straight leg raising test (SLR), femoral nerve stretch test, assessment of motor or sensory deficits, deep tendon reflexes (ankle jerk, knee jerk), spinal movements, paraspinal spasm, scoliosis, heel walking and toe walking etc. was done and the nerve roots involved were ascertained. Likely etiology was confirmed in patients with imaging (MRI) of lumbosacral spine when necessary and grouped as IVDP, LCS and listhesis. However, all patients were not imaged by MRI. X-ray of the L5 spine was taken in all cases. Patients with both acute and chronic pain were included in this study.

A common patient self-reported pain scale is visual analogue scale which has demonstrated validity and is useful for documenting incremental improvements from treatment².

Using this method, the patient was instructed to indicate the intensity of pain at rest by marking on a 10 cm line with 2 extremes: no pain (0) and worst imaginable pain¹⁰. VAS score was documented at first visit and then at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months and 6 months. VAS scores were further categorized as 0= no pain, 1-3= mild pain, 4-6= moderate pain, and 7-10= severe pain. For the analysis of outcome at 3 months and 6 months, the patients were grouped as having no pain (VAS 0) and pain present (mild/moderate/severe pain).

The Oswestry Low Back Pain Disability Questionnaire was used to assess the degree of functional disability in the patients. This questionnaire contains 6 statements in each of the 10 sections, viz. pain intensity, activities like personal care, lifting weight, walking, sitting, standing, sleeping, social life, travelling and change in degree of pain. For each section, subjects choose the statement that best describes their status. Total scores range from 0 (highest level of function) to 50 (lowest level of function). Thus each section is rated on a 0 to 5 point scale, added up, and converted into a percentage score or the Oswestry disability index (ODI). The range of possible values is from 0 to 100 (where 0 = no disability).

A total of 74 patients were recruited for this study. 37 patients were treated with Gabapentin (Group I) and 37 patients with Oxcarbazepine (Group II). Both groups received adjuvant analgesics for short periods, physical modalities and spinal stabilization exercises as indicated. Patients in Group I were given Gabapentin, starting at a dose of 100 mg two times daily and titrated up to 600 mg/day in 2 divided doses according to response assessed on biweekly follow up over phone. Patients in Group II were given Oxcarbazepine, starting at a dose of 150 mg twice daily and titrated up to a maximum of 600mg/day.

Patients were advised to continue treatment for 8 weeks. Patients were followed up biweekly over phone and seen in clinic at 2 months, again followed up over phone or in OPD at 3 and 6 months after initiation of treatment. VAS scores were noted at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months and 6 months from initiation of treatment. Measurements obtained before the study and at 8 weeks follow up included the ODI, SLR, presence or absence of motor and/or sensory deficits (hypoesthesia, hyperesthesia, or dysesthesia) of the L4, L5, or S1 dermatomes. Adverse effects if any, were noted in the follow up evaluations.

In statistical analysis, comparison of quantitative variables was done using student’s t test or Mann Whitney U test according to the nature of the data. The significance between pre and post treatment parameters was assessed by Wilcoxon signed rank test for repeated measures for non-parametric variables and Paired t test for parametric variables. Chi-square test was used for comparison of qualitative variables. The level of statistical significance was set as p<0.05

RESULTS

The study population consisted of 74 patients diagnosed clinically with lumbosacral radiculopathy. During the period of study, 2 patients were lost to follow up and 2 patients discontinued treatment due to adverse effects and hence were not followed up for the
rest of the study. A total of 70 patients completed the study.

Of the seventy four patients, 37 were males and 33 were females. In group I the majority were males (n=21, 56.8%) while in group II the majority were females (n= 21, 56.8%). The majority of patients (48.6%) belonged to the age group of 40-60 years. The mean age in group I was 47.57 ± 13.61 and in group II was 44.16 ± 12.30. Occupation wise, of the 74 patients, 36 (48.6%) were engaged in sedentary job (drivers, office workers, intellectuals, professionals). In group I, 20 (54.1%) patients were engaged in sedentary work while in group II, the majority (n=21, 56.8%) were engaged in moderate to heavy work.

Among the 74 patients, the majority (n=63, 85.1%) presented with a predominant complaint of radicular pain. Of the remainder, 4 had predominant complaint of low back ache and 7 had predominant complaint of paresthesia. No patient had sphincter complaints. Regarding the side of radicular pain, 40 patients (54.0%) had left sided pain, 25 (33.7%) had right sided pain, and 9 (12.1%) had bilateral pain. Comorbidities were present in 24 patients (32.4%) as listed - 4 patients had diabetes mellitus, 4 had hypertension, 6 had both hypertension and diabetes, 4 had hypothyroidism, 4 had dyslipidemia, 2 had bronchial asthma, 2 had valvular heart disease and 2 had fibromyalgia. The mean duration of radicular pain in months was 16.6 ± 32.3 in group I and 9.9 ± 12.6 in group II. There was no significant difference in symptoms or duration between the two groups.

Regarding clinical signs, in the 74 patients studied, 27 patients (73%) in group I and 34 patients (91.9%) in group II had positive SLR at ≤ 70 degrees on the symptomatic side. Spinal movements were restricted in 37 (50%) patients, paraspinal spasm was present in 35 patients (47.3%), scoliosis in 8 patients (10.8%) and motor deficits were present in 34 patients (46%). The majority of the patients (n= 65, 87.8%) had sensory deficits pertaining to specific dermatome innervated by affected nerve roots. Deep tendon reflexes (DTRs) were found to be absent or sluggish in 53 (71.6%) patients.

On analysis, a statistically significant difference was observed for positive SLR at ≤ 70 degree (more in group II, p value= 0.032), presence of paraspinal spasm (more in group II, p value 0.036) and reflex change (more in group I, p value 0.005). There was no significant difference in motor weakness, sensory deficits, restriction of spinal movements, heel walking and toe walking between the two groups (p value >0.05). Majority of the patients (n=34, 45.9%) had L5 radiculopathy followed by L5, S1 radiculopathy in 21 patients (28.4%). Fourteen patients (18.9%) had S1 radiculopathy and 5(6.8%) had L4 radiculopathy

Average baseline VAS score was 7.0 ± 2.1 in group I and 7.1 ± 1.8 in group II. Mean ODI was 55.1 ± 17.9 in group I and 55.1 ± 19 in group II. Both the groups were comparable according to baseline scores of outcome measures.

MRI of the lumbosacral spine was done in 52 patients (34 in group I and 18 in group II). In the majority of patients imaged (n= 41, 78.8% of patients imaged by MRI or 55.4% of the total number of patients), the cause of radiculopathy was assessed to be intervertebral disc pathology. The disc pathology identified was disc protrusion in 19 patients, extrusion in 5 patients, and disc bulges in 17 patients. The remaining 11 patients imaged were found to have one of the following degenerative pathology – lumbar canal stenosis with foraminal stenosis in 3 patients, listhesis with foraminal stenosis in 4 patients and lateral recess stenosis in 4 patients.

Mean duration of treatment for 35 patients in each group (excluding two patients lost to follow up and 2 patients who discontinued treatment due to adverse effects) was 8.9±5.6 weeks for group I and 7.5±3.8 weeks for group II. The dose of the medication was increased in 9 (25.7%) patients in group I and 5 (14.3%) patients in group II at 2 weeks. Dose titration was done at four weeks and 7.1 ± 1.8 in group II. Mean ODI was 55.1 ± 17.9 in group I and 55.1 ± 19 in group II. Both the groups were comparable according to baseline scores of outcome measures.

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The mean baseline VAS score of group I was 7.1 ± 2.1 and that at 2 weeks was 5.4 ± 2.3, at 4 weeks 4.5 ± 2.4, at 6 weeks 3.6 ± 2.1, at 8 weeks 3.2 ± 2.2, at

<table>
<thead>
<tr>
<th>VAS score</th>
<th>Group I (n=35)</th>
<th>Group II (n=35)</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<td>Pretreatment VAS</td>
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<td>2 weeks VAS</td>
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<td>4 weeks VAS</td>
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<td>6 weeks VAS</td>
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<td>8 weeks VAS</td>
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<tr>
<td>6 months VAS</td>
<td>2.9</td>
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Table 1: Comparison of VAS scores between Gabapentin and Oxcarbazepine groups (Mann Whitney U test)
3 months 3.0 ± 2.4, and at 6 months 2.9 ± 2.4. The change in mean VAS scores in successive follow up from baseline mean VAS score was statistically significant (p value <0.001) in group I.

The mean baseline VAS score of group II was 7.0 ± 1.8 and that at 2 weeks was 4.5 ± 2.1, at 4 weeks 3.6 ± 2.2, at 6 weeks 3.0 ± 2.2, at 8 weeks 2.5 ± 2.3, at 3 months 2.1 ± 1.9 and at 6 months 1.8 ± 1.9. The change in mean VAS scores in successive follow up from baseline score in group II was also statistically significant (p value <0.001).

However, there was no significant difference in mean VAS scores at these intervals between the two groups as shown in table 1.

However, the observed difference in ODI between groups was not statistically significant (p value 0.223).

Among the 70 patients studied, 33 had motor deficits, 62 had sensory deficits and 50 had reflex change at initial clinical assessment. Of the 33 patients, 8 in group I and 6 in group II had improvement in motor deficits at 8 weeks. Similarly improvement in sensory deficits was noted in 17 in each group, while improvement in reflex change was noted in 13 patients in group I and 5 patients in group II. The observed difference between the two groups was not statistically significant. On analysis, both groups showed an increase in the mean SLR values at 8 weeks. The observed increase in SLR angle between baseline value and at 8 weeks was statistically significant in each group (p value <0.001).

Analysis of adverse effects was done in 72 patients, 36 in each group, (excluding 2 patients from initial sample of 74 patients who were lost to follow up and included 2 patients who discontinued treatment due to adverse effects). Eleven (30.6%) patients experienced adverse effects in group I and 5 (13.9%) patients had adverse effects in group II. This observed difference in occurrence of adverse effects between two groups was not statistically significant (p value 0.089). The frequently reported adverse events in group I and group II respectively were: somnolence (13.9% and 5.6%), fatigue (5.6% and 8.3%), weight gain (8.3% and 2.8%) and drowsiness (2.8% in both groups). There were 2 occurrences of serious adverse effects leading to discontinuation of treatment. Two patients dropped out of the trial during the first week of treatment while on starting dose of the drug due to intolerable adverse effects. One patient in gabapentin group developed hypersensitivity reaction in the form of skin rash and edema of lips which was managed by early medical intervention. One patient in oxcarbazepine group had experienced severe drowsiness leading to drug discontinuation. He was an elderly patient and

<table>
<thead>
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<th>Variable</th>
<th>Category</th>
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<th>SD</th>
<th>p value</th>
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<td>ODI at 8 weeks</td>
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<tr>
<td>ODI in Group II</td>
<td>ODI pre-treatment</td>
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<td>54.9</td>
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<td></td>
<td>ODI at 8 weeks</td>
<td>35</td>
<td>28.5</td>
<td>20.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2. Paired comparison of mean ODI at 8 wks with baseline ODI in each group (Paired t test)
the drowsiness could have been due to hyponatremia which is a known side effect of oxcarbazepine.

In our study, male gender, sedentary work and absence of sensory deficit were significantly associated with no pain (VAS = 0) at 3 months. Younger age, shorter duration of radicular pain and achievement of 2 point reduction in VAS at 2 weeks were predictors of successful outcome with complete pain relief (VAS = 0) at 6 months.

DISCUSSION

The overlap between underlying pathophysiological mechanisms of epilepsy and neuropathic pain supports the use of certain antiepileptic drugs in the treatment of neuropathic pain6,12. In our study, we compared the efficacy of these two antiepileptic drugs with respect to reduction in pain and functional disability in a group of patients with lumbosacral radiculopathy.

Our study included 74 patients with lumbosacral radiculopathy, divided into groups receiving Gabapentin (group I) or Oxcarbazepine (group II). The patients were in the age group of 20-75 yrs. The maximum number of patients in our study was in 40-60 years age group. However there was no statistically significant difference in age distribution or gender between the two groups. The literature evidence also suggests that the prevalence of lumbosacral radiculopathy is equal among men and women in the age group of 40-60 years. With increasing age, the concentration of collagen in the disc increases and water content decreases. As a result, clefts and fissures form in the disc and disruption of annular fibers occurs, predisposing to herniation of nucleus pulposus13.

In our study, the patients in both groups were comparable with regard to their predominant complaints, side of symptoms, claudication pain, weakness and presence of comorbidities. The diagnosis of lumbosacral radiculopathy is clinical. Suzan Coster et al14. concluded in their study that dermatomal radiation, more pain on coughing, sneezing, straining and positive straight leg raising test (SLR) are of diagnostic value in clinical evaluation of lumbosacral radicular syndrome. Clinically, the majority of patients had L5 root involvement (n=34, 45.9%) followed by L5 and S1 radiculopathy in 21 patients (28.4%). This may be explained by the fact that in the lumbosacral spine, intervertebral discs affected most frequently are L4-L5 and L5-S1 because of its mobility during flexion, extension and torsion, leading to L5 and S1 radiculopathies15. In the majority of patients imaged (n=41, 78.8%), the cause of radiculopathy was assessed to be intervertebral disc pathology.

In the present study, there was appreciable progressive reduction in pain intensity compared to baseline with treatment in both the groups as assessed by VAS and ODI. Similar observations were made on efficacy of gabapentin in lumbar spinal stenosis and lumbar disc herniation patients by Yaksi et al15. Kasimcan et al16. Oxcarbazepine (150-900 mg/day) was reported to be effective in a study on patients with painful radiculopathy refractory to gabapentin where 15 out of 18 (83%) patients reported ‘good’ to ‘excellent’ responses with significant reduction in ‘burning’ and allodynia17. Efficacy of oxcarbazepine has been noted by Carrazana E. et al18. In a broad range of neuropathic pain conditions like trigeminal neuralgia, painful diabetic neuropathy and in patients refractory to other antiepileptic drugs such as carbamazepine and Gabapentin, the analgesic effects of oxcarbazepine, its generally improved safety and tolerability profile and lower cost (cost wise, 10 tabs of oxcarbazepine 300 mg costs about Rs.70 while 10 tabs of gabapentin 300 mg costs about Rs.110) suggests that oxcarbazepine will be an important addition to the pharmacological options for management of neuropathic pain.

The extent of reduction in ODI with conservative management has not been well studied. K. Yildirim et al19. noted a 15 point improvement in ODI with gabapentin treatment in patients with chronic radiculopathy. In the present study, there was statistically significant increase in mean angle at which SLR was positive from the baseline value in both the groups at 8 weeks. With respect to change in neurological deficits at 8 weeks, both groups showed statistically significant improvement. Yildirim et al19. also found improvements in motor and sensory functions and SLR with gabapentin treatment in patients with radiculopathy at 8 weeks and Yaksi et al20 noted significant improvement in sensory deficits in gabapentin treated patients with lumbar spinal stenosis.

The occurrence of adverse effects for both drugs were relatively few, with only one patient in each group developing serious side effects resulting in discontinuation of the treatment. The Cochrane review on gabapentin in neuropathic pain, 2010 (n=1468) reported the relative frequency of adverse effects as dizziness (24%), somnolence 20%, headache 10%, diarrhoea 10%, confusion 7% and nausea 8%16.

The most common adverse effects reported with oxcarbazepine are tiredness, headache, dizziness, ataxia and gastrointestinal side effects like nausea, vomiting, diarrhoea17,19. No patient in our study reported hypersensitivity reaction to Oxcarbazepine. In general, gabapentin is known to have a better safety profile and fewer serious side-effects compared to oxcarbazepine20,21. However in our study oxcarbazepine was also found to be well tolerated as gabapentin with only few adverse effects. In the present study, we found that female gender, higher age, longer duration of radicular pain, nature of occupation as moderate to heavy work, presence of sensory deficit and delayed 2 point reduction in VAS score were associated with persistent pain at follow up. Our study shares some similar observations to that noted in
previous studies. Iversen et al\textsuperscript{24} in his study identified higher age and reflex impairment as prognostic factors for non-success. Other factors identified in literature with a less favourable outcome are female gender, symptoms of depression and anxiety, long lasting leg pain, carrying heavy loads, driving at least 2 hours per day, psychosomatic symptoms and positive nerve stretch tests\textsuperscript{25,30}. However in our study no association was found for positive straight leg raising test, reflex impairment or motor deficits with treatment outcome. There was no statistically significant association between comorbidities (diabetes, hypertension, dyslipidemia and hypothyroidism) and outcome in our study.

To summarize, in our study we found that both gabapentin and oxcarbazepine are effective and relatively safe in treatment of neuropathic pain due to lumbosacral radiculopathy. The possible adverse effects and various factors affecting the outcome could be identified.

CONCLUSION

The current study suggests that monotherapy with Gabapentin or Oxcarbazepine is an effective treatment for neuropathic pain due to lumbosacral radiculopathy as evidenced by significant reduction of mean VAS and ODI scores. Like its efficacy, the safety profile and adverse effects of both drugs are comparable. The occurrence of serious adverse effects is rare. It is hoped that large, double-blind placebo controlled clinical trials will confirm the efficacy and tolerability of these drugs in lumbosacral radiculopathy. In our study we found that younger age, male gender, sedentary work, shorter duration of radicular pain, absence of sensory deficits and achievement of 2 point reduction in VAS at 2 weeks are predictors of good outcome and complete pain relief. These results on predictors of outcome should be validated in further studies before being used to inform patients.

REFERENCES

26. Edwards RR, Klick B, Buenaver L, et al. Symptoms of distress as prospective predictors of pain-related sciatica treatment out-


Mortality Predictors In Acute Coronary Syndrome Induced Ventricular Arrhythmias

Nandu M*, Gireesh Kumar K P*, Arjun Balasubramanian**, Sreekrishnan T P*, Naveen Mohan*, Bharath Prasad S*

ABSTRACT

Objective: Ventricular tachycardia and ventricular fibrillation can occur in patients presenting with Acute coronary syndrome with normal left ventricular function. We aimed to investigate the mortality predictors in Acute coronary syndrome induced ventricular arrhythmias.

Materials and methods: 201 Acute coronary syndrome patients with normal left ventricular function were included in our study.

Results: Mortality in patients with ventricular tachycardia and ventricular fibrillation have strong association with Killip III & IV, elevated serum creatinine and elevated Troponin-I.

Conclusion: Mortality was higher in patients presenting with ventricular fibrillation compared to that of ventricular tachycardia. Mortality had strong association with Killip class III & IV, elevated serum creatinine and elevated Troponin I.

Keywords: Ventricular tachycardia, Ventricular fibrillation, Serum creatinine, Troponin I, Killip class III & class IV.

INTRODUCTION

Ventricular arrhythmias are common in setting of acute myocardial infarction. Ventricular arrhythmias seen in myocardial infarction include isolated ventricular premature complexes, accelerated idioventricular rhythms, non-sustained, sustained ventricular tachycardia and ventricular fibrillation. Current therapies for acute coronary syndromes have reduced the incidence of fatal arrhythmias following Acute Myocardial Infarction. Arrhythmias have been classified based on the timing of onset following Acute Myocardial Infarction. The early stage generally includes arrhythmias originating within the first 24-48 hours after onset of Acute Myocardial Infarction. The late stage reflects arrhythmias after the initial 48 hours. In addition some studies describe a chronic stage to reflect arrhythmias arising in healed myocardial scar tissue, generally 72 hours after infarction.

Ventricular premature complexes (VPCs) may occur in any phase following Myocardial Infarction and are generally asymptomatic and hemodynamically well tolerated. PVCs have been classified as “simple” if they are unifocal, infrequent and isolated, or “complex” if they occur early (interrupting the preceding T wave) as couplets, bigeminy or are multifocal.

Accelerated idioventricular rhythm (AIVR) is generally defined as ventricular rhythm of 3 or more consecutive beats at a rate generally greater than 120 beats/min for less than 30 seconds. The presence of Non-Sustained Ventricular Tachycardia is recognized as a potential marker of electrical instability, thus predisposing to sustained ventricular arrhythmias and sudden cardiac death. The risk of Non-sustained Ventricular Tachycardia is further increased following Acute Myocardial Infarction in patients with diminished Left Ventricular Ejection Fraction< 49% .

Sustained Ventricular Tachycardia & Ventricular Fibrillation is generally defined as a regular wide complex tachycardia at a rate >= 120 beats/min, lasting for >=30 seconds or causing hemodynamic compromise. Ventricular fibrillation is generally defined as irregular ECG undulations of varying contour and amplitude with absence of distinct QRS and T wave, causing prompt hemodynamic compromise requiring DC conversion. Ventricular Fibrillation is further classified into “primary” occurring in absence of heart failure or hypotension and “secondary” which occurs in preterminal settings of heart failure or cardiogenic shock.

In our study we compare the mortality predictors in Acute Coronary Syndrome induced ventricular arrhythmias.

MATERIALS AND METHODS

A cross-sectional study was done at Department of Emergency Medicine, Amrita Institute of Medical Science using non-random sampling wherein all patients presenting within the study period of May 2014 to May 2015 were included. The study subjects were patients presenting with Acute Coronary Syndrome to the Department of Emergency Medicine at Amrita Institute of Medical Science, a tertiary teaching hospital in Kerala, India.
Inclusion criteria: All adult patients (age >= 18 years) admitted with diagnosis of acute coronary syndrome (with normal LV function).

Exclusion criteria: Patients with non-cardiovascular causes for their clinical presentation were excluded. Sample size was based on the incidence rate observed in the existing literature (GISSI – 2: Prevalence & prognostic significance of Ventricular Arrhythmias after myocardial infarction) and with 95% confidence and 25% allowable error, the minimum sample size was computed as 200.

Each patient fulfilling the inclusion criteria was subjected to a detailed history taking of the present illness, comorbid conditions, risk factors. ECG changes were noted and blood was sent for cardiac enzymes (Trop I and CK-MB), Serum Creatinine and Electrolytes.

**RESULTS**

A total of 201 patients were included in the study. Majority of the patients were males (83.58%) and belonged to the age groups of 41-60 years (48%) and 61-80 years (42%). Similarly majority of the patients had dyslipidemia (71%), while almost half the patients had diabetes mellitus (45%) and hypertension (52%). Of the 201 patients, ventricular arrhythmia was observed in 53 patients with a mortality rate of 58.5%. The mortality rate of patients without ventricular arrhythmia was 2.7%. In total, fatal outcome was observed in 35 patients (17.4%). The proportion of patients who developed Ventricular arrhythmia was 19.4% (12.4% - ventricular tachycardia; 14% - ventricular fibrillation).

Mortality in patients with ventricular tachycardia is strongly associated with Killip Class III & IV (P value = 0.017 & OR = 9.778), Serum creatinine > 1.4mg (P<0.001) and Troponin I > 0.1ng/ml (P value= 0.001 & OR = 36).

Similarly, mortality in patients with ventricular fibrillation have strong association with Killip Class III & IV (P value = 0.044 & OR = 7.00), Serum creatinine > 1.4mg (P=0.03 & OR = 9.0 ) and Troponin I > 0.1ng/ml (P value= 0.005 & OR = 17).

**Table-1: Demographic characteristics**

<table>
<thead>
<tr>
<th>Gender</th>
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<tbody>
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**Table-2: Prevalence of Risk factor**

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<th>Risk factors</th>
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**Table-3: Outcome of patients**

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<th>Presence of arrhythmia</th>
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<tr>
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<td>With ventricular arrhythmias</td>
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<td>Ventricular fibrillation</td>
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<tr>
<td>Ventricular tachycardia</td>
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<td>11</td>
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<tr>
<td>Without ventricular arrhythmias</td>
<td>144</td>
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<tr>
<td>Total</td>
<td>166</td>
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Patients with Ventricular Fibrillation or Ventricular Tachycardia had a higher risk profile than those without, suggesting that Ventricular Arrhythmias are more frequent in higher risk patients with an acute coronary syndrome. The presence of Ventricular arrhythmias per se carries a grave prognosis in patients with acute coronary syndrome. Coronary artery disease and resultant myocardial infarction are the most common etiology of ventricular fibrillation and cardiac arrest. Other causes of ventricular fibrillation include dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, valvular heart disease, congenital heart disease, proarrhythmia from drugs, acid base and electrolyte abnormalities, long QT syndrome, short QT syndrome, and atrial fibrillation in a patient with Wolff-Parkinson–White syndrome with an anterograde conduction bypass tract.

The mortality in Ventricular Fibrillation group was higher than Ventricular Tachycardia group and those without Ventricular Arrhythmia. The mortality was higher in both Ventricular Tachycardia and Ventricular Fibrillation group with Killip Class III & IV, serum creatinine > 1.4 mg% and Trop I >0.1. High degree of association was seen in Killip Class III & IV and high degree of muscle damage was evidenced by high Troponin I and high CK-MB.

Development of adverse events during acute hospitalization was most frequent with Ventricular Fibrillation, intermediate with Ventricular Tachycardia and the lowest in patients who did not develop Ventricular Arrhythmia during hospitalization, reflecting the decreasing risk profile of these populations. Adverse event were related to ischemia and left ventricular dysfunction. Patients with ventricular tachycardia have higher risk of recurrence even when heart failure and coronary ischemia are controlled.

Presence of Ventricular Arrhythmia was a strong predictor for in-hospital mortalities. Therefore, identification of patients who are likely to develop a Ventricular Arrest, and adequately treating them are important to improve their short and long term outlooks. The prognosis for Ventricular Arrhythmias is particularly poor for Ventricular Fibrillation. Most cases of Ventricular Fibrillation occurred within the 24 hrs, in accordance with another study that showed 80% of ventricular arrhythmia's requiring defibrillation, occurred within 12hrs. With every minute of delay in defibrillation for ventricular fibrillation, the chance of survival decreases by 7 to 1 percent.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
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<td>Alive [n(%)]</td>
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<td>Killip classs</td>
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<td></td>
<td>III &amp; IV 3(27.3)</td>
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<td>Creatinine</td>
<td>Normal 11(100)</td>
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<td></td>
<td>Elevated 3(21.4)</td>
<td>11(78.6)</td>
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<tr>
<td>TROP I</td>
<td>&lt; 0.1 11(92)</td>
<td>1(8)</td>
<td>36.667 (3.261 – 412.256)</td>
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<td>&gt; 0.1 3(23.6)</td>
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Table-4: Mortality predictors in Ventricular Tachycardia

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<td>Elevated 2(11.8)</td>
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<td>&gt; 0.1 2(10.5)</td>
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Table-5: Mortality predictors in Ventricular Fibrillation

DISCUSSION

Patients with Ventricular Fibrillation or Ventricular Tachycardia had a higher risk profile than those without, suggesting that Ventricular Arrhythmias are more frequent in higher risk patients with an acute coronary syndrome. The presence of Ventricular arrhythmias per se carries a grave prognosis in patients with acute coronary syndrome. Coronary artery disease and resultant myocardial infarction are the most common etiology of ventricular fibrillation and cardiac arrest. Other causes of ventricular fibrillation include dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, valvular heart disease, congenital heart disease, proarrhythmia from drugs, acid base and electrolyte abnormalities, long QT syndrome, short QT syndrome, and atrial fibrillation in a patient with Wolff-Parkinson–White syndrome with an anterograde conduction bypass tract.

The mortality in Ventricular Fibrillation group was higher than Ventricular Tachycardia group and those without Ventricular Arrhythmia. The mortality was higher in both Ventricular Tachycardia and Ventricular Fibrillation group with Killip Class III & IV, serum creatinine > 1.4 mg% and Trop I >0.1. High degree of association was seen in Killip Class III & IV and high degree of muscle damage was evidenced by high Troponin I and high CK-MB.

Development of adverse events during acute hospitalization was most frequent with Ventricular Fibrillation, intermediate with Ventricular Tachycardia and the lowest in patients who did not develop Ventricular Arrhythmia during hospitalization, reflecting the decreasing risk profile of these populations. Adverse event were related to ischemia and left ventricular dysfunction. Patients with ventricular tachycardia have higher risk of recurrence even when heart failure and coronary ischemia are controlled.

Presence of Ventricular Arrhythmia was a strong predictor for in-hospital mortalities. Therefore, identification of patients who are likely to develop a Ventricular Arrest, and adequately treating them are important to improve their short and long term outlooks. The prognosis for Ventricular Arrhythmias is particularly poor for Ventricular Fibrillation. Most cases of Ventricular Fibrillation occurred within the 24 hrs, in accordance with another study that showed 80% of ventricular arrhythmia's requiring defibrillation, occurred within 12hrs. With every minute of delay in defibrillation for ventricular fibrillation, the chance of survival decreases by 7 to 1 percent.
In conclusion, in this study the mortality of patients with ventricular arrhythmias have strong association with Killip Class III & IV, Serum creatinine and Troponin levels. So, we can conclude that Killip classification (Class III & IV), Serum creatinine levels and Troponin I levels are the most significant mortality predictors in Acute coronary syndrome induced ventricular arrhythmias.

REFERENCES
Study of Accuracy of Clinical Examination in Comparison with MR Fistulogram in Fistula in Ano

Ramu R, Riju R Menon

ABSTRACT

Fistula in ano is an elusive disease with myriad of symptoms and has been described virtually from the beginning of medical history. Fistula in ano is known for its frequent exacerbations, recurrences and its chronic disease progression. The surgeon who is fortunate enough to have the opportunity to treat the patient initially is the one most likely to affect a cure, to limit morbidity and to minimise disability. To maximise operative results and minimise recurrences and complications, accurate preoperative assessment of the fistula is necessary. It is now increasingly recognised that preoperative imaging can help identify infection that would have otherwise gone unidentified. The aim is to study the accuracy of clinical examination in a case of fistula in ano in comparison with MR Fistulogram. By clinical examination, we were able to identify internal opening in 33 out of 50 total cases. On comparing this clinical data with MRI findings, it was found that in 30 out of 33 cases, the exact findings was confirmed by MRI, thereby showing a positive predictive value a positive predictive value of clinical examination as 90.9%. Out of 17 cases, where the clinical examination could not locate the internal opening, 10 of the cases the internal opening was revealed by MRI, thereby showing a negative predictive value of clinical examination as 41.2%. The sensitivity and specificity of clinical examination was noted to be 75% and 70% respectively. The overall accuracy of clinical examination was found to be 74%.

INTRODUCTION

Fistula in ano is an elusive disease with myriad of symptoms and has been described virtually from the beginning of medical history. Fistula in ano is known for its frequent exacerbations, recurrences and its chronic disease progression. The surgeon who is fortunate enough to have the opportunity to treat the patient initially is the one most likely to affect a cure, to limit morbidity and to minimise disability. To maximise operative results and minimise recurrences and complications, accurate preoperative assessment of the fistula is necessary. It is now increasingly recognised that preoperative imaging can help identify infection that would have otherwise gone unidentified. Magnetic Resonance Imaging preoperatively, especially in patients with complex and recurrent fistulas or persistence abscess, have been shown to influence surgery and reduce the rate of recurrence. It has been found that many times, a proper clinical examination and intraoperative assessment of patient gives better results. Some patients actually do not require MR Fistulogram, if they had been properly assessed clinically.

Traditionally, these patients were diagnosed clinically, evaluation was limited to digital rectal examination, and examination under anaesthesia (EUA) was the principal method to define the extent and complexity of the disease process. However, this approach often leads to incomplete evaluation of the inflammatory process, misinterpretation of the fistula anatomy, inadvertent sphincter injury, and a failure to detect complex fistulas or sepsis, especially in those patients with recurrent disease, inflammatory bowel disease or complex disease, often leading to poor outcome after surgery. The goal of imaging includes defining the presence and cause of any secondary tracks and to gauge the extent of sphincter involvement by the fistula to plan surgery and prevent relapse.

In some patients with frank linear low and fistula, which could have been clinically diagnosed, a MR Fistulogram has been done. Investigations for this patient could have been made cost effective with only clinical examination and omission of MR Fistulogram. In the other extreme, in a few patients, there have been instances of recurrence because of a side branch or a higher internal opening had been missed and could have been defined with MR Fistulogram.

In this paper, an attempt is made to find out the accuracy of clinical examination (Digital Rectal Examination and Proctoscopy) in comparison with MR Fistulogram and to find out any clear cut indications for MR Fistulogram in a patient with anal fistula can be proposed.

MATERIALS AND METHODS

Recurrent disease, inflammatory bowel disease or complex disease, often leading to poor outcome after surgery. The goal of imaging includes defining the presence and cause of any secondary tracks and to gauge the extent of sphincter involvement by the fistula to plan surgery and prevent relapse.

In some patients with frank linear low and fistula, which could have been clinically diagnosed, a MR Fistulogram has been done. Investigations for this patient could have been made cost effective with only clinical examination and omission of MR Fistulogram. In the other extreme, in a few patients, there have been instances of recurrence because of a side branch or a higher internal opening had been missed and could have been defined with MR Fistulogram.

In this paper, an attempt is made to find out the accu-
racy of clinical examination (Digital Rectal Examination and Proctoscopy) in comparison with MR Fistulogram and to find out any clear cut indications for MR Fistulogram in a patient with anal fistula can be proposed.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software version 20. Digital rectal examination and proctoscopy and MR Fistulogram were done before surgery. Data regarding the nature of fistula, external opening and internal opening were noted during clinical examination. All patients were sent for MR Fistulogram before planning operative intervention. Patients were subjected to operative intervention. The type, nature of fistula and internal opening were documented. Data regarding clinical examination and MR Fistulogram were then compared to surgical findings. Accuracy of clinical examination was then compared with MR Fistulogram findings.

RESULTS

During the study period, 50 consecutive patients were assessed, out of which almost 84% were males. 92% of patients presented with perianal discharge as the major symptom, followed by pain and swelling in the area. 21 patients (42%) out of total 50 patients had past history of anorectal abscess. Out of these 21 patients, 12 subjects underwent incision and drainage from outside hospital. 8 cases out of 12 patients who underwent incision and drainage had complex branching fistula on presenting to us. 23 patients out of 50 gave history of previous fistula in ano, out of which 7 patients underwent surgical intervention and presented to us with recurrence. On surgical exploration; it was found that, 82% MR Fistulogram findings were correlating with surgical findings, whereas only 46% of clinical findings correlated with surgical findings. On comparing clinical and MRI findings, it was found that, out of 33 cases where internal opening was made out by clinical examination, in 30 of the subjects, it was confirmed by MRI, thereby showing a positive predictive value of 90%. It was also seen that out of the 17 cases, where the clinical examination could not locate the internal opening in 10 of these cases, the internal opening was revealed by MRI, thereby showing a negative predictive value of clinical examination as 41.2%. The overall accuracy of clinical examination was found to be 74%.

In our study, we were able to identify internal opening in 33 subjects out of 50 total cases. On comparing this clinical data with MRI findings, it was found that in 30 out of 33 cases, the exact finding was confirmed by MRI, thereby showing a positive predictive value of clinical examination as 90.9%. It was also seen that out of the 17 cases, where the clinical examination could not locate the internal opening in 10 of these cases, the internal opening was revealed by MRI, thereby showing a negative predictive value of clinical examination as 41.2%. The overall accuracy of clinical examination was found to be 74%.

In this study, it was seen that maximum incidence of fistula in ano was seen in age group 40-50 yrs. of age with nearly equal incidence in the 6th decade. There were studies by Vasilevsky and Gordon in 1984 and Bruhl in 1986, reporting the maximum incidence in the 4th and 5th decade.

In this study, the male: female ratio was 5: 1, thereby pointing out higher incidence of anal fistula in male gender. There were comparable studies in the past showing near similar gender prominence. A Study on fistula in ano conducted by Sundar Prakash S, Saravanan PS, Chandra Prabha J(2014) reported male to female ratio of 4: 1. Ani and Solamke (1976) reported male to female ratio of 8: 1 whereas Eisenhammer S (1985) reported male: female ratio varying from 1.8:1 to 8:1. No specific reason was found out as to why the female patients refrain from early consultation. Maybe the location of the diseased part makes the female patients shun from early consultation. Though we had only 8 female patients in our study, we found that out of 8 females, 5 subjects had complex disease out of which 3 had previous

<table>
<thead>
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<th>Internal opening (clinical)</th>
<th>Internal opening (MRI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>30(90.9)</td>
<td>0.092</td>
</tr>
<tr>
<td>No</td>
<td>10(58.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7(41.2)</td>
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</table>

Table 1- Comparison of clinical and MRI findings.

DISCUSSION

Fistula in ano is a condition that has been described from the beginning of medical history. But the treatment still poses a surgical problem. Many authors have presented new operative techniques and case series to minimise the recurrence rate and incontinence. But the treatment remained a challenging job for the surgeon. With the advent of high resolution imaging modalities like MR Fistulogram along with thorough clinical examination, the threat of incomplete treatment of fistula in ano and the recurrence can be brought down.

In this study, identification of internal opening was taken as a factor to compare both the clinical and MRI findings. Internal opening is the most difficult aspect in fistula in ano to be identified on clinical examination, the identification of which is very important in determining the treatment outcome. In low anal fistulas with small tract, it is easy to identify internal opening. We can also identify internal opening by palpating the induration in the suspected area by applying Goodsall’s rule. The difficulty of identifying the internal opening can be due to several factors like internal opening with crypts, fibroses internal opening or a high internal opening.

In this study, it was seen that maximum incidence of fistula in ano was seen in age group 40-50 yrs. of age with nearly equal incidence in the 6th decade. There were studies by Vasilevsky and Gordon in 1984 and Bruhl in 1986, reporting the maximum incidence in the 4th and 5th decade.

In this study, the male: female ratio was 5: 1, thereby pointing out higher incidence of anal fistula in male gender. There were comparable studies in the past showing near similar gender prominence. A Study on fistula in ano conducted by Sundar Prakash S, Saravanan PS, Chandra Prabha J(2014) reported male to female ratio of 4: 1. Ani and Solamke (1976) reported male to female ratio of 8: 1 whereas Eisenhammer S (1985) reported male: female ratio varying from 1.8:1 to 8:1. No specific reason was found out as to why the female patients refrain from early consultation. Maybe the location of the diseased part makes the female patients shun from early consultation. Though we had only 8 female patients in our study, we found that out of 8 females, 5 subjects had complex disease out of which 3 had previous
history of fistula in ano.

The major symptom with which almost 46 patients out of total 50 presented was discharge from external opening. The next common presenting complaint was pain which was noted in 36 patients. In a study, conducted in India by Das AC and Prakash Aggarwal it was noted that discharge from external opening was the most frequent and commonest symptom in the case of fistula in ano. Another recent study in 2014 by Sundar Prakash S, Saravanan PS, and Chandra Prabha J documented 86% of the subjects in their study presented with perianal discharge. In a study by Vasilevsky et al, the predominant symptom was perianal discharge. This data is comparable to our study.

Majority of the previous studies state that anorectal abscess is an acute process which marks the initial manifestation of underlying fistula in ano. Incision and drainage of the access will result in complete resolution of the infection in almost 50% of the patients, unfortunately in the rest, an anal fistula will develop. In a study by Vasilevsky et al, the cause for fistula in ano was anorectal abscess (21%), I and D (39%) and previous surgery (11%). Even though, most of literature noted history of anorectal abscess in majority of their subjects, in our study, only 21(42%) out of total 50 patients gave a past history of anorectal abscess. Out of these 21 patients, 12 underwent incision and drainage from outside hospital. 8 cases out of 12 patients who underwent incision and drainage had complex branching fistula. There are studies which show association of anorectal abscess with poor socio-economic group. In our study, we noticed a higher incidence of lower to middle socio-economic group presenting with anorectal abscess.

Almost 23 cases in our study gave history of previous fistula in ano, out of which 10 subjects had complex branching fistula. 7 out of 23 subjects underwent surgical intervention and presented to us with recurrence and all 7 had complex disease at the time of presenting to us. This clearly proves that the chance of complexity of fistula increases with previous fistula surgery.

The external opening was identified in 48 patients (96%), out of which 15 had anterior opening and 33 had posterior opening while nearly all patients had discharge from the external opening. 6 subjects had multiple exterior opening. The internal opening was not identified in 17 out of 50 patients clinically. There are studies which states identifying 100% of internal opening clinically with the help of proctoscopy. In our study, it was only 66% of the internal opening identified on clinical examination which is possibly due to the high incidence of complex fistulas (42%) in our study group.

In our study, all patients underwent MR Fistulogram and MR did not identify internal opening in 10 subjects out of 50 cases. The sensitivity and specificity of MR Fistulogram in our study is slightly on the lesser side when compared to other studies. Beckingham and colleagues concluded that DCEMRI had sensitivity of 97% and a specificity of 100% in the detection of anal fistulas. MRI in our practice has provided valuable information regarding the internal opening, presence of secondary tracts in 42% of the total cases and, it was found that 10 of the 17 patients in whom internal opening was not found in clinical examination was revealed with MR Fistulogram thereby showing poor predictability of negatives in case of clinical examination.

On surgical exploration, it was found that, 82% MR Fistulogram findings were correlating with the surgical findings, whereas only 46% of clinical findings correlating with surgical findings. In 9 cases, surgical findings proved MRI wrong. MRI could not identify internal opening in 10 cases, out of which 4 cases were surgically found to be blind ending sinus probably due to the fibrosis of internal opening due to chronicity in those cases. 2 cases underwent VAAFT and internal opening was found to be fibroses with track ending as a blind sinus with fistuloscope and we terminated the procedure with obliteration of the tract using Fibrin glue. In the rest of the 6 cases, we were able to identify internal opening on surgical exploration with the help of fistula probe and H2O2- Methylene blue.

MATERIALS AND METHODS

Clinical examination may not be an ideal predictor of the presence or absence of internal opening and secondary tracts in fistulae in ano since the predictive value of positives is 91%. MR Fistulogram is a better option to look at additional tracks and position of internal opening. The treating surgeon should discuss the MRI with a trained Radiologist preoperatively, especially in complex recurrent diseases, before planning the mode of surgical intervention. The complexity of fistula can be directly related to previous inadequate surgical intervention with resultant difficulty in identifying and eradicating the fistula tracts. When the two modalities are combined, it gives high sensitivity and specificity for planning surgical intervention especially so in a recurrent and complex fistula.

REFERENCES


Outcome and Predictors of Outcome in Patients with Pathological Node Negative Status of Breast Carcinoma

Revathy A K, Rajasekharan Pillai, Vijaykumar D K

ABSTRACT

The aim of this study is to estimate the Median Survival Rate (MSR) with respect to recurrence of pathological Node Negative (N0) breast cancer in patients, to evaluate the factors influencing the outcome of N0 breast cancer in patients and to determine the relevance of such factors in deciding the extent of adjuvant therapy. This is a partly retrospective and partly prospective study of 454 pathological N0 breast carcinoma patients, who underwent primary surgery followed by adjuvant therapy, at Amrita Institute of Medical Sciences, Kochi, Kerala, from 2004-2013. Patients who underwent neo-adjuvant chemotherapy were excluded. Prognostic factors like age, parity, breast feeding, family history, duration of symptoms, tumour size, lymphovascular emboli, ER, PR, HER2 and Ki-67 were analysed with respect to those with and without early events (recurrence, metastases or second malignancy and death). Median Survival Rate of N0 breast carcinoma patients with median follow up of 45 months is 86.1%. Majority of the patients were below 55 years of age. ER negative status has statistical significance with bad prognosis. PR negative status has borderline statistical significance with bad prognosis. Other factors like age, parity, breast feeding, family history, duration of illness, type of surgery, tumour size, histopathology, HER2/neu status and lymphovascular invasion (LVE) did not show any statistical significance. It was evident that ER-PR negativity is associated with negative outcome in N0 breast carcinoma patients who had a median follow up of 45 months. For more accurate analysis, longer follow ups are required. Cost-effective evaluation of HER2/neu status was with FISH. Assessment of Ki67 status for all breast cancer patients is required.

INTRODUCTION

Breast cancer is the most common female cancer in the world with an Age-Standardized incidence Rate (ASR) of 39 per 100,000, which is more than double that of the second ranked cancer (cervical cancer ASR=15.2 per 100,000)1. Breast cancer accounts for 23% of all newly occurring cancers in women worldwide and represents 13.7% of all cancer deaths1. Lump in the breast, dimpling of the skin, change in the shape of the breast, fluid coming out of the nipple, or red scaly patch of skin, are certain signs of breast cancer. The various factors for the development of a breast cancer include, female sex, lack of physical exercise, obesity, hormone replacement therapy during menopause, first menstruation at an early age, ionizing radiation, use of alcohol, late pregnancy nulliparity, and old age.

The developed countries with a small proportion of the world population account for almost 50% of breast cancers diagnosed worldwide 2 and 12% breast cancer occur in women between 20-34 years of age2. In the developing countries of Asia, the health care burden on account of breast cancer has been steadily mounting. It is expected that in the decades to come, these countries would account for majority of new breast cancer patients diagnosed globally. The survival rates of breast cancer vary with a high survival rate in the developed countries than developing ones. Breast cancer is most common in women than in men. In younger women, diagnosis of breast cancer is more difficult as their breast tissue is denser than in older women. The stage of cancer is often advanced by the time a lump in young woman's breast is palpable.

As per the ICMR-PBCR data, breast cancer is the most common malignancy among women in urban registries of Delhi, Mumbai, Ahmadabad, Calcutta and Trivandrum, where it constitutes to about more than 30% of all cancers in women. In the rural PBCR of Barshi, breast cancer is found to be the second most common cancer in women after cancer of the uterine cervix. The prognostic factors in breast carcinoma are lymph node status, tumour size, lymphovascular invasion, proliferation markers, ethnicity, age, ER/PR status, HER2/neu, genetic profiling, histologic type and grade. The predictive factors are hormonal status, HER2/neu status and genetic profiling.

The expected five year survival for a N0 breast cancer is over 90%. Most N0 breast cancers will be cured by surgery and RT alone, yet 30-40% of these patients relapse and ultimately die of disseminated disease. If we follow the recent guidelines of adjuvant therapy for breast cancer, more than 90% of patients with negative nodes will get treated with chemotherapy, with a possible benefit of less than 10% of all patients exposed to the side effects of chemotherapy. This is because we still do not have reliable prognostic and predictive factors which will help us to avoid unnecessary treatment. This study is an attempt to find the factors, if any, which will help to predict a favourable or unfavourable outcome in patients with Pn0 breast cancer in this part of the country.

Materials and Methods

This study included all patients with N0 breast carcinoma presenting to all surgical departments, at Amrita Institute of Medical Sciences, Kochi, Kerala. These patients included in the study were divided into two parts. The first part consisted of patients with retrospective anal-
Analysis of PN0 breast cancer, operated from 2004 till 2011. The second part was a prospective collection of data of all breast cancer patients who underwent surgery from January 2012 to December 2013. The study population consisted of all patients with PN0 status and who had a follow up of minimum 4 years in the retrospective group, and 1 year in the prospective group.

We included all patients with breast carcinoma, who underwent primary surgery, and those with histopathology reports suggestive of pathological N0 status of disease. A minimum of 6 nodes should have been sampled from the axilla to qualify for inclusion and we excluded those patients who underwent neo-adjuvant chemotherapy/radiotherapy. Patients who did not have a follow-up of at least 4 years in the retrospective group and 1 year in the prospective group were excluded.

The standard prognostic factors which affected the outcome in N0 breast cancer patients in the Indian population were mentioned as age of the patient at the time of admission, menstrual status- premenopausal/ postmenopausal, family history, size of the tumour, type of primary surgery, ER, PR, HER2/neu status, proliferative index, type of radiotherapy, chemotherapeutic schedule. This study was carried out from 2004 to 2011 as a retrospective study and prospective study from 2012 to 2013. The retrospective group was followed up for 4 years and the prospective group for 1 year. Based on the results observed from the existing literature on recurrence rate, with respect to ER-PR status, 95% confidence and 80% power, minimum sample size came to 300 for ER-PR status and 520 for HER2neu.

**Statistical Analysis:**
Recurrence rate of breast carcinoma in patients with pathological N0 status was computed for total sample, with respect to ER, PR and HER2/neu status. Chi-Square Test was done to check the statistical significance of the difference in recurrence rates between the two subgroups. Median survival time was calculated for the total sample using Kaplan-Meir survival analysis. The difference in Median Survival Rate between subgroups was tested to find the statistical significance by using Log Rank Test.

<table>
<thead>
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<th>ER</th>
<th>Recurrence</th>
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<tbody>
<tr>
<td></td>
<td>No n (%)</td>
<td>Yes n (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>154 (81.5)</td>
<td>35 (18.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>168 (90.8)</td>
<td>17 (9.2)</td>
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Table 1- ER Negativity versus Outcome.

<table>
<thead>
<tr>
<th>PR</th>
<th>Recurrence</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No n (%)</td>
<td>Yes n (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>151 (83)</td>
<td>31 (17)</td>
</tr>
<tr>
<td>Positive</td>
<td>168 (90.8)</td>
<td>21 (10.9)</td>
</tr>
</tbody>
</table>

Table 2- PR Negativity versus Outcome.

**RESULTS**
Survival rate of N0 breast carcinoma with median follow up of 45 months was found to be 86.1%. Among the patients, 13.9% had some event in form of local recurrence, distant metastasis or death. Majority of the patients were under 55 years of age. ER negativity is the only factor significantly influencing early failures in the study. Other factors like age, parity, breast feeding, family history, duration of the illness, type of surgery, tumour size, histopathology, HER2/neu status and lymphovascular emboli (LVE) did not show any statistical significance. This is probably due to the short follow up period.

**DISCUSSION**
**ER Negative Status:**
In this study, 50.8% of patients were ER negative. IHC was used to find ER status. Cut off was taken as a figure greater than 1%. It was found out that bad prognosis was associated with ER negativity. This corroborated with other studies like Crowe ‘827, Fischer ‘886, Pichon ‘968 and Helgi ‘908 which have also showed statistical significance of ER negativity with bad prognosis, in univariate analysis. In multivariate analysis like Sheshadri ‘969 and Hupperete ‘979, this observation was correct when associated with size and PR status.

**PR Negative Status:**
In this study, 48.9% of patients were PR negative, and there was borderline significance regarding the association of bad prognosis with that of PR negative status (P=0.08). IHC was used to assess PR status. Cut off was taken as a figure greater than 1%. Similar work done by Helgi et al. that studied 367 patients with a follow up of 48 months, showed significant association of PR negative status with bad prognosis.

**CONCLUSION**
ER negativity was the only factor that significantly influenced early failures. PR negativity had only a borderline significance. There was no association of positive status of HER2/neu with bad prognosis.

On the basis of comparison with other similar studies, it is evident that poor prognosis in N0 breast carcinoma is associated with larger tumour size, ER-PR negative status, HER2/neu positive status, younger age of the patient at the time of admission, presence of lymphovascular emboli and high Ki67 status.
The long term prognosis for clinically N0 women with very small tumours (<1cm) is excellent, with a 10 year disease-free survival rate of 88%\(^{11}\). Routine adjuvant therapy in this group would be difficult to justify. For N0 patients with larger tumours, ER-PR negative status and HER2/neu positive status, 5 year relative survival rate decreases to about 85% (range 82.2%-92.3%)\(^{12}\). Hence, these patients are to be initiated on adjuvant systemic therapy at the earliest, thereby reducing the rate of recurrence and increasing the disease-free survival rate.

REFERENCES

Clinical Spectrum of Lung Cancer and its Association with Smoking Habit

Veni Krishna S, Asmita Mehta, Nithya Haridas, James P T

ABSTRACT

Background and objectives: Lung cancer occurs due to the uncontrolled growth of cells in the tissues of the lungs. It can spread to the entire organ through the process of metastasis. This form of cancer remains one of the most fatal diseases across the globe causing high morbidity and mortality rates.

Methods and Materials: A cross-sectional study was done on 100 histopathologically proven primary lung malignancies at Amrita Institute of Medical Sciences, Cochin from November 2012 to October 2014. Those patients with definite histological evidence of active extra-pulmonary malignancy were excluded from the study while the inclusion criteria involved patients with a definite histopathological biopsy/cytology and those patients with indirect evidence of bronchogenic carcinoma in the form of positive sputum or pleural fluid cytology or pleural biopsy with CT thorax showing evidence of a lesion consistent with bronchogenic carcinoma. A standardized questionnaire was prepared for collecting data of patients under the inclusive criteria. The details including age, smoking history, chief complaints, radiological calculations, method of diagnosis, histopathological diagnosis and clinical stages were entered in the proforma. The Percentage distributions of case with respect to various clinical variables were computed.

Statistical Analysis: This study is mainly about the distribution of lung cancer cases in relation to demographics and clinical variables. The following statistical tests were applied for generating appropriate hypothesis. To test the statistical significance of the difference in mean value between two groups student’s t – test was applied and between three or more groups the analysis of variance was applied. In cases of small sample size for comparing groups, corresponding non parametric tests were applied. To test the statistical significance of the association between various factors with respect to smoking Chi - Square test was applied. The sample size was taken as 100.

Results: A total of 100 lung cancer patients were encountered during the study period which included 76 males and 24 females. Most patients were in the age group of 61-70 years. Mean age of study subjects was 65.25 years (SD 9.36). 60% of male subjects had smoking habits whereas the females were non-smokers. Cough was the most common symptom which was present in 85% patients. The physical evaluation revealed clubbing in 53% and effusion in 31% of the subjects. The frequent radiological finding was mass lesion (65%). The right upper lobe was the most affected area which included 26% of the subjects. Histopathologically, 90 were non-small cell lung carcinomas and 10 were small cell lung carcinomas. Trans-thoracic biopsy was the main mode of diagnosis in 48 % of the subjects. Approximately 64% of the patients were at stage IV at the time of diagnosis.

Conclusion: The study has revealed that most cases of lung cancer occur in the elderly population aged 60 years or more. Adenocarcinoma is the prevalent histological subtype in this study. Most of the patients were at the advanced stage when diagnosed. Prevalence of smoking habit was 60% in the study.

INTRODUCTION

Although smoking is considered as one of the major causes of lung cancer most of the smokers will not develop lung cancer thus indicating the role of additional factors in the case of lung carcinogenesis. Higher longevity and increasing cigarette smoking has led to a numerical rise of patients with primary lung cancer in India. The clinicopathological profile and the relative frequency of different histological subtypes of lung cancer have been changing in recent years, probably due to changes in smoking habit, growing popularity of low/ filter cigarettes and exposure to other occupational agents.

MATERIALS AND METHODS

All patients with suspected lung cancer who were referred to the outpatient department of Pulmonary Medicine and Oncology department of AIMS were included and patients with definite histological evidence of active extra pulmonary malignancy were excluded. The study group underwent initial evaluation which included history, physical examination, complete blood count, bio-chemical studies and chest X - ray PA view. Computed Tomography (CT) of the chest was done for all patients. For histopathological confirmation of lung cancer either bronchoscopic biopsy, Percutaneous USG/CT guided fine needle aspiration or biopsy or thoracoscopy was done according to the case. Bronchoscopy was done in relevant cases in bronchoscopy suite by pulmonologist using fibreoptic bronchoscope. Bronchial tree was visualized and any grave abnormality was sampled by biopsy or brushings. Bronchoalveolar lavage was sent for cytological study. Transbronchial biopsy/nodal aspiration was done in appropriate cases and was sent for histopathological examinations. Pleural fluid analysis, cytological examination of regional lymph nodes and metastatic deposits was done in appropriate cases. The subjects were classified as (group1) who have never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire lifetime and non-smokers (group2) who currently do not smoke cigarettes.

RESULTS

A total of 100 histopathologically proven primary lung cancer cases were available for clinicopathological anal-
analysis during the study period. Most patients fell in the age group between 61-70 years. Mean age of the study subjects was 65.25 years (SD 9.36). For male patients, the mean age was 67.73 (??SD) years and for females it was 62.62 (??SD) years. Male to female ratio was 3.16:1. Below the age of 50 years, 66% of the lung cancer patients were females.

Out of the total study subjects, 60% were smokers. The male smoker: nonsmoker ratio was 3.75:1. Approximately 35% of the patients were exclusive cigarette smokers. The average pack years was calculated to be 17.68 (one pack year is calculated as number of packets of cigarettes smoked per day x number of years smoked)

Cough was the typical symptom being present in 85% of subjects. Three patients were asymptomatic at presentation. Mean duration of the symptoms was found to be 10 weeks. The shortest duration of symptoms was 7 days and longest was 1 year.

General examination findings included clubbing, peripheral lymphadenopathy and features of superior venacaval occlusion. All the 100 patients had abnormal chest radiograph at presentation. Common patterns included mass lesion in 65% of cases followed by pleural effusion in 31% of cases. There was predominance of right side in 60% of cases. 54% of the cases were peripherally situated. There were 90 cases of NSCLC (Non-small cell lung carcinoma) and 10 cases of SCLC (small cell lung carcinoma). Adenocarcinoma was the common histological subtype encountered in the study. All cases of small cell carcinoma occurred in males. The diagnosis were predominantly based on transthoracic cytology or biopsy (48%) followed by bronchoscopy in 41% of cases. Among NSCLC, 64.04% patients were of stage IV. Similarly among SCLC, 9 patients had extensive disease while only 1 patient was presented with limited stage disease. 24 patients with advanced stage of disease with poor performance status were given supportive care.

DISCUSSION

The mean age of patients with lung carcinoma in the present study was 65.5 years. It was different from most of the previous Indian studies which reported a mean age range from 50 to 56.7 years. Few recent studies by Malik et al1 and Gupta2 had reported the common age

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<th>Non smokers (n=40)</th>
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Table 1: Shows the relation between smoking status and various demographic, clinical, radiological and pathological parameters in carcinoma lung patients.
The major clinical symptoms encountered in the present study were cough and dyspnoea (85% and 63% respectively). Other common symptoms included weight loss, chest pain and hemoptysis. This was in accordance with a similar study by Jindal and Behera et al. in 1990 who reported cough (88%) as the most common presenting symptom. Other findings by Jindal et al. included chest pain (52.2%) and hoarseness of voice in 29.99% of patients. According to them unexplained cough for more than several weeks would lead to a high degree of suspicion. In the present study hemoptysis was seen in only 25% of patients, which was similar to the study by Jagadish et al. in 2009 (25.12%). There was no statistically significant difference in the frequency of presenting symptoms between smokers and non-smokers.
The mean duration of symptoms was less in the present study when compared to other studies. In a study by Jindal, Behera et al, 46.4% reported symptoms between 3-6 months. Most cases were treated as Tuberculosis for varying periods of time before a diagnosis was made. In the present series also, 14 patients received prior anti-tuberculosis treatment. Wang et al observed that the diagnosis of lung cancer in 47 patients (70% of all patients below 40 years) was delayed, with an erroneous diagnosis of tuberculosis in 55% of patients. A paradigm shift is needed in the thinking of clinicians that lung cancer is not purely a smoking related disease, nor should every chest shadow raise a suspicion of only tuberculosis. Most common radiological finding in lung cancer patients in this study was mass lesion which was found in 65% of patients. It was right sided in 60% and left sided in remaining 40% patients. Khan et al (2006) also observed 63% of lesions in the right lung. In a study of 336 patients with bronchogenic patients by Jindal, et al, the most common finding was opacity with or without collapse (64%) and pleural effusion (23%). There is wide variability in these observations in different studies; however the finding of a mass lesion at the time of diagnosis of lung cancer is high. In the present study, histopathologically 90% of the patients had non-small cell lung cancer and the remaining 10% had small cell type of cancer. Among the non-small cell type, squamous cell carcinoma and adenocarcinoma constituted 30% and 52% respectively. This was similar to the other Indian authors who have reported increasing incidents of adenocarcinoma. CT guided lung biopsy gave the highest diagnostic yield, leading to a diagnosis in 47% of patients. This was different from what was observed by other authors who reported FOB (fiber-optic bronchoscopy) to be the most rewarding investigative modality. In our study, the overall yield with CT guided percutaneous biopsy was 85.71% and FOB was 85%. Percutaneous biopsies done under CT guidance is the investigation of choice for peripherally situated lesion, which has very minimal complication rates as seen in various international and Indian studies. Most of the patients in the present study were presented with locally advanced disease or distant metastasis. 70.5% patients were diagnosed in the later stage of the disease (either in stage 3B or 4). There are several studies which have similar observation (Thippanna et al 1999; Prasad et al, 2004; Mohan et al, 2007). This delay in presentation may be attributed to poor awareness about the disease, late seeking of medical attention, attribution of symptoms to underlying COPD and misdiagnosis. In multiple series from west as well as from India, it is reported that 50-70% cases of NSCLC and up to two-third of SCLC usually present in advanced stage. Although complete surgical resection has been more effective single modality treatment for early stage non-small cell lung cancer, only 37% of patients presented a resectable stage (up to 3A). Of these only 10 subjects could be offered definite surgery due to the presence of co-morbidities placing them at high surgical risk. This was similar to the study done by Mallik et al. Radiation and chemotherapy formed the main treatment modality in the present study.

CONCLUSION
In our study we found that the mean age of subjects with lung cancer was 65.2 years and the male: female ratio of the lung cancer patients was 3.16:1. Approximately 60% of the patients were smokers. The main symptom was cough. Mean duration of symptoms in lung cancer subjects was 10 weeks. Adenocarcinoma was the basic histological type. Most yielding investigation was transthoracic cytology or biopsy. Approximately 64% of subjects with NSCLC presented in stage IV at the time of diagnosis. Palliative radiotherapy or chemotherapy formed the main treatment modality.

REFERENCES


**ABSTRACT**

**Background and aims:** Rheumatoid arthritis is a chronic and the most common disease that causes pain, stiffness swelling and limited motion and function of many joints. The small joints in the hand and feet tend to be involved most. The aims of our study are to estimate the percentage of various hand deformities, to explain the possible link factors for hand deformities and to study the effect of hand deformities on patients functional ability.

**Methodology:** It is a cross sectional study for the primary objective and second of the secondary objectives; and case control study for the first of the secondary objectives.

We include all patients who were diagnosed to have RA, Patients who were on DMARD treatment or who were planning to start DMARD treatment, Patients with age >=18 years and excluded patients who were below 18 years, who were diagnosed to have other forms of arthritis e.g. psoriatic arthritis, who were pregnant, lactating, with psychiatric problems or had hearing impairment, and those who were not willing for the study, or those who did not give a written consent.

**Results:** All patients were right hand dominant. Among all patients, 13.3% of patients had ulnar deviation, 6.4% of patients had boutonniere deformity and 5.4% of patients had swan neck deformity. Only 0.5% of patients had Z deformity of the thumb alone. 4.5% of patients had a combination of ulnar deviation and swan neck and 4.0% of patients had a combination of boutonniere and swan neck deformities. 1.0% of patients had a combination of boutonniere and Z deformity. 0.5% of patients had a combination of ulnar deviation, swan neck and Z deformity. 1.5% of patients had a combination of ulnar deviation and Z deformity, 0.5% of patients had ulnar deviation and boutonniere, 0.5% of patients had ulnar deviation and fixed flexion deformity of the metacarpophalangeal joint and 1.0% of patients had a combination of ulnar deviation, swan neck and boutonniere deformity. 4.0% of patients had flexion deformity of the proximal interphalangeal joint and 2.0% of patients had flexion deformity of the proximal interphalangeal joint and 1.0% of patients had fixed flexion deformity of the proximal interphalangeal joint and 2.0% of patients had synovial hypertrophy of the metacarpophalangeal joint and 0.5% of patients had synovial hypertrophy of the proximal interphalangeal joint.

**Conclusion:** Hand deformities are prevalent in RA and the common deformities are ulnar deviation, boutonniere, swan neck deformities and a combination of them. In univariate analysis, duration of disease, delay in DMARDs and RF are potential risk factors for hand deformities in RA. In multivariate analysis, duration of disease and RF are independent risk factors for hand deformities in RA. RA patients with hand deformities have more disability and functional impairment than RA patients without hand deformities.

**INTRODUCTION**

About 1% of the world's population is afflicted by Rheumatoid arthritis, women three times more often than men. Onset is most frequent between the ages of 40 and 50, but people of any age can be affected. It can be a disabling and painful condition, which can lead to substantial loss of function and mobility if not adequately treated. It is a clinical diagnosis made on the basis of symptoms, physical examination, radiographs (X-rays) and laboratory investigations. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have published diagnostic guidelines that help the diagnosis of Rheumatoid Arthritis.

Most prevalent deformities are ulnar deviation, boutonniere and swan neck deformities. It is not uncommon that the same hand develops different deformities simultaneously. Deformities together with other deficits such as reduced grip strength and pain can have a major impact on hand function and subsequently the ability to perform activities of daily living.

In India most patients with Rheumatoid arthritis resort to other systems of medicine like Ayurveda and Holistic Medicine initially and even modern medical practitioners quite often prescribe only steroids and analgesics. Majority of these patients present with exacerbation of symptoms and sometimes deformities and initiation of DMARDs, starts later in the course of the disease, which cannot reverse but only prevent further joint damage. Administration of DMARDs at the earliest, once diagnosis is established gives a remarkable outcome, provided, the patient monitors his/her blood/liver/renal profiles, with time to time evaluation and titration of dose of DMARD is done according to the severity of disease.

Some patients develop deformities within the 1st year of onset of symptoms while others develop after a long duration on an average of 5-10 years. This disparity in presentation would be due to the aggressive nature of the disease or the ineffectiveness of the treatment.

Hand Deformities have a major impact on activities of daily living, particularly when the disease is active and is associated with inflammation. Severe deformities can also deteriorate ones quality of life.
OBJECTIVES

Primary Objective: To estimate the percentage of various kinds of deformities, with reference to hand in rheumatoid arthritis patients.

Secondary Objectives:
1. To ascertain the possible risk factors, which are, duration of disease, delay in DMARDs and serological parameters like RF and Anti-CCP for deformities in hand in RA patients.
2. To study the effect of hand deformities on patients’ functional ability.

MATERIALS AND METHODS

Study design
Cross sectional study for the primary objective and second of the secondary objectives; and case control study for the first of the secondary objectives.

Sample size: 202 patients were included.
Study period: May 2011 to January 2014
Study setting: Amrita Institute of Medical Sciences, Kochi
- Department of Rheumatology and Clinical Immunology
- Department of Physical Medicine and Rehabilitation

PATIENT SELECTION CRITERIA

Inclusion Criteria:
- Patients who were diagnosed to have RA.
- Patients who were on DMARD treatment or who were planning to start DMARD treatment. Patients with age >= 18 years

Exclusion Criteria:
- Patients who were below 18 years
- Patients who were diagnosed to have other forms of arthritis e.g. psoriatic arthritis
- Patients who were pregnant, lactating, with psychiatric problems or had hearing impairment.
- Patients who were not willing for the study, or those who did not give a written consent.

OUTCOME MEASURES AND TOOLS USED

1. The Stanford Health Assessment Questionnaire (HAQ). The HAQ Disability Index was developed at the Stanford Arthritis Center. It has been validated for use in rheumatologic disorders. The HAQ- DI assesses a patient’s usual abilities using their usual equipment (e.g. assistive devices) during the past one week. In each item there is a four – level difficulty scale that is scored from 0-3, representing normal [no difficulty]0, some difficulty1, much difficulty2, and unable to do3. There are 20 questions in eight categories of functioning – dressing, rising, eating, walking, hygiene, reach, grip and usual activities. The highest component score in each category determines the score for the category, unless aids or devices are required. Dependence on equipment or physical assistance increases a lower score to the level of 2 to more accurately represent underlying disability. The eight category scores are averaged into an overall HAQ- DI score on a scale from zero (no disability) to three (completely disabled).

2. Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH): The M-SACRAH questionnaire comprises of 12 questions to be answered on a visual analogue scale (VAS; 0-100 mm), covering the three categories of symptoms that primarily determine the clinical situation of patients with rheumatoid affections of the hand: function, joint stiffness and pain. The average score of each domain was calculated, and the overall average for the three domain scores was then obtained. The overall M-SACRAH therefore ranges between 0 and 100, 0 representing the best and 100 the worst possible status.

3. Australian / Canadian osteoarthritis hand index (AUSCAN) was published in 2002 and has been validated for the assessment of hand disability in rheumatoid arthritis patients. It comprises of 15 items covering pain, stiffness and function to be answered on a visual analogue scale (VAS; 0–100 mm).

4. Hand Dynamometer: This dynamometer measures grip force from 0 - 50lb. It was used for measuring grip strength.

5. Cylinders and Spheres
Each consists of large and small size and was used to assess hand function (hand grasp).
- Large Cylinder diameter 7cm and Small Cylinder diameter 3.5cm, Large Sphere Diameter 12 cm and Small Sphere Diameter 6 cm
All patients satisfying the inclusion and exclusion criteria were included in the study after getting a written informed consent from them. Since it is a cross-sectional study, the sample population was selected randomly based on inclusion and exclusion criteria during my study period.

For the first of the secondary objectives, a case-control study approach was adopted and 2 groups were taken. In one group RA patients with hand deformities and the other group RA patients without hand deformities. Each patient’s demographic details and medical history were collected in a specially designed proforma and included other details:

- Risk factors pertaining to Duration of disease, Delay in DMARDs, RF and Anti-CCP.
- Assessment of hand deformities by examination and with the help of goniometer. Assessment of different hand functions objectively by using spheres / cylinders and with lateral key pinch / pulp pinch. Measurement of grip strength objectively by a hand dynamometer.
- Assessment of patients’ functional ability by using HAQ-DI, M-SACRAH and AUSCAN scores.
- Duration of disease was determined from the onset of symptoms in years. Delay in DMARDs in years was determined by subtracting the time when DMARDs were initiated in years from duration of disease in years. A period of more than 3 months between the diagnosis and initiation of DMARDs was considered as delay in DMARDs. RF test was determined using latex agglutination method and value > 8 IU/ml was considered positive. Anti-CCP test was determined by Chemiluminescence Enzyme Immunoassay (CLEIA) method and value > 5.00 U/ml was considered positive.

6. **Goniometric measurement of Range of Motion**

This was done to assess restriction of movements.

**METHODOLOGY**

All patients satisfying the inclusion and exclusion criteria were included in the study after getting a written informed consent from them. Since it is a cross-sectional study, the sample population was selected randomly based on inclusion and exclusion criteria during my study period.

For the first of the secondary objectives, a case-control study approach was adopted and 2 groups were taken. In one group RA patients with hand deformities and the other group RA patients without hand deformities.

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- Assessment of patients’ functional ability by using HAQ-DI, M-SACRAH and AUSCAN scores.
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**DISCUSSION**

Statistical analysis was done using IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). For all continuous variables the results are either given in mean ± SD / median (minimum-maximum) and for categorical variables as percentage. To compare the averages of continuous variables between two groups, for those that are following normal distribution, independent sample T-Test was used and for those that are not following normal distribution, Mann-Whitney U Test was performed. Spearman’s rho correlation coefficient was used for finding the correlation between two continuous parameters. Chi-square test was used for finding the association between two categorical variables. The p-value less than 0.05, was considered as statistically significant.

**RESULTS**

**Hand Deformities**

All patients were right hand dominant. Among all patients, 13.3% of patients had ulnar deviation, 6.4% of patients had boutonniere deformity and 5.4% of patients had swan neck deformity. Only 0.5% of patients had Z deformity of the thumb alone. 4.5% of patients had a combination of ulnar deviation and swan neck and 4.0% of patients had a combination of boutonniere and swan neck deformities. 1.0% of patients had a combination of boutonniere and Z deformity. 0.5% of patients had a combination of ulnar deviation, swan neck and Z deformity. 1.5% of patients had a combination of ulnar deviation and Z deformity. 0.5% of patients had a combination of ulnar deviation, swan neck and boutonniere deformity. 0.5% of patients had ulnar deviation and boutonniere, 0.5% of patients had ulnar deviation and fixed flexion deformity of the metacarpophalangeal joint and 1.0% of patients had a combination of ulnar deviation, swan neck and boutonniere deformity. 4.0% of patients had flexion deformity of proximal interphalangeal joint, 2.0% of patients had fixed flexion deformity of the proximal interphalangeal joint and 1.0% of patients had fixed flexion deformity of proximal interphalangeal and metacarpophalangeal joints. 2.0% of patients had synovial hypertrophy of the metacarpophalangeal joint and 0.5% of patients had synovial hypertrophy of the proximal interphalangeal joint.
Boutonniere Deformity

Ulnar Deviation + Swan Neck Deformities
Delay in DMARDs and Duration of disease

On associating risk factors with hand deformities the average delay in DMARDs was significantly higher in patients with hand deformities than in patients without hand deformities (p = <0.001). The average duration of disease was significantly higher in patients with hand deformities than in patients without hand deformities (p = <0.001).

RF and Anti-CCP Positivity

The percentage of RF positivity was significantly higher in patients with hand deformities (82.1%) than in patients without hand deformities (60.2%) (p = 0.002). The percentage of anti-CCP positivity was higher in patients with hand deformities (79.5%) than in patients without hand deformities (63.8%). But the difference is not statistically significant.

Univariate and Multivariate analysis of risk factors

In univariate analysis, the percentage of hand deformities was higher in RF positive patients (56.6%) than RF negative patients (30%) (OR = 3.038, p = 0.002). The percentage of hand deformities was higher in anti-CCP positive individuals (30%) (OR = 2.207, p = 0.084), but is not statistically significant. The percentage of hand deformities was higher in patients with duration of disease more than 5 years (63.8%) than duration less than 5 years (32%). (5 years has been taken as a cut off since the average duration of disease in patients was between 5-10 years) (OR = 3.754, p = <0.001). The percentage of deformities was higher in patients with delay in DMARDs more than 1 year (54.3%) than in patients with delay in DMARDs less than or equal to 1 year (35.9%) (OR = 2.122, p = 0.022). The Odds Ratio was significantly high for RF, duration of disease and delay in DMARDs.

In multivariate analysis the Odds Ratio was high only for RF (OR = 4.30, p = 0.017) and duration of disease (OR = 3.869, p = 0.007) which shows that they are independent risk factors for hand deformities.

On associating risk factors with hand function, among the patients who have hand deformities the percentage of poor/fair hand function was higher in patients who are RF positive than in patients who are RF negative, except for GCLR, GSLL and LKPL, but is not statistically significant. In all patients right hand was dominant.

In patients with hand deformities grip strength for both right and left hands was higher in patients who are RF negative patients than RF positive patients, but is not statistically significant.
Hand function and Anti-CCP

In patients who have hand deformities, the percentage of poor / fair hand function was higher in patients who are anti – CCP positive than who are anti – CCP negative, but is not statistically significant. In patients who have hand deformities grip strength was higher in anti-CCP positive patients than anti-CCP negative patients but is not statistically significant.

Hand function and duration of disease

Among patients who have hand deformities, the average duration was high in patients who have fair/poor hand function than in patients who have good hand function. There is low negative correlation between grip strength of right hand and duration of disease (r=-0.193, p= 0.056), there is low negative correlation between grip strength of left hand and duration of disease (r=-0.168, p=0.099).

Outcome measures and duration of disease

In patients who have hand deformities the average HAQ-DI, M-SACRAH and AUSCAN were higher in patients with duration of disease more than 5 years. The average M-SACRAH was higher in patients with duration of disease less than 5 years. Except for AUSCAN the other variables do not show statistical significance.

| Deformity | Outcome measures | Number | Duration of disease>5yrs | | Number | Duration of disease<5yrs | p-value |
|-----------|------------------|--------|------------------------|--------|------------------------|---------|
|           |                  |        | Mean±SD | Median (min-max) | Mean±SD | Median (min-max) |
| NO        | HAQ-DI           | 38     | 3.00 ± 2.948 | 0.0625(0-3) | 1.33±1.260 | 0.00(0-3) | 0.580 |
|           | M-SACRAH        | 38     | 5.68±16.361 | 1.4250(0-100) | 6.27±14.915 | 0.00(0-100) | 0.980 |
|           | AUSCAN           | 38     | 5.09±16.488 | 1.300(0-100) | 6.01±14.869 | 0.00(0-100) | 0.748 |
| YES       | HAQ-DI           | 67     | 0.51±0.822 | 0.2500(0-4.13) | 0.42±0.809 | 0.1250(0-3) | 0.286 |
|           | M-SACRAH        | 67     | 12.11±23.954 | 4.500(0-100) | 12.21±27.385 | 3.0(0-100) | 0.148 |
|           | AUSCAN           | 67     | 13.74±23.628 | 5.133(0-100) | 11.58±26.936 | 1.0(0-100) | 0.010 |

Outcome measures and delay in DMARDs

In patients who have hand deformities with delay in DMARDs more than 1 year, the average M-SACRAH and AUSCAN were high, whereas HAQ-DI was low. Except for AUSCAN the other variables are not statistically significant.

Outcome measures and RF

In patients who have hand deformities the average HAQ-DI, M-SACRAH and AUSCAN were higher in patients who are RF positive, but is not statistically significant.

Outcome measures and Anti-CCP

Among patients who have hand deformities the average HAQ-DI, M-SACRAH and AUSCAN were higher in patients who are anti-CCP positive, but is not statistically significant.

Outcome measures and hand deformities

On associating outcome measures with hand deformities the average HAQ-DI, M-SACRAH and AUSCAN were higher in patients with deformities than without deformities. The average AUSCAN STIFFNESS was higher in patients with deformities than without deformities, but is not statistically significant.
Outcome measures and hand deformities

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<td>104</td>
<td>10.75±20.194</td>
<td>0.003</td>
</tr>
<tr>
<td>Auscan Pain</td>
<td>98</td>
<td>13.50±25.335</td>
<td>104</td>
<td>4.50±14.173</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Auscan Stiffness</td>
<td>98</td>
<td>15.88±26.744</td>
<td>104</td>
<td>11.38±21.385</td>
<td>0.250</td>
</tr>
<tr>
<td>Auscan Function</td>
<td>98</td>
<td>11.09±23.326</td>
<td>104</td>
<td>4.20±11.132</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

The most commonly occurred deformity was ulnar deviation followed by boutonniere and swan neck deformities. Since rheumatoid arthritis has a particular predilection for the MCP and PIP joints the common deformities that present are ulnar deviation, boutonniere and swan neck deformity and a combination of these deformities or may simply present as flexion deformity of the MCP or PIP joints and a combination of these.

105 patients had duration of disease more than 5 years. Among them 67 patients had hand deformities. Patients with duration of disease more than five years suffered more deformities and as a consequence impaired hand function, grip strength and disability. M-SACRAH was high in patients with duration of disease less than 5 years as they had both early morning stiffness and stiffness during inactivity. It was noted that most patients had resorted to other systems of medicine (like Ayurveda) which has been proved ineffective over time. Even in modern medicine, most of the time only primary treatment with steroids or analgesics was given for a long duration of time which gives them temporary relief. They only reduce the inflammatory process and do not modify the disease process, in other words they only suppress the mediators of inflammation but do not inhibit the cells responsible for the development of inflammation. By the time they present to this tertiary center significant time would have lapsed and they would have already developed deformities. Range of motion and strengthening exercises are mandatory for flexibility, maintaining normal joint alignment, prevent
RA patients with hand deformities have more disability. In univariate analysis, duration of disease, delay in DMARDs and RF are potential risk factors for hand deformities in RA. In multivariate analysis, duration of disease and delay in DMARDs and RF are independent risk factors for hand deformities in RA.

Hand deformities are prevalent in RA and the common deformities are ulnar deviation, boutonniere, swan neck deformities and a combination of them. In univariate analysis, duration of disease, delay in DMARDs and RF are potential risk factors for hand deformities in RA. In multivariate analysis, duration of disease and RF are independent risk factors for hand deformities in RA.

The M-SACRAH and AUSCAN are measures for functional assessment, the hands in particular. The former comprises of 12 items and the latter 15 items. Except for few items both measured physical function, stiffness and pain differently. While stiffness of joints was quantified more in M-SACRAH, it was pain that was more quantified in AUSCAN. Therefore the results also varied. While M-SACRAH quantified more of intricate activities like unscrewing cap of a tube of toothpaste and turning the pages of newspaper AUSCAN quantifies picking up of large heavy objects, wringing out washcloths etc. Therefore in our study M-SACRAH was showing higher scores (more disability) in patients who had deformities, delay in DMARD, RF positive, anti – CCP positive patients and in patients with impaired hand function. Meanwhile AUSCAN was high who had deformities, longer duration of disease, delays in DMARD, RF positive, anti – CCP positive patients and in patients with impaired hand function. Except for the relation between AUSCAN with duration of disease and delay in DMARD, the association between outcome measures and risk factors is not statistically significant.

LIMITATIONS OF OUR STUDY
Since this institution is a tertiary center, most patients came from other primary health centers or other systems of medicine for better management. Hence determining the delay in DMARD and duration of disease after establishing the diagnosis was difficult.

The number of patients who did anti-CCP test were relatively low, considering the cost of the test. Hence it could not be done as a baseline test. A larger sample size would have confirmed the possibility of this autoantibody as a risk factor.

Hand functions were assessed mainly with spheres and cylinders, hence deformities easily accommodated to them. The use of cubes/cuboids would have assessed mild to moderate hand deformities better.

CONCLUSIONS
• Hand deformities are prevalent in RA and the common deformities are ulnar deviation, boutonniere, swan neck deformities and a combination of them.
• In univariate analysis, duration of disease, delay in DMARDs and RF are potential risk factors for hand deformities in RA. In multivariate analysis, duration of disease and RF are independent risk factors for hand deformities in RA.
• RA patients with hand deformities have more disability.
A Study of Hand Deformities in Rheumatoid Arthritis

References


Evaluation of Second Trimester Uterine Artery Doppler in Prognosticating the Outcome of Pregnancy

M Sukanya Sankari, Radhamany K

ABSTRACT

Background and aims: The placenta is the structure that links the mother and fetus by indirect interaction with the maternal blood that spurts out of the uteroplacental vessels. The placenta begins to develop upon implantation of the blastocyst into the maternalendometrium. Our aim is to study the prevalence rate of abnormal uterine artery Doppler and to study the outcome of pregnancy in the normal and abnormal uterine artery Doppler with respect to PIH, IUGR and Preterm labour.

Methodology: It is a 2.5yr prospective study conducted at Amrita Institute of Medical Science. 100 Patients are selected according to the inclusion and exclusion criteria. USG of uterine artery Doppler in the 2nd trimester of the pregnancy was used


Results: In our study, 100 pregnant women were recruited from June 2010 to april 2013. Of 100 cases studied, 91 had normal Doppler and 9 had abnormal Doppler. Out of this 9, abnormal dopplers, 4 (44.4%) had persistence of diastolic notch with elevated S/D ratio and PI. The other 5 (55.5%) abnormal Dopplers had only elevated S/D ratio and PI. Out of 4 PIH patients with abnormal Doppler, three ie 75% developed severe Pre Eclampsia and so pregnancy was terminated at 31weeks, 33weeks and 36weeks. 6 patients with normal uterine artery doppler developed PIH and did not develop preeclampsia. In this 6 PIH patients, 3(50%) delivered preterm due to PROM and preterm labour because of maternal infections, which was confirmed by elevated counts in the mother and 5 (83%) had IUGR babies. Of this 6 PIH patients, 5 IUGR babies were contributed by the constitutionally small mothers. Among the 10 PIH patients 6(60%) had normal doppler and 4(40%) had abnormal Doppler. In 9 patients with abnormal Doppler, 4(44.4%) developed IUGR babies which was contributed by PIH and severe Preeclampsia. The 6 (66%) patients with normal uterine artery Doppler, had IUGR babies contributed by the constitutionally small mothers.

Conclusion: Second trimester uterine artery Doppler is useful in predicting PIH and IUGR.

INTRODUCTION

The placenta is the structure that links the mother and fetus by indirect interaction with the maternal blood that spurts out of the uteroplacental vessels. The placenta begins to develop upon implantation of the blastocyst into the maternalendometrium. The outer layer of the blastocyst becomes the trophoblast which forms the outer layer of the placenta. This outer layer is divided into two further layers: the underlying cytotrophoblast layer and the overlying syncytiotrophoblast layer. The syncytiotrophoblast is a multinucleate continuous cell layer which covers the surface of the placenta. It forms as a result of differentiation and fusion of the underlying cytotrophoblast cells, a process which continues throughout placental development.

The syncytiotrophoblast (otherwise known as syncytiot)ium), thereby contributes to the barrier function of the placenta.

The placenta grows throughout pregnancy. Development of the maternal blood supply to the placenta is suggested to be complete by the end of the first trimester of pregnancy (approximately 12–13 weeks). In preparation for implantation, the uterine endometrium undergoes ‘decidualisation’. Spiral arteries in the decidua are remodelled so that they become less convoluted and their diameter is increased. Primary & Secondary waves of trophoblastic invasion causing Loss of mem-

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and diabetes mellitus.

RESULTS
In our study, 100 pregnant women were recruited from June 2010 to April 2013 according to the inclusion and exclusion criteria. Gestational age of the patients was confirmed by the First trimester USG. If no dating scan was available, Second Trimester USG was used for confirmation of Gestational age. In all the selected patients, Uterine artery Doppler along with their routine anomaly scan was done. These patients were followed up till delivery. Along with the Doppler indices, other details like gestational age at termination, whether the patient developed PIH or not and birth weight of the babies were also included.

<table>
<thead>
<tr>
<th>Uterine Artery Doppler</th>
<th>No of patients</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>91</td>
<td>91.0</td>
</tr>
<tr>
<td>Abnormal</td>
<td>9</td>
<td>9.0</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 1: Distribution of normal and abnormal dopplers

Majority of the patients had normal uterine artery doppler and only 9% had abnormal uterine artery Doppler.

<table>
<thead>
<tr>
<th>Diastolic Notch</th>
<th>Uterine artery doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>No</td>
<td>91(100%)</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Distribution of Diastolic Notch among normal and abnormal dopplers

In this study, the value of uterine artery right S/D ≤ left S/D ratio ≤ 1, PI >1.45 is considered as abnormal Doppler. Presence of bilateral diastolic notch is considered significant. Out of 100 cases I studied 91 had normal Doppler and 9 had abnormal Doppler. Out of this 9 abnormal dopplers, 4 (44.4%) had persistence of diastolic notch with elevated S/D ratio and PI. The other 5 (55.5%) abnormal Dopplers had only elevated S/D ratio and PI. All the four with persistent diastolic notch developed preeclampsia. In this 3 pregnancies were terminated at 31-36 weeks for uncontrolled hypertension with severe preeclampsia and one pregnancy was induced at 38 weeks for preeclampsia. All the four pregnancies had IUGR babies.

Out of 4 PIH patients with abnormal Doppler, three i.e 75% developed severe Pre Eclampsia and so pregnancy was terminated at 31 weeks, 33 weeks and 36 weeks. All the three delivered Severe IUGR babies with weight 1.1kg, 1.2kg and 2.3kg respectively. This is statistically significant with p < 0.05. And also persistence of diastolic notch is seen in all the four patients. 6 patients with normal uterine artery doppler developed PIH and did not develop preeclampsia. In this 6 PIH patients, 3(50%) delivered preterm due to PPROM and preterm labour because of maternal infections, which was confirmed by elevated counts in the mother and 5 (83%) had IUGR babies. Of this 6 PIH patients, 5 IUGR babies were contributed by the constitutionally small mothers. Among the 10 PIH patients 6(60%) had normal doppler and 4(40%) had abnormal Doppler.

Table 1: Distribution of normal and abnormal dopplers

<table>
<thead>
<tr>
<th>Complications</th>
<th>Abnormal doppler with dn (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia</td>
<td>3</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1</td>
</tr>
<tr>
<td>IUGR</td>
<td>4</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>4</td>
</tr>
</tbody>
</table>

In 9 patients with abnormal Doppler, 4(44.4%) developed IUGR babies which was contributed by PIH and severe Preeclampsia. The 6 (66%) patients with normal uterine artery Doppler, had IUGR babies contributed by the constitutionally small mothers.

In total 11 preterm labours, 3(100%) were terminated for severe preeclampsia who had persistence of diastolic notch. And the rest, 25% were due to preterm premature rupture of membranes and 75% were due preterm labour pains. This may not be statistically significant and the second trimester uterine artery doppler did not have much value in predicting the preterm labour. The Better predictor of preterm labour could be the serial measurement of cervical length. Causes of preterm labour was found to be PPROM, Preterm contractions rather than gestational hypertension. Except for 3 preterm deliveries, which were terminated preterm due to severe preeclampsia.

DISCUSSION
One of the main goal of routine antenatal care is to identify mothers or babies at risk for adverse outcomes during pregnancy. One of the commonly performed investigation in pregnancy is the ultrasonogram as it is quiet safer during all trimesters of pregnancy. Doppler ultrasound uses sound waves to detect the flow of blood in the blood vessels. It is used in pregnancy to study the fetomaternal as well as feto placental blood flow. Impaired placentation can cause some of the most important obstetrical complications such as pre-eclampsia and intrauterine growth restriction which has increased fetal and maternal morbidity and mortality respectively. The failure to undergo physiological trophoblastic vascular changes is reflected by the high impedance to the blood flow at the level of the uterine arteries. Doppler ultrasound study of utero-placental blood vessels, using waveform indices or notching, may help to identify the mothers at-risk in the first and second trimesters of pregnancy, such that interventions might be used to reduce maternal and fetal morbidity and/or mortality. If an abnormal blood flow pattern is identified, then it is possible that
survived preterm labour because of PPROM and preterm contractions which did not contribute for IUGR. The other 4 with abnormal Doppler suffered severe preeclampsia. Second trimester uterine artery Doppler has a positive predictive value is 44.4%, negative predictive value is 93.4% with 40% sensitivity and 94% in screening for IUGR.

In predicting preterm labour, Uterine artery dopplers were not found useful as Abnormal Doppler could not predict preterm labour. It has 27% sensitivity and 93.25% specificity with positive predictive value 33.3%. So better predictor of preterm labour could be the serial measurement of cervical length.

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8. Brandão AH, Cabral MA, Leite HV, Cabral AC. Arq Bras Cardiol. Endothelial
ABSTRACT
Urinary retention is a painful side effect associated with antipsychotic drugs. Amisulpride is a second generation antipsychotic medication used in the management of psychosis and dysthymia along with depression. We wish to report a rare side effect of urinary retention associated with amisulpride therapy.

INTRODUCTION
Amisulpride, a substituted benzamide derivative, is another second-generation atypical antipsychotic medication. It is a standard treatment in dysthymia as well as in psychosis. Amisulpride is efficacious, effective and well tolerated in positive symptoms of schizophrenia: there is extensive evidence that it treats negative symptoms when given in low doses, although relative lack of EPS and an antidepressant effect may contribute. It is generally well tolerated with adverse effects that have been reported include insomnia, anxiety, agitation, dryness, gastrointestinal disorder, dry mouth, and Hyperprolactinemia.

Although urinary retention has been reported to occur with other antipsychotics, we could not find any report of urinary retention associated with amisulpride. In contrast, we found a case of amisulpride-induced urinary incontinence associated with amisulpride. We wish to report a case that developed urinary retention while on amisulpride therapy.

CASE REPORT
46 year old male presented to outpatient department with 1 year history of insidious onset of suspiciousness, reporting hearing voices not heard by others, decreased social interaction, anhedonia, decreased self care and socio-occupational dysfunction. His past, family and personal history were non significant. Mental status examination revealed rapport not established, fearful affect, delusions of reference and persecution, third person auditory hallucinations, impaired abstraction and insight grade 1. He had no significant medical history. He was diagnosed as a case of Paranoid schizophrenia according to DSM. He was started on risperidone up to 6 mg per day without any response. Subsequently, he was started on amisulpride 100 mg per day increased to 800 mg over period of next 3 weeks. The patient gradually started showing improvement in her symptoms and he tolerated the drug well. However, after about 5 weeks of amisulpride therapy, the patient developed difficulty in urination and had hesitancy. He would have to make an effort to pass urine. Subsequently, within next few hours, he developed complete urinary retention along with severe abdominal pain which increased while he tried to micturate. He was taken to emergency and catheterization was done. His USG Abdomen and pelvis was within normal limits. Physical examination and other relevant laboratory tests were normal. No local pathology was identified. The dose of amisulpride was decreased to 400 mg per day. The patient has shown improvement in his psychotic symptoms and has been stable for the last 6 months without reporting any urinary complaints.

DISCUSSION
The temporal relation between administration of Amisulpride and urinary retention indicates a highly probable chance of amisulpride induced urinary retention in this patient. The appearance of urinary retention at higher dose and disappearance with subsequent dose reduction suggests this to be a dose related phenomenon. In contrast to other typical antipsychotics where cholinergic blockade is proposed as the mechanism, it is difficult to speculate the mechanism for amisulpride induced urinary retention as it has no affinity for cholinergic receptors. Amisulpride is specific for its action on dopamine D2 and D3 receptors in the limbic rather than striatal structures. It has been reported that at higher doses (>10 mg/kg) amisulpride acts as a dopamine receptor blockade and in low doses (<10 mg/kg), amisulpride preferentially blocks presynaptic D2/D3 receptors, resulting in enhanced dopamine transmission.

We can only speculate at present the role of dopaminergic system in causing this side effect. Central acute dopamine-2 (D2) receptor stimulation has been associated with a reduction of bladder capacity and detrusor overactivity, suggesting that acute D2 blockade caused by higher dose of amisulpride may be a factor in urinary hesitancy and retention. Subsequently, lowering the dose might be beneficial for the same.

Our patient did not have any risk factor for urinary retention like prostate hypertrophy or old age; still he developed this side effect. Our report suggests that one should be cautious while using this drug and patients should be explained about this rare but possible side effect. Special care should be taken in elderly and other population prone to anticholinergic side effects. Further studies are required to characterize the urinary problems associated with amisulpride therapy and also to characterize the patients at risk for these
troublesome side effects.

REFERENCES
Special Report from WHO

Key messages:

- Depression is a common mental disorder that affects all.
- The risk is increased by poverty, unemployment, life events such as the death of a loved one or a relationship break-up, physical illness and problems caused by alcohol and drug use.
- Depression causes mental anguish and can impact people’s ability to carry out even the simplest everyday tasks, with sometimes devastating consequences for relationships with family and friends.
- Untreated depression can prevent people from working and participating in family and community life.
- At worst, depression can lead to suicide, now the second leading cause of death among 15-29-year olds globally.
- Depression can be effectively prevented and treated. Treatment usually involves either psychotherapy or antidepressant medication or a combination of these.
- Overcoming the stigma often associated with depression will lead to more people seeking help.

World Health Day, celebrated on 7 April every year to mark the anniversary of the founding of the World Health Organization, provides a unique opportunity to mobilize action around a specific health topic of concern to people all over the world. The theme of 2017 World Health Day campaign is depression.

What is depression?
Depression is an illness characterized by persistent sadness and a loss of interest in activities that you normally enjoy, accompanied by an inability to carry out daily activities, for at least two weeks.

In addition, people with depression normally have several of the following symptoms:

- Loss of energy
- Change in appetite
- Sleeping more or less
- Anxiety
- Reduced concentration
- Indecisiveness
- Restlessness
- Feelings of worthlessness, guilt, or hopelessness
- Thoughts of self-harm or suicide.

What is the burden of depression?

- Globally:
  - WHO estimates that one in four people in the world will be affected by mental or neurological disorders at some point in their lives. Around 450 million people currently suffer from such conditions.
  - An estimated 350 million people are affected with depression. At its worst, it can lead to suicide, over 800,000 people die due to suicide every year.

- In India:
  - In India, the National Mental Health Survey 2015-16 data reveals that nearly 15% Indian adults need active intervention for one or more mental health issues.

- One in 20 Indians suffers from depression. It is estimated that in 2012, India had over 258,000 suicides, with the age-group of 15-29 years being most affected.

What is the campaign?
The overall goal of this one-year campaign is that more people with depression, in all countries, seek and get help. More specifically, it is aimed at creating a better informed general public on depression, its causes and possible consequences, including suicide, and help available for prevention and treatment; encouraging people with depression to seek help; and facilitating family, friends and colleagues of people living with depression, to provide support.

At the core of the campaign is the importance of talking about depression as a vital component of recovery. The stigma surrounding mental illness, including depression, remains a barrier to people seeking help throughout the world.

Talking about depression, whether with a family member, friend or medical professional; in larger groups, for example in schools, the workplace and social settings; or in the public domain, in the news media, blogs or on social media, helps break down this stigma, ultimately leading to more people seeking help.

What is the slogan?
The campaign slogan is: Depression: Let’s talk.

Who are we reaching out?
Depression can affect anyone. This campaign is for everyone, whatever your age, sex, or social status.

While the World Health Day 2017 campaign will be broad-based, the focus will be on vulnerable population, including demographic vulnerability (young people, women, elderly), geographical and financial vulnerability etc.

Further details can be accessed at http://www.searo.who.int/india/mediacentre/events/world_health_day/whd_2017/en/
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ABSTRACT: A structured abstract of not more than 250 words should accompany each original article, systematic review or meta-analysis. Abstracts for original contributions should be divided by individual headings into paragraphs entitled: Objectives, Methods, Results and Conclusions.

Case reports should include a brief abstract describing the case(s) and literature review. Reviews must have an abstract included, which can be unstructured. Editorials need not include an abstract. Abbreviations or references to figures or tables should not be utilized in the abstract.

ORIGINAL ARTICLES: All original manuscripts should include the following:

Abstract: Structured abstract as described above.

Introduction: The specific aim(s) and a priori hypothesis need to be stated.

Methods: Must include sufficient information to judge the quality of the work, including statistical analysis and study power, where appropriate.

Results: Please do not duplicate results present in the text and tables.

Discussions: Consider including a brief statement of the major findings, the meaning of the study including possible explanations and implications for clinicians, the findings in relation to other studies and consideration of important differences in results, the strengths and weaknesses of the present study, and what are now the unanswered questions and future research needs.

Authors are required to include in addition to a structured abstract, a separate paragraph with 4-8 bulleted points under the heading: what is known on the subject and what this research adds. This information will be included as a table at the end of the article, and is to be aimed at simply explaining the study’s importance and knowledge gained from it to those who are non-experts in the particular fields.

RANDOMIZED CLINICAL TRIALS (RCTs): RCTs are encouraged and will be fast tracked in the review and publishing schedule. Randomised clinical trials must all report their data in accordance with CONSORT (Consolidated Standards of Reporting Trials) statement. This ensures that you provide enough information for editors, peer reviewers, and readers to see how the trial was performed and to judge whether the findings are likely to be reliable. Please provide the following, as described in the CONSORT statement:

Five extra sub headings section in the main text of the paper: Protocol, assignment, masking, participant flow and follow up, analysis.

A completed checklist for editors and reviewers (not for publication) showing that you have described all key points in your report.

All RCTs must meet CONSORT guidelines, and include the CONSORT checklist with submissions. We may choose not to use all of the sub headings in the published version of the paper for reasons of readability.

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DEBATES: They must be written by different authors for the pros and cons, and will be crisp and short in nature, consisting of not more than 1000 words excluding references.

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REFERENCES: All the references should be numbered consecutively and be listed according to the order in which they are referred to in the text of the manuscript. The references should be typed double-spaced and abbreviations of journals must conform to those used in Index Medicus or the National Library of Medicine. The format should conform to the example listed below.

References to an article with 3 or less authors:


References to an article with more than 3 authors:


Reference to a book:


Reference to a chapter in a book:


TABLES: Each table should have an appropriate title, self-explanatory, and should not duplicate the text. The data should be logical and well organised so that it can be used to compare or classify related items. Table should be numbered consecutively in Arabic numerals beginning with 1.

ILLUSTRATIONS: Colour illustrations are allowed, and will not usually attract a cost to authors.

One set of original illustrations should be mailed. All the illustrations of graphs, artwork, and photographs should be numbered in consecutive Arabic numerals and submitted. A label should be affixed to the back of each illustration with the name of the senior author, manuscript title, figure number and an arrow indicating the top of the figure. The legends of all figures should be typed double-spaced on a separate sheet of paper. When appropriate, arrows should be placed on photographs and drawings to indicate the portions to which reference is made. In the legends for photomicrographs, the magnification and stain utilized should be included.

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