Doctor-Patient relationship

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From time immemorial, Medicine has been considered a **noble** profession, on account of the nature of services they rendered to the suffering humanity. The sanctity of the oath taken by the professionals and the code of ethics they had imposed on themselves are considered adequate to keep the doctors on the righteous path. For a long, long time, medical profession has served the society reasonably well that the profession was rightly called a "Noble Profession" and Doctors, "next to God". People took up the profession as a vocation with a strong feeling that this job is the purpose of his life, and, a feeling that it is a call from God. They are motivated by humanitarian consideration with a strong desire to help others and relieve suffering. Even today, an overwhelming majority of professionals in medicine abide by the norms of public service and a deep sense of social responsibility thereby not permitting external temptations affect their profession.

However, due to complexities of life in the modem society, there has been commercialization in every aspect of life, in which the medical profession could not remain unaffected. The great strides of progress in modem medicine, diagnostic techniques, surgery and healthcare system, have raised various problems in respect of standard of care, extent of human right protection and adequacy of systems of accountability. Time-tested standards, conventions and practices have been questioned in the light of new knowledge and better understanding of healthcare. The consumer today, is no more fatalistic and at the mercy of the doctor or the hospital. ***I am a doctor, and I can do no wrong'*** does not stand anymore. People now want justice and compensation. These developments have caused in serious deterioration of Doctor-patient relationship. This is partly because, the amount of commitment among the professionals has been greatly submerged by other less noble considerations. Too much of commercialization and too much of compartmentalization of different specialties have depleted the milk of human kindness in the profession.

Duties of a doctor

Keeping in view the corrosion of doctor-patient relationship, it is important to remind ourselves what our duties and responsibilities are. There are four basic duties a doctor has to perform. They are:

1. Duties towards the state
2. Duties towards the society,
3. Duties towards one another, and
4. Duties towards the patient.

1. Duties towards the state

A doctor has a statutory duty towards the state in reporting birth, death and Notifiable diseases to the Public Health authority. He also has unconditional duty to perform in times of natural calamities and mass disasters. In times of emergencies, he as a moral, ethical and humanitarian duty to do his best to save the life of a patient. In medicolegal cases, he has a duty to examine the case and prepare a good medicolegal report so as to help in the administration of justice. Every person, aware of the commission of, or of the intention of any other person to commit any offence shall

forthwith give information to the nearest Magistrate or Police officer of such commission or intention.

2. Duties towards the society
A doctor has a special duty to teach and demonstrate a healthful living in a society.

3. Duty towards one another
Doctors have to cooperate with one another. Never to criticize or condemn a colleague but should extend to him the same honour, respect good behavior and cordiality as he would expect from them.

4. Duties towards the patient
As soon as a doctor undertakes to treat a patient, he becomes duty bound to exercise a reasonable degree of skill, care and competence in his treatment. There has been an implied form of contract that he will do his best for the welfare of his patient. He need not guarantee a cure, nor will he be liable for an error of judgment. He should always be courteous, sympathetic, friendly and helpful. He should use his utmost skill, care and competence to cure his patients. Even when he fails to cure, the patient should not have any doubt about the sincerity of the doctor. He should always be a source of confidence and comfort to the sick. When a patient fails to see these conducts in a doctor, suspicion arose, faith falters. Doubt, challenges, litigations, and, even assaults occurred. In recent times, we have seen several embarrassing newspaper reports: **"A doctor charged with homicide", "Let Doctors pay", "Hospital blunder" "Doctor in the Dock" "Neurosurgeon asked to pay Rs.5 lakhs" "Doctor assaulted after patient's death", "Forceps left in the patient's stomach after operation" etc.**

Remedy
The best way to avoid all these problems is to observe the CODE OF MEDICAL ETHICS very scrupulously. We should practice our profession with conscience and dignity, maintaining utmost respect to human life. Let us try to maintain the honour and noble tradition of our profession by giving the health of our patient our first consideration. Let reward and financial gain be our secondary consideration. An ideal physician should be upright, pure in character, diligent and dedicated in caring for the sick. He should be sober, patient, prompt in discharging duty without anxiety, conducting himself with propriety, humble, friendly and sympathetic. Let patient be considered the ***most important visitor of the day*** and, be hospitable to him. Holistic approach to the patient is the need of the hour in this era of litigation where **every patient becomes a potential going-to-court case.** One should realize that "healing is not merely curing certain disease". It is not like repairing and removing the defect of a machine: it deals with a person. So, let us be human, not mechanical in our approach. William Boyd has said, ***"The patient with a heart disease is not just an internal combustion engine with a leaking valve, but a sensitive human being with a disease heart".*** Therefore, disease in man is not exactly the same as disease in experimental animal, for in man the emotion comes into play.

Mushrooming of specialties and super-specialties in the modern medical science has complicated patient management. It has created too much of compartmentalization that, a time may come when a doctor is called a ***specialist in right kidney, and not for the left.*** Such multiple super-specialties have diluted the emotion and tend to be mechanical. The milk of human kindness in a doctor has been submerged in a robotic approach of a doctor, thus shattering the bond of love, friendship and trust between a doctor and the patient.

To bring back the past glory of the profession, and restore the love and trust between doctor and the patient, let us administer a **Reasonable degree of care** to the patient – spend sometime with the patient everyday, explain his problems, be friendly, give comfort, let him not feel neglected, try to understand his problems. Give to your patient what you want a doctor to give when you are a patient. A sense of commitment and a sense of stewardship are essential. To keep ourselves free from the slavery of covetousness,

Let us accept our work,

Not only as an occupation or even a profession,

But also as a *CALLING-A VOCATION*

Guest Editor

Do we need re-examining undergraduate Medical Education

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Let us analyse the post-independence scenario of medical education in our country. There seems to be an overwhelming emphasis in promoting the production of medical personnel. This has been well evidenced by the increasing number of medical colleges throughout the country. At present, the annual output of MBBS doctors exceeds twenty five thousand. Are we not overproducing doctors in the country? The matter needs to be examined carefully. On the other hand, the quality of medical training programme has not been given due attention as it should be. The training programme for the medical students should be well planned so that it is relevant, useful and responsive to the needs of the common people/ society. If we examine teaching - training programmes/ schedules for the MBBS students, there lies a number of points to be clarified.

The curriculum needs to be planned properly. If we happen to examine the present curricula, it needs analysing common disease spectrum seen at outpatient and inpatient setups at primary health centres, district hospitals, general practitioners and medical college hospital. The emphasis in our training should match fairly with the common and important health problems of the society. It will be desirable to expose medical students to health problems throughout the period of undergraduate training.[1]

Each department concerned should identify its own goals, objectives and core abilities. It should also be clearly mentioned as well as documented and be available to the medical students.

It has been seen that the present system of teaching is not active. This needs to be modified so that there is active learning where the participation of students or the learner is of utmost importance. Simply attending or listening to didactic lecture classes will not be appropriate.

There should be provision for integrated learning along with other health professionals from within the medical institute as well as from outside. This is needed to impart composite knowledge on health instead of fragmented and piece meal approach.

The undergraduate medical education should be oriented towards training of medical students to become a physician of first hand contact who is capable of looking after the preventive, promotive, curative and rehabilitative aspects of medicine.[2] The graduate doctor should possess the skills to plan and manage community health programmes. Also he/she should have clear understanding of his / her role in different National Health Programmes.

The basic doctor should invariably possess the requisite knowledge and skills to manage efficiently the clinical emergencies and medicolegal cases.

The medical personnel/ doctor should also require the leadership and managerial skills to carry out his works with the health team of primary health care centre or any health care set up. The National Health Policy (NHP)

decries the wrong priorities that crept into health care service of the country and clearly points to prepare doctors who will serve rural and urban settings and who will not give emphasis on curative aspects of medicine alone.[3]

The training of the undergraduates should be such that once graduated, he should develop humanistic attitudes in practising medicine.

The curriculum contents for teaching the medical students should contain proper guideline for evaluation of students through a valid and reliable system which can assess the minimum skills/ care abilities of the learners.

These are only a few facets of ongoing undergraduate medical teaching programme. Besides these, internship programme, methods of teaching, and use of newer and effective teaching aids etc. may be looked into properly.

Some of the suggestions for a change or modification in the curriculum of the undergraduate medical education may be mentioned.

- Faculty sensitisation and development
- Discussion with student representatives
- Identification of tasks of graduate doctor
- Review and Revision of question papers with due approval from the university with a view to setting question papers properly balanced in terms of course content and its relevancy
- Designing and Restructuring of evaluation tools/ Technique
- Implementation of teaching innovations.
- Continuous monitoring of changes by Feedback from students and faculty and modify if needed.

Medical Education unit / cell of the Institute/ College may be given the responsibility for co-ordinating and helping departments in successful implementation and achieving useful changes as suggested.

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Prophylactic antiemetic therapy with dexamethasone in patients undergoing laparoscopic cholecystectomy

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Abstract

Objective : To evaluate the effectiveness of intravenously administered dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing elective laparoscopic cholecystectomy. **Methods :** Fifty adult patients were randomly allocated to one of the two groups, to receive either 10mg (3ml) of dexamethasone i.v. (Group A), or 3ml normal saline i.v. (Group B). **Results :** The results showed that 8% of the patients in the dexamethasone group compared with 40% in the saline group reported vomiting (P<0.05). The total incidence of nausea and vomiting was 16% in the dexamethasone group and 76% in the saline group (P<0.001). **Conclusion :** Prophylactic intravenous dexamethasone 10mg significantly reduced the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

Keywords: *Surgery, Laparoscopic, Vomiting, Nausea , Antiemetics, Dexamethasone.*

Introduction

Postoperative nausea and vomiting (PONV) are frequent complications after general anaesthesia and major surgery. PONV not only causes distress to the patient, but also gives tension on sutures, potential bleeding at the operative site, unanticipated hospital admission, delayed discharge, fluid and electrolyte imbalance. In recent years, there has been a general trend towards decrease in the incidence and intensity of the problem, because of the use of less emetic anaesthetic agents, improved pre-and postoperative medications, refinement of operative techniques and identification of predictive factors.

The place of dexamethasone has been well established as an antiemetic in patients receiving chemotherapy in 1981.[1,2] Recently, dexamethasone has also been found to be effective in reducing the incidence of PONV in patients undergoing various field of surgery.[3-9] Despite recent advances in modern anaesthetic practice and surgical techniques, nausea and vomiting still occurs with unacceptable frequency and a high incidence of PONV has been reported in patients undergoing laparoscopic cholecystectomy (53-73%).[10,11] As dexamethasone has an antiemetic effect in various situations[2,5-7,11-13], it may also be effective in the prevention of emesis after laparoscopic cholecystectomy.The present study is designed to evaluate the antiemetic effect of intravenous (i.v.) dexamethasone in the prevention of nausea and vomiting in adult patients after laparoscopic cholecystectomy.

Material and methods

The study was conducted in the Department of Anaesthesiology, Regional Institute of

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Medical Sciences(RIMS), Imphal, during the period July 2003 to June 2005. After obtaining institutional ethics committee approval and informed written consent, fifty adult patients belonging to ASA grade I and II, aged 18-60 years scheduled for elective laparoscopic cholecystectomy under general anaesthesia were selected for the study.

Patients with any gastrointestinal, liver or renal diseases, psychological illness, a positive history of alcoholism or opioids addiction, those who had received steroids or antiemetic medication within 24h before surgery or complained of preoperative nausea or vomiting including motion sickness or headache, hypersensitivity to steroids and those who were pregnant, lactating, menstruating or weighing more than 90kg or suffered from a difficult intubation during the induction of anaesthesia were excluded from the study.

Patients were randomly allocated to two groups of twenty five (n=25) in each group. Group A received 10mg (3ml) dexamethasone intravenously while Group B (Placebo group) received 3ml normal saline.

Pre-anaesthetic evaluation was done for all the patients scheduled for elective laparoscopic cholecystectomy. Detailed history, physical examination and basic investigations were done in these patients. Visual analogue scale (VAS) consisting of 10 cms with 0 = no pain and 10 = most severe pain were explained to all the patients in the pre-anaesthesic visit. All patients were premedicated with oral diazepam 0.2mg/kg and ranitidine 150 mg orally the night before surgery.

On arrival in the operation theatre, routine monitoring devices were placed and used, including non-invasive arterial pressure, heart rate and pulse oximetry. A suitable peripheral vein was cannulated for administration of anaesthetic agents and intravenous fluids. All patients were premedicated with 50mg i.v. ranitidine and glycopyrrolate 0.2mg i.m. 1h before surgery. Then, study medications (3ml) were prepared. One minute before induction of anaesthesia, patients in Group A received dexamethasone 10mg (3ml) i.v. and those in Group B, normal saline (3ml) i.v.

The anaesthetic regimen and surgical procedure were standardized for all patients. Anaesthesia was induced with propofol 2mg/kg body weight and butorphanol 20µg/kg body weight i.v. Tracheal intubation was facilitated with succinylcholine 2mg/kg body weight i.v. and anaesthesia maintained with N_2O and halothane in oxygen and atracurium (0.5mg/kg body weight i.v. and repeated as required).

Ventilation was controlled manually and adjusted to maintain the end-tidal partial pressure of CO_2 ($PETCO_2$) between 4.7 and 5.3kPa (35-40 mmHg). Laparoscopic cholecystectomy was performed under video guidance and involved four punctures of the abdomen. During surgery, patients were placed in the reversed Trendelenburg position with the right side of the bed elevated and abdomen insufflated with carbon dioxide through a veress needle to a maximum of 15 mmHg. All patients received diclofenac sodium 75mg i.m. and tramadol 2mg/kg i.v., twenty minutes before the end of surgery. At the cessation of surgery, glycopyrrolate 0.5mg and neostigmine 2.5mg were administered i.v. to reverse the neuromuscular block, and tracheal tube removed. Intra-operative monitoring included continuous ECG, non-invasive blood pressure, capnography and pulse oximetry.

After surgery, data were collected up to 24h postoperatively. The follow-up of the patients during the first 2h was undertaken in the post-anaesthetic care unit (PACU) and thereafter (2-24h) in the ward. During the first 2h after anaesthesia (PACU), vital signs such as non-invasive blood pressure, heart rate, respiratory rate and haemoglobin oxygen saturation (SpO_2) were monitored in all patients. Nausea, emetic episodes, rescue antiemetic medication, pain treatment and adverse events were assessed on three occasions during the study period as follows: 1h, 2h and 24h after the end of the operation. Nausea and vomiting were evaluated on a 3 point ordinal scale (0=none; 1=nausea; 2=vomiting). The number of all emetic episodes were recorded. Rescue

antiemetic administration of ondansetron 4-8mg i.v. was given on patient request or when vomiting occurred. The number of antiemetic and analgesic doses were recorded during the study period (0-1h, 1-2h, 2-24h). Rescue analgesic was provided by a further dose of tramadol 2mg/kg i.v. and diclofenac sodium 75mg i.m., repeated if necessary. Pain intensity was assessed using a 10-cm visual analogue scale (VAS; 0 = no pain, 10 = most severe pain) during the study period (1h, 2h, 24h).

Statistical analysis of the data between the two groups was performed by student 't' test. A 'P' value of < 0.02 was considered to be highly significant.

Results

Over the study period, a total of 50 patients with 25 in each group were studied. There was no significant differences between the two groups with respect to patients characteristics, duration of CO_2 insufflation, duration of surgery and duration of anaesthesia (table 1).

Table 1. Patient characteristics, duration of CO_2 insufflation, surgery and anaesthesia in Group A and Group B.

Variables	Group A (Dexame-thasone) (n=25)	Group B (Saline) (n=25)	'P'
Age(yr)	35.1±10.2	39.5±14.1	>0.05
Weight(kg)	56.7±10.8	58.1±8.6	>0.05
Height (cm)	163.5±4.32	164.5±7.01	>0.05
Sex (M:F)	5.20	8:17	>0.05
Duration of CO_2 insufflation(min)	44.3±13.2	46.9±14.07	>0.05
Duration of surgery(min)	53.7±15.15	53.9±14.9	>0.05
Duration of anaesthesia(min)	63.5±15.0	63.4±15.7	>0.05

Table 2 showed total incidence of nausea and vomiting during 0-24h postoperatively. Only 8% of the patients in Group A compared to 36% of the patients in Group B experienced nausea with chi-square value of (x^2) 4.19 which is significant, i.e. p<0.05. Similarly, 8% of the patients in Group A and 40% of the patients in Group B experienced vomiting with chi-square value of (x^2) 5.37 which is significant, i.e. p<0.05. The total incidence of nausea and vomiting reported during 0-24h interval was 16% of the patients in Group A versus 76% of the patients in Group B with chi-square value of 15.78 which is highly significant, i.e. p<0.001.

Table 2. Incidence of nausea and vomiting during 0-24h postoperatively(po), n(%)

Variables	Group A (Dexame-thasone) (n=25)	Group B (Saline) (n=25)	'P'
Nausea only	2 (8)	9 (36)	<0.05
Vomiting	2 (8)	10 (40)	<0.05
Total	4 (16)	19 (76)	<0.001

Table 3 showed the distribution of patients with respect to their vomiting episodes during 0-24h postoperatively. In Group A 92% of the patients and 60% of the patients in Group B had no episodes of vomiting with chi-square value of (x^2) 5.37 which is significant, i.e. p<0.05. Similarly, 8% of the patients in Group A reported vomiting at least once compared to 28% of the patients in Group B with chi-square value of (x^2) 2.16 which is not significant, p>0.05. In Group A no patient reported vomiting episodes of 2-3 times compared to 8% of the patients in Group B with chi-square value of (x^2) 0.52 which is not significant, p>0.05 and none of the patients in Group A had vomiting episodes of 4-6 times compared to 4% of the patients in Group B with chi-square value of (x^2) 0.002 which is not significant, p>0.05.

Table 3. Shows the distribution of patients in relation to vomiting episodes in Group A and Group B during the first 24h po, n (%).

No.of vomiting episodes	Group A (Dexameth-asone) (n=25)	Group B (Saline) (n=25)	P
0	23 (92)	15 (60)	<0.05
1	2 (8)	7 (28)	>0.05
2-3	0 (0)	2 (8)	>0.05
4-6	0 (0)	1 (4)	>0.05

Only 8% of the patients in Group A were given rescue antiemetic compared to 40% of the patients in Group B during the 0-24hPO. Statistically, chi-square value of (x^2) 11.08 was found which is highly significant i.e. p< 0.001.

In Group A, 84% of the patients reported complete response compared to only 24% of the patients in Group B during the 0-24h interval after surgery. Statistically, a chi-square value of (x^2) 15.78 was found which is highly significant, i.e. P<0.001.

The visual analogue score (VAS) was 5.0(5.0-6.0) in Group A and Group B during 0-1hPO. However, scores came down to 4.0(3.0-6.0) in Group A and 4.0(4.0-6.0) in Group B during 1-2hPO. Between 2-24hPO, VAS were 3.0(2.0-5.0) in Group A and 3.0(3.0-5.0) in Group B. Statistically, there was no significant differences between the two groups.

Table 4 showed the analgesic requirements of patients in both the groups. In Group A, only 1 patient received 1 dose of analgesic injection during the 0-1h interval whereas those in Group B did not require any analgesic injection. Statistically, chi-square value of (x^2) 0.001 was found which is not significant i.e. P> 0.05. In the 1-2h interval, no patient in both the groups required any analgesic injection. However during the 2-24h period, 16 patients in Group A compared to 10 patients in Group B required 1 dose of analgesic supplement. Statistically, chi–square value of (x^2) 2.003 was found which is not significant i.e. P> 0.05. Eight (8) patients in Group A required two doses of analgesic injection compared to 14 patients in Group B during this interval with chi-square value of (x^2) 2.02 i.e. not significant P> 0.05 and 1 patient in both the groups required 3-6 doses with chi-square value of (x^2) 0.52 which is not significant i.e. P> 0.05.

Table 5 showed the incidence of adverse events in both groups. Drowsiness and sedation was reported as the maximum adverse effect with 21 patients in Group A and 23 patients in Group B. Sore throat was reported in 12 patients in Group A compared to 9 patients in Group B. Eleven (11) patients in Group A and 13 patients in Group B reported urinary retention. Four (4) patients in Group A complained of itching other than perineal compared to none in Group B. Headache was found in 3 patients in Group A compared to only 1 patient in Group B. Perineal itching was reported in 2 patients in Group A immediately after injection of dexamethasone whereas no patient in Group B reported perineal itching. No other side effects are observed.

Table 4. The frequency of analgesia administration with injection diclofenac sodium and injection tramadol with the number of doses administered during the three time intervals after operation.

Analgesic medication (yes/no) No.of doses	Group A(Dexamethasone)(n=25)			Group B(Saline) (n=25)		
	0-1h	*1-2h*	*2-24h*	*0-1h*	*1-2h*	*2-4h.*
	1/24	0/25	25/0	0/25	0/25	25/0
1	1	0	16	0	0	10
2	0	0	8	0	0	14
3-6	0	0	1	0	0	1

Table 5. Incidence of adverse effects. Values are numbers

	Group A (Dexamethasone) (n=25)	Group B (Saline) (n=25)
Drowsiness	21	23
Sore throat	12	9
Urinary retention	11	13
Itching (other than perineal)	4	0
Headache	3	1
Perineal itching	2	0

Discussion

Postoperative nausea and vomiting (PONV) are the most common complications after anaesthesia and surgery, with a relatively higher incidence after laparoscopic cholecystectomy. Several studies found high incidences of PONV (53-72%) in patients undergoing laparoscopic cholecystectomy. [2,10,11,14-17]

The present study demonstrated the beneficial effects of intravenous dexamethasone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy. Dexamethasone 10mg (3ml) i.v. was given one minute before induction of anaesthesia whereas other previous authors used 2 to 16 mg of i.v. dexamethasone for their studies.[3,14-17]

In the present series16% of the patients in dexamethasone group reported nausea and vomiting compared to 76% of the patients in saline group during 0-24h postoperatively. Our values were not in full agreement with those of the other authors[14-16] where the frequency

of nausea and vomiting ranges from 23 to 32.5% in dexamethsone group and 52.5 to 64% in saline respectively. This discrepancy could be due to lack of full knowledge about its aetiology, use of large dose dexamethasone, various risk factors (CO_2 insufflation, gall-bladder surgery, use of volatile anaesthetic and opiods and female sex) and less number of patient recruitment. The result shows that dexamethasone 10mg was more effective than placebo for the prevention of PONV in patients undergoing laparoscopic cholecystectomy.

In our study, 92% of the patients in dexamethasone and 60% in saline group reported no episode of vomiting during 0-24h interval. These results were identical to the previous authors [14-16] where no episode of vomiting during the same period ranges from 89 to 95% in dexamethsone group and 66 to 72% in saline respectively.

Rescue antiemetic was given to 8% of the patients in dexamethasone group compared to 40 % of the patients in the saline group. Our findings were in full agreement with those of previous investigators.[3,5] Complete response was seen in 84% of patients and 24% in saline group. The values were similar to those of previous authors.[14-16]

The antiemetic action of dexamethasone is believed to be exerted through glucocorticoid receptors in nucleus of solitary tract, raphe nucleus and area postrema which are involved in the regulation of the vomiting reflex. It also inhibits the production or secretion of serotonin in central nervous system and prostaglandin synthesis is also impaired .[1,18]

Dexamethasone has been used in the dose of 8-32 mg. for the prophylaxis of emesis related to chemotherapy and after paediatric and gynaecological surgery.[2,19] Though dexamethasone 8 mg was used most frequently, we chose 10 mg to see whether large dose increased antiemetic effect.

During the 24h study,arterial pressure,heart rate and ventilatory frequency were stable and there was no significant difference between groups. No patient had Spo_2 less than 92%. Visual analogue score (VAS) after 1h, 2h and 24h is found to be similar between the two group. Previous authors reported lower values.[15,16] This discrepancy could be due to the technique of anaesthesia and analgesia, low pain threshold in some patients and also less sample size of the present study. However in the present series, all the patients (100%) in both groups required at least one dose of analgesic injection during the 0-24h postoperative period. The percentage of patients requiring rescue analgesic in present study was higher than that of the previous studies.[14,16]

Reported side effect was similar to those of previous studies.[14,17,20] Though adverse effects related to a single dose of dexamethasone were extremely rare,we have reported a few adverse effects of dexamethasone. Perineal itching was the most unusual feature that patients complaint. Several previous authors considered that use of dexamethasone therapy for less than 24 h was safe and almost without adverse effects.[12,13,15,19-23]

Conclusion

It can be concluded from the present study that prophylactic intravenous dexamethasone 10 mg significantly reduced the incidence of PONV in patients undergoing laparoscopic cholecystectomy without any major side effects. Therefore, dexamethasone may be a useful and effective drug for the prevention of PONV after laparoscopic procedures and is recommended for routine use.

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Anti-inflammatory, analgesic and anti-pyretic effects of *Eupatorium birmanicum* DC leaves in albino rats

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Abstract

Objective: To study anti-inflammatory, analgesic and antipyretic effects of aqueous extract of Eupatorium birmanicum DC leaves in albino rats. **Methods:** Carrageenan induced paw oedema method was adopted to study the anti-inflammatory activity in albino rats. Analgesic activity was studied by the tail flick method using analgesiometer and antipyretic activity was evaluated on brewer's yeast induced pyrexia in albino rats. **Results:** Aqueous extract of Eupatorium birmanicum leaves 200 mg/kg bw, i.p. produced significant inhibition (23.08%) of carrageenan induced paw oedema (P <0.001) and significantly increased the tail flick reaction time observed at 30min as compared to respective controls in albino rats (P <0.001). Eupatorium birmanicum aqueous extract (400 mg/kg bw, p.o.) also reduced the body temperature of pyrexia induced albino rats significantly. **Conclusion:** The study demonstrates significant analgesic, anti-inflammatory and anti-pyretic effects of Eupatorium birmanicum leaf aqueous extract. The antipyretic activity of the test drug was however, less significant when compared with the standard drug.

Key words: *Eupatorium birmanicum, analgesic, anti-inflammatory, antipyretic.*

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Introduction

The diverse culture of our country is a rich source of traditional medicines. Many of these traditional medicines are of plant origin.[1] Scientific data on such plant derivatives could pave the way to the development of new chemical entities for clinical use. The leaf tea of *Eupatorium perfoliatum* is used as a substrate for Peruvian bark in the cure of intermittent fever in the United States.[2] Biswal PR et al[3] reported the wound healing effects and antibacterial effect of *Eupatorium odorantum Linn.* in rabbits. Carvalho LH et al[4] studied the effects of crude extracts of *Eupatorium squalidum* against fever and malaria. *Eupatorium birmanicum* DC (Asteraceae) is a small undershrub, found abundantly in Imphal valley. Local people use the juice obtained from crushed leaves to soothe the body in burning sensation (fever).[5] In view of the above claims relating to Eupatorium species, the study was initiated to evaluate anti-inflammatory, analgesic and anti-pyretic activities of the aqueous extract of *Eupatorium birmanicum* DC leaves.

Material and methods

Preparation of *Eupatorium birmanicum* DC leaf extract: The aqueous extract of *Eupatorium birmanicum* leaves (*AEB*) was obtained by the extraction procedure as described by Verma SC and Agarwal SL[6]. Fresh leaves of *E. birmanicum* collected during the months of June and July were cleaned and air dried at room temperature. The dried leaves were then crushed with a mechanical grinder and 100 gm of the powder

was extracted with distilled water using a soxhlet apparatus till the eluent was colorless. On evaporation of the water extract, a deep brown residue (7.2 gm) was obtained and stored in a clean porcelain jar at room temperature. Freshly prepared solution of *AEB* was used in each experiment.

The RIMS Institutional Ethical Committee approved the experimental protocol.

Experimental animals

Colony bred Wistar albino rats (NIN strain) of either sex (120-180 gm) procured from National Institute of Nutrition, Hyderabad were used in the study. The animals were kept in polypropylene cages with 12 hour light – dark cycle in ambient temperature. The animals were maintained on standard laboratory diet with free access to clean drinking water.

Acute toxicity study: No adverse effect or mortality was detected in albino rats fed upto 3 gm/kg p.o. of *AEB* during 24 hr observation period.

Drugs: Carrageenan, yeast, acetylsalicylic acid, Tween-80, paracetamol, pethidine.

Anti-inflammatory activity of *AEB*

The method of Winter CA et al[7] was followed to study anti-inflammatory activity. Carrageenan 1% in normal saline solution (w/v) was injected in a volume of 0.05 ml into the sub-plantar tissue in the right hind paw of rats. Aqueous extract of *Eupatorium birmanicum* (200 mg/kg) and acetyl salicylic acid (ASA) in 3% Tween-80 (100 mg/kg) were administered orally in equal volumes of 1ml to the test and standard groups respectively.

The animals in the control group received normal saline (10 ml/kg) 1 ml p.o. The foot volume was measured plethysmometrically as described by Ghosh MN and Singh H[8] in unanaesthetized rats immediately before and again after carrageenan injection. The difference between the two recordings was recorded as the oedema volume. The percentage anti-inflammatory activity was calculated as described by Khalaj A et al[9].

$$\text{Anti-inflammatory activity} = \left(1 - \frac{dt}{dc}\right)/100$$

Where, dt is the difference in paw volume of drug treated groups and
dc is the difference in paw volume of the control group.

Analgesic activity of *AEB*

The method of D'Amour FE et al[10], as modified by Davies OL et al[11] was followed to evaluate analgesic activity of *AEB* by Tail flick method using analgesiometer. Animals showing variation of more than 3 sec from the group mean were discarded and cut-off time was fixed at 10 sec to avoid tissue injury. The time interval taken by an animal to flick its tail from the hot nichrome wire was noted and taken as the "reaction time". *AEB* and the standard drug (pethidine) were injected intraperitoneally at 200 mg/kg and 24 mg/kg doses respectively. Distilled water (DW) 2 ml/kg i.p. was used as control. The reaction time of each rat from each group was recorded at intervals of 15 and 30 minutes after administration of the drugs.

Antipyretic activity of *AEB*

Antipyretic activity of *E. birmanicum* was studied on brewer's yeast-induced method of Brownlee as described by Burn JH et al[12]. Animals were screened and only those animals showing approximately constant rectal temperature were selected. The room temperature was maintained throughout between 18^0C and 20^0C. Animals were fasted for 18 hours and after measuring the basal rectal temperature, pyrexia was induced by subcutaneous administration of two 1 ml of 15% suspension of dried yeast (1cc. per 100 gm wt.) in 2% gum acacia suspended in normal saline. Paracetamol 500 mg/kg p.o. was used as the standard drug for comparing the antipyretic activity of *EB* 400 mg/kg p.o. Yeast induced control group received normal saline 5 ml/kg p.o. The various drugs were administered by gavage in equal volumes of 1 ml.

Statistical analysis

All values were expressed as mean ± SEM. Data were subjected to one-way ANOVA followed by Dunnett's 't' test. Kruskal-Wallis One-way ANOVA on ranks was used for the analysis of non-normally distributed data using NCSS software. *P* values less than 0.05 were considered significant.

Results

Anti-inflammatory effect: The effect of *AEB* 200 mg/kg p.o. on carrageenan induced paw edema in albino rats is shown in table 1. The mean increase in paw volume of the control group was 0.39 ± 0.01 ml whereas, it was 0.30 ± 0.01 and 0.32 ± 0.02 ml for groups treated with *AEB* and ASA respectively (*P* <0.001). The percentage inhibition of paw edema in groups treated with *AEB* (200 mg/kg, p.o.) and ASA (100 mg/kg, p.o.) were 23.08% and 17.95% respectively.

Analgesic effect*:* Mean increase in the reaction time following *AEB* 200 mg/kg i.p. was insignificant at 15 minutes (3.4 ± 0.25 sec). However, significant increase in reaction time was recorded *(P <0.001)* at 30 min. The standard drug, pethidine 24 mg/kg i.p. showed highly significant *(P <0.001)* increase in the reaction time at 15 and 30 min. as compared to the control(Table 2).

Anti-pyretic effect: The antipyretic effect was observed over a period of four hours. Paracetamol served as the reference drug. It was observed that 18 hours after subcutaneous administration of dried yeast, there was a significant rise of temperature in all groups as compared to the initial basal temperatures in each group. Significant antipyretic effect of *AEB* 400mg/kg p.o. was observed till 4th hr after induction of pyrexia *(P <0.001)*. The standard drug, paracetamol, also produced highly significant reduction of temperature in pyrexia induced albino rats till 4th hr (*P <0.001)* (Table 3).

Table 1. Anti-inflammatory effect of *Eupatorium birmanicum* aqueous extract on carrageenan induced rat paw edema.

Group	Dosage and Route	Mean increase in Paw volume (ml) ± SEM	Percentage of inhibition
I. N/saline	10 ml/kg, p.o.	0.39 ± 0.01	——-
II. *EB*	200 mg/kg, p.o.	0.30 ± 0.01*	23.08
III. ASA	100 mg/kg, p.o.	0.32 ± 0.02†*	17.95
ANOVA :	F(df) = 11.17 (2,15) *P* <0.01		H(df) = 10.76(2) *P* = 0.004

n=6 in each group; *$P < 0.001$ *Vs* control (I); †$P < 0.5$ *Vs* test drug (II)

Table 2. Analgesic effect of *Eupatorium birmanicum* aqueous extract in albino rats by Tail-flick method.

Group Drugs & doses	No. of animals. (n)	Reaction time (mean ± SEM, sec) 15 minutes	30 minutes
I. DW, 2ml/kg i.p.	5	3.4 ± 0.25	3.6 ± 0.25
II. *AEB*, 200mg/kg i.p.	6	3.7 ± 0.21	5.83 ± 0.54*
III. Pethidine, 24mg/kg i.p.	5	9.2 ± 0.37*†	9.6 ± 0.24*†
One-way ANOVA	F(df) :	116.69 (2,13) P <0.0001	53.71 (2,13) P <0.0001
	H(df) :	11.67(2) P = 0.006	13.34(2) P = 0.001

*P <0.01 *Vs* control (I); †P <0.001 *Vs* test drug (II)

Table 3.Antipyretic activity of *Eupatorium birmanicum* aqueous extract in yeast induced pyrexia in albino rats.

Group	Initial basal temperature (°F)	Temperature after pyrexia (°F)	Temperature after treatment (°F) 1st Hr.	2nd Hr.	3rd Hr.	4th Hr.
I. N/saline 5ml/kg, p.o.	98.80± 0.13	100.33± 0.36	100.23± 0.26	100.23± 0.32	100.20± 0.36	100.18± 0.31
II. *EB* 400mg/kg, p.o.	99.07± 0.11	100.98± 0.30$^{e\perp}$	100.85±0.48^{e}	100.80±0.40	100.73± 0.49$^{\perp e}$	100.00± 0.59^{e}
III. Paracetamol 500mg/kg, p.o.	98.65± 0.2	100.70± 0.45	97.87± 0.25*	97.58± 0.26*	97.35± 0.28*	97.33± 0.22*
One-way ANOVA F(df)	1.97(2,15)	2.96(2,15)	48.26(2,15)*	25.47(2,15)*	18.72(2,15)*	9.30(2,15)*
P	0.174		<0.0001	<0.0001	<0.0001	0.002
H(df)	3.53(2)	3.47(2)	12.78(2)	11.79(2)	11.55(2)	10.15(2)
P	0.17		0.0016	0.0027	0.003	0.006

Values are mean ± SEM; n = 6 in each group. †*P*<0.05; $^{\perp}$*P*<0.01*; *P*<0.001 *Vs* (I); ^{e}*P*<0.001 *Vs* (III)

Discussion

Carrageenan induced paw oedema in rats is a commonly employed method for screening anti-inflammatory activity in animals. The leaves of the *Eupatorium birmanicum* aqueous extract (200 mg/kg) reduced paw oedema in albino rats significantly *(P <0.001)* showing a percentage inhibition of 23.08% at three hours after carrageenan

injection. Acetylsalicylic acid (100 mg/kg p.o.) also significantly reduced the paw volume and its effect as anti-inflammatory agent is reconfirmed. The test drug showed no significant difference *(P >0.5)* in the mean increase in paw volumes when compared to the standard drug and appears to be as potent as acetyl salicylic acid.

In the present study it has been observed that the aqueous extract of *AEB* 200mg/kg p.o. produced highly significant increase (*P <0.001)* in the reaction time (in sec) as compared to the control group at 30 minutes. The reaction time of the control group at 30 minutes is comparable with the findings of the Palanichamy S and Nagarajan S[13]. The reaction time of the standard drug (pethidine) at 15 minutes and 30 minutes also shows highly significant *(P <0.001)* increase in the reaction time.

The antipyretic effect of *Eupatorium birmanicum* DC leaf aqueous extract was studied on dried yeast induced pyrexia in albino rats. The mean initial basal temperature of pyretic rats in our study approximates the findings of Gupta MB et al[14]. Paracetamol (500 mg/kg, orally) caused significant lowering of the body temperature upto fourth hour after its administration which was in conformity with the findings of Vimala R et al[15]. The antipyretic effect of *AEB* 400 mg/kg, p.o. caused significant lowering of body temperature at first and third hour of observation period as compared to the control group after pyrexia. The anti-pyretic activity was, however, less significant than paracetamol.

Conclusion

Results of the present study shows that the aqueous extract of *Eupatorium birmanicum* DC leaves (200 mg/kg) possess significant anti-inflammatory and analgesic activities in albino rats. *AEB* (400 mg/kg) has been also found to possess anti-pyretic activity. The anti-pyretic activity is however, less significant than paracetamol.

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Clinico-pathological study of benign breast disease

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Abstract

Objective: To study the clinical patterns of Benign Breast Disease (BBD) in females and to correlate them with pathological findings. **Methods:** One hundred females who attended Regional Institute of Medical Scieces (RIMS), Imphal with various forms of BBD during the period from May 2005 to June 2007 were studied. Clinical diagnosis was compared with cytological or histological findings wherever possible and accuracy of clinical diagnosis was evaluated. **Results :** Main presentations of BBD were a lump in the breast, breast pain and nipple discharge. The mean age at presentation was 28.26 years. Breast lumps accounted for 88 (88%) cases of which 18 (20.45%) had associated complaints like breast-pain and nipple-discharge. Of the 26 (26%) cases of breast-pain, 18 (69.23%) had an associated breast lump or nipple discharge. Nipple discharge was present in 8 (8%) case with or without a lump or pain in the breast. Fibroadenoma was the commonest lump accounting for more than half of the lumps. Fibroadenosis and galactocele came next with 22.73% and 11.36% of the breast-lumps respectively. Clinical diagnosis of breast lump, as confirmed by cytology or histology, was accurate in 76.14% of the lumps as a whole while the accuracy was about 90% in case of fibroadenoma and fibroadenosis alone. **Conclusion:** A lump in the breast is the commonest presentation of BBD. Breast pain and nipple discharge are other symptoms. More than one symptom may be present in the same patient. Commonest age-group is 21-30 years. Among breast-lumps, fibroadenoma is the commonest followed by fibroadenosis and galactocele. Clinical diagnosis of benign breast lump is accurate in 70 to 90 percent cases. Certain lumps like fat necrosis, parasitic infestation are often difficult to diagnose clinically and can be confirmed only histo-cytologically.

Key words: *Breast lump, breast pain, nipple discharge, fibroadenoma, fibroadenosis, galactocele, Cysticercus cellulosae.*

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Introduction

Benign Breast Disease (BBD) is a term for the group of breast diseases which are not cancer. It is by far the most common cause of breast problems in women. In fact, it is at least ten times more common than breast cancer in the west.[1] Up to 30% of women will suffer from benign breast disorder requiring treatment at some time in their lives.[2]

The popular classification of BBD according to the aberration of normal development and involution (ANDI) causes confusion due to lack of clarity in distinguishing between normal physiological changes and pathologic ones. One of the more satisfying classifications would be the one devised by Love S et al [3], the so called Nashville classification. According to this, BBD is classified by two

systems: Pathologically, BBD is divided into – (a) nonproliferative lesions (b) proliferative lesions without atypia and (c) atypical proliferative lesions. Clinically, BBD is classified as (a) physiologic swelling and tenderness, (b) nodularity, (c) breast pain, (d) palpable lumps, (e) nipple discharge and (f) infections or inflammation. In this study, we have profiled the incidence of BBD, the relative frequency of different types and their clinical features. Secondly, we have attempted to correlate the clinical and pathological findings, wherever possible.

Material and methods

The study was undertaken in the Department of Surgery, Regional Institute of Medical Sciences, Imphal, during the period from May, 2005 to June, 2007. The first 100 (one hundred) women treated for benign breast disease were included in the study.

Inclusion criteria: Female patients with any benign disorder/disease of the breast – for example, breast lump, breast pain, nipple discharge – were included. Women with inflammatory diseases and malignancy were excluded from the study

A detailed history and thorough physical examination were the basis of the study. After making an appropriate clinical diagnosis, one or more of the special investigations – fine needle aspiration cytology (FNAC), mammography and ultrasonography of the breasts – were carried out for confirmation of the diagnosis. Histopathological examination was routinely performed if any lump was excised. Clinical diagnosis, particularly of the benign breast lumps, was compared with cytological or histological findings and accuracy of clinical diagnosis was evaluated.

Results

The patients were broadly divided into three groups depending on their symptoms or presentations such as breast lump, breast pain and nipple discharge.

The commonest presentation was breast lump comprising 88(88%) cases out of which 18 (20.45%) had associated complaints like breast pain and nipple discharge. Among 26 patients with breast pain, only 8 (30.77%) had no other complaint. Half of these had pain in both breasts. In the remaining 18 (69.23%) patients, the pain was associated with either a breast lump or nipple discharge or both. The pain was cyclical in 12 (46.15%) and non-cyclical in 14 (53.85%) cases. Among 8 patients with nipple discharge, 3 (37.5%) presented with nipple discharge as the only complaint. The discharge was serous and bilateral in 2 and unilateral and greenish in the other. The cause was found to be duct ectasia in the latter but no definite pathology could be detected in the former two. The remaining 5 (62.5%) patients had nipple discharge associated with either a breast lump or breast pain. The different types of presentation and their incidence are shown in table 1.

Table 1. Presentations of benign breast disease

Presentation	No. of patients	Percentage
#Breast lump only	69+1*	70
#Breast lump + §Breast pain	14	14
#Breast lump + ©Nipple discharge	1	1
#Breast lump + §Breast pain + ©Nipple discharge	3	3
§Breast pain only	8	8
©Nipple discharge only	3	3
#Breast pain+ ©Nipple discharge	1	1
Total	100	100

** One patient had another lump in the axillary tail of the same side.*

No. of patients with breast lump: 88

§ No. of patients with breast pain: 26

© No. of patients with nipple discharge: 8

Age of the patients with BBD ranged from 7 to 58 years. The mean age at presentation was 28.26 years. Fifty-five (55%) patients were in the age-group 21-30 years. The youngest was a 7 year-old girl who presented with a small lump in the right breast and the oldest was a 58 year-old woman who had a lump of parasitic origin in the left breast. Forty-six (52.27%) of the 88 women with benign breast lump were between 21 to 30 years. The lump was 3 cm across in 32 cases, which happened to be the commonest size in the series. The biggest lump was a galactocele of 10cm diameter. The patient was a 47 year-old woman. The age-wise distribution of BBB has been shown in figure 1.

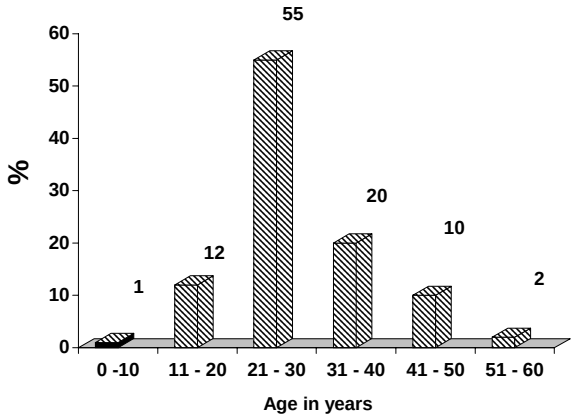

Fig 1. Age-wise distribution of BBD

Out of 100 patients, right breast was affected in 53 while the left breast was affected in 41. In 6 patients, both breasts were affected (table 2). They included 4 cases of bilateral breast pain and 2 cases of bilateral nipple discharge. Thirty-one (35.23%) of the lumps were present in the upper outer quadrants. Fibroadenoma accounted for 45 (51.14%) of the patients with breast lump(table 3). Twenty (22.73%) cases had fibroadenosis while 10 (11.36%) others had galactocele. There was one case (1.14%) of parasitic infestation (*Cysticercus cellulosae*) in a 58 year-old woman. In 2 cases (2.27%) the lumps were found to be due to normal physiological changes (nodularity).

Table 2. Side-wise distribution of BBD

Side involved	No. of cases	Percentage
Right breast	53	53
Left breast	41	41
Both breasts	6	6
Total	100	100

Table 3. Incidence of different types of benign breast lumps

Diagnosis	No. of patients	Percentage
Fibroadenoma	45 (44 +1*)	51.14
Fibroadenosis	20	22.73
Galactocele	10	11.36
Cyst	2	2.27
Fat necrosis	3	3.41
Phylloides tumour	2	2.27
Epidermal inclusion cyst	3	3.41
Parasitic infestation	1	1.14
Normal (Nodularity)#	2	2.27%
Total	88	100

***This patient had 2 lumps –one each in the breast and axillary tail of the same side.*

Subsequent cytology reported normal physiological change.

Clinical and histo-cytological correlation

Diagnosis of the lumps was confirmed either cytologically or histologically or by both. Accuracy of clinical diagnosis of fibroadenoma was 90% (45 out of 50). Clinical diagnosis of fibroadenosis was made in 22 cases and 20 (90.91%) of them were correct. Diagnosis was wrong in 3 of the 10 cases of galactocele (70% accuracy). Only in one out of the 3 cases fat necrosis could be diagnosed clinically. There was a case of *Cysticercus cellulosae* of the breast which could not be diagnosed until cytology proved it to be parasitic infestation. On the whole, the clinical diagnosis was correct in 67 of the 88 patients of benign breast lump (76.14% accuracy).

Discussion

Patients of benign breast disease generally presented with one or more of the three complaints – breast lump, breast pain and nipple discharge. Foxcroft LM et al[4] found that 87.4% of women who attended the Wesley Breast Clinic were due to a breast lump while in the series of Ratanachaikanont T[5], a breast lump was the presenting symptom in 77.35% of 371 BBD patients. The corresponding figure for our study was 88%.Fibroadenoma accounted for 51.14% of benign breast lumps in our study. Our finding is in agreement with most of the available literature on benign breast lumps where the frequency of fibroadenoma ranges from 46.6% to 55.6%.[6-9]

Many authors like Adesunkanmi AR and Agbakwuru EA[6] and Ikhewaba FN[7] found the incidence of fibroadenosis ranging from 29.5 to 42.2% of benign breast lumps. We had a slightly smaller figure of 22.73%. The incidence of breast pain in our series was 26% of BBD which is quite within the range of 12.8% to 30.3% found in most other series.[5,6] Leis HP Jr[10] reported that the incidence of breast discharge was only 9% of all breast complaints in his study, which is almost equal to 8% incidence in our study.

The mean age at presentation was 28.26 years. This is almost similar to the observation made by Adesunkanmi AR and Agbakwuru EA[6] where the mean age of BBD patients at presentation was 28.7 SD+10.6 years. Most of

the fibroadenomas were seen in the age group of 21 to 30 years. Greenal MJ[11] observed that fibroadenomas were mostly seen in girls aged 16 to 24 years. Commonest quadrant to be affected by benign breast lumps was the upper outer quadrant (35.23%). The reason behind this higher incidence is due to larger mass of tissue in this quadrant.[8,9]

In a study of 100 breast lumps by Sharma MB[12], the accuracy of clinical diagnosis for breast lumps was 89.4%. In another series by Ratanachaikanont T[5], the overall accuracy of clinical breast examination for a palpable lump was 91.44%. Both the figures are much higher than our corresponding finding of 76.14%. But both the studies included malignant cases also, which might have made the accuracy rate higher.

Conclusion

Benign breast disease is a common problem in women. A lump in the breast is the commonest presentation. Breast pain and nipple discharge are other symptoms. More than one symptom may be present in the same patient. Commonest age-group is 21-30 years. Among breast-lumps, fibroadenoma is the commonest followed by fibroadenosis and galactocele. Other lumps are relatively uncommon. Breast pain may occur alone or in association with a lump or nipple discharge. Incidences of cyclical and noncyclical pain are nearly equal. Nipple discharge, particularly if serous or greenish is usually harmless. Clinical diagnosis of benign breast lump is accurate in 70 to 90 percent cases. Certain lumps like fat necrosis, parasitic infestation are often difficult to diagnose clinically and can be confirmed only histo-cytologically.

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Study of lipid profile among ABO blood groups of ischaemic heart disease

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Abstract

Objective: To study the association between ABO blood groups and lipid profile in Ischaemic Heart Disease (IHD). **Methods:** The study was conducted during the period from October, 2005 to September 2006 in Department of Biochemistry, RIMS, Imphal. A total of 50 cases with severe acute chest pain already diagnosed and admitted in ICCU of Medicine Dept. were taken as study subjects. Thirty normal individual were taken as controls. Blood samples were taken from each study and control for ABO grouping and lipid profile, then the results were analysed statistically. **Results:** Total cholesterol (TC), tri-glycerides (TG), LDL, VLDL were increased in all blood groups of IHD when compared with control. However, HDL found to decrease significantly in all ABO blood groups of IHD cases. Fifty six percent of IHD cases were of group A where as 53.34% of controls were of group O. Among the healthy controls, TC level significantly increased in a group individuals compared to other blood groups. When lipid profile were compared among various blood groups of IHD cases, TC, TG, LDL, and VLDL were found to be significantly higher in blood group A of IHD cases. Maximum cases (14) of group A of IHD cases exhibited TC level between the range of 231-250 mg %. **Conclusion:** Serum lipid parameters are increased in IHD irrespective of blood groups. However, TC level increases significantly among group A of IHD cases compared to other blood groups, which may be the reason for susceptibility of blood group A to IHD. It can be concluded that there is a familial, probably genetic component (ABOgroup) and also environmental factors influencing incidence of the disease.

Key words: *Ischaemic Heart Disease (IHD), ABO blood groups, Lipid profile.*

Introduction

Ischaemic Heart Disease (IHD) is usually associated with hypercholesterolemia. A linear increase was been observed in coronary heart disease (CHD) with increase in total plasma level from 180mg/dl onwards[1]. The Lipid research clinics Coronary primary prevention trials has postulated that in human 1% fall inTC predicts a 2% reduction in CHD risk. Low-density lipoprotein (LDL) is the carrier of total cholesterol (TC) transporting cholesterol to tissues and thus is the most potent atherogenic agent. An inverse relation between CHD and high-density lipoprotein (HDL) was been established. Elevated very low-density lipoprotein (VLDL) and higher tri-glycerides (TG) indicates less effective intravascular lipolysis, which in turn is associated with higher atherogenic effects. Significant association between ABO blood groups and IHD was been reported by several authors[2]. Serum TC level was significantly higher in subjects of blood group A resulting in higher incidence of IHD

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than with other blood groups. The reports of various studies stated higher TC levels(at 1% significant level) among blood group A patients of IHD than those of B group patients and 0.1% significant than those of group O indicating more susceptibility of blood group A persons to IHD[3,4]. Akhund IA et al[5] found that blood group A was commonest among patients with MI and angina pectoris while these disease were least in blood group O patients. Patients with blood group O are more likely to bleed from peptic ulcer than A group[6]. The studies of many authors [5,6] found no significance association between TC and ABO blood groups and no significant predominance of group A over group O among patients with IHD. It is with this conflicting reports that this study is carried out in Regional Institute of Medical Sciences (RIMS),Imphal.

Material and methods

The study was conducted in the department of Biochemistry in collaboration with department of Medicine, RIMS during period from Oct. 2005 to Sept. 2006. A total of 50 cases with severe acute chest pain attending emergency department and subsequently admitted in ICCU were selected as study group. The preliminary provisional diagnosis of IHD was based on history, clinical findings and findings from ECG. Thirty individuals age and sex matched from normal population were taken as controls excluding cardiac, renal, hepatic, pulmonary, metabolic or atherosclerotic disorders by clinical examination,relevant investigations and ECG. Screening investigations included serum urea,creatinine and liver function test. Blood grouping was done both in controls and IHD cases using a reagent kit, suuplied by Tulip (India) employing the method of Harsh M[7]. Serum TG was estimated by the method of Gowland E [8] and serum TC by Steele et al [9] LDL and VLDL were estimated indirectly using formula of Friedwald and Fredickson.[10]

Results

The mean age ± SD was found to be 52.66 ± 11.45 yrs in the control group of 30 individuals and 59.10 ± 9.47 yrs in the study group of 50 individuals as shown in table no.1. IHD cases was found to be prevalent more in males than females with male:female ratio of 1.27 : 0.78. as revealed from table 1.

Table1. Mean age with standard deviation in both control and IHD cases.

Control(n=30)			IHD cases(n=50)		
Sex	No.of cases	Mean age ± SD (yrs)	Sex	No. of cases	Mean age ± SD (yrs)
Male	17	50.29 ± 10.37	Male	28	58.96 ± 10.82
Female	13	55.76 ± 12.44	female	22	59.27 ± 8.74
Total	30	52.66 ± 11.45	Total	50	59.10 ± 9.74

In the table 2, it can be observed that majority of IHD cases (n=16, 56%) belonged to blood group A in the study group whereas most of the control cases (n=28, 53:34%) belong to blood group O.

Table2. Distribution of ABO blood groups in control and study cases.

Blood group	Control n(%)	Study group n (%)
A	09 (30)	28 (56)
B	03 (10)	05 (10)
AB	02 (6.66)	14 (28)
0	16 (53.34)	
Total	30	50

Serum TC, TG, LDL and VLDL were significantly higher in IHD cases than the corresponding means of control group (table 3). The TC was 220.44 ± 23.05 mg% in study group whereas in controls it was 183.42 ± 15.62 mg %. Like wise the TG was 158.77 ± 29.90 mg% in study group and 121.70 ± 31.42 mg% in control group, LDL was 145.06 ± 23.52 mg% in study group and 106.35 ± 16.61 mg% in control group, VLDL found as 43.56 ± 5.87 mg% in study group and 25.85 ± 7.84 mg% in control group.

Table 3. Lipid profile in control and IHD cases (Mean ± SD)

Lipid parameters	Controls (n=30) (Mean ± SD)	IHD cases (n=50) (Mean ± SD)
Total cholesterol(mg%)	183.42 ± 15.62	220.44 ± 23.05*
Triglycerides (mg/dl)	121.70 ± 31.42	158.77 ± 29.90*
LDL (mg/dl)	106.35 ± 16.61	145.06 ± 23.52*
VLDL (mg/dl)	25.85 ± 7.84	43.56 ± 5.87*
HDL (mg/dl)	51.21 ± 7.45	31.82 ± 6.74*

*p<0.05

Comparison of TC and TG level among ABO blood groups of IHD cases revealed significantly higher value among group A compared to other groups (table 4).

Table 4. Serum TC and TG level among ABO blood groups of IHD cases.

Blood groups	TC	TG
A	221.3 ± 19.8*	164.3 ± 26.7*
B	190.4 ± 5.2	140.4 ± 9.4
AB	188.9 ± 10.72	142 ± 31.4
O	194.5 ± 11.7	140.5 ± 24

* p<0.05

Table 5 showed significantly higher values of LDL,VLDL and lower HDL among group A compared with other groups.

Table 5. LDL, VLDL , HDL levels among ABO blood groups of IHD cases

Blood groups	LDL	VLDL	HDL
A	147.5 ±19.5*	32.8 ±6.2*	40.5 ±6.2*
B	118.2 ±4.9	25.1 ±0.6	34.3 ±2.8
AB	118.6 ±8.6	30.4 ±10.3	41.8 ±4.2
O	125 ±14.8	28.7 ±4.2	41±5.4

* p<0.05

Maximum number of cases (14) in blood group O among control group showed the serum TC within 190mg/dl whereas among the IHD cases in blood group A showed the maximum number (26) were in the range of 191-230mg/dl (table 6). The multiple logistic regression analysis revealed significant association (p = <0.01) between HDL and IHD cases.

Table 6. Number of cases in ABO blood groups of controls and IHD cases in different range of mean serum TC.

Range of serum cholesterol (mg/dl)	No. of cases in different ABO group in control				No. of cases in ABO group in IHD case			
	A	B	AB	O	A	B	AB	O
Upto 190	04	03	01	14	02	02	03	03
191-230	05	01	01	01	26	01	02	11
Above 230	0	0	0	0	0	0	0	0
Total Cases	09	04	02	15	28	03	05	14

Discussion

The present study shows that there was only one case of IHD in age below 40 yrs and there were no cases above the age of 90 yrs. The findings related to age are in conformity with the findings of various investigators [11] who has reported highest incidence in the age group of 51-60 years. Preponderance of IHD in males were reported by eastern and western workers[12] which is also reflected in our study.

Prevalence of IHD among group A followed by group O in our study is in conformity with reports of various investigators[13]. However, reports on higher incidence of IHD among AB group are also available in literature.[14]

The present findings of higher serum TC, TG, LDL, VLDL and HDL in blood group A of IHD cases might be due to an increase rate of atheromatosis in blood group A as reflected by higher TC level than other groups. Blood group A subjects are reported having clinically significantly higher thrombotic potential than blood group O which is supported by higher platelet retention in group A than group O and risk of developing IHD in group A is higher.[15 16.] The relationship is influenced by diet, being most obvious after a fatty meal and uneffected by carbohydrate and protein consumption. Most of the cholesterol seemed to be derived from hepatic synthesis. Obese people are more prone to develop hypercholes-terolemia.

In this study maximum number of IHD cases with group A (26) had TC in range of 191-230mg%. Other reports[17] have also found higher TC. The findings of significantly higher platelet retention in blood group A with higher thrombotic potential is the factor for greater incidence of IHD in blood group A.[17]

Conclusion

This study reveals that among IHD cases serum cholesterol level is maximum in blood group A as compared to other blood groups. Serum TG, LDL, VLDL levels are also higher in IHD cases in blood group A. An increase correlation is observed between serum HDL level and IHD cases. It is therefore suggested that all the blood group A individuals should take precautions of IHD and preventive measures like regular check-up of TC and other lipid profile parameters should be carried out.

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Infection with Hepatitis A, B, C and E viruses in HIV infected patients in Manipur

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Abstract

Objective: To study the prevalence of hepatitis virus infection in Human Immunodeficiency Virus (HIV) infected jaundice patients and to compare its prevalence with those of HIV non-infected jaundice patients and to analyse the liver functions of HIV infected patients taking antiretroviral therapy (ART). **Methods:** 200 HIV infected jaundice (study group) and 200 HIV non-infected jaundice (control group) patients attending Regional Institute of Medical Sciences (RIMS) Hospital, Imphal during August 2005 to July 2007 were studied. 5 ml of blood was collected aseptically from all the patients. The sera were separated by centrifugation at 2000 g for 20 minutes and tested for detection of IgM anti-HAV, IgM anti-HEV, HBsAg, and anti-HCV Ab. **Results:** 186(93%) HIV infected patients had co-infections with hepatitis viruses i.e. HAV 70(35%), HBV 31(15.5%), HCV 22(11%) and HEV 63(31.5%) whereas 106(53%) HIV non-infected jaundice patients had hepatitis virus infection viz; HAV 54(27%), HBV 10(5%), HCV 6(3%) and HEV 36(18%). Hepatitis virus infection was found to be more common in HIV infected patients. Liver function test (LFT) showed higher serum bilirubin and liver enzymes among HIV infected jaundiced patients than the HIV non-infected jaundice patients. **Conclusion:** HIV infected patients are more prone to hepatitis virus infection. Hepatitis A and E virus infection may spread through unusual routes of transmission among high risk patients viz. homosexuals and IVDUs. Hepatotoxicity was found to be more in HIV patients co-infected with hepatitis virus. Therefore, screening for all hepatitis viruses in HIV infected patients whether they are on ART or naïve ART is recommended besides regular monitoring of liver functions.

Key words: *Human Immunodeficiency Virus (HIV), Hepatitis A, B, C and E Viruses, Co-infection.*

Introduction

Hepatitis virus infection in HIV patients is a growing common problem worldwide. It is increasingly recognized that HIV infection can modify the clinical course of hepatitis virus infections.[1] There are many important epidemiological and clinical interactions between HIV and the hepatotropic viruses. The pattern of hepatotropic virus infection varies according to risk group.[2] HIV infection associated with Viral Hepatitis increases morbidity, mortality and utilization of medical care resources.[3] Parenteral transmission of hepatitis A complicating transfusion of blood and blood products has now been reported many times besides its potential spread among the injecting drug-using population and homosexuals.[4] There are reports of an increased seroprevalence of anti-hepatitis E

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virus antibodies in Italian injecting drug users and homosexual men.[5] An increase in the incidence of hepatocellular carcinoma and hepatotoxic effects were associated with antiretroviral drugs in patients with HCV and HBV co-infection.[6] Liver disease due to chronic HBV and HCV infection is becoming a leading cause of death among persons with HIV infection worldwide, and the risk of death related to liver disease is inversely related to the CD_4 cell count.[7] HIV positive patients on highly active ART (HAART) regimen should be tested for hepatitis virus co-infection at baseline and monitor liver function before and/ or during antiretroviral therapy.[8]

Globally, an estimated 33 million people are infected with HIV.[9] Manipur with hardly 0.2% of India's population contributes over 2% of country's AIDS cases and nearly 8% of India's total HIV positive cases.[10, 11] Hepatitis B virus (HBV) causes an estimated 370 million chronic infections and hepatitis C virus (HCV) affects 130 million people worldwide. An estimated 2-4 million HBV and 4-5 million HCV respectively have co-infections with HIV worldwide. HBV, HCV and HIV shared common routes of transmission but they differ in their prevalence by geographic region and the efficiency of certain types of exposures.[1]

Hence this study was carried out to assess the association of hepatitis virus infection with HIV infected patients from Manipur, one of the six hard hit states of HIV/AIDS in India.[10] The study aims to find out the prevalence of hepatitis virus infection in HIV infected patients with jaundice and to compare its prevalence with those of HIV non-infected jaundice patients and to analyse the liver functions of HIV infected patients taking antiretroviral therapy (ART).

Material and methods

This prospective study consisted of 200 diagnosed cases of HIV infected jaundice (study group) and 200 HIV non-infected jaundice patients (control group) attending Regional Institute of Medical Sciences (RIMS) Hospital, Imphal. The study was conducted in the Departments of Microbiology and Medicine, RIMS, Imphal during August 2005 to July 2007. The study group consisted 169 males and 31 females, whereas 177 males and 23 females in the control group. Age of the patients was from 18 - 50 years. 43(21.5%) HIV infected patients were on HAART.

Patient suffering from the following conditions viz; alcoholic cirrhosis, chronic liver disease, hepatotoxic drugs except HAART drugs, toxins, autoimmune chronic hepatitis and other conditions like Wilson's disease, α_1 – antitrypsin deficiency etc. were not included in the study.

Diagnosis of patients was made based on careful history taking, clinical examination and liver function tests for both study and control groups. 5 ml of venous blood was collected aseptically from all the patients and serum separated by centrifugation at 2000 g for 20 minutes at room temperature. When testing was delayed, the samples were stored at 2 - 8^{O}C for 1 week and at -20^{O}C for longer storage. Highly lipemic, icteric or haemolysed samples were not used.

The serum samples were tested as per manufacturer's guidelines for detection of IgM anti-HAV by ELISA based on the principle of Microplates Enzyme "Capture" Immunoassay for the qualitative determination of IgM Class antibodies to Hepatitis A Virus in human serum and plasma (Equipar srl Diagnostici, Italy) having sensitivity at the Cut-off of =10 PEI U/ ml and specificity =98%, IgM anti-HEV by ELISA based on the principle of Microplates Enzyme Immunoassay for the determination of IgM antibodies to Hepatitis E Virus (Equipar srl Diagnostici, Italy) having sensitivity =98% and specificity =98%, HBsAg Hepacard (Biomed Industries, India), one step rapid immunoassay visual test for the qualitative detection of HBsAg based on the principle of antigen capture or "sandwich" having sensitivity of 100% and specificity of 100%, and HCV TRI-DOT (Biomed Industries, India) 4th Generation rapid visual test for the qualitative detection of antibodies to Hepatitis C Virus based on the principle of immunofiltration membrane having sensitivity 100% and specificity 99.8%. The results were interpreted and recorded as per

manufacturer's instructions.

Results

A total of 200 HIV infected jaundice patients were studied for infection with hepatitis A, B, C and E viruses. 186(93%) patients were infected with various hepatitis viruses i.e. 70(35%) from hepatitis A, 31(15.5%) hepatitis B, 22(11%) hepatitis C and 63(31.5%) from hepatitis E virus (table 1).

Of the 200 HIV non-infected jaundice patients studied, 106(53%) patients suffered from various hepatitis viral diseases i.e. 54(27%) from Hepatitis A, 10(5%) Hepatitis B, 6(3%) Hepatitis C and 36(18%) from Hepatitis E (table 2).

Table 1. Prevalence of Hepatitis Viruses in HIV infected jaundice patients

Age	Total no. of patients	HAV	HBV	HCV	HEV
11-20	8	2 (1%)	1 (0.5%)	0	3 (1.5%)
21-30	67	23 (11.5%)	12 (6%)	7(3.5%)	23 (11.5%)
31-40	79	28 (14%)	16 (8%)	11(5.5%)	29 (14.5%)
41-50	46	17 (8.5%)	2 (1%)	4 (2%)	8 (4%)
TOTAL	**200**	**70 (35%)**	**31(15.5%)**	**22(11%)**	**63(31.5%)**

% in parenthesis indicates prevalence rate

Table 2. Prevalence of Hepatitis Viruses in HIV noninfected jaundice patients

Age	Total no. of patients	HAV	HBV	HCV	HEV
11-20	17	9 (4.5%)	0	0	5 (2.5%)
21-30	53	16 (8%)	3 (1.5%)	2 (1%)	10 (5%)
31-40	68	20 (10%)	5 (2.5%)	3 (1.5%)	13 (6.5%)
41-50	62	9 (4.5%)	2 (1%)	1 (0.5%)	8 (4%)
TOTAL	**200**	**54 (27%)**	**10 (5%)**	**6 (3%)**	**36 (18%)**

% in parenthesis indicates prevalence rate

Table 3. Co-infections of hepatitis viruses in HIV infected & non-infected patients.

HIV Status	HAV + HEV	HBV + HCV	HAV + HBV + HCV	HEV + HBV + HCV
HIV infected (Study group)	17 (8.5%)	5 (2.5%)	2 (1%)	1 (0.5%)
HIV noninfected (Control group)	4 (2%)	1 (0.5%)	0	0

% in parenthesis indicates prevalence rate

Table 4. Liver Function Test of HIV infected & HIV non-infected jaundiced patients

Test parameters (average values)	HIV infected with jaundice (n = 200)		HIV non-infected with jaundice (n = 200)
	On ART (n = 43)	Naive ART (n = 157)	
Total Bilirubin (mg/dl)	5.2	3.1	2.5
ALT/SGPT (U/L)	546.9	380	332.6
AST/SGOT (U/L)	458	382.6	371.4
Alkaline Phosphatase (U/L)	106.1	70.8	79.4

A high prevalence of HAV and HEV infections were noted in both HIV infected and HIV non-infected jaundice patients; 70(35%) against 54(27%) ($p<0.05$) and 63(31.5%) against 36(18%) ($p < 0.01$) respectively. Prevalence of HAV and HEV was much higher in HIV infected jaundice patients. There were significantly high prevalence of HBV and HCV among the HIV infected jaundice patients as compared to HIV non-infected jaundice patients ($p<0.01$). Most hepatitis virus infections occurred in the (21-40) years age group. Co-infections of hepatitis viruses were found to be higher in HIV infected than HIV non-infected group ($p<0.01$). HAV and HEV co-infection occurred in 17(8.5%) in the HIV infected jaundice patients whereas 4(2%) occurred amongst the HIV non-infected group ($p<0.01$). HBV and HCV co-infection occurred in 5(2.5%) patients in the HIV infected and 1(0.5%) in the HIV non-infected ($p<0.0.5$). Co-infections of HAV, HBV and HCV were noted in 2 (1%) patients and HEV, HBV and HCV in 1 (0.5%) patient among the HIV infected jaundice patients (table 3).

Serum bilirubin and other liver enzymes were raised in both HIV infected and HIV non-infected groups. However, HIV infected jaundiced patients showed significant rise in serum bilirubin level ($p<0.05$). HIV infected patients on ART showed higher serum bilirubin levels and liver enzymes as compared to naïve ART patients (table 4).

Of the 200 HIV infected jaundice

patients, the following risk factors were found viz. 126(63%) had heterosexual exposure, 21(10.5%) were IVDUs, 8(4%) were men having sex with men (MSM), 8(4%) were heterosexual with IVDUs, 2 (1%) were MSM with IVDUs and 29(93.5%) were spouse of HIV infected husband.

Discussion

This study shows that a higher prevalence of hepatitis virus infection occurs among the HIV infected patients as compared to the HIV non-infected patients i.e. 186(93%) and 106(52%) respectively. Similar finding of higher prevalence of hepatitis virus infection among the HIV infected persons was also observed by other workers.[12] Among the HIV infected jaundiced patients, high prevalence of enterically transmitted Hepatitis A Virus (HAV) 70(35%) and Hepatitis E Virus (HEV) 54(27%) infection were found. HAV and HEV has been reported amongst the homosexual and IVDUs by other's study.[13] Therefore, possibilities of HAV and HEV transmission through homosexual and IVDUs is envisaged from this study since HIV infected patients showed higher prevalence rate ($p<0.01$) and also had history of high risk exposures. The prevalence rate of parenterally transmitted Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections were found to be 31(15.5%) and 22(11%) respectively in the HIV infected and 10(5%) and 6(3%) among the HIV non-infected patients respectively. This higher prevalence rate among the HIV infected patients is probably due to high risk exposures. Similar findings of increased risk for hepatitis viruses among high risk HIV infected patients were observed by other workers also.[1, 2]

It was observed that co-infections of HIV with HAV, HBV, HCV and HEV in different combination were observed to be higher among the HIV infected jaundice patients as compared to the HIV non-infected jaundice patients which is similar to findings of other studies.[3] There was no co-infection of HAV or HEV with HBV and HCV in HIV non-infected jaundiced patients. The higher prevalence of co-infection among HIV infected jaundice patients may indicate the presence of unusual routes of transmission among the hepatitis viruses depending upon the high risk exposure which may contribute to co-infections of HBV and HCV with HAV and HEV among these patients.

Liver function tests showed higher serum bilirubin and liver enzymes viz. alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT) and alkaline phosphatase levels in the serum of HIV infected jaundiced patients as compared to HIV non-infected jaundiced patients. Again, HIV infected patients on ART showed higher levels of serum bilirubin and other liver enzymes compared to naïve ART HIV patients. This shows that HIV infected jaundice patients whether on ART or naïve ART co-infected with hepatitis virus predisposed to more liver damage. Therefore, regular assessment of liver functions is necessary in HIV infected patients whether they are co-infected with hepatitis virus or not, and on ART or naïve ART.

Hepatotoxicity indicated by abnormal liver function tests among HIV patients co-infected with hepatitis viruses and patients on ART is not exclusively an effect of drug toxicity and the presence of hepatitis viruses co-infection is an independent risk factor.[12,15] In hepatitis virus co-infection in HIV patients,the liver damage may be caused by immune reconstitution and related exacerbation of viral hepatitis.[16] A strict follow-up for hepatotoxicity is mandatory when ART is initiated in patients with <200 CD_4+ T cells/mm^3. Anti-hepatitis pre- or co-medication could be an effective preventive or curative measure.[13] Since abnormal liver functions was noted even in HIV non-infected jaundice patients, a mere infection by hepatitis viruses is sufficient enough to cause liver damages irrespective of its co-infection with HIV. However, its co-infection with HIV enhances liver damage and more so in those patient on HAART as indicated by assessment of liver functions.

Conclusion

The study shows that HIV infected patients are more prone to hepatitis virus infection. Higher prevalence rate of Hepatitis B and C virus infection among the HIV infected patients as

compared to HIV non-infected patients were attributed to its sharing of the same route of transmission as to that of HIV and also exposure to high risk factors. However, enterically transmitted hepatitis A and E virus prevalence is equally high among HIV infected patients. Co-infection of hepatitis viruses and its co-infection with HIV were found to be significant in this study.

This study suggests that besides its usual routes of transmission of hepatitis viruses, unusual routes of transmission of HAV and HEV should also be considered in view of exposure to high risk factors amongst the homosexuals and IVDUs. Vaccination against HAV and HBV is therefore recommended for high risk patients as well as those HIV infected patients who are not co-infected with HAV and HBV. Screening for all hepatitis viruses in HIV infected patients whether they are on ART or naïve ART is recommended besides regular monitoring of liver functions.

Acknowledgement

The authors thank Director and Medical Superintendent, Regional Institute of Medical Sciences, Imphal for allowing to carry out this study.

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Study of effect of alcohol on antioxidant status in rat liver

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Abstract

Objective: To see the effect of consumption of locally distilled alcohol (country liquor) continuously for few months on hepatic antioxidant status in albino rats. **Methods**: The study was carried out on thirty six (36) albino rats aged 3 – 4 months. They were divided into six groups. The first group received only normal diet (Control No. 2). The second, third, fourth and fifth groups were given alcohol along with normal diet. The sixth group was given both alcohol and nutrient antioxidant supplements (vitamins A, C, E) along with normal diet. Additional group of six albino rats (3 -4 months old) were sacrificed at the very beginning of study (Control No. 1). After getting the antioxidant level in Control No. 1, the antioxidant level in the alcoholic group was determined by sacrificing second, third, fourth and fifth group after one week, one month, three and six months respectively. The first and sixth groups were sacrificed after six months only. **Results**: After six months of careful rearing the alcoholic groups showed much higher body weight gain of around 75 gm as compared to the first and sixth group of around 37 gm. With progress of alcohol loading, all the sub-cellular fractions showed decrease in Vitamin E and Vitamin A levels. With antioxidant supplementation in the sixth group, the levels of vitamin E and A ware increased in all sub-cellular fractions. There was gradual fall in vitamin C content with progress of alcohol loading and the fall was equal in both alcoholic and non alcoholic antioxidant groups. Vitamin C supplement group showed a very high level of these vitamins in 15000 X g, 1hr supernatant fraction. **Conclusion:** Recommending a well defined dietary antioxidant vitamin supplement to alcoholics, a through trial study in human alcoholic is still necessary.

Key words: *Alcoholic, Antioxidant, Free radical.*

Introduction

The liver injury due to acute or chronic ethanol abuse has been proved to be dependent on its oxidative effect at the cytosolic, peroxisomal and microsomal levels.[1] But despite extensive investigations, the molecular mechanism leading to hepatic damage still needs to be clarified. Based on technologically advanced procedures, it has been demonstrated that a group of reactive species known as free radicals might be taking a major role in the pathogenesis of tissue changes during hepatic ethanol loading. A free radical has been defined as a chemical species, capable of independent existence that contains unpaired electrons. They are energetically unstable, highly reactive and short lived.[2] Drugs including alcohol may exert toxic effect by promoting free radical formation during their

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metabolism and a decline of some of the antioxidant defenses like reduced gluthathione, vitamin C, vitamin E, vitamin A etc. thereby increasing the ratio between pro-oxidant and antioxidant reaction resulting to a condition known as oxidative stress.[3] Polyunsaturated fatty acids within cell membranes and lipoproteins are particularly susceptible to oxidative attack often as a result of metal ion dependent hydroxyl radical formation. Long chains of lipid peroxides may be formed causing serious disruption of cell membrane function.[4,5] Proteins exposed to free radical attack may fragment, cross link or aggregate. The consequences include interference with ion channels, failure of cell receptor etc. Free radical damage to DNA may cause destruction of bases, deoxyribose sugar and single or double strand breaks[6] and is implicated in mutagenesis, carcinogenesis and even cell death[7]. Antioxidants delay and protect against oxidative damage produced by free radicals. Vitamin A, C and E are usually known as nutrient antioxidants. Vitamin E is a lipid soluble antioxidant present on cell membrane and it suppresses free radical induced lipid peroxidation. Vitamin C, water soluble antioxidant which acts as free radical scavengers could improve liver functions in alcoholic patients.[8,9] It has been reported that Vitamin E, though a strong antioxidant may behave as a pro-oxidant if aqueous phase antioxidant falls short.[10]

The present study was undertaken to see whether the nutritional antioxidants like Vitamin C, E, A etc have got any definite role in checking liver injury in alcoholics.

Material and methods

The study was carried out in Department of Biochemistry, Regional Institute of Medical Sciences, Imphal, Manipur during June, 1999 to December, 1999. Albino rats (Wistar strain), 3 – 4 months old procured from National Institute of Nutrition, Indian Council of Medical Research (ICMR), Hyderabad reared in the Central Animal House, RIMS Imphal were the animals used for the study. Diet chart formulation was done according to the method given for preparation of pellet diets as published in LAIIS Centre, News (Nov,1984). Ethical clearance was obtained from the institutional ethical committee for conducting the animal experiment.

Thirty six male albino rats (36) with average mean weight of 165 gm were selected and divided into six groups. The first group was given only normal diet and served as Control No. 2. The second, third, fourth and fifth groups were given alcohol over and above normal diet. The sixth group was given both alcohol and nutrient antioxidant along with normal diet. An additional group (Control-I) of six albino rats (3 -4 months old) with an average mean weight of 165 gm was sacrificed at the very beginning of the study for determining antioxidant levels in various sub-cellular fractions. Determination of antioxidant level in alcoholic group was done by sacrificing the second, third, fourth and fifth groups after one week, one month, three and six months respectively. The first (Control No.2, C_2) and the sixth groups were sacrificed after six months only to determine the hepatic antioxidant levels.

All the chemicals and reagents used for the study were of analytical grade and alcohol used for feeding animals was collected from a local distiller. This sample contains 37.95% alcohol as per analysis method given by Department of Food and Technology and Biochemical Engineering, Jadavpur University, Calcutta. Four hundred I.U. of Vitamin A (Retinol procured from Eupharma Lab. Ltd. Mumbai), 0.66 I.U. of Vitamin E (alpha tocopherol procured from E. Merck, India Ltd.) and 4 mg of Vitamin C (Ascorbic acid from ABBOTT, Lab. India) were supplemented to the sixth group per day per animal.

For collection of rat liver, the abdomen was cut and tissue was dissected and then a homogenate was prepared in 20% 0.25 M sucrose solution using Potter Elvehjem type homogenizer. Differential centrifugation of the homogenate was done in high speed refrigerated centrifuge machine (Beckman's Avanti – 30) to separate the various sub-cellular fractions. All the sub-cellular fractions and 15000 X g, 1hr supernatant were used for study of antioxidant levels in them. Methods of Natelson S[11] were used to estimate the levels of vitamin E, vitamin A and vitamin C.

Results

In table 1, the sixth group and the first group (C_2) show mean body weight of 201 and 204 gm respectively showing a weight gain of 36 gm and 39 gm within a span of six months. The alcoholic group, on the other hand showed a better rate of weight gain showing the increase of 15 gm, 30 gm, 39 gm and 75 gm when recorded after one weak, one month, three months and six months respectively.

Table 1. Comparative body weight changes in different groups of animals.

Animal groups/duration	Initial weight in gms (mean)	Final weight in gms (Mean)	Weight changes (mean) in gms
1 week ALC (2nd gr)	165	180	15
1 month ALC (3rd gr)	165	195	30
3 months ALC (4th gr)	165	204	39
6 months ALC (5th gr)	165	240	75
6 months ALC + AO (6th gr)	165	201	36
6 months Control – C_2 (1st gr)	165	204	39

P-value by T test between mean values of initial weight & final weight < 0.01 (.006), significant.

ALC = Alcoholic & AO = Antioxidant

Table 2 shows the comparative values of Vitamin E in various sub-cellular fractions of rat liver under different dietary conditions. Among the sub-cellular fractions, light mitochondrial fraction accommodates the maximum quantity of Vitamin E followed by nuclear fraction. Effect of alcohol on the sub-cellular distribution of Vitamin E can be recorded only after one month of alcohol loading. The table also shows the change in Vitamin E level in homogenate (H) as well as in supernatant. The change of the Vitamin level in alchohol and antioxidant supplement group is insignificant. With the progress of alcohol loading (i.e one week, one month, three months and six months of alcohol load) all the fractions showed decrease in vitamin E levels with a greater fall in 15000 X g, 1hr supernatant, which is statistically highly significant.

Table 3 shows vitamin A distribution in all the sub-cellular fractions though the nuclear fraction and light mitochondrial fraction show slightly higher level. Effect of alcohol loading in level of vitamin A can be seen only after one month. Though, the homogenate (H) shows a negligible fall in its Vitamin A content ($P > 0.2$) the fall in the sub-cellular fractions are all significant. Heavy mitochondrial fraction shows the greatest fall ($P < 0.001$). Rearing the animal for 6 months showed decrease in the level of Vitamin A in nuclear fraction, heavy and light mitochondrial fractions in the first (Control 2, C_2) and sixth groups (Alchohol and antioxidant).

The quantity of vitamin C recovered as sum of all the fractions seems to be much higher than that of the whole homogenate. The recovery is higher in the soluble fraction than that of the whole homogenate. On alcohol loading, Vitamin C level decreases in the soluble fraction and on antioxidant supplementation in the sixth group, the level

Table 2. Comparative study of Vitamin E conc. In various subcellular fractions of alcoholic rat liver.

S.F	Control – I Mean ± SD	Alcohol				Alcohol Antioxidant 6 months Mean ± SD	Control C_2 Mean ± SD
		1 week Mean ± SD	1 month Mean ± SD	3 months Mean ± SD	6 months Mean ± SD		
H	17.10 ±0.58	16.67 ±0.66	16.10 ±0.64	14.51 ± 0.67**	14.45 ± 0.64**	17.23 ± 0.69	17.39± 0.77
N	4.83 ± 0.42	4.77 ± 0.38	4.62 ± 0.37	4.16 ± 0.32**	4.10 ± 0.33**	4.93 ± 0.40	4.85 ± 0.40
M_1	3.83 ± 0.42	3.82 ± 0.39	3.80 ± 0.31	3.47 ± 0.29*	3.34 ± 0.26**	3.97 ± 0.37	3.93 ± 0.42
M_2	7.73 ± 0.79	7.77 ± 0.71	7.52 ± 0.70	6.49 ± 1.18*	6.45 ± 1.17*	8.60 ± 0.71	7.77 ± 0.82
Sup	3.57 ± 0.35	3.49 ± 0.32	3.35 ± 0.33	2.95 ± 0.40**	2.88 ± 0.43**	3.60± 0.34	3.58± 0.40

Values expressed as mg/G liver

*P < 0.05 ** P < 0.001 S.F - Subcellular fraction, H-Homogenate, N - Nuclear fraction, M1 - Heavy mitochondrial, M2 - Light mitochondrial, Sup. - Supernatant.

Table 3. Comparative study of Vitamin A concentration In various subcellular fractions of alcoholic rat liver.

S.F	Control – I Mean ± SD	Alcohol				Alcohol Antioxidant 6 months Mean ± SD	Control C_2 Mean ± SD
		1 week Mean ± SD	1 month Mean ± SD	3 months Mean ± SD	6 months Mean ± SD		
H	68.80 ±5.00	71.35 ± 0.74	66.75 ± 1.68	60.2 ± 2.62*	52.27 ± 2.99*	76.62 ± 2.98**	68.67± 0.79
N	18.36 ±0.99	18.35 ± 0.63	14.45 ± 1.73*	14.53 ± 1.69*	13.83 ± 1.47*	22.40 ± 2.60*	17.00 ± 1.81
M_1	16.67 ±0.47	17.14 ± 0.38	12.76 ± 1.39**	12.50 ± 1.41**	12.16 ± 1.39**	20.69 ± 2.59*	14.18 ± 1.51*
M_2	18.28 ±0.34	18.11 ± 0.43	14.27 ± 1.74**	14.26 ± 1.74*	13.77 ± 1.52**	17.05 ± 1.02	17.09 ± 0.74*
Sup	15.31 ±0.67	15.88 ± 1.03*	13.67 ± 1.95	12.82 ± 1.35*	12.73 ± 1.29*	17.46± 0.52**	15.17 ± 0.85

Values expressed as mg/G liver *P < 0.05 ** P < 0.001 S.F - Subcellular fraction, H-Homogenate, N - Nuclear fraction, M1- Heavy mitochondrial, M2- Light mitochondrial, Sup.- Supernatant.

Table 4. Comparative study of Vitamin C concentration In various subcellular fractions of alcoholic rat liver.

S.F	Control – I Mean ± SD	Alcohol				Alcohol Antioxidant 6 months Mean ± SD	Control C_2 Mean ± SD
		1 week Mean ± SD	1 month Mean ± SD	3 months Mean ± SD	6 months Mean ± SD		
H	201.17 ± 6.65	189.33 ± 4.84*	189.33 ± 4.84**	186.50 ± 3.45*	172.83 ± 2.56**	203.43.62 ± 5.20**	181.83± 3.71*
N	44.95 ± 2.44	44.70 ± 2.51	43.75 ± 0.76	43.75 ± 0.76*	43.86 ± 0.71	43.47 ± 2.07	43.43 ± 1.00
M_1	43.47 ± 1.00	43.47 ± 1.00	43.75 ± 0.76	43.75 ± 0.76	44.70 ± 2.51	44.70 ± 2.51	44.70 ± 2.51
M_2	43.47 ± 2.07	43.75 ± 0.76	44.70 ± 2.51	44.70 ± 2.51	40.37 ± 5.62	43.43 ± 1.00	43.80 ± 0.71
Sup	220.50 ± 10.73	206.33 ± 4.97*	207.33 ± 2.51	267.33 ± 13.54*	203.83 ± 6.52*	244.83± 19.68**	202 ± 5.22*

Values expressed as mg/G liver *P < 0.05 ** P < 0.001 S.F – Subcellular fraction, H-Homogenate, N – Nuclear fraction, M1 – Heavy mitochondrial, M2 – Light mitochondrial, Sup. – Supernatant.

of Vitamin C increases significantly in 15000 X g, 1hr. supernatant. Sacrificing the animals after 6 months shows decreases in level of vitamin C in 15000 X g, 1hr supernatant and the decrease is similar in both alcoholic and non alcoholic groups, suggesting a negligible role of alcohol in changing the hepatic Vitamin C level (Table 4). The changes must be simply because of aging.

Discussion

In this study, we found that alcoholic animals had a better weight gain when compared to control and alcoholic groups supplemented with antioxidant vitamins. Alcohol when given in reduced dose, instead of causing any harmful hepatic changes, might have simply stimulated the whole organ system thereby increasing different vital functions leading to better appetite and food intake. This may be one of the possible reasons of getting higher weight gain in alcoholic group.[12] The rapid increase in weight may not be a good sign of healthiness because most of chronic alcoholics are always on higher side of expected normal weight. The cause of increased body weight may be due to increased deposits of hepatic lipids and also other adipose tissues. Alcohol has extra calories of its own and if taken regularly becomes an appetizer.

In this study, among the sub-cellular fractions, light mitochondria accommodates the highest quantity of the vitamins. It may be due to the fact that alpha - tocopherol is a membrane bound antioxidant associated mainly with the lipid component of the membrane. The localization of the vitamin in the 15,000Xg, 1hr supernatant must be due to microsomes present in it. The effect of regular intake of this locally distilled alcohol on the hepatic vitamin E content is seen more distinctly with the microsomal fraction when compared to that

in mitochondria. This is due to the presence of all the initial components of lipid peroxidation in the microsomes. Here supplementation of antioxidant vitamins along with alcohol feeding does not affect the hepatic vitamin E content. A marginal increase in vitamin E content can rather be seen in all the sub-cellular fractions. The increase in light mitochondrial fraction is highest. This finding shows the importance of dietary alpha tocopherol in checking the loss of this hepatic antioxidant due to ethanol mediated free radical injury. Ethanol feeding, if not supplemented by vitamin E shows a significantly reduced hepatic alpha tocopherol content.[13] The study also reaffirms that rearing the animals upto 5 to 6 months with proper dietary condition maintains the vitamin E content in all the sub-cellular fractions of rat liver showing that the effect of aging has not yet been started upto the age of 6 months. Further, in case of vitamin A low recovery after cell fractionation in the alcoholic group, it is suggested that the presence of naturally occurring protective antioxidants can work only in association with all the fractions by losing its protective nature after cell fractionation under alcoholic conditions due to alcohol mediated free radical reaction. Similar findings are reported by various other studies including that of Maria JE, et al[14]. Among non alcoholics, the recovery is almost 100%. Unlike vitamin E, the first fall in level of vitamin A is seen with mitochondrial fraction. Various authors reported that structural changes of mitochondria after administration of alcohol may be related to the early fall in its vitamin content.[14] Antioxidant vitamin supplementation increases the level of this vitamin in all the sub-cellular fractions except in the light mitochondria which may be due to its sensitivity to alcohol which distort its structural integrity. Aging also seems to affect the vitamins A status of two mitochondrial fractions sparing rest of the fractions. Vitamin C is mainly recovered from soluble fraction and its level is not affected by progress of alcohol loading. The aging process seems to be the major factor in changing vitamin levels in soluble fraction of cells. The study reaffirms that antioxidant supplementation seems to be useful in maintaining the vitamin levels affected by process of aging and alcohol.

Conclusion

From all the findings, it is suggested that antioxidant vitamin supplements will be beneficial to alcoholic population but for it to be recommended, a through trial study in human alcoholics with a well controlled dietary chart and proper assessment of health status at different stages of aging be very much needed.

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An outbreak of scrub typhus in Bishenpur district, Manipur 2006

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Abstract

Objective:To survey the outbreak of fever with rash an epidemiological and entomological investigation was carried out in Bishenpur District of Manipur in 2006. **Methods**:11057 persons were surveyed in the Bishenpur District. The multidisciplinary team investigating the outbreak included Physicians, Dermatologist, Microbiologist, Technicians and Paramedical staffs. **Results:** Out of the 11057 persons surveyed 24 cases were detected which included 5 fatal cases. The survey also showed that age group 10-45 years and both sexes were affected. The common presenting features were fever (high grade), skin rash mainly over trunk ,eschar at the site of bite, headache, body ache, hepatomegaly, splenomegaly, axillary/inguinal lymphadenopathy and altered sensorium in fatal cases. Serological tests with Weil-Felix OXK antigen showed titer >1:80. The source of infection in this outbreak was the rodents which were abundant in most of the households and surroundings. **Conclusion :** The disease outbreak occurring in Bishenpur district of Manipur was confirmed as scrub typhus. Health education regarding proper hygiene and maintenance of clean environment and improvement of health service seeking behavior of the inhabitants is essential for prevention of future outbreaks.

Key Words : *Epidemiological investigation, Entomological investigation, Orientia tsutsugamushi, Weil-Felix test.*

Introduction

Outbreak of scrub typhus, a rickettsial disease caused by Orientia tsutsugamushi has been reported from different parts of India in recent years . Recent outbreak has occurred in Southern India[1] during October 2001 to February 2003 and in Himachal Pradesh affecting 113 cases in September 2003[2] and also in Himalayan region affecting more than 100 cases in 2003[3]. The present report is the first outbreak reported from Manipur (2006) and is one of the most recent out breaks in India. A mysterious disease presenting with fever and one or more skin lesions has been occurring in Bishenpur district of Manipur since 2001. The disease followed a seasonal pattern with cases occurring in May to October months. A cluster of disease was reported in 2006. Hence an epidemiological team investigated the outbreak of the disease.

Material and methods

Study area: Few villages in Bishenpur district affected by the febrile outbreak covering a population of 11057.

Most of the villagers are involved in agricultural works and most were vegetable vendors and firewood cutters. The nearest Health Centre

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is district hospital, Bishenpur. The multidisciplinary team investigating the outbreak included physicians, dermatologist, microbiologist, technicians and paramedical staffs. Morbidity and mortality survey and house to house survey was carried out in the villages to collect information about occurrence of fever with rash during last few days. A population of 11057 from the different wards No.1, to ward No 9 was covered. Death during the outbreak was also investigated by employing verbal autopsy method to ascertain the cause (s) of the death. The following investigation method was employed. Case definition: Fever with skin lesions among residents of Bishenpur since May 2006. Case search: Interview of cases, reviewing of case records, verbal autopsy. Laboratory investigation: Weil-Felix test, demonstration of antibodies. Entomological study was carried out in the affected villages to study the prevalence and density of the transmitting agent. Indoor and outdoor collection of rodents and collection of mites from the rodents was carried out.

Results

A total of 11057 population was surveyed from May to September 2006. Twentyfour cases were detected with 5 fatal cases .Overall mortality rate was 20.83%. The demographic details of the investigated population is shown in table1.

Age group affected ranged from 10 years to 45 years, maximum occurring in 15- 44 years (n=16). Both sexes were also affected, males occurring slightly more than females. The cases were scattered almost throughout the village occurring in many wards of the district, maximum number of cases (n=8) occurring in ward no.1, as shown in table 2. Most of the villagers had the habit of open air defaection and urination which gave more possible exposures to the infected larval mites (chiggers) which are present on the scrub vegetation. All the patients presented with fever with maculopapular skin rashes with central necrosis in many lesions(Fig 1). Some of the patients were also found to have eshcar at the site of the bite (Fig 2). Lymphadenopathy involving mostly the inguinal region and cervical lymphadenopathy when lesions were on the scalp were also found. Additional signs included delirium, pneumonitis, myocarditis and encephalitis in seriously ill and terminal cases.

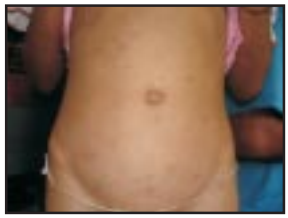

Fig 1. Skin rashes with central necrosis in scrub typhus.

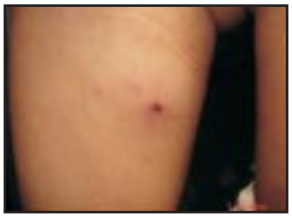

Fig 1. Eshcar at the site of the bite in scrub typhus.

Table 1. Age and sex distribution of Scrub Typhus in Bishenpur district, Manipur 2006

Age group	Population	Male	Female	Cases	Deaths	Attack rate	Case fatality rate
0-4	1105	515	505	0	0	0.0	0.0
5-9	1238	630	608	0	0	0.0	0.0
10-14	1255	645	610	4	0	0.32	0.0
15-44	5376	3376	2152	16	3	0.30	18.7
>45	2083	1150	933	4	2	0.32	50
Total	**11057**	**5736**	**5321**	**24**	**5**		

Table 2. Cases of Scrub typhus in different wards of Bishenpur municipality area.

Ward	No. of cases	No. of deaths
1	8	4
2	2	0
3	4	0
4	3	1
5	2	0
6	2	0
7-9	3	0
Total	24	5

Skin biopsy taken from the site of lesions showed nonspecific inflammatory features. Serum samples were collected and sent to NICD, New Delhi for Weil-Felix test which were found to show positive antibodies against OXK antigen (titre > 1:80) thus confirming the diagnosis of scrub typhus.

Discussion

The clinico-epidemiological and entomo-logical investigations undertaken in the

Bishenpur district of Manipur in 2006 indicated that the outbreak of fever with rash was due to scrub typhus. In recent years scrub typhus outbreak had occurred in many part of Asia including India [1,2,3]. However, the outbreak in Manipur is probably one of the most recent outbreaks of scrub typhus in India. The source of infection in this outbreak was the rodents which were abundant in most of the households and surroundings. Since most of the inhabitants had the habit of open air defeacation and urination in the surroundings with thick vegetation and decayed materials they had increased risk of exposures to the mites particularly in the covered parts. Clinical presentations of the patients in this study were mostly similar to previous reports from other areas. [1,2,3]

Most of the patients in our study did not attend health care centres and indulged in local treatment from quacks in the false belief that medication from the doctors would aggravate the disease. This may account for the high fatality rate. Although the severity of scrub typhus varies considerably, involvement of the central nervous system is seen in almost all patients and can result in meningo-encephalitis.[4] A case of scrub typhus associated with acute disseminated encephalitides (ADEM) presenting with altered sensorium (stupurous), nuchal rigidity, left hemiparesis, tonic-clonic seizure have also been reported. Serum and cerebrospinal fluid samples were positive for anti-Orientia tsutsugamushi antibidy. This was the first identifiable case of ADEM temporarily associated with scrub typhus alone[5]. Therefore meningoencephalitis may be the presenting clinical feature when cases are brought first to referral hospitals. Recently few cases of myocarditis with cardiac manifestations of scrub typhus have also been reported[6]. One of the cases admitted in RIMS Hospital presented as myocarditis with history suggestive of scrub typhus. There is also a report of acute myocardial infarction (AMI) associated with scrub typhus which was successfully treated by percutaneous interventions (PCI)[6]. Although Weil-Felix test is not a very sensitive test in the diagnosis of scrub typhus, due to lack of availability of definite tests in India, it can be a useful tool when used and interpreted in the appropriate clinical context.[7] Though polymerase chain reaction (PCR) involving the amplification of O. tsutsugamushi 165 RNA gene is taken as the definitive test for the diagnosis of scrub typhus, it has low sensitivity for the rapid diagnoses of scrub typhus in the endemic setting.[8] Because of this the Weil-Felix test may be more useful diagnostic tool in endemic settings. The treatment of choice of scrub typhus is tetracycline 500mg qid or doxycycline100mg bd given for 7-10 days. Azithromycin has also been found to be effective.[9,10] Recent reports of scrub typhus outbreaks in endemic areas, and a decreased effectiveness of antibiotics further highlights the necessity of a suitable vaccine[11] for prevention of scrub typhus.

The public health importance of this disease is underestimated because of difficulties with clinical diagnosis and lack of laboratory facilities in many geographical areas. Since scrub typhus is known to occur all over India physicians should be aware of this potentially serious but easily treatable disease.[12]

Conclusion

The disease outbreak occurring in Bishenpur district of Manipur was confirmed as scrub typhus. Almost all cases received treatment from Maibas (local quacks) who advised patients not take treatment from health facilities. This might be the reason for high mortality associated with the disease. Health education regarding proper hygiene and maintenance of clean environment and improvement of health service seeking behavior of the inhabitants is essential for prevention of future outbreaks. Furthermore awareness of such easily treatable condition is imperative amongst the health care providers for early and proper management.

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Maintenance of stability during balloon positioning in balloon dilatation of valvular aortic stenosis in paediatric cardiac cathlab - a new anaesthetic technique

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Abstarct

Objective : To evaluate the use of rapid pacing along with transient apnea in maintaining stability of balloon placement in balloon aortic valvuloplasty. **Methods :** A prospective pilot study was carried out on six paediatric patients with pure aortic stenosis requiring balloon dilatation of aortic valve. Patients who required re-inflation due to balloon dislodgement from first attempt were reinflated using rapid ventricular pacing for balloon positioning. Patients who required third re-inflation for failure from second attempt, transient apnoea along with rapid pacing was done for the positioning and inflation of balloon. Blood gas analyses done immediately before and after apnoea from both aortic root and int. jugular vein. **Results:** Balloon slipped through aortic valve in four patients using rapid pacing alone and required third reinflation. Following dilatation using rapid pacing with transient apnoea, systolic gradients across the aortic valves were significantly reduced no aortic regurgitation in the aortograms, no sustained arrhythmias or neurological deficit revealed in any patients. Tissue oxygenation was not hampered in any situation during the procedure. The time taken from placement of balloon to its deflation and re-establishment of ventilation did not exceed 16 secs in any of the patients. **Conclusion:** Rapid right ventricular pacing along with transient apnea is a safe and effective method to provide balloon stability during balloon dilatation of aortic valve.

Key words: *Balloon aortic valvuloplasty. Rapid ventricular pacing. Transient apnoea.*

Introduction

Paediatric interventional cardiology has gained serious momentum in the last few decades. Interventional cardiologists can perform complex diagnostic procedures today as well as complicated therapeutic interventions such as coil and device closures of intracardiac and extracardiac shunts, angioplasties of major vessels and balloon dilatation of cardiac valves. Improvements in cardiac anaesthesia and monitoring equipment have helped in better understanding and handling of haemodynamic disturbances during these procedures.

A number of issues are therefore pertinent to a safe anaesthetic procedure in these children. Enduring haemodynamic stability throughout the perioperative period, provision of real life circumstances, to ensure diagnostic accuracy, and an easy titratibility of anaesthetic agents in order to cope with rapidly changing cardiac loading conditions and intense haemdynamic disturbances are thus hallmarks of paediatric cathlab anaesthesia. Till date, there are no clear cut

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recommendations for the conduct of anaesthesia in these patients. Most of the techniques and concepts adopted by cathlab anaesthetists are usually established principles in other subspecialties of cardiac and paediatric anaesthesiology.

Balloon aortic valvuloplasty (BAV) is an established procedure worldwide in the management of congenital aortic stenosis. It is often a safe and effective alternative to aortic valve replacements and provides excellent results in terms of improvement of left ventricular function. Above all, the procedure is relatively safe, and can be performed under normal circulation without the use of a cardiopulmonary bypass. It involves the placement of an angioplasty balloon at the level of the aortic valve followed by balloon dilatation to relieve the stenosis. But, powerful cardiac contraction and pulsatile blood flow in the systemic circuit can cause movement of devices and balloons from their positions, leading to failure of dilatation, inadequate dilatation, valvular damage and even death.[1] Several methods for achieving balloon stability during balloon aortic valvuloplasty have been proposed, but there is no single method which can guarantee adequate balloon stability. Rapid right ventricular pacing decreasing the stroke volume at the time of balloon inflation is an accepted technique worldwide, but despite rapid pacing, balloon movement is still reported leading to complications. A study showed that rapid pacing appears to be an effective and safe procedure to stabilize the balloon during balloon aortic valvuloplasty and is thought to decrease the incidence of aortic insufficiency.[2]

Transient apnea to prevent left ventricular filling is an established concept in cardiac anaesthesia and is used in a number of cardiac surgical procedure including closed mitral valvotomy without a cardiopulmonary bypass. It prevents over distension of the left ventricle due to decreased filling as less blood returns to the left atrium from the pulmonary circulation as the lung movement ceases, also reducing the stroke volume as well.

Thus transient controlled respiratory arrest along with ventricular pacing should decrease the stroke output further leading to better stability of the balloon positioned across the aortic valve during inflation of balloon in balloon aortic valvuloplasty.

An endeavour has been made to study the effectiveness of this technique regarding balloon stability during balloon aortic valvuloplasty. The aims of this study was to find out the effectiveness of transient controlled respiratory arrest along with rapid ventricular pacing as a method of achieving balloon stability during aortic balloon valvuloplasty in patients with congenital aortic stenosis in:

1. Achieving successful placement and dilatation using apnoea along with rapid ventricular pacing in the study group.
2. Detecting changes in systolic gradient across the aortic valve before and after the procedure.
3. Detecting any procedure related complication.

Material and methods

This was a prospective pilot study of six patients with congenital aortic stenosis undergoing elective aortic balloon dilatation, performed at our tertiary paediatric cardiac care centre, of IPGME&R, Kolkata, spanned between May 2006 and August 2007.

Six paediatric patients of age between 3 and 6 years, of ASA physical status III, suffering from congenital aortic stenosis, were included in the study. In this patients balloon dilatation had failed on first attempt due to failure to place the balloon at the appropriate site across the stenosed aortic valve. Balloon placement was attempted for the second time with rapid ventricular pacing, and when a proper placement could not be achieved a third attempt was made along with transient controlled apnoea. Children with decompensated heart failure, failure to thrive, other associated cardiac lesions, and a stable balloon positioning during first attempt of balloon dilatation were not included in the study. Informed consent was obtained from parents and a detailed history regarding the symptoms of heart failure and aortic stenosis and other congenital anomalies was obtained from each

patient. A detailed physical examination was performed in every child to assess the ASA physical status, airway assessment and a complete cardio respiratory evaluation.

Preoperative investigations included complete haemogram, ASO titer and blood grouping. ECG, chest X-Ray, and echocardiography.

All children were premedicated with oral triclofos syrup 1 hour before the procedure. Infective endocarditis prophylaxis was given to all patients with inj. ampicillin 50 mg per kg body weight i.v. thirty minutes prior to the procedure or with inj. vancomycin 20mg per kg body weight i.v over two hours, being completed thirty minutes prior to procedure. Intravenous access was secured either using local application of EMLA cream prior to induction or only after inhalational induction.

All patients were pre-oxygenated with 100 % oxygen before the procedure. Induction of anaesthesia was done using a co-induction technique with inj. midazolam 0.08-0.1 mg per kg body weight i.v., inj. fentanyl 1.5 µg per kg body weight along with 0.5- 1 % halothane in O_2. Anaesthesia was maintained with 0.5 - 0.75 % halothane in O_2. Intubation and controlled ventilation was achieved with inj. vecuronium bromide 0.1 mg kg body weight i.v. Femoral artery and venous cannulation was done at the groin after induction and intubation. Through the femoral vein, a 4F bipolar pacing catheter was introduced upto the right ventricle. A single chamber pacemaker capable of rapid stimulation was connected, the VVI mode was chosen, and effective sensing and stimulation was confirmed prior to the procedure. A defibrillator was kept charged at 3 joules per kg body weight before beginning rapid ventricular pacing. Patients where the second attempt due to balloon dislodgement using rapid pacing as a sole method of achieving balloon stability for positioning had failed , were put on 0.5-1% halothane in O_2 3 minutes prior to the third attempt for re-inflation with rapid ventricular pacing and transient controlled apnoea.

The balloon dilatation system was positioned at the level of the aortic valve under fluoroscopic guidance just before ventricular pacing at a rate to establish a 50 % drop in pre-pacing aortic root blood pressure, and ventilation was stopped, the balloon was inflated till the waist disappeared and then kept inflated for 10 secs and deflated thereafter. Pressure readings were taken from the left ventricle and aortic root. SpO_2% was checked in all patients throughout the procedure. Ventilation was resumed right after balloon deflation. Total apnoea time was noted for each patient. Blood gas analyses repeated immediately before and after apnoea from both aortic root and internal. jugular vein.

Perioperative monitoring included continuous ECG/heart rate, pulse oximetry, $EtCO_2$, temperature, invasive blood pressure through appropriate left heart catheter, and blood gas analysis.

Success of the procedure was determined by decrease in left ventricular end diastolic pressure, reduction in peak systolic gradient across the aortic valve, improvement of ejection fraction and the absence of aortic regurgitation.[3]

At the end of the procedure, recovery from neuromuscular block was achieved with inj. neostigmine 50 µg per kg body weight i.v. with inj. glycopyrrolate 10 µg per kg body weight i.v. All patients were shifted to the paediatric ICCU after the procedure for monitoring.

Results

Two out of six patients had a successful balloon dilatation on second attempt using rapid pacing alone. Four of these required a third attempt.

In these four patients BAV was successfully performed on third attempt without any balloon movement during the procedure, by using rapid ventricular pacing along with transient controlled respiratory arrest with optimal improvement in LVEF and reduction of pressure gradient across the aortic valve. Fourth reinflation attempt were not required in any patient. The time taken from placement of balloon to its deflation and re-establishment

of ventilation did not exceed 16 secs in any of the patients.

Table 1. Parameters related to evaluation of procedure.

Case no.	Peak Systolic Gradient (mmHg)	Aortic Regurgitation	LVEDP (mm of Hg)	D(Aortic–Int. jugular vein) pO_2 mm of Hg
1.Before dilatation	70		30	278
After dilatation	24	Not developed	19	276
2 Before dilatation	66		26	290
After dilatation	20	Not developed	20	285
3 Before dilatation	70		28	256
After dilatation	26	Not developed	19	254
4 Before dilatation	69		30	305
After dilatation	18	Not developed	22	294

It was observed that, systolic gradient across the aortic valve after the dilatations were significantly reduced in all four patients with no post procedural aortic regurgitation in aortograms(table 1). No sustained arrhythmias after cessation of ventricular stimulation revealed in any patients. No patients developed any neurological symptom or sign at the time or after the procedure. No marked changes in arteriovenous difference in oxygen tension (D (Aortic – Int. Jugular vein) pO_2 in mm of Hg) were seen before and after the balloon dilatation using rapid ventricular pacing with transient controlled respiratory arrest. There were no procedure related complications revealed in any patient. SpO_2% maintained at 100% in all patients throughout the procedure.

Discussion

Balloon dilatation is an established method of treating congenital aortic stenosis.[4] Most catheter interventions are performed on normal circulation. Therefore use of cardioplegia, fibrillators, or clamps to stop blood flow in the working field is not required. During catheterization, contraction of hypertrophied left ventricle in valvular aortic stenosis tends to push the balloon across the stenosed valve into the aorta making proper positioning of balloon during dilatation difficult leading to various dreaded complications even death. So, balloon stability during the procedure is crucial for a successful procedure and also to reduce potential complications.

Movement of the balloon by cardiac contractions during inflation can be prevented by maneuvers such as the use of extra stiff wires and double balloons, pharmacological agents, and rapid pacing with their own merits and demerits. Stiff guide wires are sufficient to prevent balloon movement in neonates and most infants, but balloon displacement is still common in older children and adolescents, as stroke volume has increased and heart rate is decreased. Other mechanical methods include use of compliant balloons in SVC and IVC or PA.

Adenosine and esmolol are used for pharmacological maintenance of balloon stability. Adenosine is a powerful drug that creates arterial hypotension and leads to transient cardiac standstill after bolus injection. De Giovanni JV et al[5] described the use of adenosine to create transient cardiac standstill during balloon dilatation of congenital aortic valve stenosis, pulmonary valve stenosis, coarctation, and conduit stenosis. However, the dose–response to adenosine varies widely and has to be tested individually.[6] A standard adenosine dose may induce a wide range of onset and duration of asystole.[7] In addition, adenosine does not prevent ventricular extrasystoles, which may occur spontaneously or can be triggered by the intraventricular part of the guide wire or the balloon itself during inflation. Therefore, adenosine has not become a standard tool for transcatheter interventions.

Kahn RA et al[8] described cardiac standstill by induction of ventricular fibrillation to facilitate endovascular stent graft deployment in 1998. The authors claim that this technique has the advantage over high dose adenosine of being able to predict cardiac arrest time. However, defibrillation was necessary to restore synchronized cardiac activity after the procedure.

Rapid right ventricular pacing decreases stroke volume and blood pressure without

causing cardiac standstill. In older children and adolescents it may be advisable to use rapid pacing without a previous attempt at balloon inflation, as displaced balloons can still damage the aortic valve. In the study of Daehnert I et al [9] rapid right ventricular pacing was performed in 14 patients only after the balloon was displaced initially without rapid ventricular pacing. Out of these 14 patients, the balloon remained in stable position in 11 patients. In three patients the balloon was displaced again. In two of them an increase of the pacing rate to 240 beats / min provided balloon stability. In the remaining one patient stability was obtained at an unchanged pacing rate on reattempt. No sustained arrhythmias occurred. There was no other procedure related complications. Thus, the method of rapid ventricular pacing provided balloon stability facilitating success in procedures and possibly reducing the risk of complications but this procedure did not provide 100% success on first attempt.

In this study six patients were posted for balloon aortic valvuloplasty using rapid ventricular pacing for balloon stability after first attempt. Four out of these six patients required re-inflation due to balloon displacement using rapid pacing as a sole method for balloon stabilization. In these four patients balloon aortic valvuloplasty was successfully performed by using rapid ventricular pacing along with transient controlled respiratory arrest followed by optimal improvement in left ventricular ejection fraction (LVEF) and reduction of pressure gradient across the aortic valve. Further attempt to reinflate was not required in any patients. Balloon stability at time of inflation was achieved in all four cases without any balloon movement during the procedure. The time taken from the placement of balloon to its deflation and re-establishment of ventilation did not exceed 16 secs in any of the patients. Systolic gradients across the aortic valve before and after the dilatation were significantly reduced in all four patients. No aortic regurgitation in aortograms were revealed in any of the four patients before and after balloon dilatation. No sustained arrhythmias after the cessation of ventricular stimulation was seen in any patients. No patient developed any neurological symptom or sign at the time or after the procedure, no marked changes in arteriovenous oxygen gradient seen following pacing along with transient controlled respiratory arrest. There were no procedure related complications revealed in any patients. SpO_2 maintained at 100% in all patients throughout the procedure Rapid right ventricular pacing reduces stroke volume due to decreased ventricular filling for shortened diastole, loss of AV synchrony, dyskinetic ventricular contraction. Balloon inflation increases left ventricular afterload. Rapid ventricular pacing and transient controlled apnoea should decrease the left ventricular preload and thereby the afterload to compensate for that.

Transient apnea to prevent left ventricular filling is an established concept in cardiac anaesthesia and is used in a number of cardiac surgical procedure including closed mitral valvotomy without a cardiopulmonary bypass. It prevents over distension of the left ventricle and as well as reduction of stroke volume. Thus rapid pacing with apnea may significantly reduce forward ventricular ejection and prevent balloon dislodgement. Loss of ventilation further reduces stroke volume by reducing the inflow of blood into the left heart from the lungs.

During the combination of pacing and apnoea running simultaneously along with balloon inflation there is no marked increase in the duration of reduced cardiac output over and above that produced by balloon inflation alone. Moreover cessation of ventilation provides a standstill field of work in a paediatric patient for proper placement of balloon to provide balloon stability during dilatation of aortic valve. Inspite of our utmost effort we could not find any comparable study combining pacing and apnoea for balloon placement during aortic valvuloplasty, in the literature.

Limitation of the study: Small sample size, methodology not standardized and the findings not tested in other settings where low cardiac output state is desirable.

Conclusion

Rapid right ventricular pacing along with transient apnoea is a safe and effective

method to provide stability of balloon placement during balloon dilatation of valvular aortic stenosis; however it needs further studies for proper evaluation of such a technique.

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Petrified cardiac myxoma (Gamna body of the heart) mimicking atrial thrombus and causing severe mitral regurgitation : a case report

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This 52 year old female came in cardiology OPD of Regional Institute of Medical Sciences (RIMS), Imphal with history of fatigability, increasing exertional dyspnoea and palpitation since eight years, which was aggravated since last 15days. She was having in NYHA class III symptoms on initial examination. Clinical evaluation revealed irregularly irregular pulse of 92/min, blood pressure of 130/60mmHg with pan systolic murmur at apex radiating to axilla. Her electrocardiogram was suggestive of atrial fibrillation with feature of volume loaded left ventricular enlargement. X-ray chest showed dilated left atrial appendage with features of pulmonary venous hypertension. Echocardiogram revealed thickened mitral valves, severe mitral regurgitation and jet area of 21/83sq.cm on apical 4C view. Ejection fraction was 50%. There was a large left atrial mass 36x 30mm size (Fig.1), which seemed to be layered in appearance, calcified and was attached to interatrial septum(IAS).

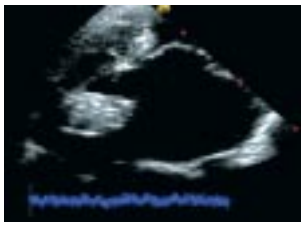

Fig.1. Apical 4C view of transthoracic echocardiogram showing calcified mass in left atrium.

She was referred to the cardio thoracic surgeons at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh for mitral valve replacement and excision of LA mass. Mitral valve replacement was done with St. Jude's (31mm) valve with excision of left atrial mass along with fossa ovali septum. Mitral annulus was found to be dilated with thickened leaflets.

The excised mass was 30x28x25mm in size, oval in shape and was calcified. It was found to be arising from IAS and posterior wall of the left atrium. On slicing, there were areas of haemorrhage and calcification.

The histopathology (Fig.2 & 3) report of left atrial mass shows extensive hyalinization, calcification and a tangled mass of thick collagen and elastic fibres impregnated with blue black pigment. This pigment stains

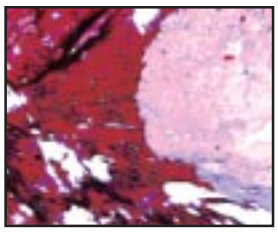

Fig. 2. Photomicrograph showing extensive calcification & hyalinization (hematoxylin and eosin stain, magnification X 550).

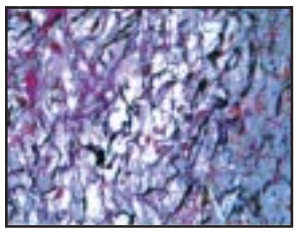

Fig 3. Photomicrograph showing hypocellular myxoid areas with few lepidic type of cardiac myxoma cells (hematoxylin and eosin stain, magnification X 280).

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positively for Prussian blue (for iron) and Von kossa (for calcium) stains. An occasional focus shows hypocellular myxoid areas with lepidic type of cardiac myxoma cell. Overall features are suggestive of a highly petrified cardiac myxoma also called Gamna body of the heart. The excised mitral valve showed no features of rheumatic affection.

Discussion

Echocardiographic differentiation between left atrial clot and myxoma may at times be difficult especially in presence of dilated left atrial appendage and atrial fibrillation with echocardiographic features of mitral valve disease. Identification of stalk and its point of attachment to the IAS and left atrial wall are important in differentiating myxoma. The thrombus present in posterior portion of left atrium and left atrial appendage has a layered appearance; whereas presence of stalk and mobility favour atrial myxoma.[1] In 75% of cases, myxoma arises from fossa ovalis of IAS.[2] Calcification is found in 10-20% of cases and microscopic calcification is less common in left atrial myxoma than in right atrial myxoma.[3] Only 10% of myxomas are reported to contain fluoroscopically detectable calcification; while approximately 28% cases have pathologically evident calcification or ossification.[2] The present index case of Petrified cardiac myxoma is an uncommon histologic variant of cardiac myxoma.[4] It has been previously described as a fibrosiderotic or sclerosiderotic nodule or Gamna bodies of the heart.[5] Such a tumor has also been often mistaken for an organized mural thrombus.[6] Petrified myxoma are composed of vascular granulation tissue with many small vessels. Macrophages, many pigment laden, and a tangled mass of thick collagen and elastic fibres impregnated with blue-black pigment are prominent features. The pigment exhibits auto fluorescence in ultraviolet light, indicating that it consists of iron, calcium and ceroid.[6] Camouflaged in this glaring morphology, the true elements of myxoma, which are myxoid areas with typical lepidic type cardiac myxoma cells are seen. Gamna's hypothesis that it occurs because of recurrent hemorrhages with subsequent deposition of iron and calcium still holds good.

The present index case also has severe mitral regurgitation, which may be due to recurrent collisions between myxoma and mitral valve causing permanent valvular damage known as wrecking ball effect.[7]

Cardiac magnetic resonance imaging plays a significant role in the evaluation of cardiac masses and is of greatest value when echocardiographic findings are equivocal or sub optimal or when the lesion has an atypical location or appearance. However, use of MR imaging generally will not help to differentiate myxoma from thrombus, as both are heterogeneous and can demonstrate variable signal intensity. Gadolinium enhancement study may be useful in differentiating thrombus from myxoma, as the former will enhance.[8]

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Primary malignant lymphoma of the spleen

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A 60 years old lady presented with mass per abdomen, generalized weakness, on and off breathlessness of over 2 years duration. She was a known diabetic, hypertensive and also was suffering from ischemic heart disease for which she was on medication.

Examination of the patient was significant for conjunctival pallor, absence of generalized lymphadenopathy, breathless at rest. There was hepatomegaly of 2 cm below the right costal margin and massive spleenomegaly of 4 cm below the left costal margin crossing the mid line. There was no ascites.

*Laboratory data included hemoglobin of 5.5 g/dl, haematocrit of 25%, total leukocyte count of 4200/*ml *(differential: neutrophil- 60, lymphocytes- 40). A peripheral smear showed pancytopenia with dimorphic anemia, platelet count of 80,000/* ml *with reticular count of 1.4% and other investigation such as LFT, Urine and Serum chemistry were within normal limits.*

Special tests such as bone marrow revealed hyperplastic megaloblastic picture with mild dyserythropoiesis, and meta-myelocytosis.

Chest X-ray showed cardiomegaly, and ECG showed sinus tachycardia with ischemic changes. USG abdomen revealed, hepatomegaly of 15cm with normal architecture, and massively enlarged spleen of 25cm, homogenous structure with pre-and para-aortic lymph- adenopathy.

The patient was taken up for splenectomy as the patient clinically showed the signs of pan-cytopenia not responding to medical management. The patient also had many co-morbid conditions such as diabetes, hypertension and ischemic heart disease which were affecting the patient's general condition. The patient underwent splenectomy through left sub costal incision under G.A, along with excision of lymph nodes at the hilum. The postoperative period was uneventful surgically except for hyperglycemia and hypertension which was controlled with aggressive medications. Grossly, the spleen weighed 2500gms, measured 28cmx13cmx7cm in dimensions(Fig 1). Cut section showed multiple small grayish white miliary nodules.

Microscopy showed large nodular areas of lymphoid aggregates both in red and white pulp(Fig 2). Nodules were varying in size and follicles were composed of monotonous population of cells. Tissue from the hilar lymph node showed similar cell pattern, adherent pancreatic tissue is free of malignancy.

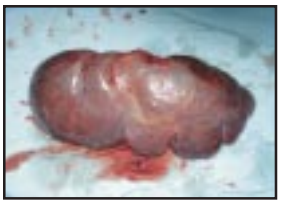

Fig 1. Splenectomy Specimen 28x13x7 cm weight 2500 gms.

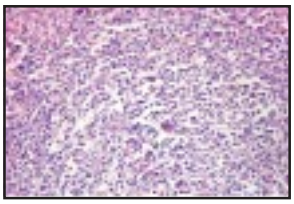

Fig 2. Microscopy 20x H &E. Small lymphocytic type, follicular arrangement.

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Histopathological report was malignant lymphoma of spleen.

Immuno-histochemistry was consistent with splenic marginal zone lymphoma, CD 20+Ve.

Liver biopsy showed normal hepatic architecture with no tumour infiltration. The patient is doing well at 9 months follow up.

Discussion

Primary malignant lymphoma of the spleen (PMLS) is an unusual malignancy. It comprises less than 1% of all Non Hodgkin's lymphomas. Cytopenia and anemia secondary to primary lymphoma of the spleen is refractory to medical therapy and responds well to splenectomy.[1]

We report a case of hypersplenism needed splenectomy which turned out to be Primary Malignant Lymphoma of the Spleen. Most PMLS are of B cell origin, most common histological picture being low grade or intermittent grade lymphomas.[2]

Clinical picture of anemia and pan-cytopenia which are usually refractory to medical therapy may be due to PMLS.

Spleen is commonly involved in disseminated lymphoma. To qualify for primary splenic lymphomas, the lesion should be confined to the spleen and /or splenic hilar lymph nodes.[3]

Non Hodgkin's lymphomas of various histologic types are represented amongst the primary splenic lymphomas. Majority of cases are of B-cell lineage and, diffuse large cell lymphomas is the commonest type.

Malignant lymphomas of the spleen may present as a case of asymptomatic spleenomegaly or result in a picture of hypersplenism.

Gross patterns are 1) Homogenous (diffuse) 2) Miliary (micro nodular) 3) Multiple masses (macro nodular) 4) Solitary masses (Macro nodular).

According to World Health Organization classification system, splenic marginal zone lymphoma is described as an indolent B-cell lymphomas which generally presents as spleenomegaly with involvement of the bone marrow and peripheral blood. Splenic marginal zone lymphoma (SMZL) is characterized by micronodular infiltration of the spleen with marginal zone differentiation.[4]

SMZL is characterized by micro-nodular infiltrate of the splenic white pulp, centered on pre-existing follicles with a peripheral rim of marginal zone B-cells, always accompanied by a variable degree of red pulp infiltration. Immuno-histochemistry is helpful in differentiating various types of lymphomas.[5]

In our case we did not make a pre-operative diagnosis of malignancy, even in the literature most of the splenic malignancy is made post-operatively by histopathology, as reported in many series.[6]

The clinical features of PMLS are characterized by nonspecific systemic symptoms, most of them are of B-cell origin and the most common picture is that of cytopenias.[7]

There are some reports implicating long standing hepatitis B infection with PMLS.[8]

Acknowledgement: The author wishes to thank Dr. V.D. Patil, Principal, J.N. medical College and Dr. M.V. Jali, MD & CE of KLES Hospital for encouragement and permission to publish the article.

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Cotard's syndrome: a case report

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A 34 years old tribal married female from Tamenglong district was referred to Dept. of Psychiatry for evaluation and treatment of her psychiatric symptoms. Her presenting symptoms, which had started 3 months before hospital admission were sleep disturbances, sad feeling, palpitation, tingling and numbness sensation, crying spells, inability to enjoy, lack of interest in her surroundings and inability to perform her daily household work. She also gradually developed nihilistic delusions and refused to take food. She believed that she did not have any stomach, intestine, brain and nerves and so she didn't need to take any food which resulted in a decrease in her weight from 68 kg to 60 kg in 1 month. Subsequently she denied existence of her body and other body parts. She also refused to take any medicines on above grounds. Subsequently, patient reportedly told her husband to under go his medical checkup as she believed that he also lacked these organs. Her problems gradually became more severe and she started saying that her children also did not have any vital organs and blood in their body, so they should be killed. She also believed that God has cursed her for her previous evil deeds and she would not be normal anymore. She also gradually stopped going outside her room and almost confined herself to her bed. She repeatedly expressed that she should be killed immediately as she is already dead without the vital organs.

Patient didn't take any psychiatric consultation before. However, she used to take tranquilizers prescribed by general physicians. She had some family problems prior to the onset of the illness. Family history revealed, one of her paternal uncle had mental problems but didn't receive any treatment. She also didn't suffer from any kind of psychiatric illness in the past.

General physical examination didn't reveal any abnormality. The results of routine hematological and biochemical tests including thyroid hormone tests were all normal. She underwent a thorough psychiatric evaluation. Mental Status Examination (MSE) revealed that she was well dressed and properly groomed. Her speech was coherent and relevant. Her mood was depressed and she had partial insights into her symptoms. We diagnosed the case as "Depression with psychotic features" according to International Classification of Diseases (ICD-10) [1] Criteria. She was prescribed a daily dose of Tablet haloperidol 10 mg, Tablet olanzapine 10 mg, Tablet lorazepam 2mg and Tablet escitalopram 10 mg. She showed gradual improvement with the treatment but she left the hospital against medical advice after 2 weeks of treatment for visiting a local faith healer and a practitioner of the traditional system of medicine.

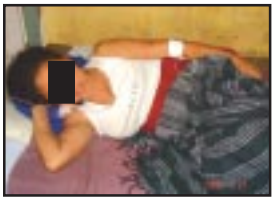

Fig 1. Patient with Cotard's syndrome

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Discussion

Cotard's syndrome was originally described in 1880 by the French psychiatrist Jules Cotard, who called it the délire des negations[2] Cotards syndrome is characterized by the presence of nihilistic delusions that one is dead or the world no longer exists. Typically, patients believe they have lost organs, blood or body parts, or even that they are dead. Patients suffering from the syndrome may deny that they exist or that a part of their body exists. They may also complain of damnation, possession or other delusional ideas, such as feeling enormous and immortal or believing that nothing exists or that another person's identity is false.[3] According to others, the syndrome can be traced in the sphere involutional melancholy.[4] Cotard's syndrome generally occurs in patients suffering from major depression with psychotic features, but it can also occur in patients suffering from schizophrenia or organic mental conditions (e.g., general paralysis, epilepsy).[5] This relatively rare syndrome is usually considered a precursor to a schizophrenic or depressive episode. With the use of antipsychotic drugs, the syndrome is seen even less frequently today than in the past.[6]

Our patient presented with the symptoms suggestive of Depression with psychotic features. Her nihilistic delusions were suggestive of Cotard's syndrome. The syndrome appeared as case report in more than 200 times over the last century according to international literature. However, there has been a dramatic decline in the appearance of it recently, probably due to the psycho-pharmacological treatment approach or/and because of the decrease in the number of institutionalized patients.[7] The syndrome is usually encountered in middle-aged or older people. But, researchers like Wani et al[8] reported this syndrome in a young pregnant female patient for the first time. Silva et al[9] also reported the syndrome with destructive behaviors directed at the self and/or others and self starvation. Cotards syndrome has been reported in a middle aged male with similar presentations by other investigators[10]. This is one of few reported cases of Cotard's syndrome in a young female patient which presented with an extreme form of nihilistic delusion of non-existence of her body parts and self starvation.

This case is being reported because of its rarity and to draw attention of its existence in this north eastern part of India and its being documented for the first time from Manipur. The patient's rejection of food was life threatening and our case also highlight the importance of an urgent therapeutic approach in patients with Cotard's syndrome who present with somatic and nihilistic delusions associated with self-starvation. The case also focuses on the need of various mental health awareness programmes in the remote areas where majority of people are still rely on local primitive system of medicine rather than accessing to the modern pharmacological method of treatment.

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Cystosarcoma phyllodes : a case report

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A 50 year old female tribal presented with a huge swelling on the left breast. She noticed the swelling 3 years back when it was small but it increased to its present size. Clinical examination revealed a well nourished woman whose left breast was replaced by a large, smooth, lobulated mass(fig 1).There was no skin ulceration. The swelling was mobile on the chest wall and there was no axillary lymph node involvement. Results of routine blood and urine analysis were normal except Hb% which was found to be 7gm% for which one unit compatible blood was transfused pre-operatively. Fine needle aspiration cytology from the mass revealed the overall features of phyllodes tumour likely of malignant variant. The patient was clinically diagnosed as cystosarcoma phyllodes of left breast. A simple mastectomy of the left breast was performed. The resected specimen weighed 3 kg and it measured 16cmx11cm (fig 2). Histopathological reports revealed it as stromal sarcoma (fig 3).

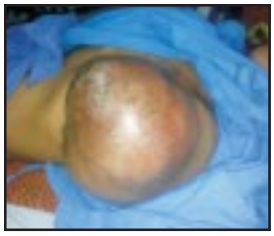

Fig 1. Cystosarcoma phyllodes of breast.

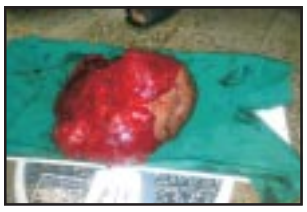

Fig 2. Resected specimen of Cystosarcoma Phyllodes of breast. Size - 16cm x 11cm.

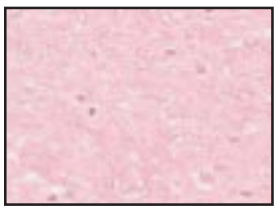

Fig 3. Photomicrograph showing pleomorphic malignant spindloid cells and increase mitotic figures, H xE, x 40.

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Discussion

Cystosarcoma phyllodes is an uncommon tumour of the breast. Cystosarcoma phyllodes tumours account only for 0.5% to 1% of breast cancers.[1] These tumours can occur in women of any age but most frequently is present between ages 35 and 55. Skin ulceration may occur secondary to pressure of the underlying mass. FNAC can not reliably diagnose these tumours. Histologically, stromal overgrowth is the essential characteristic differentiating phyllodes tumours from fibroadenomas. The biologic behaviour of the malignant type is similar to that of sarcomas. Treatment is wide local excision to tumour free margins or total mastectomy. Axillary dissection is not indicated unless nodes are clinically positive(which is rare). Currently, there is no role for adjuvant radiation; however tumours >5cm in diameter and with evidence of stromal overgrowth may benefit from adjuvant chemotherapy with doxorubicin and ifosfamide. Patients whose tumours were malignant should be followed with semiannual physical examinations and annual mammograms and chest radiographs.[1]

Based on the histopathologic criteria , several classifications of cystosarcoma phylloides have been proposed.[2,3] However, a Phyllodes

is considered malignant if the stromal component shows a clear pattern of sarcoma. Generally , 10-40% of these tumours take a malignant course, with a high tendency toward local recurrence and systemic dissemination.

Patients usually present with a large encapsulated tumour without infiltration of the surrounding tissues. The skin may be stretched over the tumour and may have a shiny appearance, sometimes with prominent veins. The mass is usually non-tender, free from overlying skin, and mobile. Pain or ulceration indicates pressure necrosis secondary to a bulky tumour.

Approximately 3-12% of malignant Phylloides tumours metastasize.[4,5] Metastasis may occur at the time of presentation or as late as 10 years later[6], spreading hematogenously to the lungs (66%), bones(28%),and brain(9%) and, in rare instances ,to the liver and heart. Regional lymph node enlargement is common, but the lymph nodes are rarely involved by tumour.[5,6]

Only a few cases of cystosarcoma phylloides with lymph node involvement have been reported in the literature. Treves N[4], in his series of 33 cases, reported only 1 case that showed metastasis to the axillary lymph nodes. In Norris HJ and Taylor HB's series of 94 patients, 16(17%) had enlarged lymph nodes, but only 1 patient had histology proven metastasis.[5]

Management of cystosarcoma has always been controversial and cannot be standardized for all patients.[7] Treatment is directed at completer removal of tumour with adequate margins. Wide total excision for small tumours and simple mastectomy for larger ones are usually satisfactory.

Excision of the pectoralis major muscle may be necessary if the fascia or muscle is infiltrated. Most of the studies showed that axillary node clearance was not required because of a very low incidence of lymph node involvement. Norris HJ and Taylor HB[5] have suggested that mastectomy with low axillary node dissection should be performed if the axillary lymph nodes are enlarged, the tumour is 4 cm or larger and biopsy shows an aggressive tumour.

The role of adjuvant radiotherapy and chemotherapy remains uncertain, but encouraging results using radiotherapy and chemotherapy for soft tissue sarcomas suggest that consideration be given for their use in cases of malignant cystosarcoma phylloides. Chemotherapy, including anthracyclines, ifosfamide (Ifex), Cisplatin, and etopovide, has been mentioned in various studies, though rarely used.[7] The use of hormonal therapy, such as tamoxifen, has not been fully investigated in cystosarcoma phylloides. However, because estrogen and progesterone receptors have been documented in these tumours, further studies with hormonal manipulation in cystosarcoma phyllodes might be warranted.

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Pumonary lymphangitis carcinomatosa, a medical enigma : report of an autopsy case

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A 30 years old male was admitted on the morning of 7th December 2002 in the department of Chest Medicine with complaints of cough for the last 2months and difficulty in breathing for a few days not associated with chest pain or fever. He had sleep disturbance. He had no significant past, personal or family history. General physical examination showed average build, no pallor, jaundice, oedema, palpable cervical lymph nodes or signs of superior vena cava syndrome. Blood pressure was recorded as 110/80mm Hg and pulse rate, 80/min.

On systemic examination, chest was clear on both sides. Cardiovascular examination revealed normal first and second heart sounds, no murmurs or jugular venous distension. Per abdominal, central nervous system examinations showed no significant findings. Routine haematological examination showed haemoglobin 13.4gm%, total leucocyte count 9000/cu mm, differential count revealed polymorph 67%, lymphocyte30%, monocyte1% and eosinophil 2% and ESR 05mm in the first hour. Chest X-ray (PA view) revealed features of pneumonitis. Urine examination showed pus 1-2/high power field, no sugar or albumin. Blood sugar(random) was 72mg%, serum bilirubin 0.7mg%, serum protein 6.4gm%, serum albumin 3.4gm%, serum globulin 3gm%, serum creatinine 0.8mg%, serum urea 38.6mg%, serum sodium 145meq/L and serum potassium 4.8meq/L. Electrocardiography findings were within normal limits. Patient was planned for contrast CT examination. He was put on antibiotics, cough suppressant, bronchodilators and intermittent oxygen. On 10th December 2002 at1.30am, patient developed persistent cough and haemoptysis. Blood pressure was 100/70mmHg and pulse was feeble. A few crepitations were detected on both sides with reduced breath sounds. Treatment continued. But at 2am patient had sudden loss of consciousness, not responding to verbal commands and painful stimuli. Resuscitation was given. But patient expired despite all maneuvers. A medical autopsy was conducted. On opening the chest, there was no evidence of pleural effusion. Right lung weighed 625gms, measured (20x13x7) cms, grossly unremarkable and floated in water. The pleura was not adherent to the underlying lung tissue. On cut section no gross area of opacity or firmness detected but frothy fluid came out. Sections were taken from upper, middle and lower lobes. 2 hilar lymph nodes were identified measuring 1cm and 0.5cm in diameter respectively. Cut surface showed homogenous brownish appearance. Left lung weighed 575gms, (18x13x6)cms, grossly unremarkable and floated in water. Cut surface showed normal appearance but frothy fluid

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came out. Sections were taken from upper and lower lobes. On microscopic examination of the lung sections, there were multiple foci of poorly differentiated adenocarcinoma predominantly within the peribronchial lymphatics(fig.1) and many tumour emboli lodged in the vessels. The involvement was bilateral and diffuse, more in the peribronchial areas. The tumour cells were composed of poorly differentiated adenocarcinoma cells with scanty to moderate amount of cytoplasm, nuclear pleomorphism with prominent nucleoli, arranged in clusters and vague acinar pattern. There were features of pulmonary congestion, oedema, chronic inflammatory cell infiltration and increased fibrosis in the interstitium and sclerosis of pulmonary vessels. Many of the vessels were thrombosed. Similar tumour cells were found in the hilar lymph nodes(fig 2).

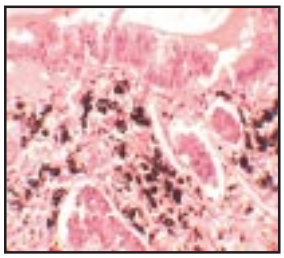

Fig1. Photomicrograph showing tumour cells in the peribronchial lymphatics. A part of the lining mucosa and numerous carbon laden macrophages are also noted.(HE stain X400)

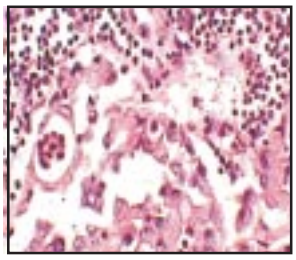

Fig 2. Photomicrograph of the lymph node section showing metastatic tumour cells (HE stainX400).

Spleen weighed 150gms, measured (12x7x3)cms and grossly unremarkable. Heart weighed 350gms, all coronary arteries were patent. Right ventricular wall was 0.3cm thick and left ventricular wall, 1.5cms. No intramural thrombi identified. Brain weighed 1200gms, measured (16x10x9.5) cms. All sulci, gyri and meninges appeared normal. Liver weighed 1650gms, surface smooth and cut surface unremarkable. Gall bladder measured (6x3) cm, filled with bile, no localized thickening of the wall or stone identified. Pancreas measured (17x3x2) cms grossly unremarkable. Stomach measured (23x14)cms. On opening, rugae appeared normal, and no growth identified. Each kidney weighed 140gms, capsule could be easily stripped. On cut section, corticomedullary junction could be easily identified, no gross abnormal appearing area identified. Prostate measured (3x4) cms and weighed 8gms. Cut surface was unremarkable. Colon appeared grossly unremarkable. Microscopic findings of the other organs were noncontributory.

Discussion

Lung is a very common site for metastatic diseases. Most metastases are multiple, bilateral and sharply defined. Some cases may present as isolated nodule with central cavitation. Lymphangitis carcinomatosa is a rare form of pulmonary metastasis where the tumour cells spread along the lymphatics. Lymphangitis carcinomatosa, as in our case, is usually adenocarcinoma[1] and often bilateral[2]. The most striking feature is progressive dypsnoea which is often disproportionate to the findings seen on chest radiographs.[3] In most cases it is thought to occur as a result of tumour microembolization. It may also result from retrograde spread from the hilar lymph nodes, though less common. Tumour emboli in the vessels, compression of the vessels by the distended lymphatics and progressive plugging of lymphatics around alveoli may account for the profound dyspnoea observed in these patients. Pulmonary lymphangitis carcinomatosa is difficult to diagnose because the symptoms, as in this case, are suggestive of pneumonia or heart failure.[4] This is made worst by the fact that in 30-50% of patients with pulmonary lymphangitis carcinomatosa the X-ray findings may be normal. The radiographic abnormalities, when present, consist of Kerley B lines[5], coarse linear, reticular and nodular basal shadowing Bronchoalveolar lavage, though helpful, may fail to yield the dignosis[3]. So, flexible bronchoscopy with transbronchial lung biopsy is diagnostic procedure of choice. Pulmonary lymphangitis carcinomatosa is reported in cases of stomach, prostate, breast and pancreatic malignancies. In many cases of pulmonary lymphangitis carcinomatosa, as in our case, the primary site of tumour may be unknown.[6] High resolution Computed Tomography is the technique of choice in the diagnosis of diffuse lung diseases including lymphangitis carcinomatosa, sarcoidosis and

Langerhans cell histiocytosis.[7] The prognosis of pulmonary lymphangitis carcinomatosa is poor, with most patients dying before 6months[1]. Lymphangitis carcinomatosa may be encountered not only in the lungs but also in other sites like bile duct wall[8] and lesser omentum[9].

Conclusion

Pulmonary lymphangitis carcinomatosa is a pattern of metastatic spread in the lungs where it tends to present as widespread neoplastic involvement of the pulmonary perivascular and peribronchial lymphatics and is also known as lymphangitis carcinomatosis. Metastases from carcinomas of the stomach, pancreas prostate and breast tend to produce this type of morphological pattern of involvement in the lungs. In some instances, the primary tumour may remain occult and even the chest X-ray findings may be within normal limits, except the development of severe dyspnoea clinically, as in this case. Pulmonary lymphangitis carcinomatosa should, therefore, be considered in cases of unexplained progressive respiratory distress with normal X-ray findings. The importance of medical autopsy underlines post mortem diagnosis of such cases after death, as in this one.

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Duplicated median cubital vein : a case report

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During dissection in the Department of Anatomy, Regional Institute of Medical Sciences (RIMS), doubling of median cubital vein was observed in the left upper limb of a male cadaver (fig.1) whose age seemed to be about 50 years . The two median cubital veins connected the cephalic vein to the basilic vein. Both of them had oblique courses and the angle of obliquity was more in the inferior one. The inferior one had a larger diameter than the superior. The two median cubital veins were found anterior to the elbow joint and the inferior median cubital vein was seen about 2.5 cm below the superior one. Despite the presence of two median cubital veins, the cephalic vein did not show any change in its usual course or diameter.

Fig 1. Duplicated median cubital vein. SM-Superior median cubital vein; IM-Inferior median cubital vein; BV-Basilic vein; CV-Cephalic vein; BB-Biceps brachii; BR-Brachioradialis.

Discussion

The median cubital vein is a superficial vein connecting the cephalic and basilic veins in the cubital fossa. It crosses the bicipital aponeurosis which separates it from the underlying brachial artery and median nerve. It will be beneficial to be conscious of its variations because of its clinical implications. It is useful for drawing blood in venepuncture and inserting a catheter for right cardiac catheterization.

To the best of our knowledge, there are only two documentations on the patterns of superficial veins in the cubital region in Indians and their inferences are contradictory. Tewari SP et al[1] noticed that the commonest pattern in Indian subjects was a median vein of the forearm dividing into two branches, one joining the cephalic vein and the other the basilic vein. On the other hand, the median cubital vein connecting the cephalic and basilic veins was found as the commonest pattern in a study on Indians by Halim A and Abdi SHM[2]. The median cubital vein connecting the cephalic and basilic vein in a H-shaped pattern is the most common pattern described in textbooks. Tewari SP et al[1] observed double median cubital vein in 4.5% of cases in their study on Indians. Presence of a double median cubital vein is reported in a Male Malay.[3]

Median cubital vein was found arising from cephalic vein below the elbow in 62% male and 49% female Nigerians.[4] If this is to be considered, then the superior median cubital vein in our report can be regarded as an extra vein.

If the median cubital vein is very large, most of the blood from the cephalic vein enters the basilic vein and thus the superior part of cephalic vein may be diminished in size or

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absent.[5] Our finding does not comply with this statement.

Duplication of median cubital vein has not been detected in the cadavers dissected from 1982 onwards in Department of Anatomy, RIMS until now. Because of its clinical utility, knowledge of this variation will be worthwhile.

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Bilateral ovarian tumour with obstructed labour: a case report

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Mrs. M.T.D., a 29 years old unbooked 2nd gravida at term pregnancy reported to the emergency OPD of the Obstetrics and Gynaecology Department on 27th Oct. 2006 with complain of pain in the lower abdomen and back.

Patient did not have regular antenatal check-up and did not receive tetanus toxoid injection. At the time of admission, on general physical examination, her vital parameters were within normal limits. Pallor, Icterus, edema and lymphadeno-pathy were clinically absent. BP was 110/70 mmHg and pulse rate was 70 bpm and regular. Body weight was 58 kgs. Systemic examination revealed no abnormality. Abdominal examination revealed a term size uterus with a single live fetus in cephalic presentation with non-engaged head. There was mild, irrigular uterine contraction. Fetal heart rate was 144 bpm and regular. On per vaginal examina-tion, cervix was 60% effaced, os 1.5 cm dila-ted, bag of forewater present and station of the head was high-up. Clinically, the pelvis appeared to be adequate for the baby.

A cystic mass with smooth surface was felt with difficulty in the posterior fornix. Gentle digital rectal examination confirmed the presence of the mass.

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Hb was 10 gm% and blood group was A Rh-positive. Routine examination of urine, blood sugar, complete haemogram and liver and kidney functions were within normal limits.

Patient went into active labour next morning. On examination, she had good uterine contraction and normal fetal heart rate. On P/V examination, cervix was 75% effaced, os 4 cm dilated, bag of forewater present and station of the head was high up.

There was no progress of labour inspite of good uterine contraction and the head was still high up. With the diagnosis of obstructed labour due to pelvic mass, emergency caesarean section was performed. A live male baby weighing 3.4 kg with Apgar score of 9/10 was delivered. The uterus was repaired in two layers and complete haemostasis maintained. Careful examination of the pelvis revealed two moderate sized cystic masses arising from both the ovaries. Left ovarian cyst was found impacted in the pouch of Douglas and it was tense, oedematous and dark-coloured due to congestion.

The right ovarian cyst was found just lateral to the left ovarian cyst. The right and the left sided cysts measured 8 x 5 x 4 cms and 6 x 5 x 4 cms respectively. Bilaterial ovarian cystectomy was done and only minimal ovarian tissue could be preserved on both

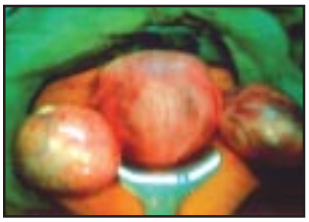

Fig 1. Bilateral ovarian tumour at caesarean section.

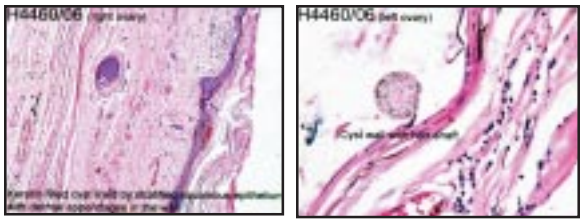

Fig 2 & 3. Photomicrograph showing features of dermoid cysts of ovary

the sides. On cut section, the right ovarian cyst was unilocular and the left one multilocular. Both the cysts contained pultaceous material and hair.

Her post-operative period was uneventful and she was discharged on 5th post operative day.

Histopathological examination revealed keratin filled cysts lined by stratified squamous epithelium. Many dermal appendages and hair shafts were seen in the wall suggesting bilateral dermoid cysts.

Discussion

After an extensive search in the PubMed and Medline, we are unable to find a similar case of bilateral ovarian cystic teratoma causing obstructed labour. Although, there are very few cases of unilateral ovarian tumour causing obstructed labour. This is the first such case among the 52394 deliveries in our institute over the last five years.

Kifle G[1] presented a case in 1987 in which ovarian cystic teratoma was reported as a cause of obstructed labour. Gupta B et al[2] reported a case of osteoma of ovary causing obstructed labour.

Ovarian tumours, though rare during pregnancy pose challenge to the obstetrician. Many of these cases are usually asymptomatic but can give rise to serious complications like torsion and haemorrhage presenting as acute abdomen.

The incidence of ovarian masses vary during pregnancy depending on the age group studied and the frequency with which prenatal ultrasonography is done. Adnexal masses complicate approximately 1 per 2000 pregnancies.[3]

Benign cystic teratomas are the most common ovarian neoplasms found in pregnancy followed by mucinous cystadenomas.[4] Teratomas represent upto 36% of adnexal masses during pregnancy.[4]

Mature cystic teratomas are most common in young women with a median age at presentation of 30 years.[5] Hence, they are commonly found to complicate a pregnancy. It is bilateral in 12% of cases.

Benign cystic teratomas in pregnant women may be responsible for complications such as torsion, rupture and obstruction of labour. These events may necessitate emergency surgical intervention with increased risk of adverse outcome for both mother and fetus.[6]

If an ovarian mass obstructs the birth canal during labour, exploratory laparotomy is indicated for both delivery of the baby and management of the ovarian neoplasm. Allowing labour to proceed while an ovarian tumour obstruct the birth canal can result in rupture of the ovarian mass or haemorrhage into the tumour followed by necrosis and suppuration.[7]

The possibilty of an undiagnosed ovarian tumour should be kept in mind amongst many other causes of obstructed labour to avoid serious complications.

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Recent advances in breast cancer management

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Introduction

Breast cancer is by far the most common female cancer worldwide accounting for 21% of all cancers diagnosed in women. The incidence of the disease vary globally with high rates in North America and Western Europe, intermediate rates in South America and Eastern Europe and low rates in Asia. But the disease is fast picking up in developing countries while it is getting stabilized or slightly down in developed countries and thus the difference in incidence and mortality is getting narrower. The reason of increased incidence in developing countries is because of urbanization while in the later it is because of more adoption of screening programmes and early detection. The focus of this review is to highlight the latest developments in the overall management of the disease.

Diagnosis

1.Newer trends in breast cancer biopsy: Newer approaches for the biopsy of non palpable breast lesions are aimed at obtaining diagnostically adequate tissue samples while minimizing invasiveness and the risk of complications.

1.1. Advanced breast biopsy instrumentation system(ABBI)

It was designed as an alternative to conventional excisional biopsy for the diagnosis of non palpable breast cancers. With 3 dimensional stereotactic localization, an axial wire is guided to the centre of the tumour. The wire is used as a guide to insert a surgical canula that removes a tissue cylinder encompassing the tumour. Tissue cylinders of varying lengths and 5-20 mm diameters can be removed. This is significantly larger tissue sample than could be removed through core biopsy and does not require multiple passes of the needle. The procedure can be carried out under local anaesthesia and on an outdoor basis.[1,2] Several institutions are testing the ABBI system with promising results.

1.2. Vacuum assisted core biopsy

This device uses the same general principle as the core needle biopsy but is capable of obtaining upto 10 times as much tissue as a core needle. Two systems currently in use are the Mammotome and the Minimally Invasive Breast Biopsy (MIBB). These devices are positioned in the breast with the aid of stereotactic or ultrasound guidance and uses high speed rotating knives to remove tissue that is removed by vacuum. False negative results are less with ultrasound guided biopsy and are preferable to stereotactic biopsy. They have the advantage of being able to obtain additional samples within one area by being turned in a circular motion. The probe may also be used to insert radio-opaque markers at the biopsy site to mark the lesion for further management. Histologic diagnostic accuracy rates of ultrasound guided large-core needle biopsy is comparable to that of open surgical

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biopsy but has the advantage of being less invasive, less expensive, and less time consuming.[3]

2. Sentinel lymph node biopsy (SLNB)
It has received much attention as possible alternative to Axillary Lymph Node Dissection (ALND) for the detection of axillary metastasis. If the sentinel lymph is negative, other nodes are presumed to be negative; thus morbidity of ALND could be avoided by voiding the axillary dissection. Sentinel lymph node (SLN) is identified by injecting either a vital dye or a colloidal suspension of radioactivity tagged substance into the periphery of the primary tumour site or intradermal injections into the skin over the tumour or the periareolar lymphatic plexus. In case of vital dye, SLN is detected during surgery but for the radioactivity, localization can be done before surgery and hence is a preferable practice. By this technique, SLN can be identified in as high as 90% of the cases.

SLNB is becoming an alternative to level I and II lymph node dissection for staging of patients with operable breast cancer.[4,5]

3. Immunohistochemistry techniques
Occult micrometastases were defined as tumour deposits not larger than 2mm in the axillary lymph nodes (AJCC). Patients who were declared node negative histologically are found to have occult nodal metastases in 10-29% of the instances when stained with immunohistochemistry techniques.[6]

4. Molecular techniques
A very fine level of resolution in the detection of isolated tumour cells and micrometastases is potentially available with the use of reverse transcriptase-polymerase chain reaction technique (RT-PCR). RT-PCR is theoretically of identifying single cells.

5. Markers for predicting and evaluating response to therapy
Modern therapies have improved the response and cure from breast cancer but at a cost life threatening toxicities. Moreover, with all the attendant toxicities, some patients may not still respond to the treatment. Now-a-days, 3 categories of tumour markers are available to predict response to a particular therapy, thereby enabling to avoid a toxic treatment if it is not going to help much. Tumour-tissue-based markers such as oestrogen receptor, human epidermal growth factor receptor (HER-2) are quite useful for selecting patients for anti-oestrogen and anti-HER-2 therapy. Circulating markers such as soluble protein markers, CA-15(3), CA-27.29, CEA and extra-cellular domain of HER-2 or circulating tumour cells may be valuable in predicting metastatic disease and response to treatment thereof. Most recently, germline markers that provide insight into inherited differences in genes that encode for the drug distribution enzymes or drug targets also may permit individualization of therapy.[7]

Advances in breast imaging
1. Digital breast Tomosynthesis : 3 Dimensional mammography. The implementation of screening mammography (MMG) had a dramatic impact in the early detection of breast cancer; however, it is well recognized that conventional MMG cannot detect all breast cancers. In fact, as many as 20% of early breast cancer can be missed by MMG. This limitation becomes more pronounced as tissue density of breast increases as in young age and big breast. The major factor contributing to the limitations of conventional MMG is the structure overlap that results on a 2 dimensional MMG. Structure overlap can not only obscure images but it can also mimic abnormalities, thus leading to reduction in both sensitivity and specificity of MMG.

Digital breast tomosynthesis is a new 3 dimensional MMG technique which can provide cross sectional imaging study of the breast that virtually eliminates confounding structure overlap, allowing more accurate diagnosis, reduces false positive results and permits precise lesion localization. One of the distinct advantages of tomosynthesis is that it extends the capabilities of conventional MMG, a modality that is affordable, easily available, well studied and well understood.[8]

2. Breast Magnetic Resonance Imaging(MRI)
The potential of breast MRI was recognized early but it is only recently that its diagnostic

power has been exploited in a major way. MRI failed to demonstrate any improvement in the diagnosis of breast disease till the advent of a contrast medium known as godalineum in Europe. Investigators found that breast cancer enhances early after a bolus of the contrast. Breast cancer enhances because of increased capillary permeability. It so happens that godalineum complex used as a contrast agent is just the right size to leak from the abnormal breast tumour capillaries to a greater extent than from normal tissue vessels.[9,10] This unique feature is the key to success of this contrast MRI and its availability to detect diseases that cannot be seen by any other method. Even in-situ carcinoma has abnormal capillary permeability. Studies have shown that the negative predictive value of breast MRI approaches 100%. Indeed the real value of breast MRI is its ability to exclude other diseases. No other imaging test can presently match this performance.[11]

3. Positron Emission Tomography (PET)
The metabolism of tumour cells take place predominatly through glycolysis. Human benign tumours display some increased glycolytic activity but much to a lesser extent as compared to that of malignant tumours. The differential is the basis of breast cancer imaging with PET. The PET tracer is a cyclotron-produced 18F-labelled glucose analog, 2-[18F]-fluro-2-deoxy-d-glucose (FDG). When FDG is taken up by the tumour cells and phosphorylated by hexokinase to FDG-6-phosphate, it is not metabolized further and remains trapped in the cells because tumour cells do not contain significant amount of glucose-6-phosphate to reverse the action. The amount of FDG uptake is inversely proportional to the degree of differentiation of the tumour cells. The major limitation of the PET is poor anatomic detail compared to CT or MRI10 but this can be overcomed by hybrid PET-CT.

Surgery
The present trend is to encourage early detection and opt for minimally invasive ablation techniques or breast conservation surgery. When more aggressive surgery is indicated, immediate breast reconstruction is the order of the day.

1. Minimally invasive ablation technique
Minimally invasive ablation of primary tumour is possible with a variety of approaches like cryotherapy, heating (e.g. radiofrequency ablation, focused ultrasound, laser interstitial therapy, microwave etc.) or chemical ablation (e.g. ethanol ablation). Techniques that are currently attracting the most attention for the treatment of breast cancer are radiofrequency ablation, laser interstitial therapy and focused ultrasound.

1.1. Radiofrequency ablation (RFA)
RFA destroys solid tumours through the generation of frictional heat by intracellular ions moving in response to an alternating current. This current flows from an electrode inserted into the tumour to a grounding pad placed externally on the skin. RFA results in cell membrane fluidity, destruction of cytoskeletal proteins and disruption of nuclear structure and DNA replication. RFA can take care of T1-2 lesions but most effectively for tumours <3 cm in diameters.

1.2. Laser interstitial therapy (LIT)
LIT destroys tumour cells by means of laser energy delivered through a fibre-optic inserted into the tumour under imaging guidance. Primary tumour lesions upto 2 cm diameter could be totally ablated with negative margins when 2,500 J/mL of heat was given or the thermal sensors recorded 600.

1.3. Focussed ultrasound (FUS)
FUS for tumour ablation was described by Harari and colleagues and by Hill and Haar. Concentrated FU was used to ablate the tumour cells. Image-guided focussed ultrasound (FUS) ablation is a non-invasive procedure that has been used for treatment of benign or malignant breast tumours. Image-guidance during ablation is achieved either by using real-time ultrasound (US) or magnetic resonance imaging (MRI). The past decade phase I studies have proven MRI-guided and US-guided FUS ablation of breast cancer to be technically feasible and safe. Successful ablation ranged from 20% to 100%, depending on FUS system type, imaging technique, ablation protocol, and patient selection[12]. At M.D. Anderson Hospital, an ongoing study is

using MRI guided focused ultrasound to treat early stage breast cancer with lesion size upto 2 cm in diameter.

2. Breast conservation therapy (BCT)
BCT has largely replaced mastectomy as the surgical treatment of choice for early stage breast cancer. Large prospective trials have shown no survival difference between the two surgical approaches, though there is a difference in the pattern of recurrence. Although loco-regional recurrences following mastectomy operations have a grim prognosis, most recurrences following BCT occur at the primary site that can be easily salvaged by additional surgery. Moreover, the psychological and cosmetic advantages of BCT are paramount especially in younger women. However, because the risk of local recurrence in conservatively treated breast is lifelong, it is important to reduce that risk through careful patient selection[13] and regular follow up.

3. Immediate breast reconstruction
In late stages when conservative surgery is not possible and also in few of the early stage patients in whom conservation is contraindicated, mastectomies needs to be done. These women can now receive an immediate breast reconstruction in the same surgery as the mastectomy. Current reconstruction techniques offer excellent cosmetic results and also provide outcomes equivalent to those of standard mastectomy. Albeit reconstructions using silicone gel or saline were initially very popular, the current trend is towards using autologous tissue - the most successful of which is the transverse rectus abdominalis muscle (TRAM) flap. In an opinion poll conducted by Sautes AS et al of patients who underwent TRAM flap, tissue expanders and implant reconstructions revealed that majority of the patients preferred TRAM flap reconstruction albeit scar is a minus point.[14]

Chemotherapy
The understanding of the fact that breast cancer is a systemic disease with as high as 60% of the overall disease and 80% in late stages by the time of diagnosis, has re-emphasized the importance of systemic treatment that chemotherapy is used more often now than ever in the past. The earlier concept that breast cancer spreads by contiguity is obsolete. It has been proved beyond doubt by a number of multicentric randomized trials that regardless of the extent or radicality of the surgical resection, the probability of cure is inversely proportionate to the initial stage or the extent of the regional nodal involvement or the presence of distant metastasis.

1. Primary systemic therapy for operable breast cancer
It may be defined as the first systemic treatment a patient receives after cancer is diagnosed and the term indicates that subsequent therapies are intended. Primary systemic therapy was first introduced in patients with technically inoperable patients. When it was noted that the majority of these patients had a remarkable response, some even a complete response, enthusiasm rose for primary systemic therapy even in operable breast cancer.[15]

National comprehensive cancer network(NCCN) 2008 recommends primary systemic therapy (PST) for women with large clinical stage IIA, IIB and T3N1M0 tumours who meet the criteria for BCT except for the tumour size and wish to have BCT. In this context, it is desirable to have FNA confirmation and not open biopsy of primary as well as palpable axillary nodes, should confirm invasive disease, sentinel lymph node biopsy for axilla negative patients and also placement of percutaneous radio-opaque clips around the tumour with mammography or ultrasonography guidance to help in future guidance for extent of surgical remova.[15]

Maur M et al[16] in a review of PST in operable breast cancer derived from the first generation clinical trials that the treatment increased possibilities of conservative surgery, proportion of patients achieving complete pathological response and that response served as a good predictor for long term outcome. The second generation trials were designed to compare PST to postoperative adjuvant chemotherapy:

here again, the rate of conservative surgery was significantly improved and the pathological response demonstrated its prognostic value, however, no progression-free or survival improvement was obtained in comparison with postoperative treatment.

The main disadvantage of this treatment are imprecise clinical and radiological staging and delay in effective local treatment.

2. Adjuvant chemo-hormonal therapy in node-negative breast cancer

In 1998, Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that the use of adjuvant chemotherapy leads to an almost equal proportionate risk reduction of relapse and death in node-negative and node-positive breast cancer patients.[17] The last EBCTCG overview presented in September, 2000 entirely confirmed the findings. These findings support the concept that node-negative breast cancer is not genetically and clinically different from node-positive patients and that nodal status is a variable prognostic factor only because it defines a time related disease stage and not because it is intrinsically associated to biologically different disease subtypes. In near future, it will be more prudent to tailor chemotherapy treatment decisions according to the following 4 main variables: molecular determinants of response to cytotoxics, pathologic and molecular determinants of disease recurrence and patient characteristics.[18]

Small primary tumours of up to 0.5 mm diameter that do not involve lymph nodes do not need adjuvant systemic therapy. Tumours of 0.6-10 mm diameter with adverse factors like nuclear grade, S phase, lymphovascular invasion and possibly HER 2/neu overexpression do need chemotherapy treatment. It tumour size is 10-20 mm and if hormone receptor is negative, combination chemotherapy is indicated and if receptor is positive, hormonal therapy ± combination chemotherapy is indicated. Here some histologies may not require systemic treatment: tubular, colloid, medullary and adenoid cystic. All other patients of lesion >20 mm diameter are managed with combination chemotherapy ± hormonal therapy.[17] For patients with HER 2/neu overexpression, combination of trastuzumab and chemotherapy gives better response.

3. Adjuvant chemo-hormonal therapy in node-positive breast cancer

Any patient of any primary size whose axillary node(s) are positive, do need chemo-hormonal therapy. Pre-menopausal patient of any primary size with positive axilla and negative hormonal status indicates combination chemotherapy (Taxane containing preferable). If more than 10 nodes are positive, high dose chemotherapy protocol must be used. In the same patient, if hormonal status is positive, combination chemotherapy and hormonal therapy is indicated. Post menopausal patients with negative hormone receptor status of any size indicates combination chemotherapy ± hormonal therapy. If HER 2/neu gene is overexpressed, trastuzumab must be added in the systemic therapy. The effects of HER 2/neu on tamoxifen resistance is unclear.[19]

Radiotherapy

NCCN guidelines in Oncology 2008 for breast cancer recommends consideration of radiation to the chest wall and supraclavicular area after chemotherapy for women with 1-3 involved axillary nodes with consideration for inclusion of the epsilateral internal mammary field, though the later had some controversy. Women with 1-3 involved axillary nodes and with primary tumour >5 cm diameter or with positive pathological margins must be given postmastectomy and postchemotherapy radiotherapy to chest wall and supraclavicular area with consideration of inclusion of the epsilateral internal mammary field. The later still had some disagreement. Women with 4 or more positive axillary nodes are at substantially increased risk of local recurrence of the disease and hence radiotherapy must definitely be recommended to chest wall and lymph node regions.[20]

Even in axilla negative patients, chest wall irradiation is recommended if primary tumour is >5 cm or with positive pathological margins or close (Less than 1 mm) pathological

margins. Radiotherapy is not recommended for patients with tumour 5 cm or smaller, negative margins and no positive axillary nodes.[20]

Axillary nodal irradiation may be as effective as axillary lymph node dissection that has an attendant morbidity in 60% of the patients - lymphoedema, numbness, limitation of arm movement and strength. The EBCTCG performed a meta-analysis of 8 trials comparing axillary nodal dissection to axillary irradiation for the treatment of early breast cancer and found no difference in mortality.[21]

Another emerging arena in radiation treatment is the consideration of partial breast irradiation (PBI) PBI can be done.

1. Partial breast irradiation (PBI)
Another emerging arena in radiation treatment is the consideration of partial breast irradiation which is an amalgamation of conservation and speed. Patients who have undergone BCT shall traditionally have to receive radiation treatment to the whole breast and needs about 6.5 weeks treatment. PBI is a recent innovation in last about 10 years that advocates treatment of a part of the breast in a short treatment time. Accelerated Partial Breast Irradiation (APBI) enables to conclude radiation treatment in a matter of 1-5 days.

The rationale of this treatment is the belief that majority of the recurrences at the primary site occurs close to the primary tumour and not more than 2 cm. beyond the edge of the tumour mass. Recht A et al[22] in an analysis found that 70-90% of the recurrences are at or near the original tumour bed in the first 5-10 years.

PBI can be done with external beam radiotherapy, delivering 34-38.5 Gy over 10 exposures treated twice daily to a target volume encompassing the tumour bed with a margin of 2.0-2.5 cm. But it is more typically treated with interstitial brachytherapy using mammoSite ballon applicator, 34 Gy over 10 exposures being treated twice daily using HDR[23]. With a median follow up of 21 months, there have been no local recurrence and 88% had good to excellent cosmetic results and 9% fair results. Another approach is to give intraoperative PBI (IOPBI) by a single exposure. The largest experience so far has been at the European Institute if Oncology, Milan using mobile linear accelerator to deliver 3-9 MeV electrons delivering 17-21 Gy. IOPBI can also been given by 50 KV x-rays.

The advantages of PBI are short treatment time, part treatment of breast thereby reducing side effects, better economy and better integration of radiotherapy and early chemotherapy. The disadvantages being need for proper patient selection, less understanding of optimal technical parameters of PBI and limited experience. Though promising, as of now, it is not a standard care yet. Only large prospective randomized studies approved by institutional research boards will answer its future.

Conclusion

Gomdalineum enhanced MRI imaging is the single, most efficient diagnostic imaging tool for breast cancer. In the surgical management, the order of the day is towards more and more conservation. When conservation is not possible, immediate surgical reconstruction is order of the day. Sentinel lymph node biopsy has shown extremely promising results in assessing lymph nodal status and thus preferable alternative to axillary lymph node dissection for sampling. In the medical management of the disease, the shift is towards the broad application of systemic therapy endorsing the belief that breast cancer is a systemic disease. This is true regardless of the nodal status. The morbidity of axillary nodal dissection can be avoided by substituting with systemic therapy and irradiation of axilla. While taxane containing regimes are preferable to anthracycline combinations to CMF, inclusion of trastuzumab for HER 2/neu gene overexpression , further enhances survival. In the radiation management, there is emerging role of partial breast irradiation particularly with mammoSite application.

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