



Guest Editor

Nanotechnology- will it revolutionize medicine?

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"Nanotechnology" which is sometimes shortened to 'Nanotech' refers to a field whose theme is the control of matter on an atomic and molecular scale. In general, nanotechnology deals with structures of the size not beyond 100 nanometers (one nanometer is one billionth or 10^{-9} of a meter) and involves developing materials or devices within that size. It is a highly multidisciplinary, drawing fields such as pharmaceutical sciences, applied physics, materials science, colloidal science, device physics, supramolecular chemistry, biological engineering, robotics, chemical engineering and many more. Nanotechnology can also be seen as an extension of existing sciences into nanoscale.

Nanotechnology in Medical Sciences

As the need for the development of new medicines is pressing and given the inherent nanoscale functions of the biological components of living cells, nanotechnology has been applied to diverse medical fields such as oncology and cardiovascular medicine. Of late, researchers are experimenting to get certain cure for AIDS using nanotech. Indeed, nanotech is being used to refine discovery of biomarkers, molecular diagnostics, drug discovery and drug delivery which could be applicable to management of these patients. To achieve these aims, nanotechnology strives to develop and combine new materials by precisely engineering atoms and molecules to yield new molecular assemblies on the scale of individual cells, organelles or even smaller

components providing a personalized medicine. Personalized medicine is individualized or individual based therapy which allows the prescription of precise treatments best suited for a single patient.

As nanotechnology is undergoing such explosive expansion in many areas, even poorer developing countries have also decided that this new technology could represent a considered investment in future economics and social well being that they cannot ignore. In the medical field, the positive sign is that nano healthcare products and other drugs are not costly. Preciously, nanotechnology has open new avenues for mankind to live a more advanced life than ever expected.

Disease and ill health are caused largely by damage at the molecular and cellular level. Today's surgical tools are, at this scale, large and crude. From the viewpoint of a cell, even a fine scalpel is a blunt instrument more suited to tear and injure than heal and cure. Modern surgery works only because cells have a remarkable ability to regroup, bury their dead and heal over the injury.

Nanotechnology "The manufacturing technology of the 21st century", should let us economically build a broad range of complex molecular machines (including, not incidentally, molecular computers). It will let us build fleets of computer controlled molecular tools much smaller than a human cell and built with accuracy and precision of

drug molecules. Such tools will let medicine, for the first time, intervene in a sophisticated and controlled way at the cellular and molecular level. They could remove obstructions in the circulatory system, kill cancer cells or take over the function of subcellular organelles. Just as today, we have the artificial heart, so in the future we could have the artificial mitochondrion.

Equally dramatic, nanotechnology will give us new instruments to examine tissue in unprecedented detail. Sensors that are smaller than a cell would give us an inside and exquisitely precise look at ongoing function. Tissue that was either chemically fixed or fresh frozen could be analyzed literally down to the molecular level, giving a completely detailed "snapshot" of subcellular and molecular activities.

Nanomaterials and nanoparticles are likely to be cornerstones of innovative nanomedical devices to be used for drug discovery and delivery, discovery of biomarkers and molecular diagnostics. Scientists are working

now to create novel nanostructures that serve as new kinds of drugs for treating cancer, Parkinson's and cardiovascular disease. Also efforts are on to engineer nanomaterials for use as artificial tissues that would replace diseased kidneys and livers and even repair nerve damage and to integrate nanodevices with the nervous system to create implants that restore vision and hearing and build new prosthetic limbs. However, as nanoparticles may also exert toxicological effects, thus development of novel nanoparticles for pharmacology, therapeutics and diagnostics must proceed in tandem with assessment of any toxicological and environmental side effects of these particles. The diversity of engineered nanoparticles and of several possible side effects represents one of the major challenges for nanopharmacology and therapeutics. Modern medical instruments alter the human body that would have been hard for people to imagine a hundred years ago.

In the future, nanobiotechnology will alter the human body (on a nanoscale) in ways that we cannot now imagine.

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A comparison between granisetron and granisetron with dexamethasone for prevention of postoperative nausea and vomiting for laparoscopic cholecystectomy

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Abstract

Objective : To evaluate the antiemetic effect of dexamethasone with granisetron in comparison with granisetron alone in patients undergoing laparoscopic cholecystectomy
Methods : Sixty six adult patients of either sex (ASA I and II, age 18-65 years) were randomly allocated into two groups (n=33). Group A received granisetron 40µg/kg IV and Group B received granisetron 40µg/kg IV plus dexamethasone 8mg IV, 1 minute before induction of general anaesthesia. Premedication and anaesthetic techniques were similar in the two groups. **Results :** Patients receiving Granisetron only had higher incidence of postoperative nausea and vomiting compared to granisetron plus dexamethasone (18% vs 6%; $\chi^2 = 2.95$; $p > 0.05$). **Conclusion :** Granisetron plus dexamethasone had better control of PONV although not statistically significant.

Key words : Postoperative nausea vomiting (PONV), granisetron, dexamethasone.

Introduction

Postoperative nausea vomiting (PONV) are

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commonly observed adverse effects of general anaesthesia. The incidence of PONV in laparoscopic cholecystectomy (LC) is unacceptably high (53-76%).^{1,2} To manage this problem, drugs like dexamethasone^{1,2}, droperidol³, metoclopramide³ were routinely used; however in the present era, some of these drugs have been replaced by selective 5-HT₃ receptor antagonists like ondansetron, granisetron, ramosetron, tropisetron etc. Moreover, granisetron and dexamethasone are also administered alone or in combination in various situations.^{1,4,5} The present study is designed to compare the effectiveness of granisetron alone or in combination with dexamethasone in controlling PONV in laparoscopic cholecystectomy.

Methods

The study was conducted in the department of Anaesthesiology, Regional Institute of Medical Sciences (RIMS), Imphal during the period July 2005 to June 2007. After obtaining ethics committee approval and written consent, 66 patients (aged: 18-65 years, ASA-I and II) scheduled for elective LC under a standardized general anaesthesia procedure were randomly allocated to two groups (n=33) with equal number of patients in each group. One minute before the induction of anaesthesia, patients in Group A received Granisetron 40µg/kg IV alone while those in Group B received granisetron 40µg/kg IV plus dexamethasone 8mg IV.

The anaesthetic regime and surgical procedure were standardized for all the

patients. Anaesthesia was induced with IV propofol 2mg/kg and butorphenol 20µg/kg. Endotracheal intubation was facilitated with succinylcholine hydrochloride 2mg/kg IV and anaesthesia was maintained with 66% N₂O in oxygen with volatile anaesthetic, halothane and nondepolarizing muscle relaxant, atracurium besylate 0.5mg/kg IV in intermittent doses. During LC, the end tidal carbon dioxide(ETCO₂) was maintained between 4.7-5.3kpa(35-40mm Hg) and maximum intra-abdominal pressure was limited to 14mm Hg. All episodes of PONV, rescue emetics and adverse events were recorded within the first 24 hr after anaesthesia. The findings were recorded and statistically analysed.

Results

Table 1 shows the distribution of patients in relation to their age, sex, ASA, weight and height in granisetron(Group A) and combination of granisetron and dexamethasone (group B). The mean age (±SD) in Group A and Group B were 43.48 ± 13.02 yr and 40.15±13.49 yr ; and the mean weight (±SD) was 55.30±9.84kg and 57.12±8.20kg respectively. It is evident from this table that both the groups have comparable profiles such as sex distribution (26:7 in both the groups) and height i.e., 158.94±7.47 cm in Group A and 158±6.90cm in Group B.

As shown in table 2, the mean(±SD) duration of surgery was 57.88 ±14.09 min in Group A and 56.06 ±20.91min in Group B. The

difference in duration of surgery is statistically insignificant(p>0.05). Similarly, the mean (±SD) duration of anaesthesia in Group A was 66.36 ± 17.65min and 65.15 ± 21.23 min in Group B. The difference in the duration of anaesthesia is also statistically insignificant (p> 0.05).

In this study, it was observed that the incidence of was higher in Group A(Granisetron only- 18%) compared to Group B(Granisetron + dexamethasone- 6%). However, its statistical significance could not be proved. It was also seen that patients in

Table 3. Showing the incidence of nausea and vomiting, median VAS and rescue antiemetics n(%) during 0-24hr postoperatively

	Group A (n=33)	Group B (n=33)	p- value
Nausea only	4(12)	2(6)	
Retching	1(3)	0(0)	
Vomiting	1(3)	0(0)	>0.05
Total	6(18)	2(6)	
Median VAS	3	3	>0.05
Rescue antiemetics	5(15%)	0(0)	>0.05

Table 4. Showing the incidence of side-effects(n(%)

Side effects	Group A (n=33)	Group B (n=33)	P- Value
Headache	3(9)	3(9)	
Drowsiness	2(6)	2(6)	>0.05
Dry mouth	1(3)	1(3)	
Constipation	1(3)	0(0)	
Perineal itching	0(0)	4(12)	

Table 1. Showing the demographic profiles of Group A(Granisetron alone) and Group B(Granisetron + Dexamethasone)

	Group A (Granisetron) n=33 (Mean±SD)	Group B(Granisetron + Dexamethasone) n=33(Mean±SD)	P- value
Age(years)	43.48± 13.02	40.15 ± 13.49	
Sex(F:M)	26 : 7	26 : 7	
ASA(I:II)	28:5	29 : 4	>0.05
Weight(kg)	55.30±9.84	57.12±8.20	
Height(cm)	158.94±7.47	158±6.90	

Table 2. Showing the duration of surgery and anaesthesia in both the groups.

Duration	Group A (Granisetron) n=33	Group B (Granisetron + dexamethasone) n= 33	p- value
Duration of surgery(min)	57.88 ± 14.09	56.06 ± 20.91	>0.05
Duration of anaesthesia(min)	66.36 ± 17.65	65.15 ± 21.23	

Group A required more rescue antiemetics (15%, table 3). The side effects and median Visual Analogue Scale (VAS) were equally observed in both the groups(table 3 and 4)

Discussion

The etiology of PONV is multifactorial viz age, sex, obesity, history of motion sickness, previous PONV, menstruation, operative procedures, anaesthetic technique and postoperative pain. The combination of

granisetron and dexamethasone has proved better than either agents alone in operative procedures such as major gynaecological surgery⁶, diagnostic laparoscopy⁷, paediatric surgery⁸, thyroidectomy⁹.

The antiemetic mechanisms of combination of these drugs could be due to the fact that granisetron is a central selective 5-HT₃ receptor antagonist acting at area postrema and nucleus of tractus solitaries and at the same time, it causes peripheral 5-HT₃ antagonism in the small intestines. On the other hand, dexamethasone produces inhibition of prostaglandin synthesis which triggers emesis. The incidence of PONV may be enhanced by opioids (odds ratio-OR = 4.18) and nitrous oxide (OR = 2.24), while propofol has antiemetic effect (OR = 0.40)¹⁰. Fuji Y et al¹¹ observed that dexamethasone 8mg IV administered in combination with granisetron 40 µm/kg body weight IV before anaesthesia was effective for prevention of PONV in laparoscopic cholecystectomy. Similar findings were observed by Biswas BN et al¹² and Khan MP et al¹³, which is in concurrence with the findings of the present study. In the present study, the incidence of PONV during 0-24h postoperative (PO) period was 18% in the granisetron group. This was in full agreement with that of Fujii Y et al¹¹ (17%) and Biswas BN et al¹² (18.3%). Our findings were lower than that of Khan MP et al¹³ (23.3%).

The incidence of PONV during 0-24h PO period in the combination group was 6% in the present study, which is comparable to that of Biswas BN et al¹² (5%) and Khan MP et

al¹³ (3%). However, our findings were higher than the values reported by Fujii Y et al¹¹ (2%).

During the 24h PO period, arterial pressure, heart rate and ventilatory frequency were stable and there was no significant difference between the groups. VAS during the first 24h PO period was found to be similar between the two groups which was insignificant statistically. In the present study, the commonest adverse event was headache (9%) in both groups. Perineal itching was the most unusual feature that some patients reported. However, all the recorded adverse effects were mild in nature. There were no significant difference between the two groups and these were comparable to those of previous studies¹¹⁻¹³.

Since both the groups were uniformly exposed to the same agents, ruling out of factors which are likely to cause PONV viz female gender, smoking, type of surgical procedure, inhalation agents like diethyl ether etc was not tried in this study. Moreover, the duration of surgery and anaesthesia were statistically insignificant.

Conclusion

It may be concluded from the present study that the prophylactic antiemetic therapy with the combination of granisetron and dexamethasone is more effective than granisetron alone for the prevention of postoperative nausea and vomiting during the initial 24h after anaesthesia in patients undergoing laparoscopic cholecystectomy.

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Chlamydia trachomatis(CT) and its co-infection with Human Immuno Deficiency Virus (HIV) in women with reproductive tract infections (RTI)

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Abstract

Objective: To study the seroprevalence of C.trachomatis and its co-infection with HIV infections attending Obstetrics and Gynaecology outpatient department, Regional Institute of Medical Sciences (RIMS), Imphal.

Methods: The study included 92 female patients with RTI. Diagnosis of RTI was made on clinical grounds with appropriate laboratory investigations - microscopy, Gram stain smear etc. Bacterial vaginosis was diagnosed using Nugent's criteria, Chlamydia trachomatis by IgG ELISA. Diagnostic serology was done for HIV by 3 ELISA/Rapid (E/R) test of different biological antigen. **Results:** Out of 92 sera tested 16 cases (17.4%) were C.trachomatis and 9 (9.8%) cases were HIV positive. Co-infection rate of HIV in C.trachomatis positives was 43.8%. 50% of C.trachomatis positives and 55.5% of HIV positives belongs to age group of 21 to 30 years. Of the C.trachomatis positives 7(43.8%) had HIV, 5(31.25%) had bacterial vaginosis, 3(18.75%) were pregnant, 11(68.75%) were unemployed, 14(87.5%) had education level below 10 standard.

Conclusion : The findings of the present study revealed a high prevalence of C.trachomatis

and high rate of co-infection with HIV infection. Our study suggest that every case of RTI must be thoroughly evaluated by laboratory testing for C.trachomatis co-infection as this has profound implications on their judicious management and aversion of complications. Early diagnosis and treatment of C.trachomatis infection will prevent progression and spread of HIV disease.

Key words : *Chlamydia trachomatis, HIV, seroprevalence, coinfection, reproductive tract infections.*

Introduction

Chlamydia trachomatis is an intracellular obligate parasitic bacterium. Serovars D to K causes oculogenital infections. Although genital infection is often low grade and chronic, it remains an important cause of pelvic inflammatory disease and its sequelae.¹ Untreated infections in women can cause extensive inflammation and scarring of female reproductive tract and studies proved that chlamydial infections may facilitate HIV transmission.² In Manipur, earlier HIV was confined to intravenous drug users (IDU) in 1990 but the epidemic is now spread to female sexual partners of IDUs and to their children. Clinic attendees of the seroprevalence rate among Sexually Transmitted Disease (STD) increased from 4.8% in 1994 to 7.4% in 2004.³ The predominant mode of transmission of both HIV infection and STIs is same including sexual transmission. Clemetson DB⁴ observed a two fold increase in HIV infection associated with sexually transmitted diseases

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or with purulent cervical secretions in women. The presence of RTI has been found to facilitate the acquisition and transmission of HIV infection by 2-10 times.⁵ Improved STD treatment reduced HIV incidence by about 40%. The STD treatment programme reduced HIV incidence by shortening the average duration of STIs, thus effectively reducing the probability of transmission of HIV.⁶

In North East India seroprevalence studies of *C.trachomatis* and its co-infection with HIV are sparse. Screening of HIV and *C.trachomatis* infections in women with RTIs will help the understanding of the reality of spread of HIV infection. As HIV and Sexually Transmitted Infection (STI) are closely interlinked, early diagnosis, treatment and control of STI offers a rational approach to control of HIV. Our main objective is to find the prevalence of *C.trachomatis* and HIV infection and the possible association between the two infections.

Material and methods

This study was conducted between November 2003 to October 2005 in the Department of Microbiology, RIMS, Imphal, Manipur. The study included 92 female patients with RTI with unknown HIV status. A written informed consent was obtained from each patient and detailed history, demographical and clinical features were recorded in a predesigned proforma. Under all aseptic precautions 5ml of

venous blood and high vaginal swabs were collected from each patient. Diagnosis of RTI was made on clinical grounds with appropriate laboratory investigations - microscopy, Gram stain smear, vaginal pH etc. Bacterial vaginosis was diagnosed using Nugent's criteria. All sera were subjected for the detection of IgG specific antibodies to *C.trachomatis* by using a commercial enzyme immunoassay kit (*Chlamydia trachomatis* IgG ELISA, Novum Diagnostica). Diagnostic serology was done for HIV by 3 ELISA/Rapid (E/R) test of different biological antigen. For testing HIV antibody the kits used were Genedia HIV 1 and HIV 2 (Green Cross Life Science Corp. Korea), SD Bioline

Table 1. Analysis of demographic, sexual and behavioural factors of Chlamydia trachomatis positives and HIV positives in RTI patients.

Variables	RTI (n=92)	CT positives (n=16)	HIV positives (n=9)
<u>Age</u>			
15 to 20 yrs	4(4.3)	0	0
21 to 30 yrs	42(45.7)	8(50)	5(55.5)
31 to 40 yrs	38(41.3)	7(43.7)	3(33.3)
41 to 49 yrs	8(8.7)	1(6.3)	
Pregnancy	27(29.34%)	3(18.75%)	1(11.1%)
<u>Contraceptive use / risk factors</u>			
IUD	1(1.08%)	6(37.5%)	0
MTP	24(26.08%)	10(62.5%)	0
OCP	2(2.17%)	0	0
Condom user	1(1.08%)	0	0
Non user	63(68.47%)	0	9(100%)
IVDU	6(6.52%)	4(25%)	6(66.6%)
Multiple partner (wife)	4(4.3%)	4(25%)	3(33.3%)
Multiple partner (husband)	13(14.13%)	7(43.5%)	5(55.5%)
<u>Occupation</u>			
Govt employed	12(13.04%)	0	0
Self employed	35(38.04%)	5(31.25%)	4(44.4%)
Unemployed	45(48.91%)	11(68.75%)	5(55.5%)
<u>Education</u>			
Under matric	47(51.08%)	14(87.5%)	9(100%)
Under graduate	30(32.6%)	1(6.25%)	0
Postgraduate	5(5.43%)	1(6.25%)	0
<u>Symptoms</u>			
Vaginal discharge	90(97.82%)	14(87.5%)	5(55.5%)
Menorrhagia	4(4.3%)	3(18.75%)	0
Postcoital bleeding	4(4.3%)	1(6.25%)	0
Low backache	21(22.82%)	10(62.5%)	2(22.2%)
Dysuria	19(20.65%)	2(12.5%)	2(22.2%)
Itching	44(47.82%)	5(31.25%)	1(11.1%)
Pain lower abdomen	15(16.30%)	7(43.75%)	1(11.1%)
<u>Vaginal pH</u>			
<4.5	38(41.3%)	0	1(11.1%)
≥4.5	54(58.69%)	16(100%)	8(88.8%)
<u>Bacterial vaginosis</u>			
	22(23.91%)	5(31.25%)	2(22.2%)

HIV 1 and HIV 2.3.0 test (SD Standard Diagnostics, Inc.) and HIV CheX (Xcyton Diagnostics). Pre-test and post-test counseling were provided for HIV testing at National Reference Laboratory (NRL) and voluntary confidential counseling and testing centre (VCCTC), Department of Microbiology, RIMS, Imphal. We have analysed the infection rates of *C.trachomatis* and HIV infection and the association between the two infections.

Results

Out of the 92 samples screened for IgG *C.trachomatis* 16(17.4%) cases were found to be positive. HIV antibody was found to be positive in 9(9.8%) cases.

Demographic, sexual and behavioural risk factors were analysed (table 1) in relation to *C.trachomatis* and HIV positivity. Both *C.trachomatis* and HIV positivity were found mostly among age group of 21 to 30 years, unemployed and lower education level and also found to be associated with risk factors like multiple sexual partners in either husband or wife and non-contraceptive user in women. Vaginal discharge was the commonest symptom, vaginal pH was mostly more than 4.5, bacterial vaginosis(BV) was positive in 22 cases of RTI , 5(31.25%) cases co-infected with *C.trachomatis* and 2(22.2%) cases co-infected with HIV infection. 3(18.75%) cases of *C.trachomatis* positives and 1(11.1%) case of HIV positives were pregnant.

Table 2. Analysis of HIV positivity in relation to CT infection

Groups	HIV positivity
CT positive = 16	7 (43.8%)
CT negative = 76	2 (2.6%)
Total n = 92	9

χ^2 - value = 25.321, df = 1, p value 0.001

Table 2 shows the analysis of HIV positivity in relation to *C.trachomatis* infection. 7(43.8%) out of 16 CT positive cases had HIV co-infection. The study revealed that HIV positivity rate was significantly high (43.8%) among those with chlamydial infection than in those without chlamydial infection (2.6%). The difference was statistically very highly significant ($p < 0.001$). Similarly the analysis

also revealed that *C.trachomatis* positivity was significantly higher in HIV positive cases than HIV negative cases (77.7% vs 10.8%).

Discussion

The high rate of *C.trachomatis* (17.4%) infection in RTI patients observed in the present study assumes significance in view of risk of HIV transmission and spread. HIV positivity and *C.trachomatis* positivity were interrelated. In the present study having multiple partner either in husband or wife were seen to be significant risk factors for both *C.trachomatis* and HIV infection. In both the cases maximum number of cases belongs to the age group of 21 to 30 years which is the most sexually active age group and it reflects the association between the sexual activity and increasing CT and HIV infection. Most of the cases had lower education level and were unemployed. Similar findings were reported by other studies.⁷⁻⁹

100% of *C.trachomatis* positives and 88.8% of HIV positives had vaginal pH more than 4.5. Hanna et al¹⁰ observed that *C.trachomatis* were 2 to 3 times more often in women with higher pH value than in those with lower value. 5(31.25%) cases of *C.trachomatis* positive and 2(22.2%) cases of HIV positive cases were co-infected with bacterial vaginosis. *C.trachomatis* is more frequently detected in women with bacterial vaginosis than without and it has been postulated that bacterial vaginosis may facilitate the entry of *C.trachomatis* to the upper genital tract through the activity of enzymes such as mucinase and sialidase.¹¹ Women with severe bacterial vaginosis had 90% increased risk of HIV.¹² Interleukin-10 concentrations are elevated in vaginal fluid of women with bacterial vaginosis and because IL-10 is known to increase susceptibility of macrophages to HIV infection.¹³

Since all the cases belongs to females of childbearing age, 3 cases of *C.trachomatis* positive and 1 case of HIV positive were pregnant who could act as a potential transmitters to their offspring. 5(55.5%) cases of HIV positive and 7(43.75%) cases of *C.trachomatis* had history of their husband

having multiple partners and they can spread to their sexual partners.

HIV infection in our study among female RTI was 9.8% which is quite alarming. 43.8% of *C.trachomatis* positives were co-infected with HIV but in a study by Joyee AG et al¹⁴ 29.5% of *C.trachomatis* positives had HIV infection. Nonulcerative STIs, including *C.trachomatis*, have been associated with an increase in numbers of CD₄+ cells in the endocervix, suggesting that HIV transmission could be increased as a result of such infection.¹⁵ The invasive intracellular pathogenesis of *C.trachomatis* can cause substantial damage to the genital epithelial layer which facilitate HIV infection.¹⁶ 77.7% of HIV positives were co-infected with *C.trachomatis* in the present

series. Immunological changes due to HIV infection may favour *C.trachomatis* infection.¹⁷ Immunosuppression due to HIV infection may lead to more aggressive chlamydial disease conditions like PID in those who are infected with *C.trachomatis*.¹⁸

Conclusion

Our study suggest that every case of RTI, be it an ulcerative or nonulcerative must be thoroughly evaluated by laboratory testing for *C.trachomatis* co-infection as this has profound implications on their judicious management and aversion of complications. The findings of present study revealed a high *C.trachomatis* and HIV coinfection rate indicating that there is a need for proper screening and management of *C.trachomatis* infection as a way of reducing the risk and spread of HIV infection.

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Bone marrow study of non-neoplastic haematologic lesions in a period of 11 years

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Abstract

Objective: To study the bone marrow involvement and evaluate the marrow status of non-neoplastic haematologic lesions for the patients who have undergone bone marrow aspiration. **Methods:** A total of 1850 bone marrow aspiration smears were examined and analysed at Regional Institute of Medical Sciences, Imphal in an 11 years period (January 1997 to December 2007) after obtaining clinical details and abnormalities in complete haemogram reports. Aspirates of inadequate material or dry tap were excluded. All the non-neoplastic haematologic lesions were selected for study. **Results :** Non-neoplastic lesions constituted 395 cases (21%), out of which Idiopathic thrombocytopenic purpura was detected in 114 cases, aplastic anaemia in 95 cases and iron deficiency anaemia in 55 cases. The least common was pure red cell aplasia detected in 2 cases only. The maximum number of total lesions were in the age group of 31-50 years (151 cases) **Conclusion :** Bone marrow examination is an important step in the diagnosis of many non-neoplastic lesions and in the exclusion of other lesions including malignancies which may cause anaemia or cytopenias.

Key words: Bone marrow aspiration, idiopathic thrombocytopenic purpura, aplastic anaemia, iron deficiency anaemia.

Introduction

The bone marrow examination is a valuable parameter in the diagnosis of many haematological conditions and certain non-haematological conditions. Diagnosis and management of many haematological diseases depend on the examination of bone marrow. Bone marrow aspiration smears are ideal for the study of cytologic details of haemopoietic cells¹. Moreover it may be involved by a neoplastic process without any abnormalities recognized in haematological parameters, conventional imaging studies, bone scans or serum chemistry.¹ So, the present study was undertaken to study the bone marrow involvement and evaluate the marrow status of non-neoplastic haematologic lesions for the patients who have undergone bone marrow aspiration.

Material and methods

The study included retrospective and prospective analysis of 1850 bone marrow aspiration smears of adequate material from January 1997 to December 2007. All the aspirations were performed by pathologists. Prior to aspiration, clinical details were obtained and abnormalities detected in the complete haemogram were recorded for every case. The principal indications were unexplained fever, anaemia and cytopenia. About 4-5 smears were made after about 0.2 ml of each aspiration, usually from the

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posterior iliac spine or sternum and for children less than 2 years from the medial tibial tuberosity, under aseptic measures. Written consent were taken for all cases. Two smears were stained by Leishman stain and the rest were kept for other stains. Iron stain was done routinely. Apart from cellularity, all the cell lineages were examined for any abnormality. Differential count from 300 nucleated cells was performed for every case. The findings were correlated with the peripheral blood picture wherever possible. Aspirates of inadequate material or dry tap were excluded from the study.

Results

During the 11-year period (January 1997 to December 2007), 1890 bone marrow aspirates were reported (table 1). Non-

Table 1. Year-wise distribution of bone marrow examination

Year	No.
1997	- 105
1998	- 123
1999	- 119
2000	- 126
2001	- 176
2002	- 182
2003	- 181
2004	- 197
2005	- 238
2006	- 197
2007	- 206

Total : 1850

neoplastic haematologic lesions constituted 395 cases (21%) and were included in the study (Table 2). The male to female sex ratio was 1.16:1 and the age varied from 1 month to 85 years. When all the lesions are combined, the number of cases were maximum in the age group of 31-50 years (167 cases) followed by 82 cases in the age group of 0-5 years (table 2). Idiopathic thrombocytopenic purpura (ITP) constituted 114 cases (28.8% of the lesions) with two peaks in 0-15 years and 31-50 years of age closely followed by Aplastic anaemia in 98 cases (24.8 %) (fig 1) including 43 cases in the age group of 31-50 years. Iron deficiency anaemia (IDA) was detected in 55

Table 2. Lesions with age-wise distribution

Lesion	0-15yrs	16-30yrs	31-50yrs	>50yrs	No. (P.C)
ITP	45	19	41	09	114(28.8)
Aplastic anaemia	10	24	43	21	98(24.8)
IDA	09	11	23	12	55(13.9)
Erythroid hyperplasia	05	07	17	09	38 (9.6)
Megaloblastic anaemia	03	05	13	07	28 (7.0)
Dimorphic anaemia	02	05	14	05	26 (6.5)
ACD	00	02	08	13	13 (3.2)
Granulo hyper	00	02	08	02	12 (3.0)
CDA	06	03	00	00	09 (2.2)
PRCA	02	00	00	00	02 (0.5)
Total	82	78	167	68	395

ITP - Idiopathic thrombocytopenic purpura,
IDA - Iron deficiency anaemia.
ACD - Anaemia of chronic disease, Granulo hyper - Granulocytic hyperplasia
CDA - Congenital dyserythropoietic anaemia,
PRCA - Pure red cell aplasia.



Fig. 1. Photomicrograph of Aplastic anaemia showing hypocellular and fatty marrow in a 17 years old patient. (Leishman Stain, X 40)

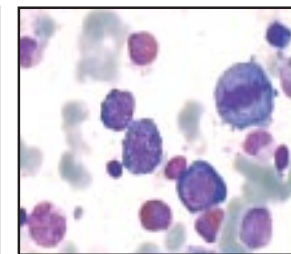


Fig. 2. Photomicrograph of Megaloblastic anaemia showing megaloblasts with open chromatin (Leishman Stain, X 100)

cases(13.9%). Erythroid hyperplasia accounted for 38 cases (9.6 %) including 15 cases of thalassaemia, 3 each of Coombs positive haemolytic anaemia, and paroxysmal nocturnal haemoglobinuria and 17 cases of non-immune haemolytic anaemias.

Megaloblastic anaemia was detected in 28 cases (fig 2) closely followed by 26 cases of Dimorphic anaemia. Anaemia of chronic disease (ACD)and granulocytic hyperplasia accounted for 13

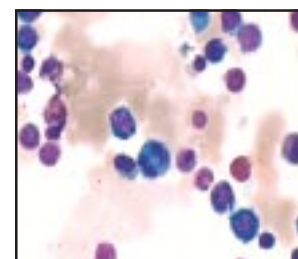


Fig 3. Photomicrograph of Congenital dyserythropoietic anaemia showing erythroid hyperplasia with marked dyserythropoiesis (Leishman Stain, X 40).

cases and 12 cases respectively. Congenital dyserythropoietic anaemia (CDA) was detected in 9 cases including 6 cases in the age group of 0-15 years (fig 3). The least common was pure red cell aplasia (PRCA) detected in 2 cases only making 0.5% of the lesions.

Discussion

In ITP, platelet associated auto-antibodies have been detected in 75 % of patients and disappearance of antibodies correlates with the appearance of normal platelet counts.^{2,3} The diagnosis of ITP is primarily by exclusion of other lesions that may cause thrombocytopenia because currently available clinical assays for platelet-associated antibodies or immune complexes are neither specific nor sensitive enough for routine clinical use. In one study the reported annual incidence of ITP was 5.5 per 100,000 persons, when defined by a platelet count of $<100 \times 10^9 /L$ and 3.2 per 100,000 using a cut-off platelet count $<50 \times 10^9 /L$, the median age at diagnosis was 56 years and the incidence increased with age.⁴ Though the exact Indian data are lacking, the diagnosis of 114 cases of ITP (28.8% of the lesions) in the present study is significant. Aplastic anaemia is more prevalent in the Far East, where the incidence is approximately 7 per 1 million in China⁵, approximately 4 per 1 million in Thailand⁶ and approximately 5 per 1 million in Malaysia⁷. The explanation for greater incidence in the orient is unclear, possibly related to environmental factors rather than genetic factors. In one series, the incidence of acquired aplastic anaemia varies bimodally with age, with one peak at older than 60 years of age.⁸ Its exact incidence in India is not known. In the present study, 98 cases of aplastic anaemia were diagnosed and a peak was observed in the age group of 31 to 50 years.

Iron deficiency anaemia is the most common anaemia in both developing and developed countries, higher among people living in chronic poverty.⁹ In India the prevalence of anaemia could be as high as 74 % in children below three years of age, 85% in expectant mothers and 90 % among adolescent girls in some population groups.¹⁰ The comparatively

lower percentage in the present study (2.9 % of total number of cases and 13.9 % of the lesions) could be due to detection of IDA from other parameters without undergoing bone marrow examination.

Megaloblastic anaemia was detected in 28 cases in the present study. This anaemia is comparatively rare in this part of the country probably because of dietary habits. Dimorphic anaemia compatible with nutritional anaemia, characterized by the presence of micronormoblastic erythropoiesis along with megaloblastic change and low iron stores was detected in 26 cases only, probably because of other diagnostic parameters without bone marrow examination. The high prevalence of infectious diseases, inflammatory and malignant disorders worldwide suggest that anaemia of chronic disease is second or third most common form of anaemia after IDA and thalassaemia.¹¹ In contrast there were 13 cases of ACD in the present study characterized by the presence of micronormoblastic erythropoiesis and normal iron stores along with low serum iron, low TIBC and high serum ferritin. This anaemia may be a cytokine-mediated process related to various cytokines associated with inflammatory or infectious causes.^{12,13}

CDA - a group of rare inherited disorders characterized by anaemia, ineffective erythropoiesis and morphologic abnormalities of the red cells was found in 9 cases with the majority in the paediatric age group (6cases).

Conclusion

Evaluation of bone marrow status is essential in the management of many haematological disorders including neoplastic and non-neoplastic lesions. Bone marrow examination is a valuable and reliable tool in the work-up of patients with anaemias and cytopenias before going into many sophisticated and costly investigations.

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Neuropsychological deficits among chronic alcoholics - a hospital based study

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Abstract

Objective: To study the neuropsychological deficits in chronic alcoholics and non alcoholic groups. **Methods:** A total no of 30 chronic alcohol dependent patients who were diagnosed according to ICD-10 criteria were selected through convenient sampling method. Another 30 matched group (Non-alcoholic Group) was also selected for the purpose of the study. **Results:** Deficits in neuropsychological components like attention, expressive speech, personality changes, focal sign and verbal comprehension were found to be insignificant at probability level. Deficit in other neuropsychological components such as scanning, ideational fluency, abstraction, block design and visual integration were found to be highly significant whereas motor task and perceptual gestalt were found to be significant at probability levels. **Conclusion:** It is concluded that the neuropsychological deficits in the components like learning and memory, ideational fluency, abstraction, visuo-spatial, executive motor function and visual integration were found to be very significant among chronic alcoholic when compared with the non-alcoholic subjects.

Key words: Neuropsychological deficit, alcoholic, neuropsychological battery.

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Introduction

Neuropsychological impairment in alcoholic is found in different studies in different countries. Studies in the US ¹⁻⁴ and Spain⁵ have shown deficits in cognitive flexibility, problem solving, verbal and non-verbal abstraction, visuo-motor co-ordination, learning, conditioning and memory. General intellectual functions seem to be impaired less frequently ^{2,6}. Studies by other researchers also found deficits in impairments in abstract reasoning ability, visuospatial and visuomotor ability and learning and memory skills⁷.

In alcoholics, the characteristic pattern of cognitive impairment, other than memory deficit, is poor performance in task of abstraction, visuospatial ability, verbal fluency, planning and organization, shifting of set and error utilization. The deficits are more severe depending on how long a patient has been an alcoholic and how much alcohol he/she has consumed⁸.

The present work aims at studying the neuropsychological deficits among chronic alcoholics that will help in framing proper treatment strategies and for better management of the alcohol dependent patients.

Material and methods

The present study was conducted in the Department of Clinical Psychology and Department of Psychiatry, Regional Institute of Medical Sciences, Imphal. A total number of 30 chronic alcohol dependent patients,

diagnosed according to ICD-10 criteria were selected irrespective of age, religion, education and marital status through convenient sampling method. Another 30 controls (Non-alcoholic Group) identical in terms of educational qualification, occupational status and age with the alcoholic group were also selected for the purpose of the study. The 30 control subjects were identified as non-alcoholic based on the subjective report and confirmed from the information's collected from family members and other important friends and relatives. 30 chronic alcohol subjects were currently abstinent in protected environment and their chronicity of drinking was 5 years and above. Both the study groups didn't have any history of significant head injury, multiple drug abuse, and any neurological or psychotic disorder. After detoxification, informed consent was taken from the subjects and the natures of the study were explained. A semi structured performa was used to collect the socio demographic variables for both the groups. The 30 alcoholic groups were diagnosed according to ICD-10 criteria of alcohol dependence⁹. Thirteen components of NIMHANS Neuropsychological Battery¹⁰ were then administered individually to find out the broad range of cognitive deficits in both the groups.

Results

The sample size consists of 60 study subjects - 30 chronic alcoholics' subjects and another 30 non-alcoholic subjects.

Table 1 shows the educational qualification for both alcoholic and non-alcoholic groups. The highest percentage for both the groups belongs to graduate with a percentage of 35% and the least belongs to higher secondary with a percentage of 15%.

Table 1. Educational qualification wise distribution of study subjects (n=60)

Education	Study Subject	%
Up to Matric	19	32
High. Sec.	9	15
Graduate	21	35
Postgraduate	11	18
Total	60	100

Table 2. Occupation wise distribution of study subjects(n=60)

Occupational status	Study Subject	%
Employed	15	25
Business	26	44
Self employed	14	23
Unemployed	5	8
Total	60	100

Table 2 shows the occupation wise distribution of study subjects. Business witnesses the highest percentage with a percentage of 44% and the least percentage belongs to unemployed.

Table 3. Age wise distribution of study subjects(n=60)

Age	Study Subject	%
20-30	4	7
31-40	26	43
41-50	30	50
Total	60	100

Table 3 shows the age wise distribution of study subject. The highest percentage of age for the study subjects belongs to the age range of 41-50 with a percentage of 50% and the least belongs to the age range of 20-30 with a percentage of 7%.

Table 4 shows the comparison of various neuropsychological components of study subjects over the groups. From this table, statistically when applied Chi-square test, it was found that neuropsychological components like attention, expressive speech, personality changes, focal sign and verbal comprehension were found to be insignificant at probability level. Other neuropsychological components like scanning, ideational fluency, abstraction, block design, and visual integration were found to very highly significant and motor task and perceptual gestalt were found to be significant at 0.020 probability level.

Discussion

The present study was a modest attempt to find out the neuropsychological impairment among the chronic alcoholics comparing with the control group (non-alcoholics) by using NIMHANS Neuropsychological battery.

Table 4. Comparison of impairment of various neuropsychological components of the two groups (n=30)

Sl. No.	Neuropsychological Components	Alcoholic (n=30)		Non Alcoholic (n=30)		Chi-square	df	P.Value	Remark
		Adequate	Impairment	Adequate	Impairment				
1	Attention	26	4	30	0	4.286	1	0.011	IS**
2	Scanning	8	22	30	0	34.737	1	0.000	VHS*
3	Ideational Fluency	12	18	30	0	25.714	1	0.000	VHS*
4	Abstract	13	17	30	0	23.721	1	0.000	VHS*
5	Motor Task	25	5	30	0	5.455	1	0.020	S***
6	Expressive Speech	29	1	30	0	1.017	1	0.313	IS**
7	Personality Change	26	4	30	0	4.286	1	0.011	IS**
8	Perceptual Gestalt	25	5	30	0	5.455	1	0.020	S***
9	Spatial Relationship	29	1	30	0	1.017	1	0.313	IS**
12	Block Design	21	9	30	0	10.588	1	0.001	VHS*
11	Focal Sign	29	1	30	0	1.017	1	0.313	IS**
12	Verbal Comprehension	26	4	30	0	4.286	1	0.011	IS**
13	Visual Integration	10	20	30	0	32.308	1	0.000	VHS*

* Very Highly Significant, **Insignificant, ***Significant

In the present study the significant impairment in neuropsychological components were found in chronic alcoholic group when compared with non-alcoholic group. The significant impairment of neuropsychological components was scanning, ideational fluency, abstraction, executive motor functions, visuospatial ability, visual integration and memory. The present findings are comparable with the findings of other authors^{1,2,4}. And the other components which were found insignificant in the study when compared with non-alcoholic group were attention, expressive speech, personality changes, focal sign and verbal comprehension. Even though the above mentioned neuropsychological components were statistically insignificant there are some individual cases who also found impaired in this area. The neuropsychological component like abstraction was also found to be very highly significant in this study. This is supported by the ground braking studies of Fitzhugh LC¹¹, demonstrated that alcoholics can have impairment in abstracting ability and in complex perceptual motor skills. The impairment of abstraction ability and concept formation has also been noted in category test^{12,13}. However there is some contradictory report on abstraction. According to the work done by Tarter RE¹⁴ on abstracting capacity in cirrhotic alcoholics concluded that deficits in reasoning ability are not invariably associated with chronic alcoholism. The

neuropsychological components like block design tests and perceptual gestalt test were also found significant impairment in chronic alcoholic group when compared with non-alcoholic group. These findings are comparable with the findings of Tarter RE². Deficits in visuo-spatial tasks have been the most consistently document deficits shown by long-term alcohol abusers. Scanning was also found very highly significant in chronic alcoholic when compared with non alcoholic. This finding can be comparable with the findings of Betera JH and Parsons OA¹⁵. They suggested that impairment of scanning was not related to motor ability but represented higher level perceptual dysfunctions. The ideational fluency was also found to be very highly significant in chronic alcoholic group when compared with non-alcoholic group and this finding is comparable with the findings of Hewelt LJ¹⁶.

Conclusion

From these findings we can conclude that the neuropsychological components like learning and memory, ideational fluency, abstraction, visuo-spatial, executive motor function and visual integration were found significantly among chronic alcoholics than non alcoholics. The findings of this study will help in framing proper treatment strategies and for better management of the alcohol dependent patients. However the findings can not be

generalized as the sample size was very small and also all the subjects were selected from a hospital based population. Therefore it is

recommended that further study involving a larger patient sample, broad based and longitudinal in nature should be undertaken.

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Comparative study of the efficacy of intravenous midazolam and propofol as induction agent to attenuate haemodynamic response of laryngoscopy and intubation

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Abstract

Objective : To compare the effect of intravenous midazolam and propofol as an induction agent on the haemodynamic response of laryngoscopy and endotracheal intubation. **Methods** : 50 adult patients undergoing elective surgery under general anaesthesia. were randomly divided into two groups of 25 each. Patients of Group A received midazolam (0.3 mg per kg body weight IV) as induction agent and patients of group B received propofol (2.5 mg per kg body weight IV) for induction. Anaesthesia was maintained using halothane (0.25% to 0.75%) in O₂ and N₂O along with supplemental doses of vecuronium. Vital signs such as pulse rate, systolic and diastolic blood pressure were monitored in all the patients. Reversal of neuromuscular blockade was done using neostigmine 0.05 mg per kg body weight IV, and glycopyrrolate 0.01 mg per kg body weight IV at the end of the procedure. **Results** : There was a sharp fall in systolic blood pressure(SBP) after induction with propofol in group B from basal SBP, 127.28 ± 9.84 mmHg. to 105.44 ± 13.19 mmHg in comparison to

group A (midazolam) from SBP, 122.2 ± 12.12 mmHg to 114.32 ± 12.71 mmHg(p,<0.05). At intubation there was significant rise in SBP in group A to 133.32 ± 14.69 mmHg compared to group B with a rise to 124.08 ± 12.38 mmHg(p,<0.05). Similarly, significant fall in basal mean diastolic blood pressure (DBP) was observed after induction in group B from basal DBP, 78.16 ± 7.74 mmHg to 69.28 ± 7.45 mmHg in comparison to group A from basal DBP, 79.52 ± 6.14 mmHg to 76.0 ± 6.73 mmHg(p,<0.05). At intubation there was significant rise in DBP in group A to 88.24 ± 8.43 mmHg compared to group B with a rise up to 78.16 ± 7.78 mmHg(p,<0.05).

Conclusion : Propofol as an induction agent proved to be more effective in attenuating haemodynamic response of laryngoscopy and intubation than midazolam in patients pre-medicated with fentanyl.

Key Words: *Midazolam, propofol, haemodynamic response, laryngoscopy, endotracheal intubation.*

Introduction

Laryngoscopy and endotracheal intubation, commonly used for patients undergoing operation under general anaesthesia, is almost invariably associated with certain haemodynamic changes such as tachycardia, increase in blood pressure and occasional disturbance of cardiac rhythm.^{1,2} These are due to reflex sympathetic discharge in response to laryngotracheal stimulation which in turn leads to increased plasma catecholamine concentration.³

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These haemodynamic changes are seen even in normotensive subjects though they are short lived.⁴ These changes are undesirable particularly in patients with hypertension and cardiac disease because it may cause myocardial ischaemia, left ventricular failure and cerebrovascular accident and may be even fatal.

Deeper plane of anaesthesia, various drugs like ganglionic blockers, local anaesthetics like intravenous lignocaine, opioids⁵ like alfentanil⁶, beta blockers like esmolol⁷ and clonidine⁸ have been used successfully to attenuate these haemodynamic changes. These various methods have their own merits and demerits.

In this study midazolam, a water soluble short acting benzodiazepine⁹ and propofol an alkylphenol¹⁰, a newer non-barbiturate intravenous anaesthetic agent were used as induction agents in two different groups of patients with the aim to evaluate their efficacy in attenuating pressure response during laryngoscopy and endotracheal intubation in patients premedicated with fentanyl.

Material and methods

After obtaining institutional ethics committee approval and informed consent from all patients the study was done with 50 adult patients of either sex and age group between 25 and 45 years. All were belonging to ASA grade I and II and undergoing elective surgery under general anaesthesia. Patients having hypertension, bronchospasm, cardiac problems and anticipated difficult airway were excluded from this study.

Patients were randomly divided into two groups of 25 each. Patients of Group A received midazolam (0.3 mg per kg body weight IV) as induction agent and patients of group B received propofol (2.5 mg per kg body weight IV) for induction.

All the patients were premedicated with glycopyrrolate 0.2 mg IV 30 minutes before and fentanyl 2 µg / kg body weight IV 10 minutes prior to induction.

A standard anaesthetic technique was followed in all patients. On arrival to the operation theatre pulse, blood pressure and SpO₂ were recorded and ECG monitoring was started. After pre-oxygenation with 100% O₂, all the patients of group-A were induced with intravenous midazolam (0.3 mg per kg body weight IV) and patients of group -B with propofol (2.5 mg per kg body weight IV). Tracheal intubation was done after achieving adequate relaxation with succinylcholine (1.5 mg per kg body weight IV), with appropriately sized cuffed endotracheal tube and fixed after confirmation of position. Anaesthesia was maintained using halothane (0.25% to 0.75%) in O₂ and N₂O along with supplemental doses of vecuronium. Vital signs such as pulse rate, systolic and diastolic blood pressure were monitored in the following intervals-

- 1) Before premedication. 2) After premedication with fentanyl. 3) After induction with study drug. 4) At intubation. 5) 1 min after intubation. 6) 3 min after intubation. 7) 5 min after intubation. 8) 7 min after intubation. 9) 10 min after intubation. Thereafter, at 5 min interval till the end of surgery.

During the study period no surgical stimulus or change in position of the patients were allowed. Reversal of neuromuscular blockade was done using neostigmine 0.05 mg per kg body weight IV, and glycopyrrolate 0.01 mg per kg body weight IV at the end of the procedure.

Statistical analysis: Softwares used: Microsoft Excel 97 (Microsoft Corporation, USA, 1985-96) PS and Sample Size Calculations ver. 2.1.30

All the data were entered into a MS excel spreadsheet and analyzed. Numerical data which were normally distributed (e.g. age, sex distribution, body weight) were analyzed using the paired 't' test (within group) and unpaired 't' test (between groups). Categorical variables (e.g. incidence of complications) were compared using the Pearson's Chi-square test. All the tests were 2 tailed. A p value <0.05 was considered as statistically significant.

Results

Table 1 shows changes in mean heart rate(per minute) with standard deviation in both the test

Table 1. Comparison of heart rate at different intervals between Group A and Group B patients (mean±SD).

Group	Group A n=25	Group B n=25	Significance p' value
Basal	80.04±6.35	79.60±2.12	>0.05
After fentanyl premedication.	76.08±5.49	76.64±0.27	>0.05
After induction	74.64±4.85	67.76±1.68	<0.05
At intubation	109.84±7.41	89.40±0.24	<0.05
1 min. after intubation.	94.40±3.91	83.76±0.45	<0.05
3 min after intubation.	94.08±4.18	83.76±0.04	<0.05
5 min after intubation	92.40±4.32	82.40±0.32	<0.05
7 min after intubation	89.68±4.42	81.44±1.33	<0.05
10 min after intubation	86.24±4.05	81.04±1.42	>0.05

p> 0.05; not significant, p< 0.05 statistically significant

Table 2. Comparison of systolic blood pressure(mm Hg)at different intervals between Group A and Group B patients (mean±SD).

Group	Group A n=25	Group B n=25	Significance p' value
Basal	122.2 ± 12.12	127.28±9.84	>0.05
After fentanyl premedication	117± 16.84	123.64±14.25	>0.05
After induction	114.32± 12.71	105.44±13.19	<0.05
At intubation	133.32± 14.69	122.48±11.09	<0.05
1 min. after intubation.	131.44± 18.28	124.16±8.12	<0.05
3 min after intubation.	130.32± 11.11	121.92±9.69	<0.05
5 min after intubation	129±10.47	121.92±9.69	<0.05
7 min after intubation	129.52±11.63	121.04±12.11	>0.05
10 min after intubation	121.04±13.51	124.56±10.63	>0.05

p> 0.05; not significant, p< 0.05 statistically significant.

Table 3. Comparison of diastolic blood pressure(mm Hg) at different intervals between Group A and Group B patients (mean ± SD).

Group	Group A n=25	Group B n=25	Significance p' value
Basal	79.52 ±6.14	78.16±7.74	>0.05
After fentanyl premedication	78.08±6.89	76.88±7.57	>0.05
After induction	76.0 ±6.73	69.28±7.45	<0.05
At intubation	88.24 ±8.43	78.16±7.78	<0.05
1 min. after intubation.	87.60± 8.71	78.56±7.01	<0.05
3 min after intubation.	84.72± 7.85	77.92± 6.51	<0.05
5 min after intubation	84.80 ±6.21	79.36±6.04	<0.05
7 min after intubation	85.04± 4.24	80.08 ± 8.13	>0.05
10 min after intubation	79.12±6.00	79.36 ± 8.93	>0.05

p> 0.05; not significant, p< 0.05 statistically significant.

groups. The basal heart rate in group A (midazolam) was 80.08 ± 6.35 per minute and in group B (propofol) was 79.06 ± 2.12 per minute. After premedication with fentanyl there was slight fall of heart rate in both the groups which was not significant. There was sharp fall of heart rate after induction with propofol in group B to 67.76 ± 1.68 per minute in comparison to group A (midazolam) to 74.64 ± 4.85 per minute. At intubation there was a sharp rise in heart rate in group A to 109.84 ± 7.41 per minute compare to group B with a rise upto 89.40 ± 0.24 .per minute. It was noted that there was statistically significant difference of heart rate between the two groups after induction, at intubation and upto 7 minutes postintubation period. At 10 minutes postintubation period the difference was not significant.

Table 2 shows changes in mean systolic blood pressure (SBP) (mmHg) with standard deviation in group A and B. The basal SBP in group A and group B was 122.2 ± 12.12 mmHg and 127.28 ± 9.84 mmHg respectively. After fentanyl there was slight fall in blood pressure in both groups, the difference was not statistically significant. There was a sharp fall in SBP after induction with propofol in group B to 105.44 ± 13.19 mmHg in comparison to group A (midazolam) to 114.32 ± 12.71 mmHg. At intubation there was a sharp rise in SBP in group A to 133.32 ± 14.69 mmHg compared to group B with a rise to 124.08 ± 12.38 mmHg. However, SBP in group B did not rise over basal value. It was noted that there was statistically significant difference between two groups after induction, at intubation and up to 7 minutes postintubation period. At 10 minutes SBP in group A touched the base line and it was still less in group B.

The difference between them was not significant.

Similarly, table 3 shows basal mean diastolic blood pressure (DBP) in group A and group B was 79.52 ± 6.14 mmHg and 78.16 ± 7.74 mmHg respectively. After fentanyl there was fall in DBP in both the groups, the difference was not significant. There was a sharp fall in DBP after induction in group B to 69.28 ± 7.45 mmHg in comparison to group A to 76.0 ± 6.73 mmHg. At intubation DBP was increased in group A to 88.24 ± 8.43 mmHg compared to group B with a rise up to 78.16 ± 7.78 mmHg, yet it was not rise over basal value. Regarding DBP there was statistically significant difference between two groups after induction, at intubation and up to 7 minutes post intubation. At 10 minutes difference between the two groups was not significant.

Table 4 shows mean changes of rate-pressure product (RPP) with standard deviation in both

Table 4. Comparison of rate pressure product(mm Hg) at different intervals between Group A and Group B patients (mean \pm SD).

Group	Group A n=25	Group B n=25	Significance p' value
Basal	9821.76 \pm 1207.07	10109.76 \pm 942.67	> 0.05
After fentanyl premedication.	8901.84 \pm 1417.43	9474.0 \pm 1245.88	> 0.05
After induction	8536.80 \pm 1130.61	7404.0 \pm 891.173	< 0.05
At intubation	14625.68 \pm 1767.57	11117.28 \pm 1277.72	< 0.05
1 min. after intubation.	12428.0 \pm 1946.46	10252.32 \pm 1082.67	< 0.05
3 min after intubation.	12268.48 \pm 1253.19	10342.88 \pm 827.36	< 0.05
5 min after intubation	11997.12 \pm 1038.72	10035.52 \pm 1005.08	< 0.05
7 min after intubation	11608.32 \pm 1124.7	9879.04 \pm 1371.75	< 0.05
10 min after intubation	10452.16 \pm 1397.05	10142.72 \pm 1162.81	> 0.05

p> 0.05; not significant, p< 0.05 statistically significant.

groups. The basal RPP in group A was 9821.76 ± 1207.07 and in group B was 10109.76 ± 942.67 . After fentanyl premedication there was little fall of RPP in both groups. After induction there was sharp fall of RPP in group B to 7404.0 ± 891.173 in comparison to group A which was 8536.80 ± 1130.61 . At intubation there was a sharp rise of RPP in group A to 14625.68 ± 1767.57 compared to group B where rise was 11117.28 ± 1277.72 . It was found that RPP difference between the two groups were statistically

significant after induction, at intubation and up to 7 minutes post intubation. At 10 minutes the difference was not statistically significant.

Discussion

Haemodynamic response to laryngoscopy and endotracheal intubation are well established. Various methods to attenuate those responses have been tried. Our study shows there was a sharp fall in heart rate after induction in group B (propofol) than in group A (midazolam). The difference between the two groups was significant. These findings were similar to that of Cullen PM, et al¹¹ who found propofol resets the baroreflex to allow slower heart rate even at lower arterial pressure.

At intubation there was a sharp rise in heart rate in group A in comparison to group B. This study is similar with that of Samuelson PN, et al¹² who found that stress of endo-tracheal intubation and surgery were not blocked by midazolam. It increases both heart rate and blood pressure.

Our study shows that there was a sharp fall in both SBP and DBP in group B (propofol) compared to group A (midazolam) after induction and the difference between the two groups were significant. This finding was similar to Wahr JA, et al¹³ who compared propofol with midazolam and found that propofol

resulted in 17% lower incidence of tachycardia and 28% lower incidence of hypertension and 17% greater incidence of hypotension.

After intubation there was sharp rise of both SBP and DBP in group A compared to group B. In group B the rise of SBP did not cross the base line value. This finding was similar to the study of Larsen R, et al¹⁴ who found that haemodynamic changes after tracheal intubation was absent in propofol group in comparison to etomidate.

In our study, the use of fentanyl as premedication helped to prevent catastrophic rise of heart rate or blood pressure after laryngoscopy and intubation. This finding was similar to Harris CE, et al¹⁵ who found that use of fentanyl resulted in arterial pressure lower than those after the induction agent alone and in an attenuation but not abolition of response to laryngoscopy and intubation. They also found that propofol alone could decrease arterial pressure significantly which did not rise above base line value after intubation. This finding was similar to our study.

Regarding the rate pressure product (heart rate x systolic blood pressure), it is a good indicator of oxygen consumption. After induction rate pressure product (RPP) falls much in group B than in group A. After intubation there was a sharp rise of RPP in

group A compare to group B and the difference between the two groups were significant.

From the above discussion it was found that propofol as induction agent was more efficient to attenuate haemodynamic response of laryngoscopy and endotracheal intubation than midazolam but care should be taken in patients with cardiovascular diseases, as the cardiovascular depression may be far less predictable and potentially, more serious.

Conclusion

In comparison to midazolam, propofol appears to be effective in suppressing the haemodynamic consequences of laryngoscopy and intubation. Premedication with fentanyl before inducing with propofol resulted in much more attenuation of blood pressure and pulse rate than propofol alone.

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Attenuation of haemodynamic changes during laryngoscopy and intubation by different doses of bolus esmolol

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Abstract

Objective: To find out the effectiveness of different doses of bolus esmolol in attenuating the haemodynamic response to laryngoscopy and intubation and to compare their relative effectiveness. **Methods:** Seventy five (75) patients of ASA I and II who were to undergo various surgeries under general anaesthesia were randomly allocated into three groups (25 patients each) to receive intravenous esmolol hydrochloride 500µgms/kg body weight, 1000µgms/kg body weight and 1500µgms/kg body weight respectively two minutes before induction of anaesthesia. Heart rate, systolic and diastolic blood pressure, mean arterial pressure, rate pressure product and ECG changes were monitored before induction, at induction, at intubation and every minute till the 9th minute post-intubation for all the three groups. **Results:** Group employing larger doses of esmolol (1500µgms/kg body weight) shows better control of laryngoscopic and intubation induced rise in heart rate, systolic and diastolic blood pressure, mean arterial pressure, rate pressure product and ECG changes even though the results are not statistically significant ($P > .05$). **Conclusion:** Haemodynamic changes during laryngoscopy and intubation can be attenuated

effectively with a larger doses of bolus esmolol.

Key words: Laryngoscopy, endotracheal intubation, stress response, bolus esmolol hydrochloride and larger dose.

Introduction

Endotracheal intubation ensures full oxygenation, ventilation of lungs and delivery of the anaesthetic gases from the anaesthetic machine to the lungs in a general anaesthetic technique. Laryngoscopy is usually performed to achieve an easy and successful endotracheal intubation. These procedures, performed even in the fully relaxed state with the use of muscle relaxants stimulate upper airway and initiate reflexes. In general, the systemic responses to laryngoscopy and intubation are increase in arterial blood pressure, heart rate and cardiac rhythmic disturbances¹ and it also increases intracranial, intra-ocular and intra-gastric pressure. These responses are thought to be initiated by lifting the base of the tongue and epiglottis by the laryngoscope blade and tracheal stimulation while intubating.^{2,3} These responses are associated with an increase in sympathoadrenal discharge, as manifested by the rise of catecholamine levels³.

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In most patients, these responses are transient, highly variable and probably of little consequences but, at times, may have serious effect on patients with pre-existing cardio-vascular and cerebrovascular diseases especially in patients with hypertension and cardiac disorders with the danger of

pulmonary oedema and myocardial infarction⁴, cerebral aneurysm rupture⁵ and precipitation of convulsion in pre-eclamptic patients⁵. Various efforts were made to attenuate these cardiovascular responses to laryngoscopy and intubation especially in those susceptible patients. Some of the methods are beta-adrenergic blockers like intravenous metoprolol⁶, topical anaesthesia with lignocaine spray to pharynx and vocal cord⁷, intravenous administration of lignocaine⁸, hypnotic drugs like droperidol⁹, vasodilators like sodium nitroprusside⁸ and hydralazine¹⁰, topical and systemic nitroglycerine¹¹, anti-arrhythmic agents like mexillentine¹², and narcotic agents like intravenous fentanyl¹³ and buprenorphine¹⁴. So far none of these agents/methods proved entirely satisfactory.

The results of using various agents in attenuating cardiovascular responses are variable with different authors, some claiming useful while others unsuccessful. Different drugs were used to attenuate the cardiovascular response during laryngoscopy and intubation and found that only esmolol provided consistent and reliable protection against increase in both heart rate and systolic blood pressure accompanying laryngoscopy and intubation¹⁵. Different beta-adrenergic blockers (esmolol, metoprolol and propranolol) were administered intravenously at three doses chosen to produce comparable degrees of beta blockade. In spite of achieving comparable beta blockade, esmolol, an ultrashortacting cardioselective β -blocker, produced a greater reduction in blood pressure than the other beta-blockers.¹⁶ The present study was designed to compare effectiveness of different doses of bolus esmolol hydrochloride in the quest for a better/optimal dose of the said drug to prevent untoward cardiovascular responses associated with intubation and laryngoscopy.

Material and methods

After obtaining institutional ethics committee approval and written informed consent, seventy five patients aged between 18 to 62 years of ASA I and II were randomly distributed into three groups of twenty five each to receive bolus esmolol hydrochloride in the dose of 500 μ gm/

kg body weight (Group-I), 1000 μ gm/kg body weight (Group-II) and 1500 μ gm/kg body weight (Group-III) respectively. Hypertensive patients, anticipated difficult intubation, significant cardiac, respiratory, hepatic, renal and neurological disorders, history of drug allergy etc. were excluded from the study.

After preanaesthetic evaluation, all the patients were premedicated with tab. alprazolam 0.25mg and tab. ranitidine 300mg, the night before the surgery. Glycopyrolate 0.04mg/kg body weight and promethiazine 0.5mg/kg body weight were also given intramuscularly 45 minutes before the induction of anaesthesia.

Heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP), rate pressure product (RPP) and ECG changes were recorded non-invasively prior to induction, at induction, at intubation and every minute post-intubation till the 9th minute for all the patients. The three different doses of bolus esmolol were given intravenously over a period of 15-20 seconds, 2 minutes before induction of anaesthesia depending on the groups. A uniform anaesthetic technique with thiopentone sodium (5mg/kg body weight) for induction of anaesthesia and succinylcholine (2mg/kg body weight) to facilitate tracheal intubation was employed in all the cases. Anaesthesia was maintained through intermittent positive pressure ventilation (IPPV) with oxygen, nitrous oxide, halothane and vecuronium bromide (0.08mg/body wt.). At the end of the surgery, residual neuromuscular blockade was antagonized with glycopyrolate and neostigmine and tracheal tube removed after the return of protective airway reflexes. The patients' parameter which was recorded were entered in a data based programme and descriptive analysis with Student "t" test using SPSS version 12 software was done and $p < .05$ was considered to be significant.

Results

The three study groups are comparable and there was apparently no difference in the age, sex, weight and ASA distribution. The heart rate increased significantly from the preinduction value right from the intubation till the 9th minute

Table 1. Showing distribution of patients' heart rate per minute in the three groups at different time intervals.

Group	Time interval	Mean±SD(rate/min)	t' value
I	Baseline	80.80±8.45	
	At Induction	92.80±20.70	3.04*
	At Intubation	113.80±21.43	7.39*
	1 st min	114.80±16.90	10.62*
	2 nd min	110.08±12.33	13.06*
	3 rd min	106.72±10.26	12.04*
	4 th min	113.12±11.75	8.88*
	5 th min	101.28±12.60	7.12*
	6 th min	99.52±12.19	6.97*
	7 th min	96.12±10.95	5.86*
II	Baseline	77.28±9.62	
	At Induction	85.08±11.92	2.91*
	At Intubation	107.92±11.42	13.56*
	1 st min	102.24±13.31	11.35*
	2 nd min	97.40±15.45	7.76*
	3 rd min	92.92±16.57	5.40*
	4 th min	87.28±15.30	3.90*
	5 th min	84.80±14.31	3.02*
	6 th min	82.72±13.50	2.26*
	7 th min	80.76±13.13	1.52
III	Baseline	81.64±9.66	
	At Induction	91.20±15.62	3.98*
	At Intubation	105.68±11.70	10.19*
	1 st min	102.48±13.99	9.06*
	2 nd min	99.80±15.59	7.55*
	3 rd min	95.80±15.92	5.59*
	4 th min	92.80±16.43	4.32*
	5 th min	90.48±15.59	3.61*
	6 th min	88.04±14.82	2.77*
	7 th min	86.12±15.17	1.84
8 th min	83.52±14.58	0.84	
9 th min	82.36±14.29	0.31	

*significant value (p<0.05)

in Group I, and till the 6th minutes in both Group II and Group III (table 1). Intergroup comparison (table 4) between Group I and II and Group I and III shows significant difference from the 1st minutes till the 9th minute. In between Group II and III, the increase in heart rate from the baseline value till the 9th minute is not significant.

The SBP increased significantly above the baseline value from the intubation till the 5th, 4th and 3rd minutes respectively in Group I, II and III respectively (table 2). Their intergroup comparison between Group I and II, Group I and III and Group II and III does not show any significant changes (table 5). The changes in the DBP followed the same trend as that of the SBP (table 2 and 5).

Table 2. Showing distribution of SBP & DBP*** in the three groups at different time intervals.**

Group	Time interval	Mean±SD (**SBP in mmHg)	t' value	Mean±SD (**DBP in mmHg)	t' value
I	Baseline	120.68±11.17		77.72±8.53	
	At Induction	120.00±12.52	0.30	81.40±8.68	2.24*
	At Intubation	163.36±24.46	8.16*	121.28±15.68	12.09*
	1 st min	148.72±28.63	5.14*	107.72±17.92	7.77*
	2 nd min	137.76±27.63	2.57*	95.44±19.97	3.95*
	3 rd min	136.60±26.83	2.43*	89.60±18.83	2.80*
	4 th min	132.56±27.45	2.35*	85.80±19.09	2.52*
	5 th min	131.32±21.75	2.15*	81.60±18.05	2.30*
	6 th min	120.80±19.62	0.32	82.06±17.48	2.28*
	7 th min	117.04±17.91	1.00	78.88±16.10	0.32
II	Baseline	120.48±8.85		77.48±9.32	
	At Induction	124.52±10.72	2.04*	82.60±7.59	3.32*
	At Intubation	166.76±13.49	15.03*	118.52±12.07	13.67*
	1 st min	148.48±15.32	9.57*	103.80±11.05	9.28*
	2 nd min	137.96±16.84	5.17*	93.68±12.85	5.48*
	3 rd min	129.40±18.63	2.36*	85.44±12.63	2.93*
	4 th min	124.52±16.82	2.31*	79.48±12.19	2.53*
	5 th min	120.52±17.45	0.01	77.56±13.65	0.03
	6 th min	117.72±16.26	0.86	75.80±12.82	0.68
	7 th min	116.24±15.97	1.27	75.20±14.37	0.84
III	Baseline	118.92±9.46		76.52±6.06	
	At Induction	122.20±12.73	1.15	82.72±10.41	1.87
	At Intubation	168.84±16.30	15.33*	119.32±13.70	13.95*
	1 st min	154.80±18.44	10.56*	106.00±13.10	10.59*
	2 nd min	141.68±20.30	6.60*	95.20±14.22	6.12*
	3 rd min	133.00±16.84	4.91*	88.60±11.64	4.58*
	4 th min	124.52±16.66	1.93	83.52±11.78	1.77
	5 th min	123.56±16.09	1.59	82.36±11.39	1.70
	6 th min	121.52±15.92	0.88	81.04±9.33	1.38
	7 th min	119.64±15.80	0.25	77.20±10.30	0.58
8 th min	117.56±15.41	0.47	76.40±11.03	0.90	
9 th min	115.92±14.39	1.07	75.52±10.32	1.31	

*significant value (p<0.05), **systolic blood pressure, ***Diastolic blood pressure

The changes in the MAP showed significant increase from the baseline value till the 6th, 4th and 3rd minutes postintubation in Groups I, II and III respectively (table 3). The RPP rise significantly from the baseline value till the 8th, 6th and 5th minute postintubation respectively in Groups I, II and III (table 3). The MRP and RPP does not show any significant differences at their corresponding time interval when intergroup comparison was done (table 6). There were no noticeable ECG changes such

Table 3. Showing distribution of MAP & RPP*** in the three groups at different time intervals.**

Group	Time interval	Mean±SD (**MAP mHg)	t value	Mean±SD(***RPP)	t value
I	Baseline	91.80±9.13		9761.20±1478.51	
	At Induction	93.84±9.27	1.25	91120.8±3294.20	2.39*
	At Intubation	136.16±16.32	12.00*	18505.6±4879.40	9.67*
	1 st min	121.48±20.17	7.30*	17111.60±4884.53	8.87*
	2 nd min	109.9±20.92	4.00*	14924.7±4149.70	6.34*
	3 rd min	102.88±20.18	2.60*	13992.7±3915.51	5.66*
	4 th min	98.76±20.49	2.40*	12785.4±4542.90	3.35*
	5 th min	95.16±18.37	2.23*	12422.9±3429.72	3.87*
	6 th min	94.7±17.88	0.79	12192.3±3167.03	4.08*
	7 th min	91.40±16.78	0.11	11339.1±2732.93	2.85*
II	Baseline	92.4±7.36		9810.40±1544.11	
	At Induction	96.48±8.11	2.48*	10505.40±17948.4	3.26*
	At Intubation	134.56±11.74	16.42*	18004.3±2490.99	18.98*
	1 st min	118.6±12.17	11.05*	15315.2±2730.78	13.37*
	2 nd min	108.6±13.91	5.87*	13520.8±2999.47	7.92*
	3 rd min	99.88±13.90	2.68*	12135.4±3144.89	4.70*
	4 th min	96.2±13.26	2.31*	10672.2±2604.76	2.84*
	5 th min	91.80±13.97	0.25	10283.2±2484.42	2.09*
	6 th min	89.16±13.77	1.25	9644.7±2167.15	20.7*
	7 th min	90.3±16.27	0.63	9432.4±2143.26	0.29
III	Baseline	91.16±7.05		9727.6±1423.68	
	At Induction	95.68±10.90	1.97	10739.0±2910.68	2.01*
	At Intubation	135.4±13.24	15.87*	17805.8±2745.37	14.96*
	1 st min	120.9±14.59	10.82*	15826.4±2664.64	12.06*
	2 nd min	109.7±15.38	6.57*	14056.9±2702.34	8.80*
	3 rd min	102.40±13.31	4.61*	12748.8±2696.30	6.24*
	4 th min	96.3±12.77	1.92	11760.7±2720.49	4.14*
	5 th min	95.5±13.41	1.70	11247.0±2749.98	3.17*
	6 th min	92.00±13.13	0.29	10772.5±2370.66	1.98
	7 th min	90.80±11.93	0.16	10379.6±2566.26	1.50

*significant value (p<0.05), **mean arterial blood pressure, ***rate pressure product

as ectopic beats, dysarrhythmias etc. in all the studied groups.

Discussion

Though endotracheal intubation ensures full oxygenation, ventilation of the lungs and delivery of the anaesthetic gaseous mixture to the patient in a general anaesthetic process, laryngoscopy and intubation are considered a stressful situation to the patient and causes sympathoadrenal stimulation producing rise in arterial blood pressure, heart rate and arrhythmias which may prove fatal. Employment of intravenous bolus doses of 100-200mg of esmolol for the attenuation of the responses to laryngoscopy and intubation were done in most studies where the results are controversial. Wang SC et al¹⁷ found that 200 mg bolus esmolol was a better choice than 100 mg bolus esmolol for the control of haemodynamic changes during laryngoscopy and endotracheal intubation. Bensky KP et al¹⁸

Table 4. Showing intergroup comparison of **MHR per minute in the three groups at different time intervals.

Group	Time interval	Mean±SD(rate/min)	t' value
I & II	Baseline	79.04±9.14	1.37
	At Induction	88.94±17.17	1.62
	At Intubation	110.86±17.25	1.24
	1 st min	108.52±16.34	2.92*
	2 nd min	103.74±15.25	3.21*
	3 rd min	99.82±15.32	3.54*
	4 th min	95.20±15.69	4.12*
	5 th min	93.04±15.72	4.23*
	6 th min	91.12±15.30	4.62*
	7 th min	88.44±14.26	4.49*
I & III	Baseline	81.22±8.48	0.35
	At Induction	92.00±18.17	0.31
	At Intubation	109.74±18.26	1.60
	1 st min	108.64±16.57	2.81*
	2 nd min	104.94±14.85	2.59*
	3 rd min	101.26±14.36	2.88*
	4 th min	97.96±15.06	2.56*
	5 th min	95.88±15.05	2.69*
	6 th min	93.78±14.63	3.00*
	7 th min	91.12±14.03	2.67*
II & III	Baseline	79.46±9.33	1.68
	At Induction	88.14±14.09	1.56
	At Intubation	106.80±12.53	0.63
	1 st min	102.36±13.51	0.06
	2 nd min	98.60±15.41	0.55
	3 rd min	94.36±16.15	0.63
	4 th min	90.04±15.96	1.22
	5 th min	87.64±15.08	1.34
	6 th min	85.38±14.28	1.33
	7 th min	83.44±14.29	1.34

*significant value (p<0.05), **mean heart rate

showed that small doses of esmolol (0.2 mg/kg and 0.4 mg/kg) blocked the increase in heart rate and blood pressure resulting from laryngoscopy and intubation. Similar finding was found with the studies of Miller DR et al¹⁹ and Sharma S et al²⁰.

In our study, the highest dose group (Group III) employing 1500µg/kg body weight, is able to bring the heart rate near the baseline value effectively even though it is not statistically significant. However, all the three studied groups were not able to control the rise in heart rate completely. Similar findings have also been reported by Tan PH et al²¹.

The SBP changes in our study showed that higher dose of esmolol used in Group III helps in bringing down effectively near the baseline value from the 4th minute onwards as

Table 5. Showing intergroup comparison of **SBP & *DBP in the three groups at different time intervals.**

Group	Time interval	Mean±SD(**SBP in mmHg)	t' value	Mean±SD(***DBP in mm Hg)	t' value
IS: I	Baseline	120.58±9.98	0.07	77.50±8.84	0.10
	At Induction	122.26±11.76	1.37	82.00±8.10	0.52
	At Intubation	165.06±19.62	0.61	119.90±13.92	0.70
	1 st min	149.10±22.73	0.12	105.76±14.87	0.93
	2 nd min	136.36±22.70	0.12	94.56±16.64	0.37
	3 rd min	128.02±22.90	0.50	87.52±16.01	0.92
	4 th min	122.04±22.52	0.44	82.64±16.17	1.40
	5 th min	120.92±19.52	0.16	79.58±15.97	0.90
	6 th min	119.26±17.90	0.14	78.98±15.50	1.47
	7 th min	116.64±16.80	0.60	77.04±15.22	0.85
IS: II	Baseline	119.80±10.28	0.60	78.12±7.34	0.49
	At Induction	121.10±12.55	0.62	82.06±9.51	0.47
	At Intubation	166.10±20.76	0.93	120.30±14.60	0.39
	1 st min	151.76±24.03	0.89	106.86±15.56	0.50
	2 nd min	138.22±24.25	1.01	95.32±17.16	0.05
	3 rd min	129.80±22.40	1.01	89.10±15.51	0.23
	4 th min	124.54±22.56	0.62	85.16±15.71	0.29
	5 th min	122.44±18.97	0.41	82.98±15.00	0.65
	6 th min	121.16±17.68	0.14	81.60±13.87	0.28
	7 th min	118.34±16.77	0.54	78.08±13.40	0.42
IS: III	Baseline	119.70±9.10	0.60	78.00±7.80	0.47
	At Induction	123.36±11.71	0.70	82.66±9.02	0.05
	At Intubation	167.80±14.85	0.50	118.92±12.79	0.22
	1 st min	152.14±16.99	1.20	104.90±12.05	0.64
	2 nd min	139.82±18.56	0.71	94.44±13.44	0.40
	3 rd min	131.22±17.67	0.71	87.02±12.13	0.92
	4 th min	124.02±16.76	1.10	82.00±12.13	1.49
	5 th min	122.04±16.68	0.64	80.96±12.90	1.91
	6 th min	119.62±16.04	0.84	78.42±11.41	1.65
	7 th min	117.94±15.82	0.76	76.24±12.42	0.59
IS: III	Baseline	116.54±16.37	0.44	74.54±13.90	0.43
	At Induction	115.46±16.23	0.20	74.86±13.63	0.34

*significant value (p<0.05), **systolic blood pressure, ***diastolic pressure product

compared with Group I and II. Similar changes in DBP and MRP were also observed in our study. Our findings were comparable with that of Wang SC et al¹⁷, Sharma S et al²⁰ and Rathore A et al²².

The RPP(heart rate x SBP), which is a better indicator of myocardial oxygen demand and whose value should be below 12000 was observed to be low (near the baseline value) in the highest dose group (Group III) as compared with Group I and II. This effectiveness of esmolol has also been observed with the works of Rathore A et al²², employing incremental doses of esmolol hydrochloride (50 mg, 100 mg and 150 mg) and Ebert TJ et al²³ employing bolus doses of esmolol 100 mg and 200 mg esmolol.

Unsatisfactory effects in checking the cardiovascular response completely to laryngoscopy and intubation in the present study may be due to employment of smaller doses of esmolol. A more satisfactory result

could have been achieved if a larger dose of the drug is used as in the study of Miller DR et al¹⁹ and Sharma S et al²⁰ or a combination of bolus esmolol with continuous infusion of the drug as reported by Figueredo E et al²⁴. A better result could also have been achieved if combined with opioids^{17,19}, nitroglycerine²⁵, lignocaine²⁶ or calcium channel blockers like nicardipine 30µgm/kg body weight²².

Conclusion

Esmolol hydrochloride helps in attenuating the pressure response during laryngoscopy and intubation without any untoward side effects. However, for effective control of the haemodynamic response during laryngoscopy and intubation, a higher dose of the drug greater than 1.5mg/kg body weight may be required, considering the safety limits of the drug.

Table 6. Showing intergroup comparison of **MAP and *RPP in the three groups at different time intervals.**

Group	Time interval	Mean±SD(**MAP in mm Hg)	t' value	Mean±SD(***RPP)	t' value
IS: I	Baseline	92.12±8.21	0.27	9535.82±1513.39	1.05
	At Induction	95.16±8.73	1.07	10857.14±649.38	1.00
	At Intubation	135.36±14.09	0.40	16255.02±3525.13	0.50
	1 st min	120.08±16.55	0.59	16213.44±3727.14	1.74
	2 nd min	109.28±17.59	0.26	14222.82±3652.90	1.37
	3 rd min	101.38±17.12	0.62	13064.06±3637.78	1.85
	4 th min	96.00±17.31	1.13	11728.88±3817.16	2.02*
	5 th min	93.48±16.24	0.73	11353.08±3154.77	2.53*
	6 th min	91.14±16.04	1.23	10918.52±2978.03	3.32*
	7 th min	90.86±16.37	0.23	10385.76±2614.54	2.75*
IS: II	Baseline	91.48±8.08	0.28	9744.44±1436.57	0.08
	At Induction	94.76±10.06	0.64	10973.98±3085.62	0.53
	At Intubation	135.80±14.71	0.17	18155.74±3634.62	0.67
	1 st min	121.20±17.43	0.11	16469.00±3648.97	1.25
	2 nd min	109.84±18.14	0.03	14490.86±3493.31	0.88
	3 rd min	102.64±16.82	0.10	13370.76±3385.96	1.31
	4 th min	98.54±16.90	0.09	12273.10±3741.83	0.97
	5 th min	95.34±15.92	0.08	11834.98±3133.40	1.34
	6 th min	93.36±15.58	0.61	11482.42±2943.41	1.74
	7 th min	91.10±14.41	0.15	10859.40±2668.00	1.28
IS: III	Baseline	91.80±7.16	0.63	9591.02±1484.92	1.00
	At Induction	96.08±9.52	0.29	10622.24±2396.11	0.34
	At Intubation	135±12.39	0.25	17905.08±2596.32	0.27
	1 st min	119.80±13.35	0.59	15570.84±2682.69	0.67
	2 nd min	109.20±14.53	0.27	13788.92±2838.43	0.66
	3 rd min	101.14±13.53	0.66	12442.10±2915.66	0.74
	4 th min	95.78±13.14	1.38	11216.50±2692.65	1.46
	5 th min	93.66±13.68	0.96	10765.14±2638.97	1.30
	6 th min	90.58±14.00	0.75	10208.62±2421.06	1.68
	7 th min	90.56±14.12	0.12	9906.04±2388.40	1.41
IS: III	Baseline	88.02±13.27	0.71	9453.70±2353.79	1.30
	At Induction	87.18±13.36	0.68	10111.94±2452.72	1.01

*significant value (p<0.05), **mean arterial pressure, ***Rate Pressure Product

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Dalteparin in the treatment of deep venous thrombosis

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Abstract

Objective: To review the efficacy of dalteparin, a low molecular weight heparin in the treatment of deep venous thrombosis (DVT). **Methods:** The study was conducted in the Cardiovascular and Thoracic Surgery Section of the Department of Surgery, Regional Institute of Medical Sciences (RIMS), Imphal over a period of seven years and consisted of 128 patients of deep venous thrombosis treated with dalteparin. **Results:** 128 patients with DVT were treated with dalteparin and warfarin. There was no bleeding episodes or pulmonary thromboembolism during the treatment and the resorption of venous thrombosis was satisfactory. **Conclusion:** Low molecular weight heparin (dalteparin) is safe and effective in the treatment of DVT.

Key words : *Low molecular weight heparin, dalteparin, heparin, deep vein thrombosis.*

Introduction

Low molecular weight heparin (LMWH) is a relatively recent addition to the list of therapies for prophylaxis and treatment of deep venous thrombosis (DVT). Traditionally, treatment for

DVT required patients to be hospitalized for administration of intravenous heparin. With subcutaneous injections of low-molecular-weight heparin, treatment of DVT can be initiated or completed in the outpatient setting with no increased risk of recurrent thromboembolism or bleeding complications.

Venous thromboembolic disease has an estimated annual incidence in developed countries of one in 1000 people.¹ The disorder commonly manifests as deep vein thrombosis of the leg, but deep venous thrombosis may also occur in other veins (cerebral sinus, arms, retina, and mesentery). The sequelae of deep vein thrombosis vary from complete resolution of the clot without any ill effects through to death due to pulmonary embolism. Morbidity due to deep vein thrombosis includes post-thrombotic syndrome, encompassing chronic venous hypertension causing limb pain, swelling, hyperpigmentation, dermatitis, ulcers, venous gangrene, and lipodermatosclerosis. Pain or swelling of a lower limb is a common presenting complaint, and a wide differential diagnosis exists.

Several recent articles have reported the safety and efficacy of LMWH in the treatment of pulmonary embolism, which is a very serious complication of deep vein thrombosis.^{2,3} Because pulmonary embolism is sometimes suspected in patients with DVT, appropriate treatment is essential for deep venous thrombosis. Treatment with low-molecular-weight heparin may still be considered in patients with DVT and

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suspected pulmonary embolus.

We present a brief review of the outcome of deep venous thrombosis treated with dalteparin, a low molecular weight heparin.

Methods

An observational study was carried out in the Cardiovascular and Thoracic Surgery Section, RIMS during the period May 2001 to April 2008.

All the patients (n=128) suspected of having DVT or documented DVT were included in this study.

Patients with recurrent DVT, any venous thromboembolism in the past 2 years, renal or hepatic insufficiency, active bleeding, bleeding disorders, and active peptic ulcer were excluded from this study.

All the patients were administered LMWH (dalteparin, 5000 - 7500 IU BID) subcutaneously for 5 - 7 days. Warfarin 5 mg was also started along with LMWH. International Normalized Ratio (INR) were checked on the 5th - 7th day and the dose of warfarin adjusted to keep the INR at the therapeutic level of 2 - 3. Complete haemogram of all the patients were checked during the hospitalization. All the patients had undergone colour coded Doppler ultrasonography during the hospital stay. Warfarin was continued for 3 - 6 months. However, in two cases of DVT with pregnancy warfarin was not given and LMWH was administered for 14 days.

All the patients were closely observed for any complications - bleeding episodes, features of pulmonary embolism, ecchymosis at injection sites.

Results

There were 128 patients. Males outnumbered female patients. Intravenous drug abuser (IVDU) constituted the maximum number of patients in the age group below 30 years, out of which there were twenty two young patients below 20 years. Three patients presented at age more than 60 years. Age distribution of patients is shown in fig 1.

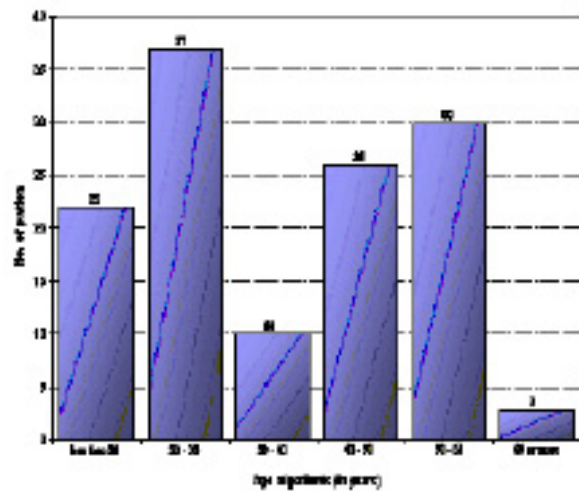


Fig 1. Age distribution of patients

There were 54 intravenous drug abuser comprises. In 51 patients the cause of DVT could not be identified. Three patients of axillary-subclavian vein thrombosis were due to excessive stressing of the arm during exercise. In this study, DVT was found in two pregnant women. Causes of DVT in this study have been shown in fig 2.

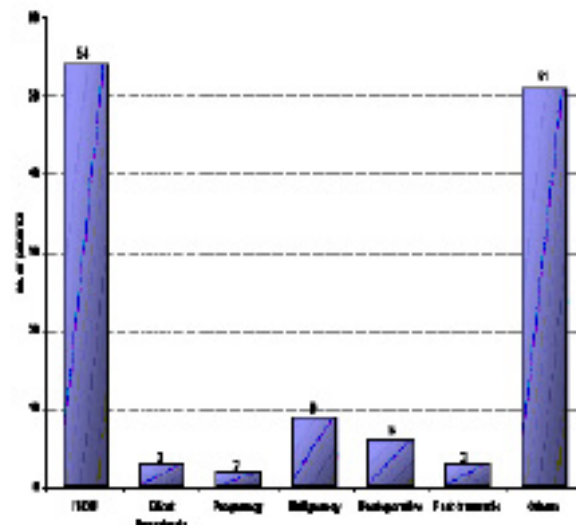


Fig 2. Causes of deep venous thrombosis.

After 5 - 7 days of initiation of therapy (subcutaneous injection of LMWH and oral warfarin), the swollen limbs were reduced to normal size in 16 patients of IVDU, 2 pregnant cases, all 3 patients of effort thrombosis, 2 patients of cancer, 2 patients of trauma, all 6 postoperative patients, and in 22 patients of unknown cause (table 1).

Seventyfive patients presented with swollen lower limbs but the swelling subsided in size at the time of discharge. This group of patients

Table 1. Results after 5-7 days of initiation of therapy (SC LMWH and oral warfarin)

Group	Number of patients with normal limbs	Number of patients with swollen limbs
IVDU	16	38
Pregnancy	2	1
Effort thrombosis	3	-
Cancer	2	7
Post-traumatic	2	-
Postoperative	6	-
Others	22	29
Total	53(41.4%)	75(58.6)

includes 38 intravenous drug abusers. Length of hospital stay was 5 - 15 days.

During the treatment with LMWH, there were no cases with bleeding episodes or pulmonary embolism. In 2 patients, there was ecchymosis at the injection sites, which resolved spontaneously.

Eighty five patients(66.4%) were followed up for 3-6 months. Only 11 intravenous drug abusers whose limbs were swollen at the time of discharge were followed up. Out of these 11 drug abusers, the swollen limbs were returned to normal size in five patients at 6 months followed up. Forty three IVDU did not turn up. At 6 months follow up, the swollen limbs returned to normal size in other group except in 5 patients.

Discussion

With advent of LMWH, the initial management of suspected or documented DVT is simple subcutaneous injection of LMWH instead of intravenous standard heparin. This removes the requirement of monitoring activated partial thromboplastin time (aPTT), and the dosage does not need to be adjusted.

The clinical advantages of LMWH include predictability, dose-dependent plasma levels, a long half-life and less bleeding for a given antithrombotic effect.⁴ During the treatment with LMWH (dalteparin) in the present study, there was no episode of bleeding in the patients which is in consistent with other studies.⁴ Furthermore, immune-mediated thrombocytopenia is not associated with short-term use of LMWH,⁴ and the risk of heparin-

induced osteoporosis may be lower than the risk with the use of standard heparin. Low-molecular-weight heparin is administered according to body weight once or twice daily, both during the high-risk period when prophylaxis for DVT is recommended and also when waiting for oral anticoagulation to take effect in the treatment of DVT.

Whereas standard heparin has a molecular weight of 5,000 to 30,000 daltons, low-molecular-weight heparin ranges from 1,000 to 10,000 daltons, resulting in properties that are distinct from those of traditional heparin. LMWH binds less strongly to protein, has enhanced bioavailability, interacts less with platelets and yields a very predictable dose response, eliminating the need to monitor the aPPT. LMWH like standard heparin binds to antithrombin III. However, LMWH inhibits thrombin to a lesser degree (and Factor Xa to a greater degree) than standard heparin.⁵

In our study the IVDUs constitute the maximum number of patients followed by a significant number of DVT whose cause could not be ascertained.

The efficacy and safety of LMWH for the initial treatment of DVT have been well established in several trials.⁶ 58.6% of our patients had swollen limbs whereas 41.4% had normal sized limb at the time of discharge (5 - 15 days). Only 66.4% were able to follow up for 3 - 6 months because majority of the drug abuser patients did not turn up for follow up. At six months follow up all the non-IVDU patients had successfully responded to the anticoagulant therapy.

Conclusion

Though there are many therapeutic options for treatment of DVT, administration of low molecular weight heparin is the most convenient and effective treatment with very less complication of bleeding and can be administered without monitoring the aPTT as it should be if conventional unfractionated heparin is used. Because of this safety profile of LMWH, many trial of treating DVT in the out-patient setting with the molecule are in the pipeline.

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A comparative study of epidural tramadol hydrochloride and epidural buprenorphine hydrochloride for postoperative analgesia following combined spinal epidural anaesthesia

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Abstract

Objective: The study was conducted to compare the efficacy of postoperative analgesia of epidural tramadol hydrochloride and buprenorphine hydrochloride. **Methods:** One hundred patients of either sex of ASA I and II who were to undergo routine lower abdominal and lower limb surgeries under combined spinal and epidural analgesia (CSEA) were chosen randomly for the study in the department of Anaesthesiology, Regional Institute of Medical Sciences(RIMS), Imphal and divided into two groups of 50 patients each - Group I, to receive 50 mg of epidural tramadol hydrochloride while Group II received 150µg of epidural buprenorphine hydrochloride. **Results:** The pain scores (VAS and verbal rating scores) at different corresponding time interval was better (lower) and statistically highly significant with p value<0.001 in Group II as compared with Group I. The onset of analgesic action was significantly faster (P<0.001) in Group II(8.00±0.00 mins) than in Group I(9.96±0.50 mins). Group II(14.55± 1.11hrs) also had longer duration of analgesia as compared with Group I(11.17±1.21hrs) which was found to be highly statistically significant (p-value< 0.001). **Conclusion:** Epidural buprenorphine hydrochloride offers superior analgesic effect/

quality than epidural tramadol hydrochloride for relieving post-operative pain in lower abdominal and lower limb surgeries.

Key words: Combined spinal epidural, buprenorphine hydrochloride, tramadol hydrochloride, superior postoperative analgesia.

Introduction

Pain, as defined by the "International Association for the Study of Pain", is "an unpleasant sensory and emotional experience associated with the actual tissue damage or described in terms of such damage". Pain following surgery is probably one of the most severe types of pain suffered by man. The unequivocal duty of the medical profession is to relieve human suffering due to pain and the greatest service one can do to mankind is to give relief from pain.

The only way of ensuring rapid relief of pain in the post-operative period is to administer an analgesic intramuscular or intravenous. However, with the advent of regional analgesic techniques like regional nerve blocks, spinal/ epidural procedures, etc. long acting local anaesthetic drugs or opioids have provided new opportunities to relieve post-operative pain in lower abdominal and lower limb surgeries with lesser side effects compared with intramuscularly and intravenously administered drugs. Combined spinal and epidural anaesthesia(CSEA) is a recent innovation of regional anaesthesia by which the main advantage of subarachnoid and

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epidural anaesthesia are retained and combined^{1,2}.

Various drugs of opioids family like morphine and pethidine were used in the CSEA procedures in the past with many limitations due to its side effects. However, more recently, other opioids like tramadol hydrochloride and buprenorphine hydrochloride which are moderately potent analgesics without severe typical opioids side effects like respiratory depression, etc. are used for post-operative pain management through CSEA.

The present study was undertaken to compare between epidural tramadol hydrochloride and epidural buprenorphine hydrochloride for their efficacy and safety in relieving post-operative pain.

Material and methods

After the approval of the Institute ethics committee, one hundred (100) patients of ASA I and II who were to undergo routine lower abdominal and lower limb surgeries under combined spinal and epidural analgesia (CSEA) in the department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal were randomly allocated into two groups of 50 patients each, Group I (n=50) to receive 50mg of epidural tramadol hydrochloride and Group II (n=50) to receive 150µg of epidural buprenorphine hydrochloride.

A routine pre-anaesthetic check up was carried out in all the patients. Patients outside the age range of 20-60yrs, outside the weight range of 35-65 kg, uncooperative and deranged mental function and those who had received analgesic drug were excluded from the study. Patients were explained of the procedure and anaesthetic technique, the type of pain relief. Written informed consent was taken for every patients. All the patients were also explained about the pain scoring (Visual analogue scale, VAS 0-10 and verbal rating score, VRS as 0= no pain; 1= very slight pain; 2= slight pain that can be forgotten temporarily; 3 = permanent and tolerable that cannot be forgotten; 4= marked pain that leads the patient to request analgesia; 5= intolerable pain with screams and restlessness).

A uniform anaesthetic technique was used in all the patients. All patients were premedicated with oral diazepam 10mg on the night before surgery, fasted and consumed no caffeine-containing foods or beverages from 10pm of the preceding night. Basal parameters like blood pressure, pulse rate, etc. were recorded. On the day of operation, an intravenous drip of lactated ringer's solution was preloaded before the application of epidural catheter and premedicated with ranitidine (50mg) and ondansetron (4mg) IV.

The patient was kept in sitting or lateral position and helped to maintain a position which ensured maximum exposure of lumbar region. Taking all aseptic and antiseptic precautions, the L2-3 space was identified and after injecting 1-2cc of 2% lignocaine hydrochloride solution to the skin, an epidural needle fitted with stylet introduced into the interspace with the bevel-end facing head till sudden loss of resistance was encountered. After confirming the needle position in the epidural space through loss of resistance technique, the stylet was withdrawn and corresponding size of epidural catheter was passed through a few millimetre beyond the tip of the needle in the epidural space. The needle was then withdrawn gradually without disturbing the position of catheter, which is later tapped to prevent dislodgement. Another space L3-4 was identified and spinal anaesthesia with 3ml of 0.5% bupivacaine heavy given using a 25G Whitacre spinal needle on each and every patient.

Following the first complaint of pain in the recovery room or in the ward, the following analgesic solution were administered through the epidural catheter- Group I (n=50) received 50mg of tramadol hydrochloride with 10ml normal saline and Group II (n=50) received 150µg of buprenorphine hydrochloride with 10ml of normal saline.

The time at which the epidural analgesic was given has been taken as time "0". The parameters observed in each individual were pulse rate, blood pressure, VAS score and verbal rating score for pain, respiratory rate and the duration of action, which were

recorded every three hourly. The onset time of the analgesics and its side effects were also recorded. All the datas collected were entered in a data based programme and analysed statistically using student's't' test. The significance level is fixed at $p < 0.05$.

Results

All 100 patients completed the analysis. The age, sex, weight, ASA and the type of operation performed were uniformly distributed in the two groups and found to be statistically insignificant ($p > 0.05$). The changes in the heart rate, blood pressure, respiratory rate and percentage saturation of oxygen at their corresponding time intervals were also evenly distributed in both the groups where the difference is statistically insignificant ($p > 0.05$). The pain scores(VAS and VRS), which are shown in table 1, figures 1 and 2, measured at three hourly time interval of the two groups showed better response(lower score) in Group II as compared with Group I, which is statistically highly significant ($p < 0.001$).

Table 1. Showing the distribution of Mean (\pm SD) pain scores (VAS and verbal rating scores) before and at different time intervals after administration of the trial drugs in Group I and II.

Time of measurement	Group I Tramadol (n=50)		Group II Buprenorphine (n=50)		p-value
	VAS (mean \pm SD)	VRS (mean \pm SD)	VAS (mean \pm SD)	VRS (mean \pm SD)	
0 hr	5.83 \pm 0.72	3.92 \pm 0.46	5.74 \pm 0.55	3.96 \pm 0.38	P=0.05
3 hr	3.70 \pm 0.81	2.06 \pm 0.37	2.78 \pm 0.86	1.66 \pm 0.59	0.001*
6 hr	2.82 \pm 0.83	1.66 \pm 0.63	0.80 \pm 0.99	0.38 \pm 0.57	0.001*
9 hr	4.46 \pm 0.46	2.82 \pm 0.52	3.60 \pm 1.20	2.06 \pm 0.59	0.001*
12 hr	4.92 \pm 0.35	2.88 \pm 0.49	3.73 \pm 1.29	2.21 \pm 0.67	0.001*
15hr	5.58 \pm 0.64	3.68 \pm 0.55	4.92 \pm 1.14	3.10 \pm 0.79	0.001*

*Significant

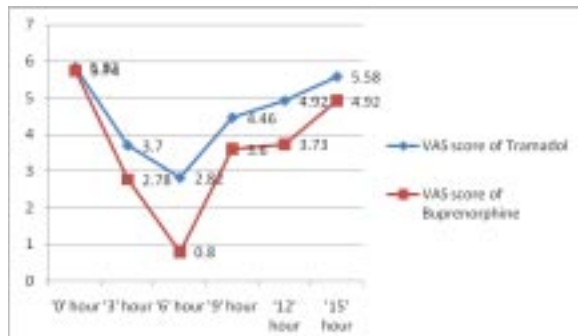


Fig 1. Showing the distribution of mean VAS scores of the two groups at different 3hourly intervals.

Group II(8.00 \pm 0.00 mins) has faster onset of analgesic effects as compared to Group I(9.96 \pm 0.50 mins) where the difference is

Table 2. Showing the distribution of Mean(\pm SD) onset time(in seconds) and Mean(\pm SD) duration of action(in hours) of the trial drugs in Group I and Group II.

	Group I Tramadol (n=50) (mean \pm SD)	Group II Buprenorphine (n=50) (mean \pm SD)	p-value
Onset time (mins)	9.96 \pm 0.50	8.00 \pm 0.00	0.001*
Duration of analgesia(hours)	11.17 \pm 1.21	14.55 \pm 1.11	0.001*

*Significant

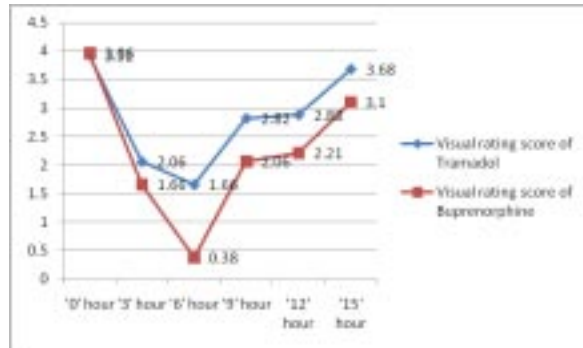


Fig 2. Showing the distribution of mean Visual rating scores in the two groups at 3hourly intervals.

statistically highly significant with $p < 0.001$ (table 2). The duration of analgesia(table 2) is comparatively longer in Group II(14.55 \pm 1.11394 hours) than Group I(11.17 \pm 1.21266 hours) and the difference is statistically highly significant ($p < 0.001$).

The adverse effects recorded in both the groups (table 3) were minimal and comparable which are statistically not significant ($p < 0.05$). There were no cases of respiratory depression in both the study groups.

Discussion

The ideal drug for post-operative pain relief should have a rapid onset, a fairly long duration of action and no undesirable or dangerous life threatening side effects.

One of the most alarming side effect of epidural opioid is delayed and unpredictable respiratory depression attributed to the rostral spread of the drug. Bromage PR et al³ have reported that most of the respiratory depression have occurred with poorly lipid soluble opiates like morphine which spread

Table 3. Showing the distribution of adverse effects

Side effects	Group I(n=50) Tramadol		Group II(n=50) Buprenorphine		P value
	No. of pt.	%	No. of pt.	%	
Nausea/vomiting	10	20	7	14	P>0.05(NS)
Headache	5	10	6	12	P>0.05(NS)
Urinary retention	4	8	4	8	P>0.05(NS)
Respiratory depression	-	-	-	-	
Hypotension	-	-	-	-	
None	31	62	33	66	P>0.05(NS)

NS= not significant

widely in CSF and gradually reach the brainstem medullary area causing respiratory depression. Bromage PR et al³, and Cousins MJ and Mather LE⁴ concluded that buprenorphine being highly lipophilic was likely to migrate more rapidly from CSF to spinal cord when bound to lipid leading to less rostral spread.

In the present study, no cases of respiratory depression was seen in both groups, which may probably be due to the lower doses of the drug used for buprenorphine and non-opioids receptors stimulation of analgesic action of tramadol⁵. This offered the main advantage of the epidurally applied drugs used in our study, providing excellent quality of analgesia with lower dose, thereby reducing side effects.

It was also demonstrated in our study that epidural buprenorphine produced more prolonged duration (14.55hours) and intense analgesia compared to epidural tramadol hydrochloride (11.17hours) without any major adverse effects. This finding is consistent with the reports of independent studies conducted by Endoh M and Matsuda A⁶ on epidural buprenorphine hydrochloride(15.25 hours) and Pan AK et al⁷ on epidural tramadol hydrochloride(10.68 hours).

The present study also showed that the epidural tramadol like buprenorphine, could provide adequate and prolonged post-operative analgesia in patients undergoing major abdominal surgery. Hennies HH et al⁸ reported that the analgesic effects of tramadol were

mediated by opioids as well as non-opioid receptor mechanism of action. Dharmana KM et al⁵, on the other hand, observed that tramadol inhibited nor-adrenaline uptake and stimulated serotonin release which, in turn, are transmitters in the descending pathways enhancing analgesia.

The study also showed that the onset of analgesic action of buprenorphine(8.00 mins) is faster than tramadol(9.96 mins) which may be explained due to the more lipophilic character of epidural buprenorphine as reported in the independent studies conducted by Bromage PR³ and Cousin Mj and Mather LE⁴ with mean onset time of 8.82 minutes and 7.36 minutes for epidural tramadol and buprenorphine respectively.

The characteristics of haemodynamic and incidence of side effects among the two study groups are comparable, without any untowards effects, to those of previous studies conducted by Delikan AC⁹ and Ichiishi N et al¹⁰.

On the overall assessment, it has been found that epidural buprenorphine hydrochloride (150µmg) produced better and prolonged relief of pain than epidural tramadol hydrochloride (50mg).

Conclusion

Epidural buprenorphine hydrochloride (150µgm) produced better and prolonged post-operative analgesia than epidural tramadol hydrochloride(50mg) without much side effects. However, epidural tramadol hydrochloride is a safe alternative considering its availability in the preservative free form and that it is not a control drug. The two drugs, because of their rapidity of onset of action, potency of analgesia, reliability of effects and their absence of major side effects when used epidurally, should be recommended routinely for post-operative pain management in lower abdominal and lower limb surgeries.

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Airway management in vallecular cyst - a case report

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A 42 year old female patient presented to the ENT outpatient department of the Regional Institute of Medical Sciences, Imphal with the complaints of dysphagia and hoarseness. On examination, a round swelling was seen in the vallecular region on the right side, almost covering the laryngeal inlet (Cormack and Lehane's Grade II, fig 1). She was planned for excision of the cyst under general anaesthesia. Preoperative assessment of the case revealed that the physical and laboratory findings were within normal limits, and there was feasibility of ventilation with a face mask.



Fig 1. Showing vallecular cyst in direct laryngoscopy.

On the day of operation, she was premedicated with glycopyrrolate 0.2mg (0.004mg/kg) i.m and ranitidine hydrochloride 50mg i.v, 45 minutes prior to the scheduled time. After informing the surgical team, emergency tracheotomy kit was kept ready in the event of any emergency like intubation failure. The patient was pre-oxygenated with

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100% oxygen after placing the routine monitors in place. Anaesthesia was induced with slow intravenous injection of 1% propofol with incremental halothane in oxygen. Intravenous succinylcholine hydrochloride (1.5mg/kg) was given to facilitate direct laryngoscopy for endotracheal intubation. Then, direct laryngoscopy was attempted with a Macintosh blade-size 3; however, the growth was obstructing the glottic opening. Immediately, it was decided to introduce a Miller blade-size 4 by the right molar approach and right paraglossal technique. The right vallecula along with the swelling was visualized with this maneuver. The patient was intubated



Fig 2. Showing endo-tracheal tube in situ after laryngoscopy.

with a poly-vinylchloride (PVC) - size 7.5 endotracheal tube and the proper placement of the tube was confirmed by auscultation and end tidal carbon-dioxide (EtCO₂) (fig 2). Anaesthesia was maintained with 66% N₂O in O₂ along with traces of volatile anaesthetic, intermittent boluses of non-depolarizing muscle relaxant with intermittent positive pressure ventilation via circle absorber. The course of the surgical procedure and the post-operative period remained uneventful.

Discussion

Vallecular cyst is a unilocular cystic mass arising out of the lingular surface of the

epiglottis, containing clear, sterile fluids.¹ It is a ductal cyst (mucous and retention cyst) and is believed to originate from obstructed submucosal gland and is found most frequently in the vallecula.² At the same time, it is an uncommon pathology in the larynx which may cause airway obstruction depending on the size of the cyst. Direct laryngoscopy may be difficult in a case of vallecular cyst because of the following factors: the epiglottis cannot be easily exposed, the swelling may impinge against epiglottis and displace it backwards, bleeding may occur from the fragile cyst, and repeated attempts may cause edema and bleeding with subsequent difficult intubation³. Fiberoptic nasal intubation, preoperative aspiration of cyst, anterior commissure blade laryngoscope or needle cricothyrotomy followed by emergency cricothyrotomy and

tracheostomy are some of the other available methods. In the present case, endotracheal intubation by the right molar approach utilizing straight blade with paraglossal technique improved the view due to - (i) reduction of soft tissue compression (ii) lowering of proximal end of line of sight and (iii) obstruction in the line of sight by the curvature of Macintosh blade is overcome by the use of straight Miller blade^{4,5}. Similar approach has also been adopted by several workers for securing the airway in such type of cases.^{3,6,7}

There are various alternative methods for intubation for such a condition. However, the use of straight Miller laryngoscope blade by right molar and right paraglossal technique can be an option in cases where growth in the airway prevents the use of conventional intubation techniques and fiberoptic endoscope is not available for routine use.

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Botryoid rhabdomyosarcoma - a case report

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A normally delivered 1 year old female child presented with a mass on the right side of vagina of 3 months duration. The lesion began as a painless small swelling which grew in size to a thumb-sized mass within 2 months. The patient had to strain at times for micturation. She also had history of occasional cough and wheezing. There was no significant family history or history suggestive of child abuse.

The vaginal mass was elongated, non-tender, soft to firm, fleshy, broad-based with small lobulations and 6 cm x 4 cm in size (fig 1).

There was no vaginal discharge. Per vaginal examination was not done as the patient was a minor. There was no lymphadenopathy. An irregular firm non-tender mass of about 3 cm x 3 cm was also palpable in the lower abdomen. Liver and spleen were not palpable. Chest examination was normal. Examination of other systems revealed no abnormal finding.



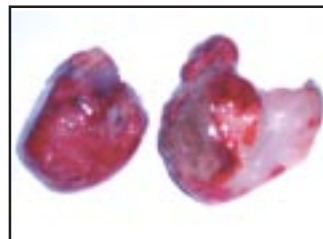
Fig 1. Showing elongated, non-tender, soft to firm, fleshy, broad-based with small lobulations vaginal mass. (6 cm x 4 cm in size)

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A presumptive diagnosis of soft wart was made. Systemic and topical antibiotics imiquimod 5% was applied on the lesion. Three hours later, as the child was crying two fleshy masses with attached membranous structure came out spontaneously one after another from the vagina (fig 2) The extruded masses were soft to firm each measuring 4cm



x 3cm. There was no per vaginal bleeding following the expulsion of the masses.

Routine blood examination showed Hb 9 g/dl, TLC 12,000/dl, ESR 20 mm 1st hour, platelet count 2 lakh, microcytic and hypochromic RBC. VDRL and retroviral tests were non-reactive. LFT and KFT were within normal limit. Chest X-ray was normal. Ultrasonography of whole abdomen showed a mass in the lower abdominal.

Histopathologic examination of the extruded mass showed racket-shaped ovoid, tumour cells with hyperchromatic nuclei and also necrosis of cambium layer below the vaginal mucosal lining (fig 3a and 3b). The findings are suggestive of botryoid rhabdomyosarcoma. Specimen from the vaginal growth revealed inflammatory granulation tissue.

Based on the histopathologic finding, a diagnosis of botryoid rhabdomyosarcoma was

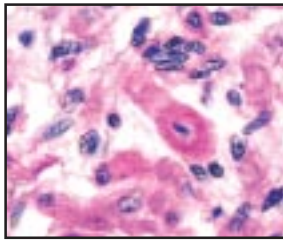


Fig 3a. H/P report of the extruded mass from vagina showed racket-shaped ovoid, tumour cells with hyperchromatic nuclei.

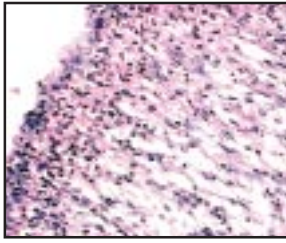


Fig 3b. Showing necrosis of cambium layer below the vaginal mucosal lining.

made. In consultation with the gynecologist and radiotherapist, chemotherapy was planned but the patient party refused it. The patient was discharged on request and did not turn up for follow-up.

Discussion

Embryonal rhabdomyosarcoma (ER) is a malignant childhood sarcoma, 50% of the cases occurring in children below 5 years of age.¹ Common sites are head and neck, retroperitoneal area, the soft part of limbs and hollow organs. It is a spindle cell tumour. The cells may reveal cross-striations (pleomorphic type), alveolar reticulin network (alveolar type), or multilayered band of cells called cambium

layer (botryoid type).² Botryoid type presents as protuberant grape-like nodules in mucosal cavity such as the vagina or nasopharynx. ER has a high mortality rate as it grows and metastasizes rapidly primarily to lymph nodes and lungs³. The mean survival is estimated to be around 15 months². Tumour that involves the head and neck, nose and sinuses requires urgent attention to avoid serious complications⁴. Prompt chemotherapy and whenever possible, surgical debulking of the mass may mitigate the condition⁵.

Botryoid rhabdomyosarcoma in the vagina can be mistaken for warts, condyloma lata, hemangioma or fungal lesions. Any soft mass from a hollow viscus, especially in a child should always be examined and investigated thoroughly to avoid diagnostic pitfall. Careful clinical and laboratory examinations will help in making a diagnosis. Histopathologic examination of the lesion will always help in such case.

This case was further complicated by the presence of retroperitoneal lesion. Chemotherapy and surgical exploration were the options considered in this case. However, the patient party were not convinced and refused to accept any form of treatment.

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Camouflaging a mandibular defect by a heat-cure acrylic implant : a simple technique

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A 30 years old male presented with asymmetrical, unaesthetic chin with recession in the left aspect (fig 1). His past medical records suggested that he had comminuted fracture of the mandible due to an alleged road traffic accident three years back. On palpation, the residual defect was felt as a notch like



Fig 1. Pre-operative anterior profile of the chin region.

concavity at the lower border of left parasymphysis region of the mandible. P-A view of x-ray mandible showed a step defect at the lower border of the left parasymphysis region. A suitably shaped heat-cure acrylic implant (methyl-methacrylate) was placed subperiostally over the defect, via an intra-oral approach, under local anesthesia to camouflage the defect and improve the appearance of the patient.

Preparation of the patient

An impression of the anterior profile of his face was taken by alginate impression material, then a cast model was prepared from it. Modeling wax was used to build up the

concavity in the chin region of the cast model to achieve symmetry (fig 2). The wax pattern was then invested in Plaster of Paris. A mould was created by the set Plaster of Paris after dewaxing and the mould was packed with the mixture of powder and liquid of methyl-methacrylate and treated to a temperature of 74°C for 8 hours to achieve polymerization which is known as heat cure polymerization to



Fig 2. Wax build-up over the stone model of the face to improve the profile.



Fig 3. Heat-cure acrylic implant prepared from the mould of the wax pattern.

obtain a heat-cure acrylic resin implant (fig 3). Multiple pores were prepared on the implant surface to facilitate fibrous tissue ingrowths for implant stability. The implant was then polished with pumice powder and auto-claved.

Operative procedure

Anesthetic technique: Bilateral mental nerve block and local infiltration in the labial sulcus at the site of surgery were given using 2% lignocaine with adrenaline.

Surgical technique: A 5cm incision was given slightly above the vestibule extending from

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lower right central incisor to lower left premolar region with the direction of scalpel towards the bone. The posterior end of the incision was raised superiorly to protect the mental nerve. The bony defect was exposed after periosteal stripping. The implant was then placed over the defect to check the fit and elevation of the contour (fig 4). Revision of shape and size of



Fig 4. Implant placed and closely adapted over the bony defect.

The implant was done intra-operatively by a micro-motor mounted acrylic trimmer for accurate fit and contour. The margin of the implant was adjusted and smoothed so that the edges of the implant merge finely with the bone. The cut edges of the periosteum were brought over the periphery of the implant to hide the implant edges. The wound was closed in 2 layers. A strip of leucoplast was placed over the surface of the chin to act as pressure band. The patient was then sent off after 2 hours of monitoring.

Follow-up

Follow-up was done at an interval of 1 month, 6 months, 1 year and 2 years (fig 5). An orthopantomogram view of radiograph of the mandible was taken at each follow-up.



Fig 5. Anterior profile of the chin two years after the surgery.

Discussion

Autologous bone graft has found its greatest use in oral and maxillofacial surgery because of good host tissue response and its osteogenic property.^{1,2} But it has drawbacks related to limited source, requirement of surgery at additional site and difficulty in shaping for the correction of larger defects.^{1,2} Various bone repairing materials have been used as alternative to autologous bone graft. They are allograft, xerograft, collagen, sea coral and alloplastic materials like, hydroxyapatite, silicon rubber, silastic, polyethylene and methyl-methacrylate (acrylic resin).¹⁻⁴

In our case, the defect was a contour deficiency of small size, and adequate amount of autologous bone could have been conveniently harvested. Our choice of heat-cure acrylic resin (methyl-methacrylate), which is familiar to dentists, as an implant material instead of a bone graft in this case, may be discussed in the context of the two types of bone defects in the maxillofacial region.

Segmental and cystic defect : In such defects, there is breach in the continuity of bone, and the bone graft acts as temporary scaffold which resorbs gradually as new bone is formed simultaneously by the ingrowth of capillaries and connective tissues from the host bone, the process being known as creeping substitution.² Biodegradability of the graft is important in this situation. Autologous bone graft is the ideal material for reconstructing such defects because of its osteoinductive potential and biodegradability.²

Contour defect: In this type of defect there is deficiency in the surface contour of the bone and bone grafting is done to augment the lost contour. When an autologous bone is used as an onlay graft to augment the lost contour, 60% of the new bone formed after autologous grafting is lost on resorption.² This implies the futility of the reconstructive effort for such type of defect with a bone graft. Methyl-methacrylate as an implant material was polymerized by chemical activation when the powder and liquid were mixed at room temperature and directly moulded into the bone defect and such resins are known as cold-cure resins. Widespread use of cold-cure acrylic for bone repair has been reported because of its various advantages.⁵ But serious disadvantages have also been reported when used in large amounts because of leakage of free monomer which can be resorbed systemically causing allergy, severe hypotension, severe pyrexia, cardiac arrest and hepatotoxicity.⁵⁻⁷ Resins polymerized via chemical activation display 3 to 5% free monomer, whereas heat activated resin is a stable compound after polymerization and exhibits 0.2% to 0.5% free monomer.⁸ Heat-

cure acrylic resin is a variant in which the polymerization is achieved when the mixture of powder and liquid is activated by heat as was done in our case during the implant preparation.⁸ Reports of sporadic use of heat-cure acrylic as an implant in the malar, calvarial and orbital regions are available though there was no special mention of its advantages and disadvantages as compared to the cold-cure resin, except about its high strength.^{5,9,10} Based on the premise that heat-cure acrylic would be even safer than cold-cure acrylic because of its relative stability after polymerization, and the fact that it is familiar to dentists, we decided to use the heat-cure resin in our case. After a follow-up period of two years of our case, we found that camouflaging the bone defect by a heat-cure methyl-methacrylate implant provided a durable result because they are non-biodegradable, well tolerated by soft tissue and

bone without any signs of implant rejection, and have adequate strength, low thermal conductivity and radiolucency. But there was the disadvantage of an inaccurate fit since the implant was prepared from an indirect impression of the soft tissue of the face, though its shape and size could be adjusted intraoperatively by rotatory cutting instruments.

In our case, the heat-cure acrylic implant, after a follow-up period of 2 years showed good tissue tolerance, non-biodegradability, and improved the psycho-social wellbeing of the patient by improving his appearance. Considering the disadvantage of autologous bone as an onlay graft and because of the high cost of other alloplastic materials, dental surgeons can consider heat-cure methyl-methacrylate implant a viable option as an onlay implant.

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Infantile hemangioendothelioma of liver

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This patient, a female baby was born on the 30th August 2008 as full term delivery. She was brought to surgical OPD, Regional Institute of Medical Sciences(RIMS), with history of abdominal distension noted by the mother since birth. Her mother also noted that the abdominal distension was slowly increasing and baby had developed shorthness of breath for the last 5-7 days. The baby was on breast feeding and was taking feeds well otherwise.

Clinical examination showed a 2 ½ months old baby with weight of 6 kg had mild pallor and tachypnoea. Respiratory rate was 32 per minute and pulse rate was 140 per minute with bounding peripheral pulse. There were no jaundice, no oedema, no lymphadenopathy. Abdomen showed huge distension with massive hepatomegaly reaching right iliac fossa(fig 1). There



Fig 1. Huge hepatomegaly

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Fig 2. Cutaneous hemangioma of umbilicus.



Fig 3. Cutaneous Hemangioma of right finger.

was no bruit over the liver. Umbilical hernia was present, besides there were cutaneous hemangiomas over the umbilicus(fig 2) and the right fingers (fig 3).

Investigations recorded Hb 6.6gm%, total leucocyte count 7400/cu mm with segmented neutrophils of 27%, lymphocyte of 63%, eosinophils of 3%, monocytes 1% and transformed lymphocytes of 6%. RBC morphology showed normochromic normocytic with few microcytes, anisocytosis and poikilocytosis.

There were also nucleated RBC's of 2/100. M.P was negative. Liver function test showed ALT of 13 U/L, AST 14 U/L, alkaline phosphatase 275 U/L and bilirubin 0.8 mg/dl. Chest X-ray showed cardiomegaly with CT ratio of 70% and prominence of bilateral upper lobe vessels (fig 4). USG of abdomen showed diffuse hepatomegaly with a span of 14 cms, with multiple hypoechoic and a few hyperechoic lesions involving both lobes of liver (fig 5). Size of the lesions ranged from 18mm x 18mm to 20mm x 23mm. Intrahepatic biliary ducts were not dilated. Gall



Fig 4. Chest X-ray showing cardiomegaly with prominent bilateral upper lobe vessels.



Fig 5. USG of liver showing diffuse hepatomegaly with multiple hypoechoic and hyperechoic lesions.

bladder, portal vein, hepatic veins and IVC were all normal. Colour Doppler imaging showed internal flow. MRI showed hugely enlarged liver with smooth outline and multiple well rounded space occupying lesions (SOL) of varying sizes (fig 6).

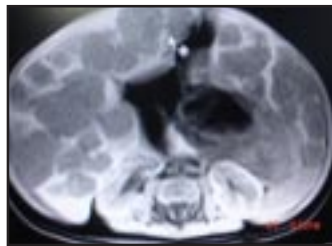


Fig 6. MRI showing enlarged liver with smooth outline & multiple well rounded SOL.

With the overall picture of clinical, USG, Doppler and MRI findings, a diagnosis of infantile hemangioendothelioma was made. As the patient was having anaemia and CCF, a packed cell transfusion (10ml/kg body wt) was given along with i.v. frusemide 5mg after completion of blood transfusion. After blood transfusion patient became comfortable and shortness of breath got settled. For further management regarding the underlying liver tumor, all available mode of treatment and the probable outcome were discussed with the parents and finally baby was started on oral prednisolone at the dose of 2mg/kg/day. Baby was kept in the hospital for 3 days after starting prednisolone and then was discharged with advice for follow-up in the surgical clinic after 10 days.

In the follow-up clinic so far, baby was seen 4 times at the interval of about 10 days. So far baby's condition remain stable otherwise and however liver enlargement had not shown any change till the last follow-up. The plan was to continue the prednisolone therapy and to monitor the progress of disease for at least a total of 6 months on prednisolone therapy.

Discussion

Infantile hemangioendothelioma is a rare benign vascular tumor of the liver. Small hemangioendotheliomas are asymptomatic.^{1,2} However majority of the cases are symptomatic and behave aggressively.³ The presence of a large lesion is recognized clinically by the diagnostic triad of enlarged liver, high output cardiac failure and multiple cutaneous hemangiomas. When hemangiomas occur diffusely through out the liver, as they usually do, their combined effect is to act as large peripheral arteriovenous shunts. Such large shunts are also responsible for the cardiac failure in many cases.^{1,2} Anaemia is also quite common in such cases and it may contribute to the cardiac failure. Anaemia in this condition is caused partly by the diluitional effect due to increased circulating plasma volume secondary to large peripheral arteriovenous shunts and partly by microangiopathic hemolytic anaemia which may occur in this condition.² The presence of transformed lymphocytes and the nucleated RBC's in the peripheral smear of our present case may reflect the picture of microangiopathic hemolytic anaemia. Our patient presented with CCF as evident by chest X-ray, picture of cardiomegaly with prominence of bilateral upper lobe vessels which could be contributed both by large arteriovenous shunting - the basic pathology of the lesion and anaemia (Hb-6.6gm%). The diagnosis of the condition is made clinically by the presence of triad of enlarged liver, high output cardiac failure and multiple cutaneous hemangiomas.^{1,2} Our case showed clearly the presence of these triad. USG of the liver showed hypoechoic in relation to normal liver, but on occasion it may be hyperechoic. The matrix may be homogenous, or it may be heterogenous related to the presence of calcification.⁴ In our patient liver was enlarged. Parenchyma showed multiple well defined hypo- and hyper-echoic lesions involving both the lobes of the liver. MRI findings were usually of multiple SOLs of varying sizes with low signal and high signal intensities in both T1 and T2 weighted images. Contrast MRI showed findings in conformity to infantile hepatic hemangioendothelioma.

Infantile hemangioendotheliomas are typically multifocal and produce a nodular deformity of the whole liver.^{1,2,5,6} These nodules range in size from a few millimeters to many centimeters and are well-demarcated without being encapsulated. At laparotomy, the nodules can be seen to pulsate. Microscopically it is composed of plump endothelial cells.^{1,2,5} They may show hemorrhages, fibrosis or calcification.

The course of infantile hemangioendothelioma is one of growth during the early months of life, followed by gradual involution.^{1,7} If the child survives, the tumour may disappear completely.⁸ The life threatening aspects are intractable congestive cardiac failure and to a lesser extent tumor rupture. Cardiac failure should be treated by conventional means in the first instance, but if this fails more drastic form of treatment should be tried.^{1,2,9} Corticosteroid have been successful in many patients.¹⁰⁻¹³ Irradiation has seldom been beneficial. In some children ligating or embolizing the hepatic artery has resulted in disappearance of the cardiac failure.^{10,14} When tumor is confined to one lobe, surgical resection is curative, even in the presence of cardiac failure.² If the infantile hemangioendotheliomas are diffused and

multifocal and without extrahepatic involvement, liver transplantation should be considered as treatment option.^{15,16} Liver transplant may be complicated with bleeding especially in neonates. It also has been reported that, interferon both alpha 1 and alpha 2B may be a useful approach in the management of this rare potentially fatal condition. It is found that rapid regression of tumor is observed with interferon therapy. It is also a relevant approach to avoid liver transplantation. In our case, the patient has already been treated with oral prednisolone. In the follow-up about 6 weeks after starting prednisolone, baby had shown stable general condition, no shortness of breath anymore. However liver size had remained still large. The final outcome of prednisolone therapy will be known after about 5 months and if by then patient does not show significant reduction in liver size then our plan is to institute interferon therapy.

This case is reported because of the rarity of this disease and difficulty in treatment. Corticosteroid is often recommended and successful in many patients. However, other approaches like irradiation, ligating or embolizing the hepatic artery, surgical resection, liver transplantation and interferon may be necessary.

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Odontogenic infection complicated by uncontrolled diabetes - a case report

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A 45 years old female patient from Ukhrul attended the Dental OPD, Regional Institute of Medical Sciences (RIMS), Imphal with complains of swelling on the left side of the face, inability to open the mouth and pus discharge beneath the lower jaw for 10 days. She gave a long history of swelling of the gum and loose teeth. After chewing a hard substance, she developed swelling at left lower jaw, lasting for a few days, followed by pus discharge and erosion of the left side of the face. She was treated with antibiotics at home but her condition deteriorated to the present level. The patient gave no history of any past medical problem. On examination, the patient was anemic and toxic appearance. The trismus was marked. There was loss of soft tissues overlying the submassetric space and the submandibular space due to necrosis. The medial pterygoid space was involved and communicated with the oral cavity because of soft tissue loss in the retromolar and the pterygomandibular fossa region. The preauricular and temporal region on the left side was tender and swollen indicating involvement of the temporal space. On removal of the slough, the submandibular and the submassetric space were exposed along with a part of the angle and ramus of the mandible (fig 1), and pus was visibly draining



Fig 1. Necrosis of the cervical soft tissues with pus discharge.



Fig 2. Pus draining through an incision in the temporal region.

inferiorly from the medial aspect of the mandible to the submandibular region. Complete hemogram revealed low hemoglobin level. Her fasting and post prandial blood glucose level were 180 mg % and 430 mg % respectively. Ringer lactate was started as IV fluid. Cefoperazone and sulbactam (Zostum) 2gm was given IV, 12hrly. 10 units of Human Actropid insulin added to 500ml of 5% Dextrose was infused 8hourly. Parenteral Vitamine B-complex was given once daily. Surgical management consists of incision and drainage in the temporal region (fig 2), debridement of the necrotic tissue from the cervical region and daily cleansing of the raw surface with chlorine water and normal saline.

Irrigation of the open medial pterygoid, submassetric, submandibular space and the oral cavity was done daily with hydrogen peroxide diluted with normal saline using a Ryle's tube (fig 3).



Fig 3. Irrigation of fascial spaces with Ryles tube.

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The gauze pad was soaked in sodium hypochlorite and squeezed dry before covering the wound daily. Nasogastric feeding was started. There was no let up in the pus discharge during the 1st week of our treatment regimen. Closure of the intraoral communication at the floor of the mouth and retro-molar region was done in the 2nd week by suturing in order to seal the oral cavity from the rest of the infected zone. Nasogastric feeding and infusion of insulin with 5% dextrose were still continued. Secondary suturing was done during the 4th week due to failure of healing. Blood sugar was able to control near normal level after 10 days of insulin therapy. After the 5th weeks following the successful closure of the oral communication, healthy granulation tissue ingrowth appeared narrowing the defect, without any visible pus. Daily dressing was continued without primary closure of the extra-oral wound to permit secondary healing. The NG tube was removed and oral intake was permitted. All infusions were stopped and the insulin regimen was changed to 4 units of Actrapid given subcutaneously thrice daily before breakfast, lunch and dinner. The patient was finally discharged on the 45th day with instruction to attend the diabetic clinic at RIMS, Imphal. The mandible was naturally closed when the healing was complete in the next follow-up. Extraction of the lower 2nd and 3rd molars, which were the source of the infection, was done in the next appointment, and mouth opening exercise programme was started to correct the trismus.

Discussion

Odontogenic infections are commonly the result of pericoronitis, carious teeth, periodontitis, or complications of dental procedures.¹ Management of multi-space orofacial odontogenic infections involves identification of the source of the infection, the anatomical spaces encountered, the predominant microorganisms found, the state of the host immune system, using laboratory data and imaging studies, and an understanding of the contemporary antibiotics and supportive care.¹ Many patients who have deep cervical infections also have some compromise in their host defence

mechanisms such as diabetes.² Increase susceptibility of infection in diabetes has been attributed to polymorph nuclear lymphocyte defect leading to decreased chemotaxis, defective phagocytosis, or impaired adherence. No alteration of IgA, G or M has been found in diabetes.³ Neutrophils phagocytose poorly and have impaired intracellular killing in a diabetic.⁴ Well controlled diabetics are not predisposed to infection but there is difficulty in containing them once it occurs, failing to show consistent improvement of the infection even after proper surgical and medical approach.^{5,6} Glucose leads to the formation of advanced glycation end products (AGES) as a function of glucose concentration and time.⁷ AGES are excessive in hyperglycemia and leads to the formation of cross-linked collagen, making it less soluble and less likely to be normally repaired and replaced. Increase collagenase activity and decrease collagen synthesis are found in individual with chronic hyperglycemia. Collagen in poorly controlled diabetes is aged and more susceptible to breakdown. Cumulative effects of altered cellular response to local factors, impaired tissue integrity and altered collagen metabolism make a patient susceptible to infection and destruction.³ Necrotizing soft tissue infections are caused most commonly by opportunistic organisms and are usually associated with diabetes or immunosuppression. Potential complications include septic shock, disseminated intravascular coagulation, acute renal failure, adult respiratory distress syndrome, mediastinitis, and pericarditis.⁸ The patients with multi-space infections require hospitalization, constant monitoring of the airway, parenteral antibiotics and fluids and utilization of the laboratory and diagnostic imaging studies, and control of possible surgical complications.¹ Computed tomography or magnetic resonance imaging is usually necessary to locate the infection and to detect suppuration that will be amenable to surgical exploration and drainage.⁹ In our case, we have not done any diagnostic imaging because the involved spaces were exposed to the surface and no surgical intervention was required for draining the pus in the cervical region. The submandibular space

communicates posteriorly with the masticator space, which consists of a group of fascial spaces bounded by the muscles and fascia of mastication, namely the masseteric, the pterygomandibular and the temporal space. Involvement of one space may lead to the involvement of the others because they communicate freely with one another.¹⁰ In our case, the periodontal infection of the lower molars possibly led to the spread of the infection to the submandibular space which then proceeded to involve the masticator space. The characteristic features of our case were necrosis of the soft tissues, prolonged period of pus discharge, marked trismus, and involvement of multiple fascial spaces. The leakage of the oral ingestions into the fascial space was an added problem. Even after a prolonged course of antibiotics and daily dressing of the site, there was no let up in the

pus discharge in our patient. It subsided gradually followed by granulation only after lowering the blood glucose level and sealing of the oral communication. There was no change in the antibiotics and the dressing regimen until the discharge of the patient confirming that the improvement was related to her blood sugar level.

The case showed that, even with proper surgical management, broad spectrum antibiotics and proper supportive therapy, odontogenic infection can have an exaggerated clinical manifestation and an unduly prolonged course when the patient has hyperglycemia. Immediate administration of insulin to control hyperglycemia is important, as was evident in our case, to control the infection and prevent serious life threatening complications.

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Renoprotective antihypertensives - a new insight

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Introduction

A large epidemiological screening investigation found blood pressure to be a predictor of end stage renal disease in the general population.¹ Specially, diastolic blood pressure was found to be associated with end stage renal disease. However, a systolic blood pressure of 127 mm Hg and diastolic blood pressure of 82 mm Hg, the values well within normotensive range is also found to be a remarkable renal risk. In patients with proteinuria greater than 3g/day an even lower targeted blood pressure 125/75 mm Hg (MAP of 92mm Hg.) offers an even additional benefit.^{2,3} There is an association between blood pressure and rate of age-related decline in renal function. In normotensive subjects the creatinine clearance falls by $0.75 \pm 0.12 \text{ ml/min/yr}$, when the same is aggravated by $0.92 \pm 0.32 \text{ ml/min/yr}$ in hypertensive subjects.⁴ Age related decline in renal blood flow is more pronounced in hypertensives. Even in the normotensive range effective renal blood flow is inversely related to the blood pressure.⁵ Therefore reduction of blood pressure is of prime importance to renoprotection. However the choice of a particular antihypertensive drug for long-term renoprotection, independent of reduction blood pressure is a matter of debate.

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Discussion

The following antihypertensives are generally used in practice. Certain drugs have superior benefits regarding haemodynamic efficacy reducing glomerular pressure, reduction in proteinuria, reduction events in rate of retardation of renal function, reduction of mortality and cardiovascular events in diabetic patients. Some other drugs have the advantage of ameliorating atherosclerosis and a few of the drugs also have therapeutic efficacy of controlling volume with reduction of blood pressure. On certain clinical conditions the combination therapy of these renoprotective antihypertensive offers the better expected outcome.

1. Angiotensin-Converting Enzyme Inhibitors (ACEI)

ACEI are the antihypertensive drugs which have the following main actions :

(i) Cleavage of the decapeptide angiotensin I to angiotensin II, the main effector hormone of RAAS (Renin - angiotensin - aldosterone system), (ii) inhibition of the inactivation of bradykinin and breakdown of other peptide. Haemodynamic effects include fall of blood pressure, reduction in glomerular pressure by vasodilation of glomerular efferent arterioles. Renoprotective mechanism is mainly due to reduction of proteinuria with concomitant reduction in the trafficking of macromolecules through the mesangium. Angiotensin II stimulate various growth factors and inflammatory cytokines involved in the process of glomerular and interstitial sclerosis.⁶

Attenuation of the angiotensin II induced processes of cell growth and repair and extra cellular matrix formation may contribute to renoprotection. ACE inhibition reduces not only the risk of nephropathy but also overall mortality and cardiovascular event in diabetic patients with high cardiovascular risk. ACEI based regimen will allow one to hope not only postpone but perhaps altogether prevent end-stage disease at least in some patients.⁷

2. Angiotensin (AT₁) - receptor blockers

Renoprotective efficacy of specific AT₁ receptor blockers is due to renal vasodilatation predominantly on efferent arterioles.^{8,9} The comparative studies between ACEI and AT₁ receptor blockers have also reported that renoprotective effects of AT₁ receptor blockers were less than that of ACEI.^{10,11} It may be relevant that AT₁ receptor blockers, unlike ACE inhibitors, induce a large increase in angiotensin II levels leaving AT₂ receptors unblocked.¹² Some evidences indicate that AT₂ receptors affect processes of cell proliferation¹³ and apoptosis.¹⁴

3. Renin inhibitor

Aliskiren is the first renin inhibitor to reach the market. It is like ACEI and ARBs (Angiotensin receptor blockers) and blocks 90% to 95% of plasma rennin. Dose is 150g to 300mg per day orally .

4. Aldosterone blocker

Spirolactone can produce specific cardioprotective effect in renal patients as well. It has antiproteinuric efficacy which may be due to specific aldosterone blockade or just its effect on volume control.¹⁵ Torsemide is a new loop diuretic with maximum hepatic excretion (safer in renal diseases) with minimum potassium excretion.

5. β -Blocker

The renoprotective effects of β -blockers is by virtue of their effect on blood pressure. These drugs can retard the rate of retardation of renal function. Well controlled studies have found a similar rate of loss of renal function with β -blockers and ACE inhibitors in dialysis.¹⁶

6. Diuretics

In hypertensive renal patients, the use of diuretic may be associated with more rapid loss of renal function. However diuretics are useful in controlling volume status and blood pressure with overt renal disease. Poor therapeutic efficacy of ACE inhibitors during high sodium intake can be used by adding hydrochlorothiazide.¹⁷

7. CCB (Calcium channel blockers)

Nifedipine (dihydropyridine) impair afferent arteriolar autoregulatory vascular tone thereby leading to transmission of systemic blood pressure to glomerular capillary bed whereas verapamil and diltiazem (non-dihydropyridine) leave autoregulation intact. Non-dihydropyridine improve glomerular membrane permeability characteristic and also effective in retarding the rate of renal function loss.¹⁸ Sodium status appear to modify the efficacy of CCBs regarding the renal effects.¹⁹

8. Lipid lowering drugs

These drugs in combination with antihypertensive agents are effective in atherosclerotic renovascular disease.²⁰ HMGco-A reductase inhibitors effectively reduce total cholesterol, LDL-cholesterol, apo B, and triglycerides in renal patients with and without proteinuria. During statin therapy HDL level is improved.²¹ Fibrin acid derivatives most effectively reduce triglycerides in renal patients.

9. Camostat mesilate

Camostat mesilate might represent a new class of antihypertensive drugs with renoprotective effects in patients with salt-sensitive hypertensives.²²

Conclusion

Certain comparative studies have shown advantage of certain drugs than others in specific aspects of renoprotection. AASK trial (African American study of kidney disease)²³ shows better renoprotection with ramipril than with amlodipine in proteinuric hypertensive nephropathy. Van Essen and colleagues²⁴ have found the rate of loss of renal function with enalapril and atenolol (-1.92 versus -1.32 ml/min/yr. However, Hannedouche and

associates²⁵ have found a difference in favour of enalapril, with loss of renal function -3.96 ml/min/yr versus -6.84 ml/min/yr with β -blockade. The practical implication produced by these studies is that we can use β -blockers when enalapril is not favourable in certain clinical settings or just the reverse can be tried in certain other clinical settings in view of renoprotection in hypertensives. Another comparative study have reported that renoprotective efficacy is less in AT₁ receptors blockers than in ACEI, Irbesartan and Losartan are the trial tested renoprotective ARBs.²⁶⁻²⁸ Non-dihydropyridine CCBs are found to be equally effective as lisinopril in reducing blood pressure and retarding the rate of the renal function loss, whereas β -blockers are less effective in both respects. β -blockers are less effective than ACEI for long-term renoprotection in non-diabetic patients and NIDDM patients. In practice the combination of RAAS blockade and aldosterone blockade will require close consideration of safety in light of the risk of development of hyperkalaemia. Telmisartan is more effective than amlodipine

for protecting renovascular functions and potentially for ameliorating atherosclerosis in hypertensive CKD with moderate renal insufficiency²⁹. Aliskiren, in combination with a diuretic appears to lower blood pressure more than an aliskiren-ARB combination³⁰. Hypertension associated with renovascular hypertension poses a major clinical challenge. In these patient antihypertensive therapy works best with ACEI, however most patients may require multiple agents³¹. Clonidine and Methyldopa (brain stem α_2 adrenergic agonist) can reduce the secretion of renin and thereby can maintain renal flow and GFR (glomerular filtration rate). These drugs are practically used as additional therapy to the other renoprotective drugs when needed. Eplerenone is the recently used drug which has the property of selective aldosterone blockade and reduction of microalbuminuria in renal patients which can block adosterone escape. In CKD with accelerated or malignant HTN. IV labetalol (α,β -blocker) and IV fenoldopam (D₁ receptor selective agonist) can be used.³²

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Forthcoming events

1. **TOT Workshop** 12 days (13-24th July 2009) TOT Workshop on enhancing institutional & counselling capacities of counsellor training institutes for NE regions - Organised by Department of Psychiatry, RIMS, Imphal
2. **Foundation day, RIMS, Imphal** 14th September 2009
3. **ASIMANICON 2009** 11th - 12th October 2009, 14th Annual Conference of Association of Surgeons of India, Manipur State Chapter Venue - Jubilee Hall, RIMS, Imphal (Contact - Prof. G.S. Moirangthem, State Chapter President, Dr. N. Sanjib, Hon. Secy., Dr. S. Jugindra, Organising Secretary)
4. **SELSICON 2009** 24th and 25th October 2009, 2nd Annual Conference of Society of Endoscopic and Laparoscopic Surgeons of India, Agra, UP (Contact - Prof. GS Moirangthem, Vice President, SELSI)
5. **ISAJAC 2009** 9th - 11th October 2009, Puri, Orissa
6. **International College of Surgeons** 1st - 3rd November 2009, 55th Annual Conference of Indian Section of International College of Surgeons 2009 Venue - Dhaliwal Hospital, 3 - Batiata Road, Amritsar (Contact - Dr. US Dhaliwal, Organising Secy.) Tel : 0183 - 2275002, e-mail : dhaliwalhospital@rediffmail.com
7. **AROI 2009** Annual Conference of AROI, November 2009, Venue - Hyderabad
8. **ISGCON 2009** 9th - 13th December 2009, Golden Jubilee Conference of Indian Society of Gastroenterology Venue - School of Digestive and Liver diseases, IPGMER, Rowald Ross Building, 4th Floor, No. 17, 244, A.J.C. Bose Road, Kolkata - 700020 Tel : 033 - 2223-4744, e-mail: info@isgcon2009
9. **ASICON 2009** 25th - 30th December 2009, Annual Conference of Association of Surgeons of India, Coimbatore, Tamilnadu
10. **ISACON 2009** 26th - 29th December 2009, 57th Annual National Conference of Indian Society of Anaesthesiologists Venue - Chennai Convention & Trade Centre (Contact Dr. Ganapathy Asokan, Organising Secy., Dept. of Anaesthesiology, Room No. 250, 5th Floor, Tower Block 2, Govt. General Hospital, Park Town, Chennai - 600 003, Tel : +919445447766, e-mail: isacon2009@hotmail.com, www.isacon2009chennai.com
11. **AICOG 2010** 18th - 22nd January 2010, 23rd All India Congress of Obstetrics and Gynaecology, Guwahati