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Welcome to the Middle-East Journal of Internal Medicine
This is the second issue this year and has a good mix of papers. A prospective and double blind clinical study from Jordan attempted to compare between the influence of postintubation dexamethasone and preintubation dexamethasoe administration, in terms of decreasing the frequency and intensity of postoperative laryngeal edema. The authors found no significant discrepancies in the frequency of hoarseness at 24 hours postoperatively nor the intensity scores of hoarseness at 1 and 4 hours postoperatively between the two groups. They concluded that Dexamethasone 16 mg administered preintubation or postintubation has almost the same effect on the frequency and intensity of postoperative laryngeal edema.

A study from Saudi Arabia was carried out to estimate the smoking prevalence, and to determine the smoking behavior, as well as provide information on knowledge and attitudes regarding smoking among physicians working in the primary health care centers. A self-administered questionnaire was distributed by researcher to 55 physicians. Prevalence of smoking was 21.8 %. This study demonstrated that less than one quarter (21.8%) of the physicians in the primary health care centers are currently smokers, which indicates a severe public health problem throughout the country. Steps need to be taken at a national level to address the fight against tobacco.

A case report from Kuwait looked at Hypercalcemia as it is not an uncommon presentation for hepatic granulomatosis. The authors report on a thirty year old Indian gentleman who presented for the first time with renal colic and was discovered to have renal calculi and hypercalcemia. Disseminated TB was found to be the underlying cause of hypercalcemia. The diagnosis was made after liver biopsy which demonstrated histological features of hepatic tuberculous granuloma. After treatment with anti-tuberculosis medication, his serum corrected Calcium fell back to normal.

A Prospective descriptive study of 27 cases from Egypt looked at renal involvement by leukemia or lymphoma in the pediatric age group. All patients presented with odema whether generalized or localized, 12 had ascitis, 11acute renal failure (ARF), three tumor lysis syndrome e(TLS), three hypertension, five with decreased urine output, and 14 with bilateral renal involvement as diffuse or focal infiltration of the kidney by ultrasound. The authors concluded that their patients present late at diagnosis with advanced disease, and renal involvement should be considered in every case of leukemia and lymphoma and to anticipate renal complications.

A paper from Jordan and the USA looked at the use of midazolam and morphine as premedication for elective intubation in neonates, and to compare the intubation conditions with these combinations versus awake intubation. The authors concluded that Morphine and midazolam decrease the time and number of attempts needed for intubation, however premature babies should have cardiorespiratory, oxygen saturation, and blood pressure monitoring during intubation.

A paper from Saudi Arabia looked at Glucose homeostasis. The author pointed out that it is a dynamic process varying between health, disease and in between conditions. Several mechanisms are responsible for keeping the equilibrium in balance. Any disturbances in these mechanisms produce abnormal conditions such as prediabetes or different degrees of frank hyperglycemia. The review discusses variations in glucose tolerance in health and disease, especially prediabetes and early type two diabetes.

An unusual presentation of chylothorax in a newborn infant was reported from Prince Hashem Military hospital. The authors report a 7 day old, full term male newborn baby with severe right sided pleural effusion which was confirmed to be a case of congenital chylothorax. Chylothorax is a rare condition in neonates and it is defined as an abnormal accumulation of lymphatic fluid in the pleural space . Chylothorax causes severe respiratory and nutritional problems and it is associated with a high mortality rate. Octreotide is a long-acting somatostatin analog that reduces lymphatic fluid production and it has been used as a new strategy in the treatment of chylothorax.

Smoking Prevalence, Knowledge, Behavior, and Attitudes among physicians working in primary health care centers, In Jeddah, Saudi Arabia

ABSTRACT

Background: Tobacco smoking is one of the leading preventable causes of death in the world and considered a major public health problem in both developed and developing countries. Health professionals in general and physicians in particular, have a key role through the health care system to motivate and advise smokers to quit. Since physicians are well regarded and have a reputable position in society, they are the most likely persons whose advice on quitting smoking would be accepted by smokers.

Objectives: This study was carried out to estimate the smoking prevalence, to determine the smoking behavior, as well as information on knowledge and attitudes regarding smoking among physicians working in the primary health care centers, belong to Ministry of Health (MOH), in Jeddah.

Methods: A validated Questionnaire was adopted from the WHO Global Health Professional Survey. A self-administered questionnaire was distributed by researchers to 55 physicians working in Primary Care Centers in Jeddah, Saudi Arabia in 2006.

Results: Prevalence of smoking was 21.8 %. With respect to knowledge and attitudes, all respondents agreed that smoking is harmful to health and almost all physicians agree that the health professionals should serve as role models for their patients and the public (96.4%), and they should routinely ask about their patients' smoking habits (98.2%) and advise patients who smoke to quit smoking (98.2%) and to avoid smoking around children (100%). Also, it was realized that 80% of physicians agree that health professionals who smoke are less likely to advise people to stop smoking.

Conclusions: Our study demonstrated that less than one quarter (21.8%) of the physicians in the primary health care centers are currently smokers. This indicates a severe public health problem throughout the country. Steps need to be taken at a national level to address the fight against tobacco.

Key words: Smoking, Physicians, Behavior

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Introduction

Tobacco smoking is one of the leading preventable causes of death in the world and considered a major public health problem in both developed and developing countries since approximately 4 million people die prematurely from smoking-related illnesses each year, with deaths expected to rise to be one in six, or 10 million each year by 2030, (1,2) more than any other cause and more than the projected death tolls from pneumonia, diarrhea diseases, tuberculosis, and the complications of childbirth for that year combined. (3)

Current statistics indicate that it will not be possible to reduce tobacco related deaths over the next 30-50 years, unless adult smokers are encouraged to quit. In this regard, health professionals in general and physicians in particular have a key role through the health care system to motivate and advise smokers to quit. Since physicians are well regarded and have a reputable position in society, they are the most likely persons whose advice on quitting smoking would be accepted by smokers. (4,5)

Internationally, there is an increased public awareness about the health risks of cigarette smoking which is reflected in the declining rates of cigarette smoking behavior in the developed countries, while in developing countries, the rates are increasing. (6)

Smoking rates among the general population in the Kingdom of Saudi Arabia are extremely high; 71% of young people have experimented with cigarette smoking. (7)

So, primary care physicians have the potential to decrease morbidity and mortality for many smoking-related diseases if they provide effective smoking counseling.

Important smoking cessation concepts will aid primary health care physicians to implement practical aspects of health promotion and disease prevention in their practice and improve the overall health for their patients.

However, physicians who smoke are less likely to counsel their patients regarding the hazards of smoking. (8,9)

And if the physician is a smoker, a negative image will be formed from the public toward the concept and attitude of their physician toward smoking; this attitude encourages people to smoke freely and increases the acceptance of these phenomena in the society.

Given the important role that doctors have to educate their patients about good health practices, the smoking figure for physicians is disturbing. Doctors are often seen as symbols of good health practice. (10) Moreover, they can, and should, play a crucial role in influencing the smoking habits of their patients.

In particular, family physicians have a key role in counseling their patients on smoking cessation strategies; as they are the first point of medical contact for most patients, they have an ongoing relationship with their patients, and they come into contact with a large number of smokers. (11)

Smoking is fairly widespread among health professionals. Health professionals who are assumed to be role models for the public have to be considered primarily in cigarette control programs. (12)

Therefore, physicians can and should utilize the window of opportunity during their contact with patients to offer smoking cessation interventions not only in the developed world but also in the developing world. (13)

This study therefore seeks to estimate the smoking prevalence and determine the behavior of the physicians toward smoking and to determine how well prepared they feel toward counseling their patients on smoking cessation strategies.

Methodology

A cross sectional study of physicians working in primary health care centers belonging to the MOH in Jeddah, Saudi Arabia, was designed. Physicians working in primary health care centers belonging to the MOH in Jeddah, Saudi Arabia were invited to participate in the study. The primary health care centers in Jeddah city are distributed and divided into 6 geographical areas; each area consists of (5-7) centers, so the representative samples were 3 centers from each area selected by every third center; the total was 18 primary health care centers including all physicians working in these centers.

A Questionnaire was adopted and modified from the WHO Global Health Professional Survey, a self-administered questionnaire developed by the Tobacco Free Initiative, a project of the World Health Organization, in collaboration with the Centers for Disease Control and a number of additional partners. (14)

The questionnaire consists of 41 questions with 4 Sections. The 1st section of the questionnaire is made up of basic demographic questions.

The 2nd section concentrates on personal smoking behavior. The definitions used to describe the smoking behavior are based on WHO standardized definitions for tobacco use. Respondents were classified as:

A “current smoker” is someone who at the time of the survey smoked any tobacco product daily.

An “ex-smoker” is someone who was formerly a daily smoker but currently does not smoke at all.

An “occasional smoker” is someone who smokes but not every day.

“A non-smoker” is someone who, at the time of the survey, did not smoke at all.

A “never-smoker” is someone who either never smoked at all, or have never been a daily smoker or have smoked less than 100 cigarettes in his/her lifetime. (15)

The 3rd section consists of 22 questions that assess knowledge of and attitudes towards the adverse affects of smoking, the role of health professionals regarding smoking cessation in their patients, and some policy issues of smoking.

The final section evaluates the training they may have received in smoking cessation counseling, as well as their comfort level in counseling patients to stop smoking.

The responses to knowledge and attitude questions were on a scale of 1-5, (1 strongly agree, 2 agree, 3 unsure, 4 disagree and 5 strongly disagree).

The inclusion criteria were:

- Any Primary health care physicians working in primary health care centers belonging to the MOH in Jeddah, Saudi Arabia in 2005.
- Both male and female doctors.
- Both Saudi and non-Saudi doctors.

The exclusion criteria were:

- Those who are not working during the research
- Those who don't want to participate.

The questionnaire was distributed to physicians in the selected primary health care centers. The data were collected and verified by hand and then coded for entry. Each physician was approached 2 times before being considered as a non-respondent. Data was entered into a personal computer by the researcher and it was analyzed by SPSS version 10. T-test was used for continuous variables.

Chi square was used for non continuous variables. Written permission from the director of the Primary Health Care Centers in Jeddah city was obtained.

Questionnaires were given to physicians with personalized cover and verbal consent.

All individual information was kept confidential.

Results

The current study was conducted in the Primary Health Care Centers in Jeddah Governorate where 55 physicians were selected randomly to assess their knowledge, attitude and practice of smoking.

Characteristics of the study group (Table 1 below):

The majority of physicians (78.2%) were non-smokers, and the smokers constituted less than one quarter (21.8%) of the whole physicians.

Table 2 (below) demonstrates the smoking behavior of the smokers.

Table 2 demonstrates that one quarter of the smokers used to consume cigarettes alone, while one third were using Shesha and 41.7% used to consume combined (more than one type).

Characteristics	No.	%
Age (years):		
25-29	21	38.2
30-34	18	32.7
35-39	8	14.5
40-44	3	5.5
45-49	3	5.5
50+	2	3.6
Gender:		
Male	26	47.3
Female	29	52.7
Specialty		
General practitioner	32	58.2
Family physician	16	29.1
Pediatrician	1	1.8
Dentist	4	7.3
Others	2	3.6

Table 1: Characteristics of the study group (n=55)

	No.	%
Type of smoking:		
Cigarettes	3	25
Shesha	4	33.3
Combined (more than one type)	5	41.7
Have ever tried to quit smoking:		
Yes	9	75
No	3	25

Table 2: Smoking behavior of the smokers (n=12)

Gender	Non smoker		Smoker		Total	
	No	%	No	%	No	%
Female	26	89.70	3	10.30	29	100.00
Male	17	65.40	9	34.60	26	100.00
Total	43	78.20	12	21.80	55	100.00

Chi sq = 4.734
df = 1 p = 0.034

Table 3: Smoking status of physicians according to gender

Specialty	Non smoker		Smoker		Total	
	No	%	No	%	No	%
GP	23	71.90	9	28.10	32	100.00
Family physician	15	93.80	1	6.30	16	100.00
Others	5	71.40	2	28.60	7	100.00
Total	43	78.20	12	21.80	55	100.00

Chi sq = 3.207 df = 2 p = 0.201

Table 4: Smoking status of physicians according to specialty

It was recognized that the majority of the smokers (75%) had previous trials to quit smoking.

Table 3 (above) shows that smoking behavior was more prevalent among male physicians (34.6%) if compared with females (10.3%). This difference was statistically significant ($p<0.05$).

Table 4 (above) demonstrates that there was only one family physician (6.3%) who was a smoker, meanwhile, it was observed that smoking was relatively quite prevalent among other physicians; it accounted for 28.1% GP physicians and 28.6% among other specialties. However, these differences were not statistically significant ($p>0.05$).

The majority of smokers (75%) think about quitting the smoking habit, while there were 16.7% who were ready to quit smoking. On the other hand, there was only one smoker (8.3%) who was neither ready nor thinking about quitting the smoking habit.

From the tables it can be seen that almost all physicians agree that the health professionals should serve as role models for their patients and the public (96.4%) and set a good example by not smoking (94.5%), and they should routinely ask about their patients' smoking habits (98.2%) and advise patients who smoke to quit smoking (98.2%) and to avoid smoking around children (100%). In addition it was realized that 94.5% of physicians agree that health professionals should speak to community groups about smoking. Also, it was realized that 80% of physicians agree that health professionals who smoke are less likely to advise people to stop smoking. Meanwhile it was found that the majority of physicians (83.6%) agree that the patient's chances of quitting smoking are increased if a health professional advises him/her to quit.

Table 6 (page 8) describes the knowledge of the physicians about the risks of smoking. It was noted that all physicians agree that smoking is harmful to health. However, it was realized that similar percentages of physicians (85.5%) agree that passive smoking increases the risk of lung disease in non-smoking adults and they agree that paternal smoking increases the risk of lower respiratory tract illnesses such as pneumonia in exposed children. Moreover, relatively lower percentages of the physicians (76.4%) agree that passive smoking increases the risk of heart disease in non-smoking adults.

Table 7 (page 8) shows that almost all physicians (96.4%) agree that health warnings on cigarette packages should be in big print, and a similar percentage agree that sport sponsorships by the tobacco industry should be banned. Meanwhile, it was noted that 94.6% of physicians agree that smoking in enclosed public places should be prohibited and an equal percentage agree that there should be a complete ban on the advertising of tobacco products. Also it was realized that 98.2% of physicians agree that tobacco sales to children and adolescents should be banned. On the other hand it was recognized that there were 5 physicians (9.1%) who disagree that hospitals and health care centers should be "smoke-free", and 4 physicians (7.3%) disagree that the price of tobacco products should be increased sharply.

Discussion

The study demonstrated that less than one quarter (21.8%) of the physicians in the primary health care centers were currently smokers. This figure was much less than what was found in a study conducted in Turkey to estimate the prevalence of smoking among doctors and medical students, where the researchers pointed out that the range of the

Items	Agree No (%)	Not sure No (%)	Disagree No (%)
Health professionals should serve as role models for their patients and the public.	53(96.4%)	2(3.6%)	--
Health professionals should set a good example by not smoking.	52(94.5%)	3(5.5%)	--
Health professionals should routinely ask about their patients' smoking habits.	54(98.2%)	1(1.8%)	--
Heath professionals should routinely advise their smoking patients to quit smoking.	54(98.2%)	1(1.8%)	--
Health professionals should routinely advise patients who smoke to avoid smoking around children.	55(100%)	--	--
Health professionals should speak to community groups about smoking.	52(94.5%)	1(1.8%)	2(3.6%)
Health professionals who smoke are less likely to advise people to stop smoking.	42(80%)	6(10.9%)	5(9.1%)
Patient's chances of quitting smoking are increased if a health professional advises him or her to quit.	46(83.6%)	6(10.9%)	3(5.5%)

Table 5: Response of physicians to items reflecting their opinion about role of health professionals towards smoking

prevalence accounted for 32.6-66.2% (16) , also, the percentage of smokers in the current study were almost half of that among physicians in Bosnia and Herzegovina (40%) (17), in Kuwait in 1990 (45.3%) (18) , and in the United Arab Emirates (43.9%)(18). However, the smokers in the current study were comparable with what was found among physicians in Fukui in Japan (26%) (19) and male physicians in Estonia (24.9%) and in all physicians in Mexico (26.9%). On the other hand, the percentage of smokers in the current study was slightly higher than what was found in Kuwait in 2000, where the percentage declined from 45.3% in 1990 to 18.4% in 2000, and in Bahrain (14.6%). Meanwhile, the findings in our study were in accordance with what was found in Al-Kharj military hospital, KSA, where the prevalence of smokers among physicians accounted for 19%. These differences could be attributed to the variations in the cultures and traditions in different communities in addition to the differences in the legislation governing smoking. In the Kingdom of Saudi Arabia, there is a law which bans smoking inside all the governmental buildings especially the health institutes. This law could explain the low prevalence of smoking among physicians in the current study.

Although the physicians know the risks and drawbacks of smoking however the majority of smokers (75%) in the current study indicated that they were just thinking about quitting the smoking habit, and there were only (16.7%) who were ready to quit smoking. These figures reflect the magnitude of the problem, as it points to an important observation that quitting in most instances is beyond the ability of most of the smokers, which could be explained by the addictive effect of nicotine. This fact was shown in a report from the CDC which emphasized that the nicotine in tobacco products is highly addictive (20,21), moreover, it was cited that a greater percentage of casual users graduate to addictive patterns of use than occurs with cocaine, morphine or alcohol-containing substances (21, 22) and the regular use of tobacco products is commonly associated with difficulty in achieving and sustaining abstinence, even when advised strongly by health professionals. Nicotine is the addicting

Items	Agree No (%)	Not sure No (%)	Disagree No (%)
Smoking is harmful to health.	55(100%)	--	--
Passive smoking increases the risk of lung disease in non-smoking adults.	47(85.5%)	7(12.5%)	1(1.8%)
Passive smoking increases the risk of heart disease in non-smoking adults.	42(76.4%)	11(20.0%)	2(3.6%)
Paternal smoking increases the risk of lower respiratory tract illnesses such as pneumonia in exposed children.	47(85.5%)	6(10.9%)	2(3.6%)

Table 6: Response of physicians to items reflecting their knowledge about risk of smoking

Items	Agree No (%)	Not sure No (%)	Disagree No (%)
Health warnings on cigarette packages should be in big print.	53(96.4%)	2(3.6%)	--
Sport sponsorships by the tobacco industry should be banned.	53(96.4%)	1(1.8%)	1(1.8%)
Smoking in enclosed public places should be prohibited.	52(94.6%)	2(3.6%)	1(1.8%)
There should be a complete ban on the advertising of tobacco products.	52(94.6%)	3(5.4%)	--
Tobacco sales to children and adolescents should be banned.	54(98.2%)	1(1.8%)	--
Hospitals and health care centers should be "smoke-free".	50(90.9%)	--	5(9.1%)
The price of tobacco products should be increased sharply.	46(83.6%)	5(9.1%)	4(7.3%)

Table 7: Response of physicians to items reflecting their opinion about measures taken to abandon smoking

agent in tobacco products and is present in sufficient quantities in all commercially available tobacco products to cause and sustain addiction (23) All tobacco products are addictive; however, cigarettes appear to maximize the addictive potential of nicotine by requiring the user to inhale the smoke into the lungs, thereby resulting in extremely concentrated doses of nicotine being rapidly transmitted to the brain (21, 24). Smoking only became widespread in Saudi Arabia in recent times. In fact, smoking was totally prohibited by King Abdulaziz in 1926 as being un-Islamic. However, since the 1950s, cigarette smoking has become widespread in Saudi Arabia from 1961 to 1987 when tobacco imports increased forty-fold. Tobacco is used in many forms but mostly as "Jerak" or shesha or in the form of cigarettes (23). The results showed that one quarter of the smokers used to consume cigarettes alone, while one third (33.3%) were using Shesha and 41.7% used to consume combined (more than one type).

Seventy five percent of the smokers in the current study indicated that they had tried to quit smoking, but by being current smokers at the time of the study meant that they failed; this observation again emphasizes the addictive effect of nicotine.

Literature showed that there is an almost general consensus that the current and future physicians should be "exemplars" to their patients and communities; the physician should act as role model by not smoking and by creating a smoke-free environment in his or her office. It was observed that the majority of the physicians (80%) agree that health professionals who smoke are less likely to advise people to stop smoking. These findings were in accordance with what was cited in a study conducted in Sweden (25,26), where they found that doctors who themselves are smokers inquire about their patients' smoking habit less than their non-smoker colleagues.

Conclusion

Although the physicians know the risks and drawbacks of smoking however, the study illustrated that one quarter of the physicians in the primary health care centers were currently smokers, the majority of the smokers (75%) indicated that they are just thinking about quitting the smoking habit, which emphasizes on the difficulty of quitting smoking which was attributed to the addictive pattern of the nicotine in addition to the habit itself. This fact was supported by the indication that 75% of the smokers in the study had tried to quit smoking, but being current smokers at the time of the study indicates that they failed.

Nevertheless, the promising observations were that almost all physicians including the smokers agree that they should serve as role model for their patients and the public, and also, almost all physicians agree that they should routinely ask about their patients' smoking habits and advise patients who smoke to quit smoking.

There was almost general consensus of the physicians about the policies and measures that must be taken to combat smoking; however, the physicians pointed out that half of the health centers (45.5%) were not following antismoking policies.

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Comparison between preintubation and postintubation dexamethasone 16 mg administration in decreasing postoperative laryngeal edema after direct laryngoscopy

ABSTRACT

Objective: To compare between the influence of postintubation dexamethasone and preintubation dexamethasone administration in terms of decreasing the frequency and intensity of postoperative laryngeal edema.

Methods: Our prospective and double blind clinical investigation included 134 subjects between 37 and 71 years old, of both genders and who underwent direct laryngoscopy at King Hussein Medical Centre (Amman) and Prince Ali hospital (Karak) Jordan, during the period Jan 2010-July 2010 and July 2010-Aug 2011, respectively.

The subjects were classified in a random manner into two groups. Subjects in the preintubation group (GI, n = 69) received intravenous administration of 16 mg of dexamethasone 60 minutes preoperatively and subjects in the postintubation group (GII, n =65) who received dexamethasone 16 mg intravenously after endotracheal intubation.

The subjects were followed up at 1, 4 and 24 hours postoperatively. The frequency and intensity of postoperative hoarseness were recorded.

Results: There were no significant discrepancies in the frequency of hoarseness at 24 hours postoperatively, neither in the intensity scores of hoarseness at 1 and 4 hours postoperatively, between the two groups.

Conclusion: Dexamethasone 16 mg administered preintubation or postintubation has almost the same effect on the frequency and intensity of postoperative laryngeal edema.

Keywords: Complication, Dexamethasone, Edema, laryngeal, Hoarseness, Intubation, Pre post, Larygoscop; direct, microscopic

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Introduction

In the immediate postoperative period, airway obstruction is seldom and was found to be as 0.17-0.19%. The causes of the majority of these were divided as secondary to anesthesia related factors, or true physical airway obstruction. Postoperative airway obstruction secondary to physical factors could be related to hematoma compression, bilateral recurrent laryngeal nerve palsies, huge tongue edema, paradoxical vocal cord motion and obstruction by a mucous cast. Angioedema may cause acute postoperative upper airway obstruction. Airway edema is to be expected in surgical techniques and postoperative airway compromise is not uncommon. Obstruction of the airway is seldom complete however, and generally takes some hours to develop allowing time for intervention before life threatening obstruction happens(1).

Dexamethasone is an effective glucocorticosteroid with analgesic and anti-inflammatory actions (2). To our knowledge, 8 and 10 mg of dexamethasone were used pre and post-intubation in the aim of reducing postoperative hoarseness(3). The operating microscope has revolutionized the treatment of laryngeal disorders. The Kleinsasser laryngoscope with the operating microscope allows detailed examination and assessment of the larynx. Complications of direct laryngoscopy may be mechanical or cardiovascular and may happen early or late. Early complications include dislocation of arytenoids;, laryngeal trauma may produce postoperative croup or laryngeal spasm. Mechanical complications may be avoided using a careful method. Late complications include trauma to vocal cords which may result in ulceration. Cord trauma may be more common in the presence of upper respiratory tract infection(4). Direct laryngoscopy is a diagnostic procedure that may also be therapeutic for removal of foreign bodies or tumours. It is considered to be one of the safest procedures .Among the few complications that may occur are failure of vocal cords to heal after biopsy. Voice changes or hoarseness are possible after any vocal cord surgery. Any time the airway itself is instrumented, there is always a change of swelling or edema in the airway.

Postoperative laryngeal edema can cause a great discomfort and sometimes it is difficult to control. Hoarseness is a generic term used to describe many kinds of dysphonia. It is frequently used to define a vocal quality that is rough or harsh.(5). This should not be confused with sore throat. It is almost always associated with laryngoscopy and is caused predominantly by abduction and pressure on the vocal cords. However, traumatic laryngoscopy can cause direct trauma to the vocal cords resulting in prolonged hoarseness.(6). The prevention of postoperative laryngeal edema is vital.

The aim of our investigation was to compare between the potency of preoperative dexamethasone and postintubation dexamethasone in decreasing the frequency and intensity of postoperative laryngeal edema.

Methods

Our prospective and double blind investigation enrolled 141 subjects of both sexes, aged between 37 and 71 years and assigned for direct microlaryngoscopy after obtaining written informed consent, at King Hussein medical centre (Amman) and Prince Ali hospital (Karak)-Jordan, during the period Jan-July 2010 and July2010-Aug 2011, respectively. Subjects with a history of new respiratory infection, preoperative administration of corticosteroids and who needed more than one trial for endotracheal intubation during the investigation, were excluded from the trial.

Preoperatively, subjects were allocated in a random fashion into two groups using sealed envelopes. Subjects in the preventive group (GI, n =69) were administered 16 mg (4 ml) dexamethasone intravenously, 60 minutes preoperatively and preintubation, while patients in the postintubation group (GII, n =65) received the same 16 mg (4ml) dexamethasone but after intubation. All anesthetic techniques were accomplished by an experienced anesthesiologist unaware of the study. All subjects were unaware of the investigation. Balanced induction of anesthesia was performed using a non-depolarizing muscle relaxant, 3 minutes after which endotracheal intubation was executed with a high volume/low pressure flexometallic endotracheal tube with an internal diameter of 6.0 mm (outer diameter 9.7 mm) for both men and women subjects. Immediately after intubation, the tracheal tube cuff was inflated with room air until there was no air leakage. Direct microscopic laryngoscopy was performed using B (medium) blade for females and C (large) blade for males. Balanced anesthesia was maintained to keep end tidal CO2 between 35-40 mmHg. At the end of surgery, patients were reversed from anesthesia using neostigmine until the subjects were fully awake. After suction of oral secretions, the cuff was deflated and the patients were extubated and removed to the recovery room. All subjects received intravenous morphine 0.05 mg/kg after the operation.

The duration between intubation and extubation was recorded. The frequency of postoperative laryngeal edema evidenced by hoarseness was measured using direct questions at 1, 4 and 24 hours postoperatively. The intensity of hoarseness was graded using a 4 point scale. (Table 1) opposite page.

Statistics

The data are presented as mean+/- SD and number. The student t test was used for comparisons between differences in age, weight and duration of intubation. The X2 test was used for comparisons in gender, frequency of hoarseness during 24 hours postoperatively and intensity of hoarseness. $P<0.05$ was considered significant.

Results

There were no significant differences between the two groups regarding number (GI, 51.5%-GII, 48.51%), gender (M: GI, 49.3%,GII, 47.7%-F:GI, 50.7%,GII, 52.3%), age (31-50 yr:GI,82.6%, GII,80%-51-71 yr: GI, 17.4%,GII, 20%) and duration of intubation (GI,66 min,GII,62 min) .$P>0.05$. (Table 2 - opposite).

Seven patients were ruled out from the trial including a total of 141 patients as they needed more than one intubation trial (4 in group I and 3 in group II)

There were no significant differences between the two groups in terms of the frequency of hoarseness at 24 hours postoperatively. No hoarseness was found in 42 cases in GI and in 36 in GII at 24 hours postoperatively. No hoarseness was found in 21 cases in GI and in 17 in GII at 1 hour postoperatively. At 4 hours postoperatively, the frequency of no hoarseness was 20 in GI and 14 in GII. $P>0.05$. Female percentage was more as in frequency and intensity regarding the postoperative hoarseness. In group I at 1 hour postoperatively, female preponderance was 9, 4, 10 and 12 while male preponderance was 12, 10, 4 and 8 in terms of grade 0, 1 ,2 and 3 respectively. In group II at 1 hour postoperatively, female preponderance was 6, 3, 12 and 13 while male preponderance was 11, 5, 5 and 10 in terms of grade 0, 1, 2 and 3, respectively.

There was no significant discrepancy between the groups regarding the intensity scores at all time intervals. Grade 1 hoarseness was found in 14, 20 and 15 cases in group I at 1, 4 and 24 hours postoperatively, respectively and in 8, 13 and 13 cases in group II, at 1, 4 and 24 hours postoperatively, respectively. Grade II hoarseness was found in 14, 21 and 5 cases and in 17, 26 and 7 cases in groups I and II, at 1,4 and 24 hours postoperatively, respectively. Grade III hoarseness was found in 20, 9 and 5 cases and in 23, 12 and 6 cases in groups I and II, at 1,4 and 24 hours postoperatively, respectively .$P<0.05$. (Table 3).

Discussion

Laryngeal edema is a frequent complication of intubation and laryngoscopy. It often presents shortly after extubation as post-extubation hoarseness and results from damage to the mucosa of the larynx. Mucosal damage is caused by pressure and ischemia resulting in an inflammatory response. Laryngeal edema may compromise the airway. Laryngeal edema is a common cause of airway obstruction and is thought to arise from direct mechanical trauma to the larynx. The severity of airway obstruction due to laryngeal edema varies. Pressure and ischemia are thought to contribute to mucosal edema which may subsequently progress and

Score	Description
0	No hoarseness
1	Hoarseness recorded only by patient
2	Mild readily apparent hoarseness
3	Severe readily apparent hoarseness

Table 1: Hoarseness score

		GI	GII
N =		69	65
Sex	M	34	31
	F	35	34
Age (yr)	37-50	57	52
	51-71	12	13
Duration of intubation (min)		66+/-9	62+/-6

Table 2: Patient demographics (mean+/-SD, number)

Grade	Sex	GI			GII		
		1 hour	4 hours	24 hours	1 hour	4 hours	24 hours
0	M	12	13	22	11	9	20
	F	9	7	20	6	5	16
1	M	10	11	8	5	7	7
	F	4	8	8	3	6	5
2	M	4	7	2	5	10	2
	F	10	13	4	12	16	7
3	M	8	3	2	10	5	2
	F	12	7	3	13	7	6

Table 3: Frequency and intensity of hoarseness (number)

present as hoarseness within hours of extubation. Although laryngeal edema occurs in nearly all intubated patients, only some of them develop clinical symptoms. Laryngeal edema is therefore usually transient and self limiting. Clinical signs associated with laryngeal edema develop rapidly following extubation. Post-extubation hoarseness is accepted as a clinical marker of laryngeal edema following extubation. Hoarseness is differentiated from stridor, as the latter is a high pitched sound produced by air flow through a narrowed airway.(7)

Incidence of laryngeal edema varies between 2.3 and 6.9%, and clinically relevant post-extubation laryngeal edema occurs in up to 30% of extubated patients. Because laryngeal edema after tracheal extubation is likely to result from an exudative response, corticosteroids often are given routinely as a preventive treatment(8). Hoarseness after an operation is relatively common and has been reported in as many as70% of patients after operation. Typically the hoarseness disappears after a few days and neither the patient nor the surgeon remains concerned about the quality of the voice. However in some cases hoarseness persists associated with pain on swallowing. The following factors contribute to the development of postoperative hoarseness: the act of intubation, the endotracheal tube during the operation, the indwelling ETT after operation, intubation in concomitant bronchitis or bronchopneumonia, an allergic reaction involving the larynx and any operation in the neck or upper thorax (9). Female sex is a risk factor for laryngeal edema due to the female mucous membrane being less resistant to trauma and thinner than that in males.

Although we used double the dose of dexamethasone (16 mg) compared to 10 mg as in S. Y. Park (3), there were no significant differences in frequency and intensity of postoperative hoarseness between the two studies and between the two groups. The confounding factors were controlled such as: the dose of dexamethasone, type and size of ETT, type of cuff and intra-cuff of pressure, type of operation and duration of intubation. The same analgesics were used in all groups to exclude potential distraction effects. Therefore the differences if any between the groups will be attributed to the differences in the timing of dexamethasone administration.

Park et al (10) showed that the preventive use of 0.2mg/kg of dexamethasone significantly reduced the frequency and intensity of hoarseness at 1 and 24 hours after extubation. The potential mechanism is based on the anti-inflammatory activity of dexamethasone which includes inhibition of

leukocyte migration and maintenance of cell membrane integrity(11). This effect may be increased if dexamethasone is given before intubation. In our study, the administration of dexamethasone before intubation gave a greater, but not significantly beneficial effect on postoperative hoarseness supporting the preventive use of dexamethasone.

Potential side effects of dexamethasone include: hyperglycemia, peptic ulcer, increased susceptibility to infection and electrolyte imbalance. However the risk of side effects from single dose steroid therapy is negligible (12).

In our investigation, the tracheal tube might have been relatively small for our patients, the male group was almost equal to the female group and patients received relatively adequate doses of systemic analgesics. These factors could have an effect on our results. Further studies are recommended to clarify the role and timing of dexamethasone in reducing the postoperative laryngeal edema.

In conclusion

The preventive 16 mg dexamethasone administration gave better impact on postoperative hoarseness after direct microlaryngoscopy procedures, but not significantly compared to the same dose but after intubation.

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Midazolam and Morphine for Elective Intubation in NICU

ABSTRACT

Objective: **To assist the use of midazolam and morphine as premedication for elective intubation in neonates, and to compare the intubation conditions with these combinations versus awake intubation.**

Methods: **A non blind randomized prospective study was conducted between November 2009 and December 2010. Forty premature babies admitted to the neonatal intensive care unit and requiring non-emergency intubation were assigned to receive 0.1 mg /kg IV morphine followed by 0.1 mg/kg IV midazolam two minutes before intubation (study group) or awake intubation (control group). Number of attempts, duration of procedure, heart rate and blood pressure were monitored.**

Result: **Forty intubations were enrolled in this study (20 premedication or study group and 20 control groups); there were no significant differences between the two groups. Successful intubation on first attempt was achieved in 16 (80 %) of intubations in the premature babies under sedation versus 8 (40%) of control. After 10 minutes post intubation the median increase of mean blood pressure in the premedication group was -5.9, versus 0.15 in the control group. Mean time for intubation in the study group was significantly reduced, 38.05 sec versus 123.05 sec in the awake group. Incidence of bradycardia in the awake group was 50% versus 60% in the study group. Nearly all infants developed hypoxemia during intubation,;70% of the study group had hypoxemia after one minute, versus 55% of the control group; 45% of the study group had severe hypoxia versus 30% of the control group.**

Conclusion: **Morphine and midazolam decrease the time and number of attempts needed for intubation, however premature babies should have cardiorespiratory, oxygen saturation and blood pressure monitoring during intubation.**

Keywords: **Premedication, elective endotracheal intubation, awake intubation.**

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Introduction

Intubation is the placement of a flexible plastic tube into the trachea to maintain an open airway or to serve as a conduit through which to administer certain drugs. Premature infants likely have an increased sensitivity to pain(1), which can lead to chronic pain or neurobehavioral and developmental sequelae (2,3). Tracheal intubation of both the term and preterm newborn is a frequently performed stressful procedure in the Neonatal Intensive Care Unit (NICU), and has the potential for airway injury. The experience of being intubated is unpleasant and painful and seriously disturbs physiologic homeostasis (4,5). Endotracheal intubation is associated with acute increases in blood pressure and intracranial pressure, bradycardia and hypoxemia (6), and a potential risk of intraventricular hemorrhage in preterm infants (7, 8, 9). Bradycardia is presumed to be vagal in origin, because the very rapid onset is suggestive of a reflexive etiology(10).

Several studies that evaluated the success rate of neonatal endotracheal intubations have reported that successful intubations frequently require more than 1 attempt and are rarely accomplished within the currently recommended time frame.(11, 12, 13).

The risks and benefits of using premedication for intubating unstable newborns are hotly debated, although several trials have demonstrated that the use of premedication for intubation of the newborn significantly improves intubating conditions, decreases the time and number of attempts needed to complete the intubation procedure, and minimizes the potential for intubation-related airway trauma.(14-18)

As midazolam and morphine has been used for years in neonates with apparent efficacy for pain and sedation, we aimed to evaluate the efficacy of morphine and midazolam, in achieving better intubation conditions and success while maintaining vital signs stability.

Methods

In King Hussein medical center with level III NICU and in Prince Hashim Hospital which is a military hospital in the east of Jordan, infants of all gestational age admitted to the NICU were eligible for inclusion in this study. Informed consents were obtained from parents before the need for intubation. Exclusion criteria were infants with airway abnormalities, absence of an intravenous access, known or family history of a neuromuscular disorder, renal impairment, liver dysfunction and cyanotic congenital heart disease. When intubation was required the infant was given 100 mcg/kg morphine intravenous slowly over one minute followed by 100 mcg/kg midazolam slow intravenous bolus, to avoid severe hypotension and seizures reported by rapid injection (19) This relatively low dose of medication was chosen to avoid the side effects of both drugs. One to three minutes after infants received medication, positive pressure ventilation was done by self resuscitation bag or neopuff and oxygen as needed; also suctioning of the airway was done as necessary. All intubations were conducted by the same neonatologist fellows. Information about intubation situations, complications, intubation time and results of each attempt, were recorded on a worksheet following each intubation. Fractional inspired oxygen concentration (FiO2) was set to 40% for the first 10 minutes after procedure. Hypoxemia defined as O2 sat<85%, bradycardia defined as HR <100b.p.m, hypotension as mean blood pressure (MBP) >2SD below the age. All intubation attempts were made within 5-8 minutes of administration of the medication. An intubation attempt was defined as insertion and removal of the laryngoscope blade; intubation time was measured from the introduction of endotracheal tube until removal of the blade after successful intubation. In case there was more than one attempt, the time recorded continued between attempts until successful intubation was confirmed by auscultation. Successful intubation was confirmed if there was appreciable and bilaterally equal air entry on auscultation, rising of oxygen saturations and heart rate, visible vapor present in the ETT and confirmed by chest radiograph.

Elective intubation was done due to blocked tube, self extubation, increasing respiratory depression and failed planned extubation. Awake intubation was performed in half of the neonates (n=20) as the control group, to compare the result between the premedication group (study group) and awake intubations group.

Heart rate and oxygen saturation was continuously monitored by Masimo pulse oximeter monitors and recorded 5 minutes prior to the procedure or any drug administration, through the procedure, 1, 5 and 10 minutes after the intubation. Mean blood pressure was recorded, non-invasively, every one minute by cuff pressure connected to PC monitor (Philips) of the premature.

Data obtained for each infant included birth weight, gestational age, age at time of intubation, weight at time of intubation, gender and reason for intubation, and any complications were also recorded. All the intubations were done by the oral route, for both groups, termination of the intubation attempt was required if SpO2 fell below 65% or the attempt exceeded 38 sec.

Results

A total of forty infants needing elective intubation were enrolled in this study (27 to 37 week GA). An equal number of infants were randomized to each study group. 20 neonates received 100 mcg/kg IV morphine followed by 100 mcg/kg IV midazolam, and 20 infants received no premedication as a control group. Both groups were comparable in mean gestational age; weight at time of intubation, vital sign, age at intubation and gender.

Table 1 presents the demographic characteristic for both groups. All intubation was done by the same intubater-neonatologist fellow. Successful intubation on first attempt was achieved in 16 (80 %) of premature intubations under sedation versus 8 (40%) of controls. A second attempt at intubation was needed in four infants infused with morphine plus midazolam and in ten awake intubations; two prematures in the control group needed three attempts to achieve successful intubation. Mean time for intubation in the study group was significantly reduced, 38.05 sec versus 123.05 sec in the awake group; number of attempts in the treatment group was 24 versus 34 in the control group, see Chart.1. Regarding the hemodynamic variables, bradycardia in the awake group was 50% versus 60% in the study group. After10 minutes post intubation the median increase of mean BP in the premedication group was -5.9, versus 0.15 in the control group, dropping of blood pressure was mild and no-one needed medical treatment .All infants during the procedure developed hypoxemia (O2 sat. <85%); 70% of the premedication group had hypoxemia after one minute versus 55% of the control group; 45% of the study group had severe hypoxia, versus 30% of the control group. The influence of heart rate mean blood pressure and SpO2 is shown in Figures 1, 2, 3 (pages 17, & 18).

Discussion

Intubation is a painful, distressing procedure and uncomfortable for the patient. In fact, premature infants and newborn infants may have increased pain sensitivity compared with older infants and age groups, (20) and it is often accompanied by transient hypoxia, acidosis, and bradycardia. As a result of this stress, unfavorable changes in blood pressure, oxygen saturation (21) and heart rate have been observed. Premedication is not a common practice for the intubation of infants and most intubations in NICU are performed with the infants awake, without analgesia or muscle relaxation, possibly due to fear of producing cardiovascular or ventilator depression(22) , however after accounting for inter and intra individual variation, premedication had a beneficial effect on the intubation procedure. Anand (23) suggested that tracheal intubation without the use of analgesia or sedation should be restricted to life-threatening situations when intravenous access is not available.

Midazolam is a short acting benzodiazepine; the benzodiazepines are a class of sedatives that act on specific

Characteristics		Midazolam and morphine group (n=20)	Control group (n=20)
Gender	Female	9	13
	Male	11	7
Gestational age, week		32,2±2,68	31,6±2,97
Age at time of intubation, days		4,5±3,86	4,9±4,87
Birth weight, grams		1715,5±583	1639,5±579
Birth weight at time of intubation, grams		1658,5±570	1626,5±546
Mode of delivery	Vaginal delivery	11	10
	Cesarean	9	10
Reason for intubation	• Respiratory depression	3	2
	• Blocked tube	7	7
	• Self extubation	8	7
	• Failed extubation:	2	4

Table 1: Demographic Characteristics of premedication group (morphine plus midazolam) and awake group (control)

receptors in the central nervous system. These receptors, which are present in the fetus from seven weeks gestation, (24) potentiate the neuronal inhibitory pathways mediated by gamma aminobutyric acid (GABA) (25). The pharmacokinetics of midazolam in neonates has been studied. It is preferred over other benzodiazepines because of its water solubility and rapid clearance, (26) although its elimination half-life is significantly shorter than that of other benzodiazepines such as diazepam. The mechanism of midazolam-induced hypotension was thought to be vasodilation related to levels of extra vascular prostanoids and calcium (27). Anesthesia induction occurs in 1.5 to 2.5 minutes when the drugs is administered IV(28). Morphine is the most frequently used opioid analgesic in all ages, and is the most commonly used drug for analgesia in ventilated neonates(29). Morphine has a slow onset of analgesia. Its mean onset of action is at 5 minutes and the peak effect is at 15 minutes.

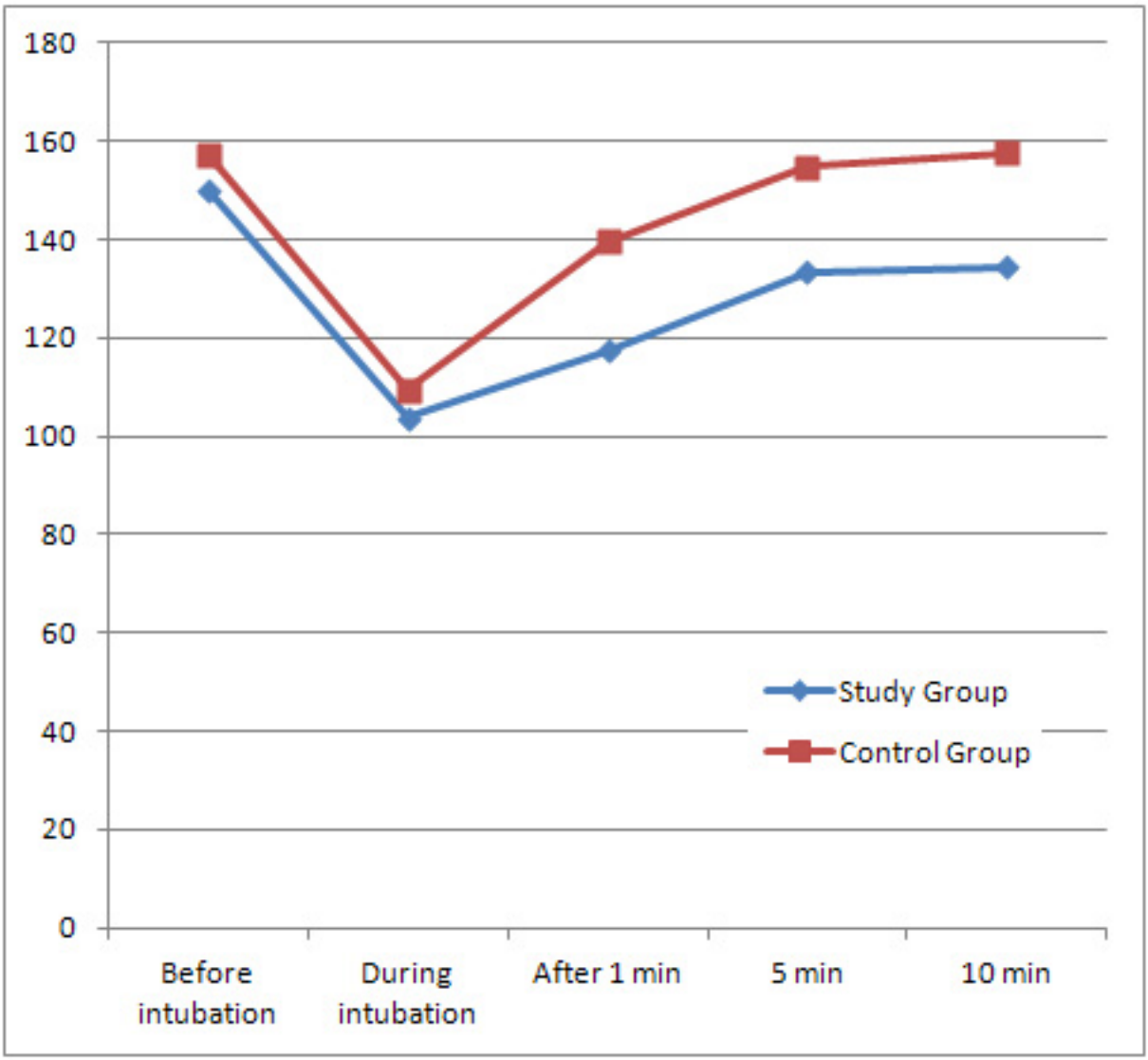


Figure 1: Change of heart rate in different stage of intubation

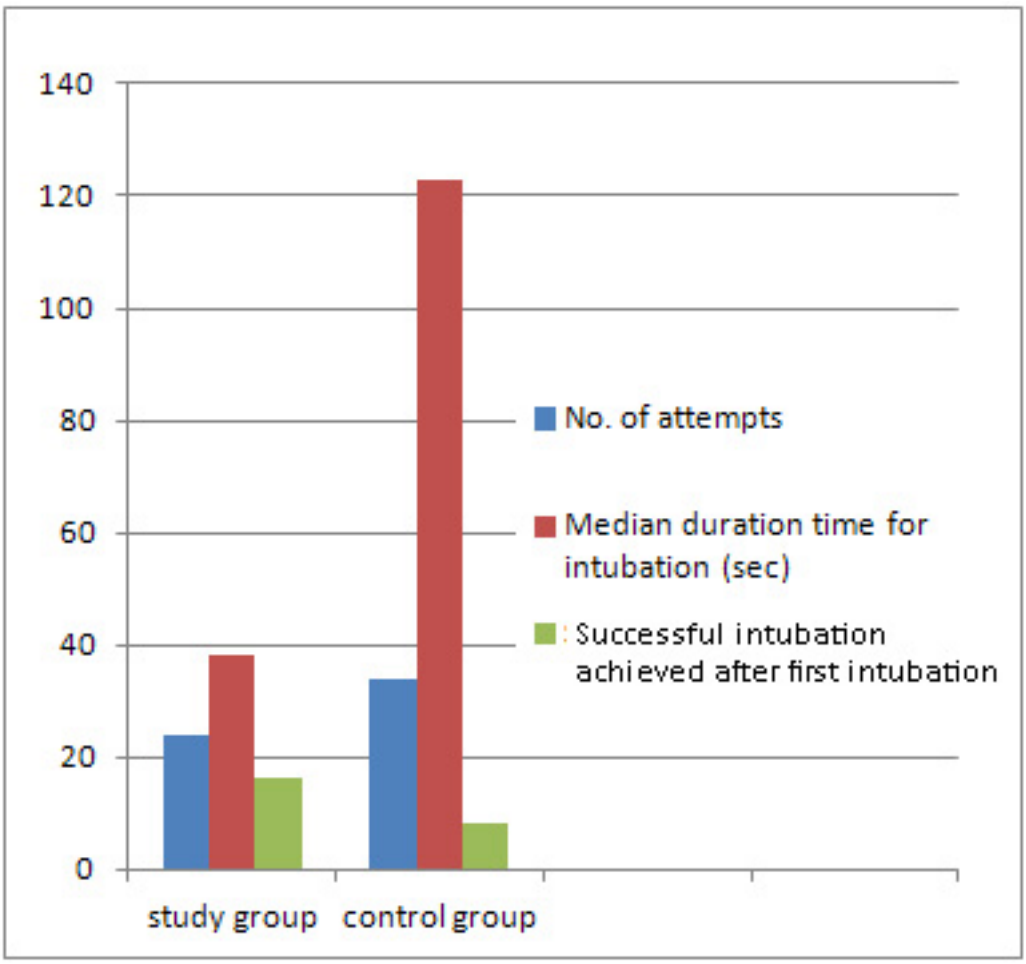


Chart 1: Number of attempts, duration time and rate of successful intubation in both groups

Figure 2: Change of O2 sat. during different stage of procedure

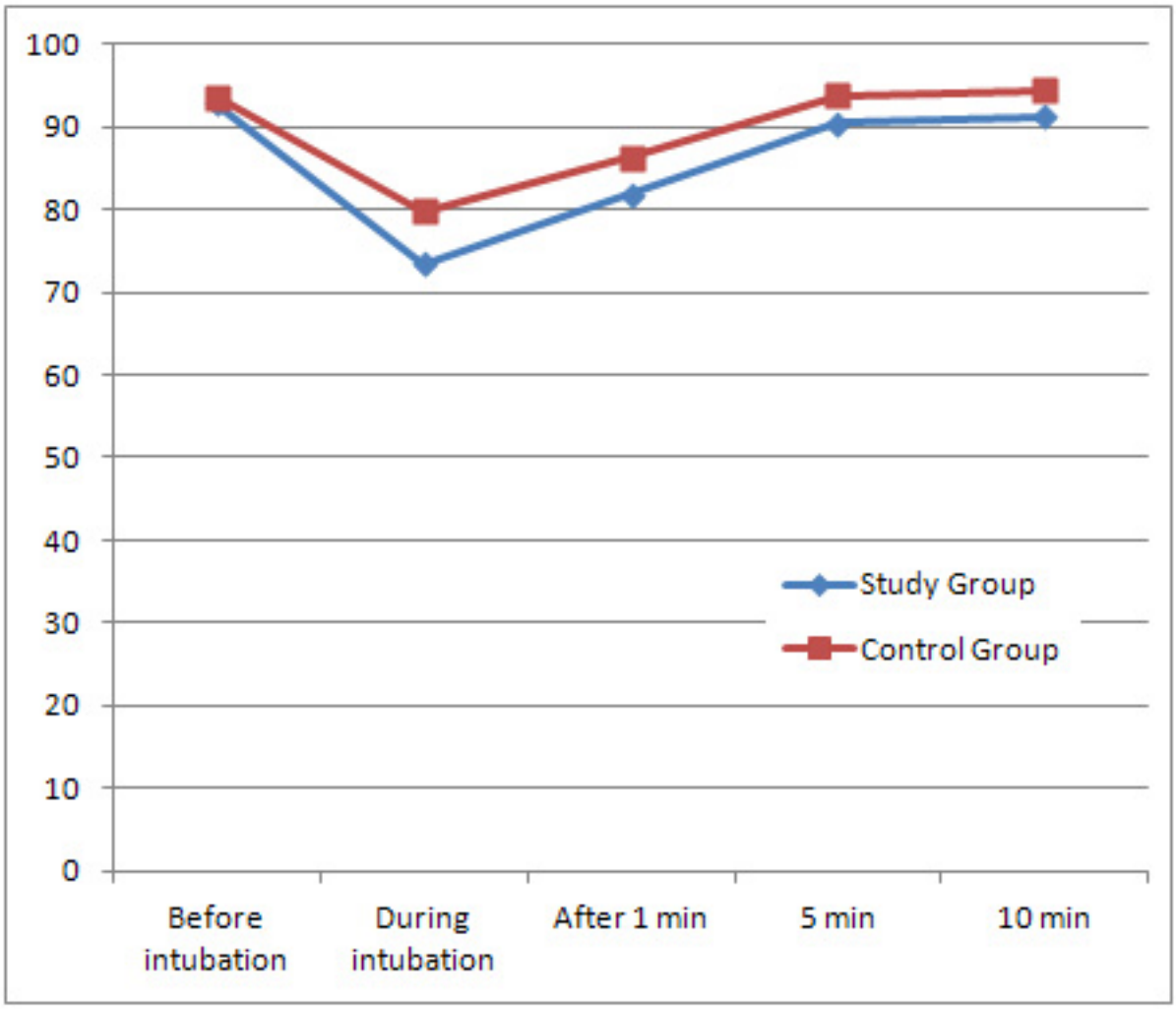
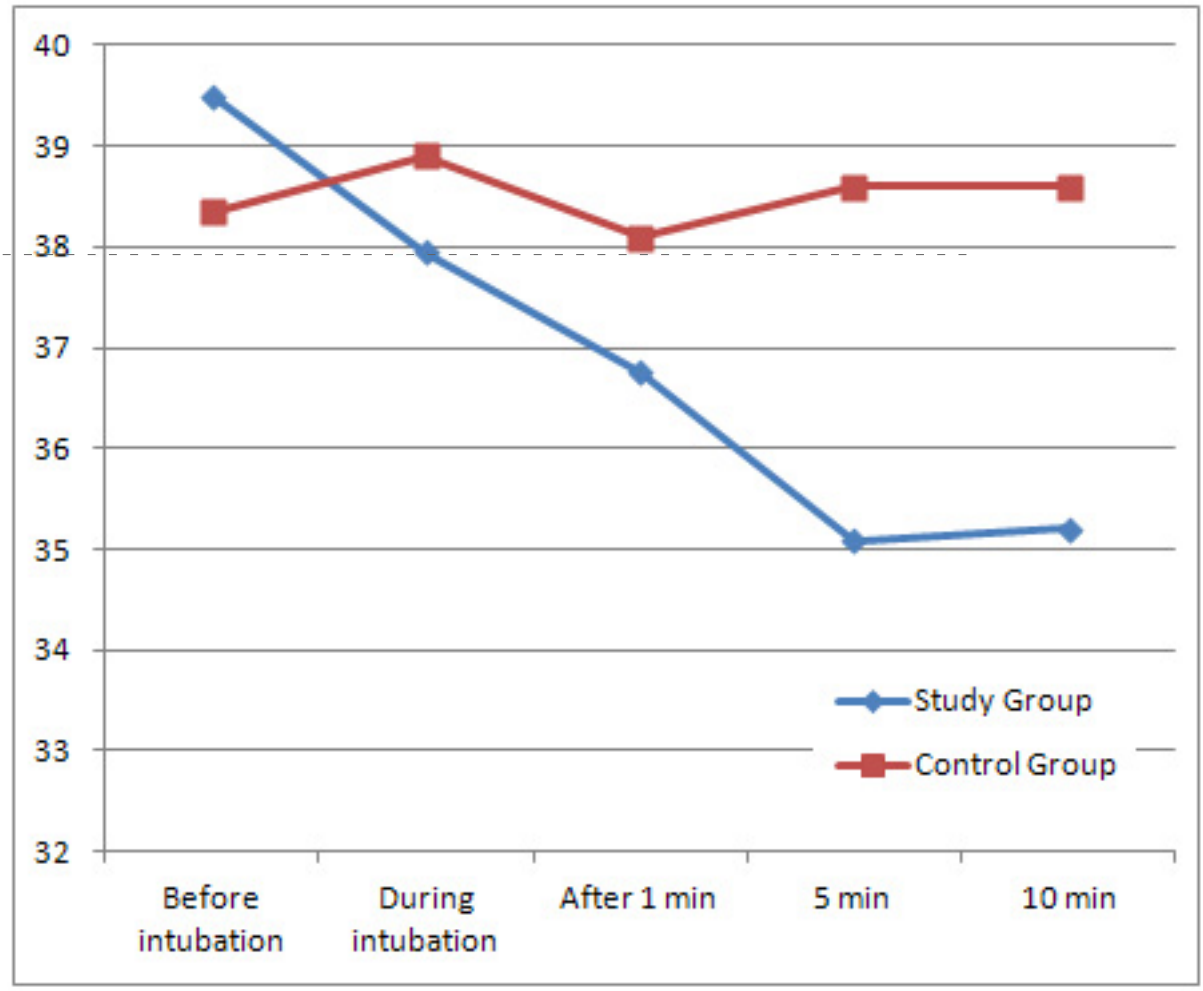


Figure 3: Change of mean blood pressure in different stage of intubation



Our study showed that the combination of midazolam and morphine facilitate intubation .but the duration of hypoxemia and bradycardia is longer in the treatment group; also the decrease in blood pressure is more.

Previous studies have used various combinations of drugs for premedication.Kelly(30) and Barrington(31), using atropine and a muscle relaxant, demonstrated a reduction in vagal bradycardia and a dampening in the rise in intracranial pressure. In a randomized, double-blind trial (stopped after only 16 intubations because of adverse events and reported in a letter to the editor), preterm infants who received midazolam and atropine for intubation had more desaturations, and 29% required cardiopulmonary resuscitation compared with those in the groups that received either atropine alone or no premedication(32) . In our study we use a low and a slow dose of midazolam in order to avoid these complications.

In the Lemyre study, the use of morphine alone for elective intubation was studied in 34 premature infants in whom infants were given either morphine or placebo 5 minutes before the intubation. The study failed to demonstrate the effectiveness of morphine in reducing the physiological instability or time needed to perform elective intubations. (33) This lack of effect is thought to be because of the delayed onset of action of morphine(34).

There is no consensus about the drug, combination of drugs or doses for premedication mainly regarding tracheal intubation in NICU.(35, 36, 37)

Midazolam and morphine showed to be a good combination, although there is a concern about the transient hypotension and bradycardia; however the small number of patients in this study may be a concern. Further study may be needed to prove that or to find a better combination as premedication.

Conclusion

Morphine and midazolam, decrease the time need for intubation, and decrease the number of attempts needed for intubation, however desaturation, bradycardia and hypotension are a known side effect of these drugs. Premature babies should have cardiorespiratory, oxygen saturation, and blood pressure monitoring during intubation.

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Renal involvement in childhood leukemia and lymphoma

ABSTRACT

Background and objective: Lymphoma and leukemia are the most solid and hematological cancers and may involve the renal parenchyma, with various degrees of renal failure with hypertension and protein urea with no other evident cause of renal abnormality. Histological pattern of renal involvement in cases of lymphoma/leukemia is either of infiltrative or nodular patterns.

The aim of this study is to focus on renal involvement by leukemia or lymphoma in the pediatric age group.

Patients and methods: A Prospective descriptive study of 27 cases diagnosed as 17 leukemia and 10 lymphoma for the period 2004-2007 at the central teaching hospital for children in Baghdad, who had the criteria of renal manifestation at presentation. Review was done of medical records of 27 patients to determine the type of leukemia or lymphoma at presentation and patients' outcome, proper past medical history was taken to exclude any related renal disease, base line complete blood picture, biochemistry, general urine exam (GUE) for protein urea (trace-4+), tissue biopsy, ultra sound and CAT of renal system if available, bone marrow aspiration(BMA) and biopsy.

Result: All patients presented with odema, whether generalized or localized, 12 had ascitis, 11 acute renal failure(ARF), three tumor lysis syndrome (TLS), three hypertension, five with decreased urine output,14 with bilateral renal involvement as diffuse or focal infiltration of the kidney by ultrasound , blood urea increase in 11, creatinine in 10, cholesterol in eight, total serum protein decrease in 18, low albumen in 17, heavy protein urea in six. Average age was 22 months, average duration of illness is two months.

Conclusion: Our patients present late at diagnosis with advanced disease. Renal involvement should be considered in every case of leukemia and lymphoma and to anticipate renal complications.

Key words: leukemia, lymphoma, renal failure, renal involvement

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Introduction

Solid and hematological cancers may involve the renal parenchyma. Clinical sequelae are usually not prominent ; lymphoma and leukemia are the most common such cancers (1). Recognized clinical definition of renal involvement in the cause of Non-Hodgkin lymphoma (NHL) are bilateral localization, various degree of renal failure with hypertension and protein urea with no other evident cause of renal abnormality . Histological pattern of renal involvement in cases of lymphoma/leukemia is either infiltrative or nodular patterns (1-5).

Nephrotic syndrome (NS) has been associated with malignancy, immune complex composed of tumor antigen and tumor specific antibodies presumably mediate to the renal involvement. NS may develop before or after the malignancy is detected. It also develops during therapy with numerous drugs or chemicals (1,6).

The appearance of multiple bilateral renal masses in lymphoma was heavily prevalent in children with renal disease and may be present at time of diagnosis or at time of recurrence of lymphoma(7); extra renal signs and symptoms of lymphoma are frequently present(8).

The aim of this study is to focus on renal involvement by leukemia or lymphoma in the pediatric age group and to avoid any complication during induction chemotherapy .

Patient and methods

A prospective descriptive study of 27 cases (17 leukemia and 10 lymphoma) out of an average 375 cases diagnosed as leukemia or lymphoma for the period 2004-2007 at the central teaching hospital for children in Baghdad who had the criteria of renal manifestation at presentation as : puffy eyes, pre orbital swelling, pitting edema of hands or legs, or generalized edema, decreased urine output , hypertension, sign of acute renal failure (ARF), albumin urea, hypo proteinemia, increased serum uric acid, increased serum creatinine and blood urea, clinical and laboratory tumor lyses syndrome (CTLS, LTLS). Review of medical records of 27 patients to determine the type of leukemia or lymphoma at presentation and patients' outcome; proper past medical history was taken to exclude any related renal disease, base line complete blood picture, biochemistry, general urine exam (GUE) for protein urea (trace-4+)(6(a)), tissue biopsy,

ultrasound and CAT of renal system if available, bone marrow aspiration (BMA) and biopsy was done. Normal values are considered as such(6(b)):

Serum protein 6.1mg- 8.1mg/dl	{1-7y ▸ 6.1-7mg/dl}	{8-12y ▸ 6.4-8.1mg/dl} (6a)
S. cholesterol 45-189/dl	{1-3y 45-182 mg/dl},	{ 4-6y ▸ 109-189mg/dl}
S. uric acid 2.2-6.6mg/dl	{1-5y ▸ 1.7-5.8mg/dl}	{6-11y ▸ 2.2-6.6mg/dl]
Blood urea	5-18mg/dl	
S. Creatinine	0.3-0.7mg/dl	
S K	3.5-5 mmol/L	
S Na	138-145 mmol/l	

The dipstick is reported as negative, trace (10-20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (1000-2000 mg/dL). Nelson nephrology(6a)

Renal biopsy was not done for any patient if it was inconvenient to the patient and where there was unavailability of an expert histopathologist. There were 21 cases of newly diagnosed leukemia and lymphoma, only one leukemia case and 5 cases of lymphoma who had been treated for more than 2-3 years with single or multiple relapse, who presented with the same findings designed in this study. The classical or typical presentation of leukemia and lymphoma are not included.

Results

All patients presented with odema, whether generalized or localized; 12 had ascitis, 11 acute renal failure(ARF), three tumor lysis syndrome (TLS), three hypertension, five with decreased urine output,14 with bilateral renal involvement as diffuse or focal infiltration of the kidney by ultrasound , blood urea increase in 11, creatinine in 10, cholesterol in eight, total serum protein decrease in 18, low albumin in 17, heavy protein urea in six. Average age was 22 months, average duration of illness is two months.

Table 1 (next page) shows all patients presented with generalized edema; 12 with ascitis, 11 ARF, 3 CTLS, 3 Hypertension, 5 with UO, one with tea color urine, 2 with neurological manifestation as extra renal involvement.

Table 2 (pages 25 and 26) shows that 14 cases had renal involvement by ultra or CAT, mild to moderate enlargement with diffuse or focal infiltration, of the kidney in most of the pt, echogenicity in some, normal in 11 cases, while jaw mass in five children, most cases had ascitis, while LN enlargements, mediastinal mass or abdominal masses with or without organomegaly was the extra renal manifestation.

In Table 5 (pages 27 and 28) we notice S uric acid (u ac.) 12, blood urea in 11,S. creatinine in 10, cholesterol in 8, total serum protein(TSP) in 18, S. Albumen in 17, heavy protein urea in 6, -ve in 4 , anuria in 1, electrolytes, hyponatremia in 2, hypokalemia in 6 (not all pt. had done the electrolytes).

Discussion

Secondary involvement of the kidney often occurs as a result of direct invasion or metastatic spread. It is more commonly involved in NHL than HL. The most affected organ is the kidney then the bladder and testis (2-5). Renal disease may be presentat the time of diagnosis and does not necessarily portend a poor prognosis (7). Renal involvement occurs through retroperitoneal extension or hematological metastasis. It is more common in non Hodgkin lymphoma (37%-92.3%) and leukemia (50%-65%) than HL(9). The most expeditious way of diagnosis of renal involvement by lymphoma is kidney biopsy and extra renal signs and symptoms are frequently present (8). In a Turkish study the involvement of the kidneys with non Hodgkin lymphoma was 7.6% and renal involvement in Burkett's lymphoma (BL) has been reported to be 6.3% (10). The involvement is unilateral and or bilateral renal involvement at initial presentation. Such involvement is almost invariably secondary and primary renal NHL is extremely rare. The most common appearance of renal lymphoma in children on ultrasound or CAT is bilateral renal masses with solitary masses or diffuse renal enlargement (7,10-11). Enlargement of the involved kidney or both kidneys may be the only finding on CT (9). In our study we had 14 patients with bilateral renal enlargement, of mild to moderate renal enlargement with nodular or diffuse pattern of infiltration with increase in echogenicity, which could be explained by the infiltrative process of malignancy, and this could be explained also by the process of tumor lysis syndrome (1-5, 7, 11-12) resulting in the enlargement of the kidneys while others had normal kidneys. We had 14(51%) cases of bilateral enlargement (10/21 of new cases all of them of Burkett's type and 4/6 of old cases mainly HL) .

Bilateral renal involvement was frequently present with acute renal failure (ARF). Dense tumor infiltration of renal parenchyma may cause compressive alteration of tubules and impaired renal vascularization (2-5,11-12); we had 11 out of 27 cases of ARF (4 old, 7 new). Tumor lyses syndrome (TLS) may contribute to renal failure along with bilateral dense parenchyma infiltration. TLS prevalence varies among different malignancies. In studies of frequency in patients with intermediate-grade or high-grade non-Hodgkin lymphomas, laboratory evidence of tumor lysis syndrome (42%) occurred much more frequently than the symptomatic clinical syndrome (6%). In children with acute leukemia receiving induction chemotherapy, silent laboratory evidence of tumor lysis syndrome occurred in 70% of cases, but

Ref.	edema	↓ UO	others, ARF, TLS
1	General o	No	ARF
2	Pre orbital o	No	
3*	Puffy face, leg o	Yes	Ascitis, ARF
4	Puffy eyes, leg o	No	Facial palsy
5	Puffy eyes	No	
6	Generalized o	No	Ascitis
7	General o	Yes	TLS , ARF, ascitis
8	General o		TLS, ARF, Ascitis
9	Puffy eyes, leg o		
10	Puffy eye, scrotal, leg o	No	Ascitis (bloody)ARF
11	Puffy eye, general o	No	Tea color urine, ascitis, ARF
12	General o	No	Granular casts
13	Puffy face	No	TLS, hypertension, ARF
14*	General o	No	ARF, ascitis
15*	Leg o	No	Off chemotherapy
16*	General o	Yes	Ascitis, ARF
17	General o	No	
18	Periorbital o	No	Hypertension
19*	General o	Yes	Ascitis, ARF
20	General o	Yes	ARF, acidosis, ascitis
21	General o	No	Ascitis
22	General o	No	
23	Periorbital o	No	
24	Periorbital o	No	Sequant
25	Bilat. leg o, scrotal swelling	No	Hypertension, ascitis
26*	Hand and feet o	No	
27	Peri orbital o, hand and feet o	No	Ascitis

Table 1: Early clinical signs on presentation

It shows all patients presented with generalized edema; 12 with ascitis, 11 ARF, 3 CTLS, 3 Hypertension, 5 with UO, one with tea color urine, 2 with neurological manifestation as extra renal involvement.

Ref	Ultrasound finding	Extra renal	Type and survival in months
1	Bilat. kid. Enlargement, Infiltration, loss of differentiation, ↑echogenicity	Nil	L3, alive, 9
2	Mod. Enlargement of kid.	H&S	L2, alive, 18
3*	No renal enlargement	Huge organomegaly	HL, alive, 20
4	Slight renal enlargement	H&S, focal masses in liver	NHL(BL), alive 10
5	Mild renal enlargement, ↑density of urinary tracts	H&S	L1, alive, 25
6	Normal kid.	RT. jaw swelling, H&S	L1, alive 36
7	Normal kid.	Multiple abd. Mass.	NHL, alive 3
8	Bilat, renal enlargement, nodular masses	RT.jaw swelling, abd. Masses,	NHL(BL), alive,2
9	Not done	L. jaw swelling, L axilla, mass, H&S, mediastinal mass	L3(ALL), alive10
10	Bilateral renal enlargement	H&S	(NHL), alive,8
11	Bilateral renal enlargement infiltrative	Thick bowel, RT. L Effusion,	L3(ALL), alive,3
12	Normal kid.	Abdominal masses, para aortic LN, S, cervical LN.	L2,alive,19
13	Normal kid.	Med. Mass, cervical LN,H&S	L1,alive,15
14*	Normal kid.	Tonsillar NHL	NHL,alive,10
15*	Normal kid	Bone marrow remission	L1,alive, 48 cure

(continued next page)

*old cases, bilat: bilateral ,kid: kidney, H&S: Hepatosplenomegaly, LN: lymphadenopathy, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, BL: Burkitts Lymphoma, mod: moderate

Table 2 (this page and top of next page) : Shows the renal and extra renal presentation

16*	Bilateral enlargement	Ascitis	HL, alive 18
17*	Mild enlargement	Splenomegaly	M4, lived 36 cure
18	Normal	Huge organomegaly	L1, alive 11
19*	Increase bilat. renal echogenicity	RT cervical mass, med. Mass,	HL, alive 20
20	Bilat. renal enlargement	R&L jaw swelling, retrobulbar swelling, abd. Mass, thyroid mass	NHL Died, <1
21	Normal	Huge H&S, ascitis	L2 alive 4
22	Normal	H&S	L2 alive 3
23	Normal	H&S	L1, alive 24
24	Bilat, kid enlargement	H&S, seqAnt, abd. mass	L2 alive, 12
25	Bil. enlargement, R focal involvement	Jaw swelling, H&S, porta hepatitis mass	NHL (BL) Alive 6
26*	Normal	Cervical L N	HL, alive, 20
27	Bilateral kid enlarge., multiple cyctic masses	Cervical LN, scalp mass, H&S	L3 alive, <3

Newly diagnosed cases				Old diagnosed cases			
Ref.	Age y	Sex	Duration day	Ref.	Age y	Sex	Duration day
1	5	M	40	1	8	F	5
2	3	M	20	2	3.5	M	14
3	12	M	30	3	14	F	30
4	2	M	4	4	10	M	30
5	7	M	60	5	5	M	90
6	3	F	20	6	14	M	30
7	3.5	M	30				
8	5	M	25				
9	4	M	10				
10	3	M	14				
11	3	M	30				
12	8	F	21				
13	2	M	90				
14	5	F	40				
15	5	M	60				
16	7	F	30				
17	3	M	60				
18	2	M	14				
19	4	M	10				
20	5	M	21				
21	3	M	10				

Male: female 1.7, and mean age 3.6y , average duration of illness is 2 months

Table 3: characteristics of the patients and duration of illness in days

New	AML(M4)	ALL(L1)	ALL(L2)	ALL(L3)	NHL	HL
	1	6	5	4	5	0
Old	AML(M4	ALL(L1)	ALL(L2)	ALL(L3)	HL	HL
		1				5

New cases (leukemia 16, NHL 5), Old cases (HL 5, ALL 1)

Table 4: Number of patients with different pathology, new and old cases Leukemia and lymphoma

Ref.	urea	U ac.	S. creatinine	TSP	S.ALP	Cholesterol	U.alb	S Na	S.K
1	216	12.5*	2.5-	4*			Trace	133	2.2
2	26	4.9	0.7	2.6*	170,	170	++++		3.3
3	15	6.5	0.5	4.5*	140,	140	Trace		3.5
4	37	9.4*	1.05-	6			Trace	130	3.1
5	22	2	0.7				Trace	127	3
6	15	?	0.8-	5.6*	140,	140	++		3.6
7	45	20*		5.3*	190,	190	Trace	135	4.1
8	56	14.4*	2.3-	3.4*	180,	180	++++		
9	29	7.9*		6.5	170,	170	++		
10	45.3	15.5*	2.2-	5.1*	220,	220	+++		4.8
11	13.7	8.8*	0.8-	5.2*	150.5,	150.5	+	140	2.2
12	?	3.5	0.6	2.6*	108,	108	Trace	136	3
13	3.7	11.3*	1.1-	4.8*			Trace		
14	27	6	0.5	4*	200,	200	+++		
15				4*	360	360	++++		
16				3.6*	180,	180	++++		
17				2*	200,	200	++++		
18	24.5	4.5	0.9-	7.6	199,	199	++++	141	4.3

Table 5 (and continued top of next page): Biochemical findings at presentation

19					280,	280	++++		
20	250	20*	2.8-		180,	180	Anuria	140	5
21	27	3.8	0.7	5.2*	299,	299	--ve		
22	25	4.6	0.5	6.2	120,	120	+	139	3.5
23	27	6	0.6		136,	136	+		
24	29	7.6*	0.7	2.6*			--ve		
25	50	4.3	1.5-	7	227	227	+		
26	50	8.9*		5.5*	100	100	--ve		
27	22	8.3*		6*					

Table 5 (continued): Biochemical findings at presentation

In this table we notice S uric acid (u ac.) 12, blood urea in 11,S. creatinine in 10, cholesterol in 8, total serum protein(TSP) in 18, S. Albumen in 17, heavy protein urea in 6, -ve in 4 , anuria in 1, electrolytes, hyponatremia in 2, hypokalemia in 6 (not all pt. had done the electrolytes).

(Discussion continued)

clinically significant TLS occurred in only 3%(13). This agrees with our study; we had 3 clinical TLS (11%) and 10 laboratory TLS(37%) , TLS was noticed in 3% in leukemia, and 25% of children had advanced stage B L lymphoma (9) in our study. Again we had more TLS with lymphoma than with leukemia and this may be because of the small sample studied and the lymphoma cases presented late with complications.

We had 4 cases of hypertension could be explained by renal compression of renal arteries by lymphoma (8) . Our patients had protein urea ranging froma trace to four + and this indicates glomerular involvement of the disease(8-9).

A few of patients fulfilled the nephrotic syndrome criteria(NS), as generalized edema, puffy eyes or face, pitting leg edema, decreased urine output ,protein urea, hypercholesterolemia, in different levels as shown in Table 4.

The explanation of this picture, is that membranous nephropathy is the most common malignancy associated with nephropathy occurring with many cancers and occasionally with leukemia and lymphoma , the mechanism may involve deposition of tumor antigen in the sub epithelia space with in situ immune complex formation and subsequent complement activation (1,6,9,12). The association between minimal changes of disease and HL well established (1,6,12). We had one patients with tea colored urine and generalized odema, 2 patients with HL presented with typical minimal changes of NS which responds to steroids dramatically case numbers 16 and 19 , only one case with leukemia who was in remission and off of her chemotherapy and presented with NS which is resistant to induction with steroids, (case no. 15).

Again glomerular disease during the course of malignancy could be explained by the paraneoplastic syndrome phenomena ., It can precede or accompany the clinical diagnosis of malignancy(12). NS is the most frequent paraneoplastic association. Alteration of T cell function allows the increase in permeability and causes nephrosis. It is observed in patients who have HL, NHL, Leukemia or other malignancy(12). Urinary symptoms related to paraneoplastic syndromes are characterized by edema resulting from Hypoalbuminemia, proteinuria (>3g/24h) due to neoplastic hypoalbuminemia which is related to reduced albumin synthesis, with hypercholesterolemia. Hypokalemia, hyponatremia or hypernatremia, hyperphosphatemia and alkalosis or acidosis may result from other types of tumors that produce adrenocorticotrophic hormone (ACTH), antidiuretic hormone (ADH). ADH released by blast cell or tumor may cause generalized edema.(14) This explains the edema in all of our patients.

We had 4 cases with jaw swellings at presentation, similar to endemic BL while the others were sporadic with obvious extra renal manifestations. The four HL cases with NS were old cases with multiple relapses on different chemotherapy agents like ifosfamide, methotrexate, and platinum compound which can permanently impair renal function, as well as antibiotics because of recurrent infections, and use of steroids, and analgesics as well the disease itself(15). Not all patients had their Na and K level done because of infrequent availability in the hospital laboratory. Even though they are in the

hyponatremic and hypokalemic side, and may be due to the malignant process or to the ADH secretion by the blast cells (14) most children present late with an average of two months , because of ignorance and denial of signs and symptoms , as well as difficult and unsafe transportation in Iraq during the period of the war at the time of the study, as well the mismanagement by the medical and para medical staff or inexpert doctors in the peripheral system.

The pattern of appearance in children showed similar characteristics to that described in adults which is a prevalence of 5-8% of cases and the appearance of multiple bilateral renal masses was heavily prevalent in children. Multiple small bilateral masses can be seen in patients with leukemia, practically AML (7), cases (17); none of our patients had renal biopsy because of absence of histopathology during that period of war, so we depended mainly on ultrasound and CAT sometimes.

Renal involvement should be considered in all newly diagnosed cases. 60% of our cases were both new leukemia and lymphoma cases, while 16% were old cases. In one study (9) on renal involvement in lymphoma (37-92.3%) and leukemia it was 50-65%, while in our study 42% were leukemia cases and 38% were lymphoma, which is comparable to this study. The small sample size may affect the result. Therefore, decisions about starting chemotherapy should be made on an individual basis16). Oliguria during initial fluid management should alert physicians to patients who may require dialysis during the induction period.(17)

Patients with a high serum lactate dehydrogenase level or renal insufficiency are at increased risk for metabolic complications after chemotherapy and should be closely monitored (18). In pediatric NHL-patients, Burkitt's lymphoma and B-ALL appear to be the commonest cause of metabolic complications early in chemotherapy. Patients with advanced stages and large tumor mass are at high risk for renal failure. Impaired renal function predisposes patients to further complications and toxic death. Prospective studies on renal function prior to and during therapy are required in order to develop a clinical profile reliably detecting patients at risk for developing renal failure and subsequent complications. (19)

Conclusion

Our patients presented late with advanced disease. Renal involvement should be considered in every case of leukemia and lymphoma and routine biochemical studies and ultra sound considered with ± CT as part of base line investigation prior to any chemotherapy.

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Variation in Glucose Tolerance in Health and Disease: Especially "Pre-diabetes" and Early Type 2 Diabetes

ABSTRACT

Glucose homeostasis is a dynamic process which varies between health, disease and in between conditions. Several mechanisms are responsible for keeping the equilibrium in balance. Any disturbances in these mechanisms will produce abnormal conditions such as pre-diabetes or different degrees of frank hyperglycemia. In the following review we will discuss variations in glucose tolerance in health and disease, especially pre-diabetes and early type two diabetes.

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Glucose Tolerance in Health

Glucose tolerance means the ability of the body to properly metabolize and administer glucose load.

To keep the glucose level in constant range despite wide fluctuations in the delivery (e.g. meals) and removal (e.g. exercise) the body needs to integrate different mechanisms.

The glucose pool inside our body receives two tributaries of glucose.

The first one brings the glucose from outside the body as a result of eating. The transport of glucose is uniquely affected by the amount of Sodium in the intestinal lumen. This is because glucose and sodium share the same co-transporters (Sodium-dependent Glucose Transporter - SGLT 1&2) (1).

The second tributary brings glucose synthesized by the body itself.

It was thought that the liver was the sole source of glucose entering the circulation, except during acidosis and after prolonged fasting. Recent studies in human and experimental animals clearly indicate that both liver and kidney release glucose under physiologic conditions (4). Although other organs can produce glucose, only these two organs contain enough glucose-6-phosphatase to make significant amounts of free glucose available for release. The glucose-6-phosphatase enzyme is the enzyme responsible for liberating trapped phospholerated glucose from inside the cells (5).

Glucose is released from the liver by two mechanisms; Glycogenolysis and Gluconeogenesis (6).

Normally the kidney contains little glycogen. The renal cells which make glycogen lack glucose -6- phosphatase enzyme.

Consequently, virtually all the glucose released by the kidney is the result of gluconeogenesis (7).

Glucose transporters (GLUT)

These are 10 transporters ordered according to their date of discovery (2). Among them GLUT-2 and 4 are the most important (2).

GLUT-2 is the glucose sensor of the beta cells. It is not dependent on insulin for its activation (3). The GLUT-4 is expressed mainly in the tissues sensitive to insulin, such as skeletal, cardiac muscles and adipose tissue (3). The GLUT-1 is considered the major glucose transporter in the post absorptive state (3).

Hormonal regulation of normal glucose tolerance

Numerous hormones are working together to regulate the range of glucose concentration in the blood within normal range (8).

Insulin, Glucagon and Catecholamines are the most important acute regulatory hormones. They are able to change glucose release in minutes. Growth hormone,

Cortisol and thyroid hormone are other glucose regulatory hormones. They are able to change glucose release in hours.

Blood glucose regulation:

The liver functions as an important blood glucose buffer system, that is, when the blood glucose rises to high concentration after a meal and the rate of insulin secretion also increases due to that, as much as two thirds of the glucose absorbed from the gut is almost immediately stored as glycogen (9). During the succeeding hours, when the secretion level falls, the liver releases the glucose back into the blood. Both insulin and Glucagon function as important feedback control systems for maintaining a normal blood glucose concentration (9). In severe hypoglycemia, direct effect of low blood glucose on the hypothalamus stimulates the sympathetic nervous system. Epinephrine secreted by the adrenal glands causes release of glucose from the liver and helps in protecting against severe hypoglycemia. The growth and the Cortisol hormones are secreted in response to prolonged hypoglycemia and they both decrease the rate of glucose utilization by most cells of the body (9). Other glucose dependent systems such as the Incretin system participated effectively in glucose regulation after meals (10).

Glucose tolerance in pre-diabetes and early type 2 diabetes

Normoglycemia is maintained by the balance interplay between insulin action and insulin secretion.

Beta cells dysfunction is a critical component in the pathogenesis of impaired glucose tolerance (11).

In the pre-diabetes state and early course of type 2 diabetes, postprandial beta cell action becomes abnormal, as evidenced by the loss of immediate insulin response to a meal which leads to hyperglycemia (12).

The glucose tolerance during the pre-diabetes state and early type 2 diabetes was affected by:

Beta cell dysfunction

This is a condition of the function of the pancreatic beta cell such that insulin secretion is insufficient to match the degree of insulin resistance (13).

Causes of beta cell dysfunction:

- Genetic predisposition

- Glucose toxicity:

This is potentially irreversible beta cell damage due to chronic exposure to supraphysiological glucose concentration (14).

- Lipid toxicity :

Free Fatty Acids and cholesterol may alter the intracellular calcium signaling and generating ceramide, which induces apoptosis (15).

Peripheral insulin resistance:

Insulin resistance is said to be present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose production primarily in the liver. Hepatic insulin resistance is the driving force for hyperglycemia.

Insulin resistance is strongly associated with obesity particularly abdominal obesity (16). An increased mass of stored triglyceride, especially in visceral or deep subcutaneous depots, leads to large adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. This results in increased release and circulating levels of Non-Etherified Fatty Acids (NEFA) and glycerol, both of which aggravate insulin resistance in skeletal muscle and liver (15).

Increased circulation of NEFA and inflammatory cytokine release by expanded visceral adipose tissue adversely affect the insulin signaling cascade (17).

IFG and IGT differ in their site of insulin resistance. People with IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance (18).

Loss of the rapid phase of insulin secretion:

In healthy individuals, insulin is secreting in a pulsatile manner and the insulin response occurs in a biphasic pattern; the rapid and latent phase.

The rapid phase reached its peak in 3-5 minutes and lasts for 5-10 minutes. The latent phase starts 10-20 minutes after exposure to glucose and can last for hours (8).

Physiological functions of the rapid phase of insulin secretion:

i. Suppress endogenous glucose production (19).

ii. Primes insulin sensitive tissues (20).

iii. Suppress endogenous glucose production indirectly through inhibition of lipolysis in adipose tissue (21).

Conclusion

Blood glucose regulation controlled by multiple pathways which is running together in synchronous to keep our glucose level within normal range. Any disturbance in these pathways will lead to disturbance in the process of glucose homeostasis.

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Hypercalcemia is not an uncommon presentation for hepatic granulomatosis. A case report in Kuwait and review of the literature

ABSTRACT

Hypercalcemia is not uncommon in patients with active TB, but is often mild and asymptomatic in most cases. Regardless of the frequent highlighted causes of hypercalcemia, it is important to consider other unusual causes including various causes of granulomatosis in certain clinical situations when the underlying cause of hypercalcemia cannot be attributed to primary hyperparathyroidism or overt malignancy. We report a thirty year old Indian gentleman who presented for the first time with renal colic and was discovered to have renal calculi and hypercalcemia. Disseminated TB was found to be the underlying cause of hypercalcemia. The diagnosis was made after liver biopsy which demonstrated histological features of hepatic tuberculous granuloma. After treatment with anti-tuberculosis medication, his serum corrected Calcium fell back to normal.

Key words: **Hypercalcemia, Renal stones, Hepatic granuloma, Tuberculosis**

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Introduction

The association between tuberculosis (TB) and hypercalcemia is well recognized. Even though the incidence of hypercalcemia in tuberculosis has been reported to be as high as 28 percent, other studies suggest a much lower incidence of 2.3 percent or less [1]. This variation among different nationalities could be attributed to differences in vitamin D and calcium intake, amount of sun exposure, prevalence of tuberculosis, and various laboratory diagnostic criteria for hypercalcemia [2] .

Hypercalcemia could be a clue to the presence of unsuspected systemic illness. With liver involvement in tuberculosis, though common both in pulmonary and extrapulmonary tuberculosis, the diagnosis is often overlooked because hepatic tuberculosis can have a relatively nonspecific clinical presentation [3] .

Case Report

A thirty year old Indian gentleman was admitted to the urology department in Jahra hospital Kuwait, with right loin pain radiating to the groin and was discovered to have right renal stone for which nephrostomy was done followed by DJ stent fixation. One week later the patient was referred to the medical team for persistent fever, hypercalcemia and thrombocytopenia. He had no history of cough, expectoration or hemoptysis, no body swelling or skin rash, no arthralgia, arthritis or photosensitivity, no dyspnea, orthopnea or paroxysmal nocturnal dyspnea (PND). Apart from the renal colic he hadprior, and anorexia over the past three months, there were no other gastrointestinal symptoms. He didn't report any TB contact. On examination he looked toxic. He had cervical and inguinal lymphadenopathy, small in size firm, mobile, non tender. His temperature ranged from 37.8 - 39 °C. The BP was within normal range with no postural hypotension. He had mild diffuse abdominal tenderness and hepatosplenomegaly. Neurological, chest and cardiac examination were unremarkable. Laboratory workup showed high ESR of 80 mm/h, thrombocytopenia with platelet count around 60.000/mm3, mild normocytic normochromic anemia; his RFT and LFT was normal apart from mild hypoalbuminemia with albumin level of 3.2 gm%. He had hypercalcemia with normal Phosphorus and alkaline phosphatase level; the corrected Ca level was up to 3 mmol/L. Unfortunately, parathyroid hormone level and vitamin D level were not available to us. His CXR revealed fibrotic lesion in the left mid lung. In his abdominal US there were hepatosplenomegaly with multiple lymph nodes in the porta hepatis which was further confirmed by CT abdomen.

His serum calcium level remained elevated above the upper normal limit despite intravenous hydration with normal saline and his platelet count improved spontaneously reaching up to 130.000 /mm3 before starting the specific treatment. A bone marrow biopsy was performed and

showed hypercellular bone marrow with adequate megakaryocytes. FNAC from cervical LN showed non-specific Lymphadenitis. The diagnosis was made after liver biopsy which revealed epithelioid cell granuloma formation with caseous necrosis and giant cells of Langerhans. Although staining for acid fast bacilli was negative, the granulomatous changes were likely of tuberculous etiology (Figures 1-2 opposite page).

Figures 1-2

Microscopic view of the liver of the patient, showing features of tuberculosis with chronic granulomatous inflammation with caseation and giant cells (hematoxylin and eosin stained, with magnification).

Anti-tuberculosis chemotherapy including daily isoniazid (300 mg), rifampin (450 mg), ethambutol (800 mg), pyrazinamide (1 gram), and pyridoxine (50 mg) were initiated. The patient showed excellent response to antituberculous treatment where the serum calcium level dropped back to normal and the patient generally improved. Ethambutol and Pyrazinamide was discontinued after two months of therapy while the rest of medications were recommended to be continued for 12 months.

Discussion

We have reported a patient presenting with hypercalcemia complicating tuberculous hepatic granuloma. We based our diagnosis of tuberculosis in this case on the presence of symptomatic hypercalcemia, presence of renal calculi, liver biopsy showing histological features of hepatic tuberculous granuloma and improvement with antituberculous chemotherapy.

The first presentation of our patient was with renal colic; probably he had previous genitourinary tuberculosis manifested as renal calculi. Hematogenous spread to the liver and flaring up of the infection could follow urinary tract manipulation following insertion of DJ stent fixation. Previous reports have described the onset of miliary tuberculosis after urinary tract manipulation, such as extracorporeal shock wave lithotripsy [4] and ureteral catheterization [5]. Concerning the mechanism of hypercalcemia in tuberculosis it could be attributed to the enhanced extrarenal 1a hydroxylase activity that causes increased hydroxylation of 25-hydroxyvitamin D to calcitriol in the macrophage. CD8 +T lymphocyte at the granulomatous side is another source of active TB metabolite [6]. Such calcitriol is considered a beneficial local paracrine factor as it has an immunomodulatory function through enhancing all cell-mediated immunity to TB and improving the capacity of activated macrophages to kill mycobacteria. Hypercalcaemia occurs when calcitriol is produced in large quantities with spillage into the circulation [7]. Others found normal level of calcitriol in a similar case [8].

Unfortunately Serum 25-hydroxyvitamin D and calcitriol were not available to us to clarify the underlying mechanism leading to hypercalcaemia in our patient and whether it is related to abnormal vitamin D metabolism. However the dramatic response of the patient to the anti-tuberculous treatment with normalization of the serum calcium supported our view that the elevated calcium level in such a case was related to the underlying disease he had.

Up on presentation, the patient had mild hypoalbuminemia. In a previous study 66 percent of patients with active TB had hypoalbuminemia at the time of diagnosis [9]. Other authors reported a much lower incidence where hypoalbuminemia was present in 36% of their patients with TB at admission [2]. The reason for hypoalbuminemia being observed in our patient before starting anti TB chemotherapy is related partly to the chronic illness he had as well as protein caloric malnutrition owing to the poor socioeconomic setting.

It was suggested, that thrombocytopenia in patients with TB might be due to the active tuberculosis and possible peripheral destruction of platelets by the bacterium or hyperactive splenomegally [10]. We can't relay the cause of thrombocytopenia observed in our patient to such reasons as it recovered spontaneously before starting anti TB treatment. Prior use of other medications could be the cause.

In our patient, even though the bone marrow biopsy was not decisive, the liver biopsy was diagnostic. Liver biopsies have the highest yield as demonstrated in a previous study[11]. Although staining for acid fast bacilli was negative, the granulomatous changes were likely of tuberculous etiology. Guided percutaneous liver biopsy was successful in demonstrating AFB in only two of 21 cases of local hepatic tuberculosis in previous reports [12]. Demonstration of AFB is more common in tubercular abscess rather than solid tuberculomas because AFB are abundant in liquefied caseous material.

Conclusion

Keeping in mind that hypercalcemia may complicate serious treatable diseases, the rare associations should be considered. Nowadays tuberculosis is growing with the appearance of MDR strains and so it is important to detect the disease and treat it adequately. The case presented here would be overlooked if the differential diagnosis of tuberculosis which may present with different biochemical and hematologic manifestations was not considered. Diagnosis may be difficult and delayed, often necessitating histological confirmation by biopsy of expected involved organ.

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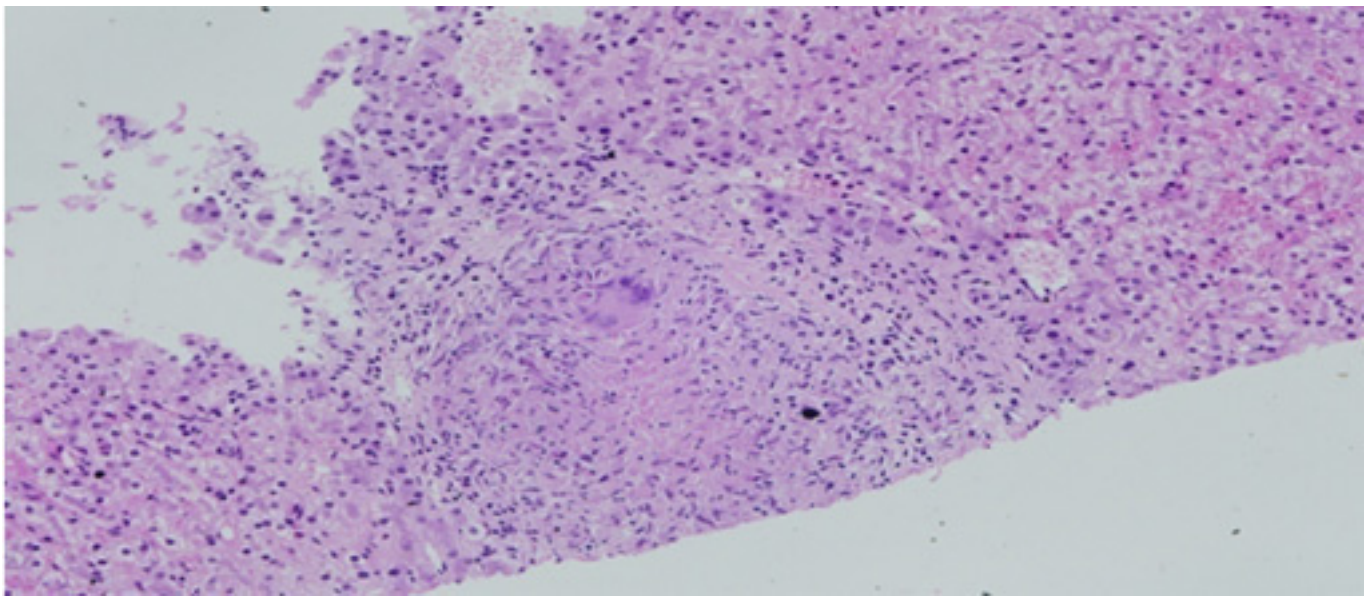

Figure 1

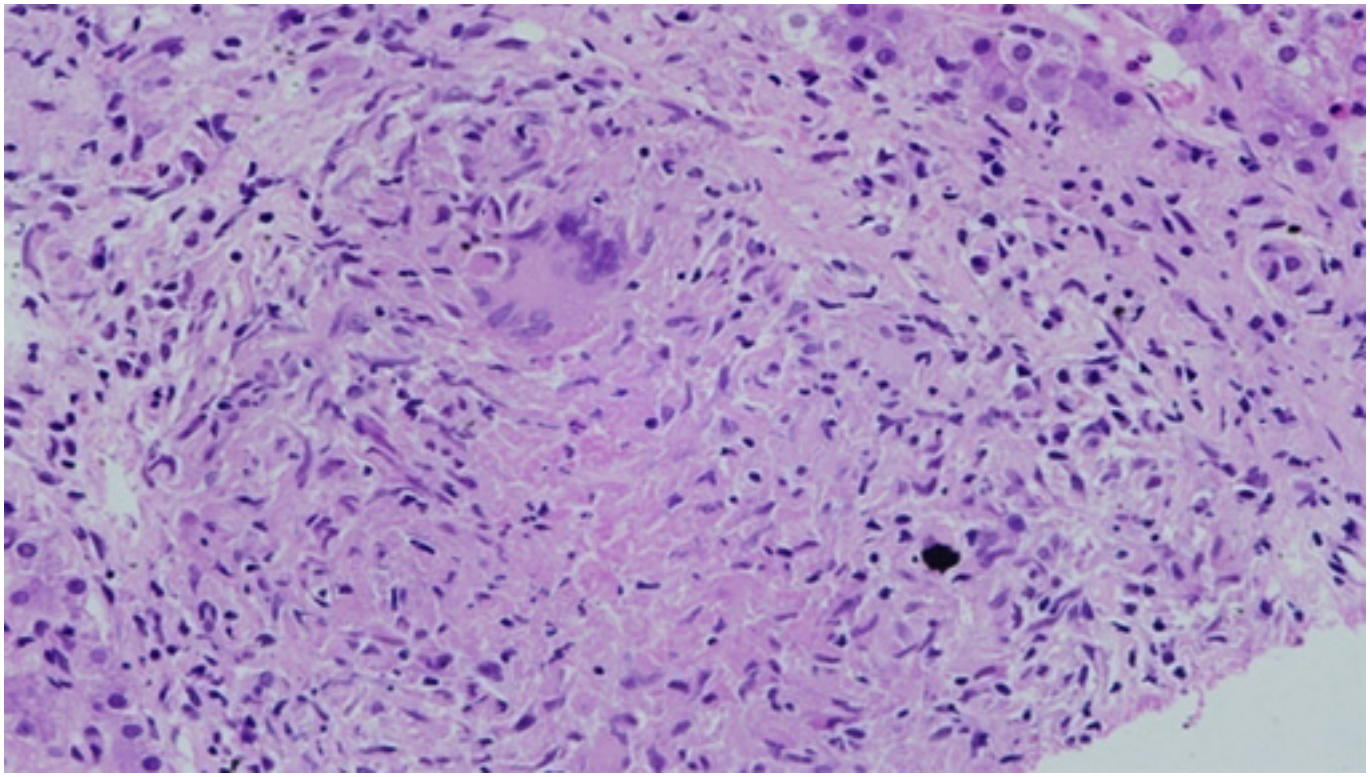

Figure 2

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Unusual presentation of chylothorax in a newborn infant - case report

ABSTRACT

Chylothorax is a rare condition in neonates and it is defined as an abnormal accumulation of lymphatic fluid in the pleural space. Chylothorax causes severe respiratory and nutritional problems and is associated with high mortality rate. Octreotide is a long-acting somatostatin analog that reduces lymphatic fluid production and it has been used as a new strategy in the treatment of chylothorax. Here, we report a 7 day old, full term male baby with severe right sided pleural effusion which was confirmed to be a case of congenital chylothorax.

Key words: newborn, chylothorax

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Introduction

The accurate and efficient diagnosis of chylothorax depends on the understanding of the anatomy of the thoracic duct, the constituents of chyle, and the diverse etiologies of chylothorax.

ANATOMY OF THE THORACIC DUCT

Generally, the thoracic duct ascends from the cisterna chyli (sac at the lower end of the thoracic duct into which the intestinal and two lumbar lymphatic trunks drain), which lies just anterior to the first or second lumbar vertebra, and passes through the aortic hiatus of the diaphragm to enter the posterior mediastinum, although wide anatomic variation exists [1]. The thoracic duct continues cephalad in a rightward position between the aorta and azygos vein until it reaches the approximate level of the fifth thoracic vertebra, where it crosses over the vertebral column behind the esophagus and continues in the left posterior mediastinum. The thoracic duct in this region is 2 to 3 mm in diameter and passes behind the aortic arch adjacent to the left side of the esophagus and behind the left subclavian artery. It then arches over the subclavian artery in the anterolateral superior mediastinum, descending to empty into the venous circulation in the region of the left jugular and subclavian veins. As the thoracic duct passes through the mediastinum, it also receives nonchylous lymph from tributaries that drain regions of the pulmonary parenchyma and parietal pleura [2]. The sum of these sources accounts for a total lymphatic flow through the thoracic duct of 1,500 to 2,400 mL/day [3]. This flow increases with dietary intake of fat, particularly long-chain triglycerides.

CHYLE COMPOSITION

Chylothorax is caused by disruption or obstruction of the thoracic duct that results in leakage of chyle (lymphatic fluid of intestinal origin) into the pleural space. The fluid typically has a high triglyceride content in the form of chylomicrons, lymphocytes (primarily T lymphocytes) as the major cellular component, and the electrolyte content of chyle is similar to plasma, and the protein concentration is usually greater than 3 g/dL. Chyle is also rich in immunoglobulins and contains all of the fat soluble vitamins absorbed from the intestine and often has a turbid or milky white appearance.

ETIOLOGY OF CHYLOTHORAX

In infants and children, chylothorax may occur as a complication of surgery or birth trauma, in association with pulmonary tumors and pulmonary lymphatic abnormalities or in association with various syndromes. However, most commonly, the etiology remains unknown and the chylothorax is considered ‘’idiopathic’’. Up to 50% of all incidents of chylothorax are recognized in the first week of life, but idiopathic neonatal chylothorax may be recognized even up to several weeks of age [4,5]. It occurs twice as often in males, and the incidence has been reported as 1/10,000-15,000.

TREATMENT

Although thoracostomy drainage is the first-line therapy in the treatment of chylothorax, octreotide, a long-acting somatostatin analog that may act on somatostatin receptors in the splanchnic area to reduce lymph fluid production, has been used in chylothorax in infants and older children.[6,7]

Herein we report a neonate who had an unusual right sided spontaneous chylothorax and was treated with octreotide.

Case Report

7 day old male infant, product of full term normal vaginal delivery, Apgar score at birth, 1st minute and 5th minute 8/10; birth weight 4kg, length 50 cm and head circumference 34 cm. The baby was discharged home after 24 hours.

The mother was 27 years old. Gravida 4, Para 4. She didn't receive any medication during pregnancy. There was no consanguinity between parents.

The baby was brought to the clinic with history of hypo activity, difficulty of feeding and attacks of cyanosis of two days duration.

Clinical examination revealed no dysmorphic features, no fever, but signs and symptoms of severe respiratory distress (Temperature 37º C , Heart rate 160 beat/min, Respiratory rate 55 cycle/min. Mean arterial pressure 35, O2 saturation 83%). Chest Xray revealed large right sided pleural effusion (see Figure 1) and Chest CT scan revealed right side massive pleural effusion accompanied by compressive atelactasis involving right lung along with shift of mid line structure to other side, 2D-ECHO revealed normal heart and Abdomen ultrasound revealed normal finding. Serum CBC and electrolyte were normal.

The baby was admitted to the intensive care unit where he was maintained thereafter on mechanical ventilation.

A thoracostomy tube was placed on the right side and a deep yellow fluid was drained (see Figures 2 and 3).

The fluid had the following characteristics : protein 3.5 g/dl, LDH 532 IU/l, Glucose 111 mg/dl, Triglyceride 864 mg/dl, cholesterol 54 mg/dl, WBC 12,000, RBC 10,000. Neither blood nor pleural fluid cultures revealed bacterial growth.

The neonate was diagnosed to have chylothorax. Enteral feeding was discontinued and total parenteral nutrition was started. The amount of pleural effusion (190 ml/day) decreased gradually and resolved on the 2nd day but the pleural effusion reappeared on the day after. Therefore intravenous octriotide 20 microgram single dose /day (1-10 microgram/Kg) was started. On the 3rd day after institution of octriotide, pleural effusion stopped and the chest tube was removed (see Figure 4 - next page) and enteral feeding was restarted with human milk. After 10 days of admission the patient was discharged from hospital in a good condition.

Discussion

Our case had no dysmorphic features and no known risk factor for the occurrence of chylothorax, such as history of thoracic surgery or placement of a central venous catheter to cause thrombosis in the superior vena cava. In addition it was on the right side when the most common occurrence is on the left side. Therefore our case was considered to be a spontaneous right sided neonatal chylothorax, and the right sided involvement in our case could be explained by the fact that the anatomy of the thoracic duct determines the location of the effusion seen with duct injury or obstruction and because the thoracic duct crosses the mediastinum at the fifth thoracic vertebral body, lymphatic injury or obstruction below this level results in a right-sided pleural effusion. In contrast, disease above this level usually leads to a left-sided effusion [8].

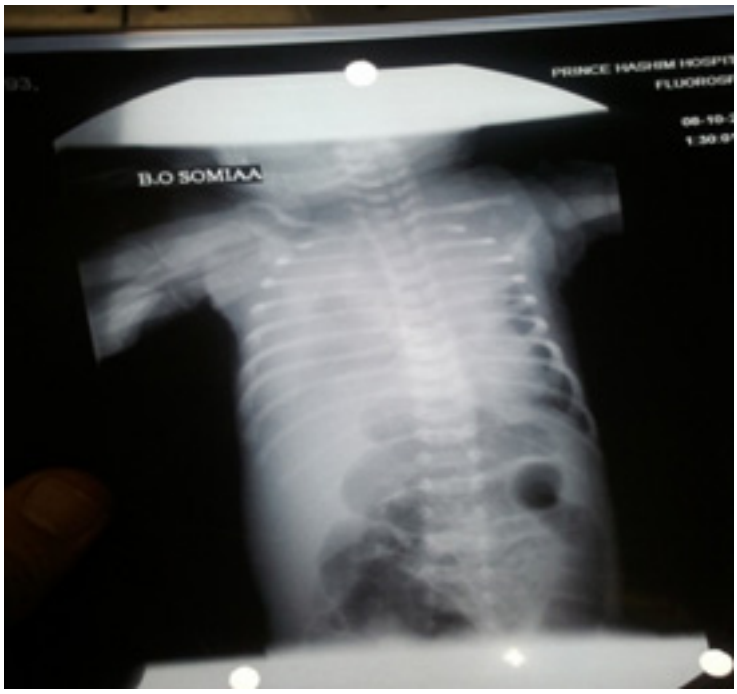

Figure 1: Chest X-Ray showed the large right side pleural effusion

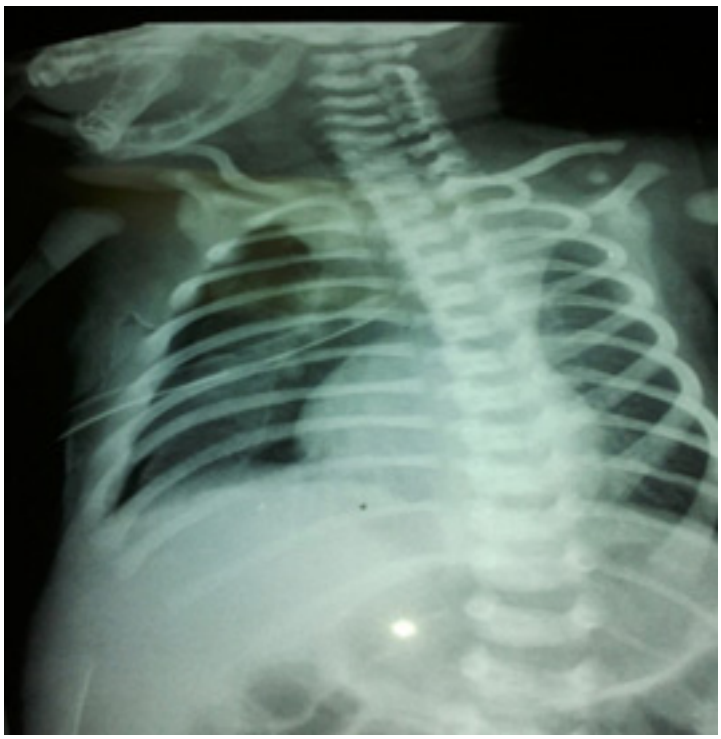

Figure 2: Chest X-Ray of the Baby after thoracostomy was done, with right side chest tube

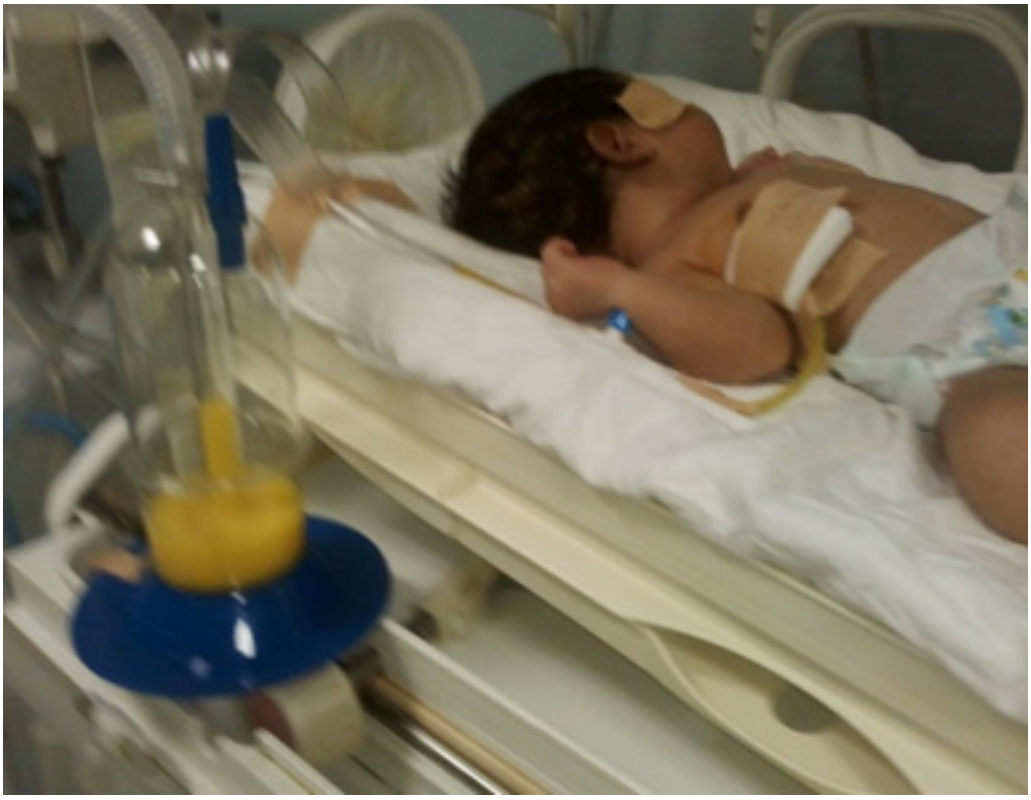

Figure 3: The baby with right side chest tube: notice the deep yellow color pleural effusion

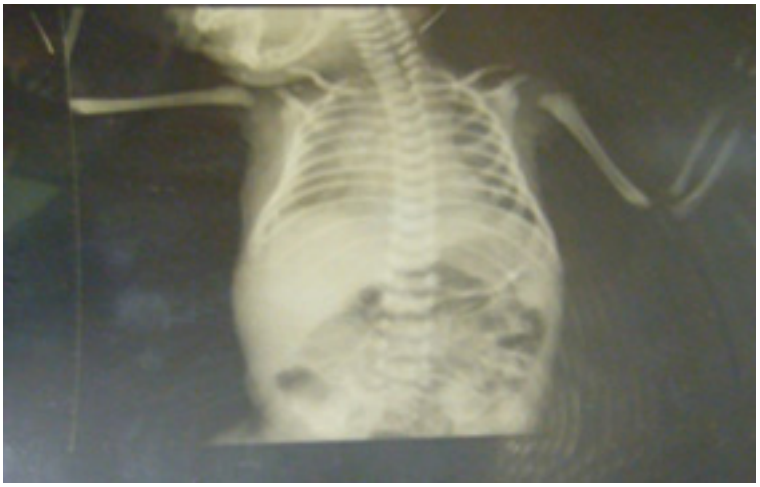

Figure 4: Chest X-Ray showed the baby after resolution of pleural effusion and removal of chest tube

of the effusion seen with duct injury or obstruction and because the thoracic duct crosses the mediastinum at the fifth thoracic vertebral body, lymphatic injury or obstruction below this level results in a right-sided pleural effusion. In contrast, disease above this level usually leads to a left-sided effusion [8].

Etiology is unknown in the majority of neonatal chylothorax cases. Idiopathic congenital chylothorax is mostly associated with lymphangiomatosis,[9] congenital lymphangiectasia,[10] Down's syndrome,[11] and maternal polyhydramnios.[12] These neonates are born with a weak thoracic duct or lymphatic anomalies. Therefore, any increase in venous pressure (e.g. during delivery) would lead to a break of the duct.

Spontaneous neonatal chylothorax is usually a transient condition that resolves by cessation of the lymphatic flow in the thorax.

Somatostatin is a peptide that acts as a neurohormone. Use of somatostatin to treat chylothorax was first reported in 1990 in an adult,[13] and in 2003 in a neonate[1].

Octreotide is a synthetic somatostatin analog. Although the exact mechanism of action of octreotide is not understood, it may act on somatostatin receptors in the splanchnic circulation, and decrease lymph fluid production through a reduction in gastric, intestinal, and pancreatic secretions or by a decrease in hepatic venous pressure and splanchnic blood flow. Response of our patient to somatostatin showed that somatostatin is an effective method of chylothorax treatment.

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