Medicinski arhiv

Medical Archives

Journal of the Academy of Medical Sciences in Bosnia and Herzegovina

• Year 2010 • Volume 64 • No 6 •

Journal is indexed in medline (www.pubmed.gov), ebsco (www.ebscohost.com) and index copernicus - ic (www.indexcopernicus.com)

Esad Cizmic, Street in Old town, 1990

p ISSN 0350-199 X
eISSN 1986-5961

contents

ADDRESS OF THE BOARD

Sarajevo, Cekalusa 90,
Tel: 033 444 714,
e-mail: avicena@lol.ba
www.amn.ba
www.avicenapublisher.org

PUBLISHED BY

AVICENA, d. o. o.., Sarajevo,
Zaima Sarca 43,
Bank account:
UNION banka Sarajevo, br.:
1020500000020077
SWIFT Code UBKSBA22,
Deutsche Bank AG, Franfurt am Main (DEUTDEFF), Account No. 9365073 10 (EUR), IBAN BA 39 1020500000020077
Medical Archive journal is published five to six times per year (Feb, Apr, Jun, Oct, Dec). Subscription for individuals is 50 euros, for institutions 100 euros, and includes VAT and postal services.

Journal is indexed in MEDLINE, EBSCO and
INDEX COPERNICUS–IC
(ICV for 2009 is 5.85

PAPERS

ORIGINAL PAPER

Post-corrosive Late Complications in Esophagus and Stomach – Role of the Esophageal Rest

Andon Chibisev
University Clinic for Toxicology, Clinical Centre, Skopje, Republic of Macedonia

Acute corrosive poisonings cause severe chemical injuries of the upper gastrointestinal tract, the most common location being the esophagus and the stomach. There are different opinions concerning the question of taking food and liquids by mouth immediately after caustic ingestion. This prospective study comprised 146 patients aged between 14 and 75 years divided in two groups. In the examined group prevailed those with esophagitis gr.IIb (n=36; 54,54 %), esophagitis gr.III (n=30; 45,45 %), gastritis gr. IIb (n=42, 63,63 %) and gastritis III (n=24;36,36%). In the controlled group prevailed those with esophagitis gr III (n= 52; 65 %) and esophagitis gr IIb (n= 28; 35 %), gastritis gr. IIb(n= 55; 68,75 %)and gastritis gr III (n= 25; 31,25 %). Analysis of the results has shown a high percentage of esophageal stenosis in both groups 25 days after poisoning (31.82% v.s 43.75%), three and six months after poisoning (36.36% v.s. 52.50%) and also gastric injuries 25 days after the poisoning (37,88 % v.s. 46,25 %), three and six months after the poisoning (40,91% v.s 53,75%) In spite of the not significant difference, the results of our investigation have shown that the group with "esophageal rest" (NPO) had a smaller percentage of post-corrosive complications than the patients who were given food or liquids immediately after poisoning. **Key words:** caustic poisonings, caustic injuries, esophageal rest, post-corrosive stenosis

Corresponding author: Andon Chibisev, MD, PhD. University Clinic for Toxicology, Clinical Centre, Vodnjanska 17, 1000 Skopje, Republic of Macedonia, Tel: +389 2 3211 072, +389 2 3237 504, +389 2 3147 635, +389 70 387 040, +389 75 223 223, E-mail: toksikourgentna@gmail.com

1. INTRODUCTION

Acute corrosive poisonings appear as a result of ingestion of acids, bases, oxidants, heavy metal salts and other chemical substances. They cause chemical injuries of the upper gastrointestinal track, the most common location being the esophagus and the stomach. The patients present with a serious clinical picture; clinical examinations are difficult to be conducted and therapy and final outcome are often uncertain (1,2). The most serious lesions occur in the esophagus and the stomach since the poison remains there a long time due to the specific anatomic structure of these organs. If the patient survives the acute phase of the poisoning, regenerative response may result in esophageal and/or gastric stenosis and increased risk for esophageal and gastric cancer (3,4).

In establishing the diagnosis and therapeutic approach of corrosive poisonings, the severity of the post-corrosive endoscopic changes of the esophagus, stomach and duodenum is of major importance. It is detected with esophagogastroduodenoscopy, which is conducted 12-24 hours after ingestion of the corrosive agent (5,6).

We usually use the classification of endoscopic post-corrosive injuries in the upper GIT suggested by Kikendall:

- First grade: erythema and edema of the mucosa;
- Second (A) grade: erosions, blisters, superficial
- ulcers (transversal and linear), exudation, hemorrhage;
- Second (B) grade: circumferential lesions;
- Third grade: multiple deep brownish-black or grey ulcerations and necrosis;
- Fourth grade: perforation (7).

Severity of the lesions depends on the nature, quantity and concentration of the corrosive substance, and the duration of exposure . The damaged mucosa, submucosa and muscle layer regenerate with great difficulty because of the surrounding inflammation, necrosis and secondary complications. Tissue fibrosis, adhesions or circular stenosis appear, which greatly disturb the normal functioning (impeded peristaltic, impeded passage). All these complicate the entire general condition of the patient, including inadequate normal food intake, loss of body weight, prostration, cachexia (8).

There are different opinions concerning the question of taking food and liquids by mouth immediately after caustic ingestion. Many authors recommend NPO (nill per os) or the so-called

"esophageal rest" until the first endoscopic control (10 – 15 days). During the "rest", the patient is fed completely parenterally by peripheral or central vein, or enterally by nasogastric or nasoenteral tube, gastrostoma or jejunostoma (9).

There is another group of authors that recommend taking liquids 48 hours after ingestion if the patient can swallow his/her saliva (10).

The aim of this paper was to present the influence of the esophageal rest i.e. NPO in development of post-corrosive stenosis in the upper gastrointestinal tract.

2. MATERIAL AND METHODS

This prospective study included a group of 146 patients, at the age between 14 and 75 years, hospitalized and treated at the University Clinic of Toxicology in Skopje in the period 2007-2009. The patients were divided in two groups:

Group 1: consisted of 66 patients, with mean age in the interval 42.9 ± 16.5 years, who were fed enterally (nasojejunal tube or feeding enterostoma) and were not given food by mouth in the first 10-15 days (NPO or esophageal rest). This was the examined group.

Group 2: consisted of 80 patients,with mean age in the interval 32.9 ± 15.6 years, who were given liquid food by mouth in addition to parenteral nutritional support in the first 48 hours after admission to the hospital. This was the control group.

Follow-up period lasted for 6 months.

In all patients diagnostic esophagogastroduodenoscopy was done in the first 12-14 hours after caustic ingestion, control esophagogastroduodenoscopy 15-25 days, three or six months after caustic ingestion. During urgent esophagogastroduodenoscopy in patients of group 1 with II B grade of injury nasojejunal tube was inserted under endoscopic control for post-pyloric nutrition. In patients with III grade of injury, after consulting an abdominal surgeon, a feeding enterostoma was implanted laparoscopically in the first 96 hours for artificial post-pyloric nutrition. Patients were analyzed according to their clinical findings, gender, way of poisoning (suicidal and accidental), chemical structure of the corrosive agent (acids, alkalis, other caustic substances).

Category	Admission		15 days after ingestion		25-30 days		3 months		6 months	
	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)
Esophagitis	/	/	51 (77,27)	69 (87,25)	3 (4,55)	4 (5,0)	/	/	/	/
Esophagitis gr.II b	30 (45.45)	42 (52,50)	5 (7,58)	7 (8,75)	1 (1,52)	9 (11,25)	/	/	/	/
Esophagitis gr.III	36 (54.55)	38 (47,50)	8 (12,12)	4 (5,0)	1 (1,52)	2 (2,5)	/	/	/	/
Stenosis	/	/	1 (1,52)	/	21 (31,82)	35 (43,75)	24 (36,36)	41 (51,25)	24 (36,36)	42 (52,50)
Normal finding	/	/	1 (1,52)	/	40 (60,61)	30 (37,50)	42 (63,64)	39 (48,75)	42 (63,64)	38 (47,50)
Total	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)

Table 1. Endoscopy/esophagus (esophageal rest v.s. liquid diet) E.R.- esophageal rest L.D.- liquid diet

Category	Admission		15 days after Ingestion		25-30 days		3 months		6 months	
	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)	E.R. (n)(%)	L.D. (n)(%)
Gastritis	/	/	51 (77,27)	60 (75,0)	4 (6,06)	3 (3,75)	1 (1,52)	/	1 (1,52)	/
Gastritis gr.II b	42 (63,64)	46 (57,50)	10 (15,15)	11 (13,75)	1 (1,52)	2 (2,5)	/	/	/	/
Gastritis gr.III	24 (36,36)	38 (47,50)	3 (4,55)	9 (11,25)	/	/	/	/	/	/
Stenosis antri	/	/	/	/	4 (6,06)	9 (11,25)	5 (7,58)	8 (10,0)	4 (6,06)	10 (12,5)
Stenosis antropylori	/	/	1 (1,52)	/	10 (15,15)	13 (16,25)	11 (16,67)	16 (20)	12 (18,18)	16 (20)
Stenosis pylori	/	/	/	/	11 (16,67)	15 (18,75)	11 (16,67)	17 (21,25)	11 (16,67)	17 (16,67)
Normal finding	/	/	1 (1,52)	/	36 (54,54)	38 (47,50)	38 (57,58)	39 (48,75)	38 (57,58)	37 (46,25)
Total	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)	66(100)	80(100)

Table 2. Endoscopy/gaster (esophageal rest v.s.liquid diet) E.R.- esophageal rest L.D.- liquid diet

The following statistical methods have been applied:

- Chi-square test (X^2 test) was used to determine the significance of difference in the onset of stenosis in the examined and control groups (post-corrosive esophagitis gr. IIb and III and post-corrosive gastritis gr. IIb and III);
- Relative risk (RR) was used to determine the risk for onset of stenosis in the examined and control groups (post-corrosive esophagitis gr. IIb and III and post-corrosive gastritis gr. IIb and III).

3. RESULTS

The examined group consisted of 66 patients, of whom 15 (22.72%) were males and 51 (77.27%) females; the youngest patients being 18 years old and the oldest 71 years old (± 95.000 Confid. Interval from 37.3 to 48.4 years.).

Days when patients received no food by mouth (NPO) varied in the interval 10.39±1.49 days, minimum 8 days and maximum 14 days.

The control group consisted of 80 patients, of whom 16 (20%) were males and 64 (80%) females. The youngest patients were 14 years old and the oldest 75 years old (± 95.000 Confid. interval from 29.4 to 36.3 years).

These patients were given liquid food by mouth 48 hours after esophageal rest.

The largest number of the examined group of patients – 43 (65.15%) ingested HCl, 15 (22.72%) used NaOH and 8 (12.12%) CH_3COOH.

The majority of patients – 61 (92.42%) had suicidal intent and 5 (7.57%) ingested caustic agent accidentally.

In the control group of patients, prevailed those who ingested hydrochloric acid – 51 (63.75%), 13 (16.25%) used acetic acid, 9 (11.25%) ingested sodium hydroxide whereas 7 (8.75%) sulphuric acid.

Analysis of the results in both groups of patients showed a high percentage of esophageal stenosis 25 days

Variable	Stenosis	Normal	RR	95%CI
15 days				
EG	1	65		
CG	0	80	Infinity	Nan<O.R.<Infinity
25-30 days				
EG	21	45		
CG	35	45	0.73	0.47-1.12
3 months				
EG	24	42		
CG	41	39	0.71	0.49-1.04
6 months				
EG	24	42		
CG	42	38	0.69	0.47-1.01

EG- examined group; CG- control group; RR-Risk Ratio;
CI- Confidence interval

Tabela 1a. Determination of risk for occurence of stenosis in patients with post-corrosive injuries (esophagitis IIA and III) in the examined and control group

Variable	Stenosis	Normal	RR	95%CI
15 days				
EG	1	65		
CG	0	80	Infinity	Nan<O.R.<Infinity
25-30 days				
EG	24	36		
CG	37	43	0.86	0.59-1.28
3 months				
EG	27	39		
CG	41	39	0.80	0.56-1.14
6 months				
EG	27	39		
CG	43	37	0.76	0.53-1.08

EG- examined group; CG- control group; RR-Risk Ratio;
CI- Confidence interval

Tabela 2a. Determination of risk for occurence of stenosis in patients with post-corrosive injuries (gastritis IIA and III) in the examined and control group

after poisoning (31.82% vs 43.75%) and three and six months after poisoning (36.36% vs 52.50%) (Table 1).

Analysis of the results in both groups of patients has shown a large percentage of post-corrosive gastric injuries 25 days after caustic ingestion (37.88% vs 46.25%) and three and six months after caustic ingestion (40.91% vs 53.75%) (Table 2).

Table 1a. shows the results of the risk for onset of post-corrosive injuries (esophagitis IIB and III) in the examined and control groups of patients.

Fifteen days after initiation of therapy, for chi-square=1.22 and p >0.05 (p=0.27), there was no significant difference in the distribution of the results between the examined and control group.

After administration of therapy for 25-30 days, the chance for occurence of stenosis in patients fed by tubes was 0.73 times smaller / RR=0,73 (95%CI 0.47-1.12)/, in comparison with patients given liquid diet, although the difference was not significant.

Three months after treatment, the chance for occurence of stenosis in patients feb by tubes was 0.71 times smaller / RR=0,71 (95%CI 0.49-1.04)/, in comparison with patients given liquid diet, although the difference was not significant.

After 6 months, the chance for occurence of stenosis in patients feb by tubes was 0.69 times smaller / RR=0,69 (95%CI 0.47-1.01), in comparison with patients given liquid diet, although the difference was not significant.

Table 2a. presents the results of the risk for onset of stenosis in patients with post-corrosive injuries of the stomach (gastritis IIB and III) in the examined and control groups of patients.

Fifteen days after initiation of the therapy, for chi-square=1.22 and p >0.05 (p=0.27), there was no significant difference in the distribution of the results between the examined and control group.

After administration of therapy for 25-30 days, the chance for occurence of stenosis in patients fed by tubes was 0.86 times smaller / RR=0,86 (95%CI 0.59-1.28)/, in comparison with patients given liquid diet, although the difference was not significant.

Three months after treatment, the chance for occurence of stenosis in patients feb by tubes was 0.80 times smaller / RR=0,80 (95%CI 0.56-1.14)/, in comparison with patients given liquid diet, although the difference was not significant.

After 6 months, the chance for occurence of stenosis in patients feb by tubes was 0.76 times smaller / RR=0,76 (95%CI 0.53-1.08), in comparison with patients given liquid diet, although the difference was not significant.

4. DISCUSSION

Corrosive agents cause tissue destruction due to coagulation or liquefaction necrosis, which intensity depends on the type and concentration of the corrosive agent, duration of exposure, quantity of the ingested agent, etc. (11). A retrospective study conducted in 239 patients who ingested sodium hydroxide (NaOH) detected post-corrosive esophagitis in 89.3% of the patients and esophageal or gastric stenosis in 72.6%. One percentage of the patients died in the acute phase of poisoning (in the first 24 h) and 1.4% in the chronic phase of the poisoning. It is interesting to emphasize that the incidence of stenosis in female patients was 80.8% and in male patients 62.5%. Percentage of stenosis in patients who ingested a larger amount of corrosive agent (two or several spoonfuls) was 93.6%; post-corrosive carcinoma of the upper GIT was found in 1.8% of the patients, fistulas in 9.9% and perforation in 4.6% of the patients (12).

Intensity and mucous damage of the upper GIT in caustic poisonings are of huge importance in decision making on the therapeutic approach. The majority of authors think that hyperalimentation (enteral or parenteral) and antibiotic therapy have the biggest effect in successful healing. In contrast to post-corrosive injuries of grade I and II A that usually do not develop post-corrosive complications, 50-70% of patients with II B grade of injury develop stenosis in the first 6 months after ingestion and all (100%) of patients with III grade of injury (13).

Extensive damage of the upper gastrointestinal tract of grades II A and III hinder physiological nutrition in these patients and, within a short period of time, they fell into a severe general condition due to hypercatabolic state and negative alkali balance. Artificial nutrition is life-maintaining therapy in patients who cannot take food and are disposed to a risk of malnutrition. The type of the artificial nutrition depends on the degree of esophageal or gastric damage (14).

In many studies, patients with II B and III grades of injury are recommended the so-called esophageal rest. It may be possible only if the patient does not take food by mouth (NPO or nill per os). During the "rest", the patient is fed enterally by nasogastric or nasoenteral tube, gastrostoma or jejunostoma and parenterally by peripheral or central vein. The positive effect of not taking food by mouth for a certain period of time is explained by the fact that food particles do not enter granulocytes of the esophageal wall and do not exacerbate the inflammation which is in a positive correlation with late post-corrosive complications (15,16).

One study which examined 522 patients demonstrated positive effects of the esophageal rest in the first 10 days after caustic ingestion regarding the percentage of the severe late post-corrosive complications (17).

Another study performed on 118 patients examined the relation of the esophageal rest with the percentage of late post-corrosive complications and revealed a positive relation between not taking food by mouth (NPO) and number of patients who had stenosis of the upper GIT as a final outcome of the poisoning (18).

Many authors recommend avoiding food intake by mouth (NPO) until the 10th day after ingestion and some other authors recommend it until the 15th day, that is, until the first endoscopic control (19).

There is a group of authors who advocate taking liquids 48 hours after corrosive ingestion if the patient can swallow his/her saliva. These authors also think that 48 hours after corrosive ingestion the patients can take food by mouth (20).

Deskin R. (21) supports the so-called esophageal rest in patients with acute corrosive poisonings. This rest is possible if the patient does not take food by mouth (NPO or nill per os). During the rest, the patient is fed by nasoenteral tube, gastrostoma or jejunostoma. This author explains that taking food by mouth exacerbates the infection of GIT post-corrosive burns and thus, delays and complicates the healing of the lesions. If enteral nutrition is impossible, then he advises TPI.

Kikendal (22) advises the so-called esophageal rest of minimum 10 days since the endoscopic diagnosis of the poisoning and permanent control of the nutritional status of the patient for maintenance of the good general condition.

Eric Kardon (23) does not recommend taking food by mouth (NPO) in acute corrosive poisonings until the first endoscopic control (between 15 and 20 days).

Katzka A. David (24) thinks that in all corrosive poisonings of II B and III grades of injury of upper GIT, it is necessary to implant feeding tube (jejunostoma) for nutritional support and to avoid food intake by mouth (NPO) for 15 days.

One study examined 118 children with severe post-corrosive esophageal and gastric burns who, in addition to the usual therapy, received nothing by mouth for 7 days in order to prevent colonization of bacteria on the necrotic parts and to reduce the possibility of infection. Seventeen percentages of them developed post-corrosive stenosis. Since physiological nutrition was not possible, feeding gastrojejunostoma was installed until the adequate surgical treatment (25).

5. CONCLUSION

Acute corrosive poisonings are a serious clinical, socio-economic and diagnostic-therapeutic problem, which, in spite of the modern sophisticated diagnostics and treatment, cause a serious invalidity in patients. These poisonings are most common in subjects who are in their most creative period of life; they burden the social community because of the expensive diagnostic and therapeutic programs and prolonged hospital stay.

In spite of the not significant difference of the results obtained in our study, it was shown that the group of patients with "esophageal rest" (NPO) had a smaller percentage of post-corrosive complications than the patients who were given food or liquids immediately after caustic ingestion. This might be a result of avoiding additional injuries during NPO status as well as of less frequent infections that would compromise the healing of post-corrosive injuries.

REFERENCES

1. Allakhverdian AS, Maurin VS, Antisecretory therapy for prevention of stenosis of bouginage after burn of esophageal strictures. Eksp Klin Gastroenterol, 2003;114(4):36-9.
2. Andreoni B, Biffi R, Padalino P, Marini A, Marzona L, Belloli S, Farina ML, Tiberio G. Artificial nutrition in the management of lesions caused by caustic ingestion. Chir Ital, 1994;46(6):42-8.
3. Zwischenberger, Joseph B. Clare Savage, Bidan A, Surgical Aspects of Esophageal Disease . Am J Respir Crit Care Med, April 2002;165(8):1037-40.
4. Arévalo-Silva C, Eliashar R, Wohlgelernter J, Elidan J, Gross M. Ingestion of caustic substances: a 15-year experience Laryngosc, 2006;116(8):1422-6.
5. Berthet B, Bernardini D, Lonjon T. Treatment of caustic stenoses of the upper digestive tract. Chir (Paris), 1995;132 (11): 447-50.
6. Abakumov MM, Kostiuchenko LN, Kudrichoba NE. Enteral infusion-nutrional correction of homeostasis in patients with postburn cicatrial stenosis of the esophagusand stomach.Vestn Khir Im II Grek, 1999;155(5):30.
7. Alinejad A. Caustic injury to upper gastrointestinal tract,Shiraz university of medical sciences, Depertment of internal medicine, Available from:pearl.sums.ac.ir/semj/vol4/jan2003/causticinj.htm

8. Atabek C, Surer I, Demirbag S, Caliskan B, Ozturk H, Cetinkursun S. Increasing tendency in caustic esophageal burns and long-term polytetrafluorethylene stenting in severe cases: 10 years experience. J Pediatr Surg, 2007 Apr;42(4):636-40.
9. Post-corrosive injuries of upper gastrointestinal tract, Chibishev A, Simonovska N, Shikole A, Contributions, 2010 Jul;31(1):297-316.
10. Ramasamy K, Gumaste VV. Corrosive ingestion in adults, J Clin Gastroenterol, 2003 Aug,37(2):119-24.
11. Chibishev A, Chibisheva B, Bozinovska C, Naumovski J. Oesophageal and gastric stenoses are common complications after acute oral poisoning with corrosive agents. Maced J Med, 2005;51(1-2):139-46.
12. Mamede RC, De Mello Ficho FV. Treatment of caustic ingestion: an analysis of 239 cases. Dis Esophagus, 2002;15 (3):210-3.
13. Conforto F, Gercitano M, Tanga I. Emergency treatment of esophago-gastric lesion in caustic ingestion patiens. Critical Care, 2004,(Suppl 1)8:P 284.
14. Di Costanzo J, Noirclerc M, Jouglard J, Escoffier JM, Cano N, Martin J, Gauthier A. New therapeutic approach to corrosive burns of the upper gastrointestinal tract. Gut, 1980 May;21(5):370-5.
15. Kochhar R, Poornachandra KS, Puri P, Dutta U, Sinha SK, Sethy PK, Wig JD, Nagi B, Singh K. Comparative evaluation of nasoenteral feeding and jejunostomy feeding in acute corrosive injury: a retrospective analysis. Gastrointest Endosc, 2009 Nov;70(5):874-80.
16. Katzka A, David MD. A standardised protocol for the acute management of corrosive ingestion in children. J Pediatr Surg. 2005;40(7):1214-5.
17. Cibisev A, Nikolova-Todorova Z, Bozinovska C, Petrovski D, Spasovski G. Epidemiology of severe poisonings caused by ingestion of caustic substances. Prilozi, 2007;28(2):171-83.
18. Andreoni B, Farina ML, Biffi R, Crosta S. Esophageal perforation and caustic injury, emergency menagment of caustic ingestion. Dis Esophagus, 1997;10 (2):95-100.
19. Sarfati E, Gossot D, Assens P. Management of caustic ingestion in adults. British Journal of Surgery, 2005;74 (2):146–8.
20. Zabelegui A, Mijan de la Torre. Severe gastroesophageal lesions due to caustics; the role of nutritional support. Nutr Hosp, 1995;10 (6): 364-7.
21. Deskin R. Caustic ingestion. com [homepage on the Internet]. U TMB, Grand Rounds Dept.of Otolaryngology; 1995 [updated 2001 april 17; cited 2010 june 30].Available from:www.utmb.edu/otoref/grnd/ Aerodigestive-Tract-2001-04.htm
22. Kikendal JW. Caustic ingestion injuries. Gastroenterol Clin North Am, 1991; 20(4): 847-57.
23. Kardon E. Caustic ingestion, com [homepage on the Internet]. Emergency Medicine Toxicology. [updated 2010 May; cited june 2010]. Available from: emedicine.medscape.com
24. Katzka A, David MD. Caustic Injury to the Esophagus. Current Treatment Options in Gastroenterology, 2001;1(4):59-66.
25. Schmittenbecher P. A standardised protocol for the acute management of corrosive ingestion in children. J Pediatr Surg, 2005;40(7):1214-5.

ORIGINAL PAPER

Role of Intravenous Omeprazole on Non-variceal Upper Gastrointestinal Bleeding After Endoscopic Treatment: a Comparative Study

Indrit Këlliçi[1], Bledar Kraja[2], Iris Mone3, Skerdi Prifti[2]
Endoscopy Unit, University Hospital of Durres, Albania[1]
University Clinic of Gastrohepatology, University Hospital Center "Mother Theresa", Tirana, Albania[2]
Laboratory Department, University Hospital Center "Mother Theresa", Tirana, Albania[3]

Aim: To evaluate and compare the clinical efficacy of intravenous omeprazole versus intravenous ranitidine therapy for the treatment of non-variceal upper gastrointestinal (UGI) bleeding after endoscopic therapy. **Methods:** 108 patients (72 males and 36 females) admitted with non-variceal UGI bleeding in the Intensive Care Unit of the University Hospital of Durres, Albania, from 2004 to 2008, were included in the study. Patients with gastro-duodenal malignancy and those who were previously receiving anti-secretory drugs were excluded. All patients were treated endoscopically by injecting epinephrine (diluted 1:10.000) followed by ethanol and subsequently were randomized to receive either intravenous omeprazole (with an initial dose of 80 mg, followed by 8 mg/h infusion [n = 54]), or intravenous ranitidine (100 mg bolus, followed by 100 mg boluses every 6 hours for the next 72 hours [n = 54]). **Results:** The re-bleeding rate 72 hours after endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1 –7.2; P<0.01). Less volume of blood transfusion was needed for the omeprazole group than for the ranitidine one (1.1 ± 1.8 units vs. 2.3 ± 2.9 units, P=0.03). The hospitalization period was shorter among patients treated with omeprazole than among those treated with ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). The need for surgery and the mortality rate were not statistically different between the two groups. **Conclusion:** After endoscopic treatment of non-variceal UGI bleeding, intravenous omeprazole reduced the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the period of hospitalization. Intravenous omeprazole should be used in patients with non-variceal UGI bleeding after effective endoscopic treatment. ***Key words:*** bleeding, omeprazole, peptic ulcer, ranitidine.

Corresponding author: Bledar Kraja, MD. University Clinic of Gastrohepatology, University Hospital Center Mother Theresa, Tirana, Albania E-mail: bledarkraja@yahoo.com

1. INTRODUCTION

Non-variceal upper gastrointestinal (UGI) bleeding remains a major reason for hospitalization and mortality. Its overall incidence is approximately 150 hospital admissions per 100.000 inhabitants per year and the most common cause of UGI hemorrhage is peptic ulcer (1, 2). Most ulcers stop bleeding spontaneously as a result of intrinsic haemostatic mechanisms, but in one fifth of cases these mechanisms may fail, and the bleeding continues (2).

Endoscopic therapy for bleeding peptic ulcer is an important modality of treatment. A meta-analysis has shown that endoscopic treatment in such cases reduces the rates of recurrent bleeding, surgery and mortality (3). However bleeding recurs within 72 hours after endoscopic therapy in approximately 20% of patients and overall mortality of UGI bleeding remains around 10% (4, 5).

Pharmacological treatment is an attractive adjuvant to endoscopy therapy in UGI bleeding. The major goal of the medical therapy is the inhibition of gastric acid secretion. The studies have shown that a high intragastric pH could facilitate platelet aggregation and removal of proteolitic influence of pepsin on thrombus (2, 6, 7). The intragastric pH above 6.0 for a minimum period of 72 hours is necessarily for clot stability at the ulcer site (8).

The intravenous use of Histamine H2-receptor antagonists (H2RA) or Proton Pump Inhibitors (PPI) inhibits the gastric secretion but the intravenous infusion of PPI maintains in-

tragastric pH above 6.0, showing better effect than H2RA administration (6, 9). Thus, the intravenous use of PPI is theoretically superior in preventing recurrent bleeding.

Several studies have evaluated the effect of PPI on the non-variceal UGI bleeding (10-13). Unfortunately in some of them the results are not very clear because of including a heterogenic group of patients (10, 11), or not performing any endoscopic treatment (12, 13).

2. GOAL

The aim of our study was to evaluate the clinical effectivity of intravenous PPI therapy compared with intravenous H2RA for the treatment of non-variceal UGI bleeding after endoscopic therapy.

3. METHODS

Study population

Between June 2004 and August 2008, 173 patients with upper GI bleeding were admitted at the Intensive Care Unit of the University Hospital of Durres, Albania. All of them were diagnosed and eventually treated endoscopically. We included in our study the patients with non-variceal UGI bleeding older than 16 years in whom haemostatic endoscopy had been successful. We excluded patients with gastroduodenal malignancy and those previously treated with antisecretory drugs (H2RA or PPI).

Endoscopic therapy

Endoscopic examinations were performed using a video-endoscope (FUJINON 2200) within the first 24 hours of admission. Patients were treated endoscopically by injecting 10–25 cm^3 of adrenaline (epinephrine) (diluted 1:10 000) around the ulcer crater and absolute alcohol on the ulcer bed to stop the bleeding. Haemostasis was considered as established if bleeding had stopped and bleeding vessels were flattened or cavitated. In patients with non-bleeding visible vessels, haemostasis was considered as established when the vessel disappeared.

Data collection

After endoscopic treatment, patients were randomized to receive intravenous infusions of omeprazole or ranitidine for a period of 72 hours. They were divided into two groups according to the medical therapy: group I had received 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for 72 hours, and group II had received intravenous ranitidine 100 mg bolus, followed by 100 mg boluses every 6 hours for a period of 72 hours.

The following data were recorded on every patient: age, sex, location of the ulcer (stomach or duodenum), bleeding stigmata (visible vessel, oozing hemorrhage, spurting or clot), presence of shock, hemoglobin and hematocrit level, previous ulcer bleeding or ulcer disease, non-steroid anti-inflammatory drugs or aspirin use, and comorbid conditions. The Rockall scoring system was used to assess the severity of bleeding in both groups (14).

The primary end-point was 72-hours re-bleeding rate. Re-bleeding was defined as new hematemesis, melaena, or hypotension (< 100 mm Hg systolic blood pressure) associated with a drop in hemoglobin and/or endoscopic evidence of fresh re-bleeding. Volume of blood transfusion, hospital stay, need for surgery and mortality were considered as secondary end-points.

Statistical analysis

Data were entered into a personal computer and analyzed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means (± standard deviations). The results of the two treatment groups were compared by chi square ($\chi 2$) test (categorical variables), and Student's t test (numerical variables). To test the association between outcomes and clinical co-variables, we estimated risk ratios and 95% confidence intervals (95%CI). In all analyses, statistical significance was considered at $P \leq 0.05$.

4. RESULTS

During the study period, a total of 173 patients with upper GI bleeding were admitted to our Unit. We excluded

Variable	Omeprazole Group (N=54)	Ranitidine Group (N=54)
Sex (no. of patients) Male Female	 35 19	 37 17
Age (in years)	55.4 4 17.3†	55.8 4 16.9
Hemoglobin (g/dl)	8.24 4 1.4	8.29 4 1.5
Hematocrit level (%)	27.7 4 4.2	27.5 4 3.7
Shock at presentation (no. of patients)‡	7	6
Location of ulcer (no. of patients) Stomach Duodenum	 15 39	 16 38
Endoscopic signs of bleeding (no. of patients) Visible vessel Oozing hemorrhage Spurting hemorrhage Clot with underlying vessel	 16 20 4 15	 12 19 3 19
Size of ulcer (in cm.)	1.06 4 0.8	1.12 4 1.0
Previous ulcer disease (no. of patients)	11	12
Previous ulcer bleeding (no. of patients)	5	4
Risk factors for bleeding ulcer (no. of patients) Use of NSAID Use of aspirin	 10 18	 11 26
Rockall score	5.2 4 1.8	5.1 4 1.7
Coexisting illnesses (no. of patients) Ischemic heart diseases Cerebral stroke Diabetes mellitus Hypertension Other diseases	 8 3 3 4 2	 10 2 2 5 4

Table 1. Base-line characteristics of the 108 patients. There was no statistically significant difference between the two groups. † Means 4 standard deviations. ‡ Shock was defined as a systolic blood pressure of 90 mm Hg or less, or a pulse rate of 110 beats per minute or more.

Variables	Omeprazole Group (N=54)	Ranitidine Group (N=54)	Relative Risk (95% CI)	P value
Recurrent bleeding (%)	6 (11.1)	14 (25.9)	3.4 (1.1-7.2)	<0.05
Volume of blood transfusion (units)	1.1 4 1.8*	2.3 4 2.9	___	<0.05
Hospital stay (days)	5.4 4 2.6*	6.8 4 3.3	___	<0.05
Surgery (%)	2	5	0.5 (0.09-2.8)	NS†
Death (%)	1	2	1.9 (1.5-2.3)	NS

Table 2. Clinical outcomes after endoscopic therapy and medical treatment * Means 4 standard deviations.† Not statistically significant (P>0.05).

from the study 28 patients with other gastro duodenal lesions who were not treated endoscopically or underwent surgery because of profuse bleeding, 23 patients with esophageal varices, 6 patients with gastric tumors, and 8 patients who had previously received antisecretory drugs, H2RA or PPI. Only 108 patients fulfilled the criteria to be included in our study. The mean age of the patients was 55.6 years (range: 17 – 85 years). We had 54 patients in group I (taking intravenous omeprazole) and 54 patients in group II (taking intravenous ranitidine).

There were no statistically significant differences between the two study groups on regard of age, the severity of bleeding at presentation, the location of ulcer, endoscopic signs of bleeding, risk factors for ulcers, and coexisting illnesses (table 1).

Table 2 shows the clinical outcomes of this study. The re-bleeding rate after 72 hours of endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1 –7.2; P=0.003). The mean (±SD) number of units of blood transfused after endoscopy and medical treatment was significantly smaller in the omeprazole group than in the ranitidine group (1.1 ± 1.8 vs. 2.3 ± 2.9 units, P=0.03). The difference was probably related to treatment, since the mean number of units transfused before endoscopic treatment was similar in the two groups (0.9 ± 1.2 and 1.0 ± 1.4 units, respectively; P=0.45). The hospitalization period was shorter among patients treated with intravenous omeprazole than those treated with intravenous ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). Twenty patients (6 in the omeprazole group and 14 in the ranitidine group) who had recurrent bleeding underwent a second endoscopy. The endoscopic retreatment stopped the bleeding in 67% of the patients in omeprazole group (4/6), and in 64% of the patients in ranitidine group (9/14). The need for surgery was lower in the omeprazole group (two vs. five), but the difference was not significant (P=0.17). Also, the mortality rate was not statistically different between the two groups of the study. One patient (1.8%) died in the omeprazole group compared with 2 (3.7%) in ranitidine group (P=0.14). All the patients died because of coexisting illnesses.

5. DISCUSSION

The main findings of our study indicate that aggressive acid suppression with intravenous omeprazole significantly reduces the rate of recurrent bleeding, if compared with intravenous ranitidine in patients with non-variceal UGI bleeding after endoscopic schlerotherapy. Patients who were treated with intravenous omeprazole required fewer blood transfusions and had significantly shorter period of hospital stay. The need for surgery and the mortality rate were also lower in the omeprazole group, but these differences were not significant.

Several studies have evaluated the use of PPI in patients with non-variceal UGI bleeding. These studies have shown that patients who received intravenous PPI had significantly lower rate of recurrent bleeding than those who received H2RA or placebo (10, 15, 16). PPI also decreases the need for blood transfusions, the need for surgery, the mortality rate, and shortens the time of hospitalization (9, 17).

In second reports, the use of intravenous omeprazole is shown ineffective in patients with upper gastrointestinal haemorrhage either with (18) or without endoscopic therapy (12). The study of Daneshmend et al. included patients with variceal bleeding, tumours, and peptic ulcers, but in these two studies, the authors used an 80 mg intravenous bolus of omeprazole followed by 40 mg every 8 hours. Two other studies found that intravenous omeprazole reduced the need for surgery if it was accompanied with endoscopic therapy, but they did not show if it reduced the rate of recurrent bleeding or mortality (19, 20)

In our study, we enrolled patients with gastro-duodenal bleeding ulcers. All the patients were treated with endoscopic epinephrine and ethanol injection within the first 24 hours of admission. Adrenaline in doses of 20 ml solution 1: 10 000 leads to about 85-90% suppression of non-variceal UGI bleeding (21, 22).

After endoscopic therapy we used 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for the next 72 hours. PPI are continuously being generated, and the half-life of omeprazole in the circulation is short (50 minutes), therefore it needs to be given more frequently (e.g. every 3 hours) or continuously (23). Recommended dose of PPI for prevention of non-variceal bleeding recurrences is 80 mg in bolus and subsequently through next 72 hours dosage of 8mg/hour (7, 8). We used intravenous omeprazole because oral omeprazole may suppress acid production to a similar degree, but it may take several days before the pH is consistently above 6.0.

Omeprazole acts on K^+-H^+-ATPases pump situated in parietal cells and outside gastric sites, in renal and vascular smooth muscles (23, 25). This can result in decreased renal function and vasoconstriction in blood vessels. In our patients the mortality rate was not significant between the two groups and the deaths were caused only by co-morbid conditions.

Our study had some limitations. We did not measure intra-gastric pH in our patients because the high dose of omeprazole, like the one we used, can maintain intra-gastric pH above 6.0 (6). Our patients were not examined for Helicobacter pylori presence. The prevalence of H. Pylori in Albanian population is very high (26, 27) and therefore

we did not examine for this bacteria in this group of peptic ulcer patients.

6. CONCLUSION

We found that intravenous omeprazole reduce the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the hospital stay in patients with non-variceal UGI bleeding after endoscopic epinephrine injection. It should be used in these patients after effective endoscopic treatment.

REFERENCES

1. Gilbert DA. Epidemiology of upper gastrointestinal bleeding. Gastrointest Endosc, 1990;36:S813.
2. Laine L, Peterson WL. Bleeding peptic ulcer. N Eng J Med, 1994;331:717-27.
3. Cook DJ, Gujatt GH, Salena BJ, laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Gastroenterology, 1992;102:139-42.
4. Van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between, 1993/1994 and 2000. Am J Gastroenterol, 2003;98:1.494-9.
5. Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subject. Gut, 2002;50:460-4.
6. Netzer P, Gaia C, Sandoz M, et al. Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. Am J Gastroenterol, 1999;94:351-7.
7. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal hemorrhage: guidelines. Gut, 2001; 51(Suppl. 4): IV1-IV6.
8. Barkun A, Bardou M, Marshall JK. Consensus recommendation for managing patients with non-variceal upper gastrointestianl bleeding. Ann Intern Med, 2003;1399(10): 843-57.
9. Martin JE, Macaulay SS, Zarnke KB, et al. Proton Pump Inhibitors versus H2 antagonists or placebo for upper gastrointestinal bleeding with or without endoscopic hemostasis: a meta-analysis. Gastroenterology, 2003; 124 (Suppl.1):A625.
10. Khuroo MS, Farahat KL, Kagevi IE. Treatment with proton pump inhibitors in acute non-variceal upper gastrointestinal bleeding: a meta-analysis. J Gastroentrol Hepatol, 2005;20(1):11-25.
11. Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. Proton pump inhibitors versus H2-antagonists: a meta analysis of their efficacy in treating bleeding peptic ulcer. Aliment Pharmacol Ther, 2001;15(7):917-26.
12. Daneshmend TK, Hawkey CJ, Langman MJS, Logan RFA, Long RG, Walt RP. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. BMJ, 1992;304:143-7.
13. Khuroo MS, Yattoo GN, Javid G, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med, 1997;336:1054-8.
14. Rockall TA, Logan RFA, Devlin HB, Northfield TC and the steering committee and members of Natl Audit of acute upper gastrointestinal haemorrhage. Risk assessment following acute upper gastrointestinal haemorrhage. Gut, 1996; 38:316-21.
15. Bardou M, Toubouti YM, Benhaberou-Brun D et al. High dose intravenous proton pump inhibitors decrease both rebleeding and mortality in high-risk patients with acute peptic ulcer bleeding: a series of meta-analyses. Gastroenterology, 2003;124(Suppl 1):A625.
16. Andriulli A, Annese V, Caruso N et al. Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of metaanalyses. Am J Gastroentrol, 2005;100:207-19.
17. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis: proton-pump inhibitor treatment for ulcer bleeding reduces transfusion requirements and hospital stay-results from the Cochrane Collaboration. Aliment Pharmacol Ther, 2005;22:169-74.
18. Villanueva C, Balanzo´ J, Torras X, et al. Omeprazole versus ranitidine as adjunct therapy to endoscopic injection in actively bleeding ulcers: a prospective and randomized study. Endoscopy, 1995; 27:308-12.
19. Schaffalitzky de Muckadell OB, Havelund T, Harling H, et al. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers: randomized double-blind placebo-controlled multicentre study. Scand J Gastroenterol, 1997; 32:320-7.
20. Hasselgren G, Lind T, Lundell L, et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding: results of a placebo-controlled multicenter study. Scand J Gastroenterol, 1997;32:328-33.
21. Calvet X, Vergara M, Brullet E, Gisbert JP, Campo R. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. Gastroenterology, 2004; 126:441-50.
22. Lin HJ, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. A prospective, randomized trial of large–versus small–volume endoscopic injection of epinephrine for peptic ulcer bleeding. Gastrointest Endosc, 2002;55:615-9.
23. Brunner G, Luna P, Thiesemann C. Drugs for pH control in upper gastrointestinal bleeding. Aliment Pharmacol Ther, 1995; 9(Suppl 1):47-50.
24. McCabe RD, Young DB. Evidence of a K+-H+-ATPases in vascular smooth muscle cells. Am J Physiol, 1992;262:H19558.
25. Christensen PB, Albertsen KEP, Jensen P. Renal failure after omeprazole. Lancet, 1993;341:55.
26. Megroud F, Bouchard S, Brugmann D, et al. Seroprevalence of Helicobacter pylori infection in six countries of Eastern Europe using a common methodology. Gut, 1995;1(39):A283.
27. Resuli B, Agimi F, Hoxha L, Bega B, Kraja B. The prevalence of Helicobacter pylori infection in Albanian children. Helicobacter, 2004;9:515.

ORIGINAL PAPER

Evaluation of Medical and Surgical Management of Critical Extremity Ischemia Caused by Atherothrombosis

Nedzad Rustempasic[1], Emir Solakovic[1], Medzida Rustempasic[2], Izet Masic[3]
Clinic for Vascular Surgery, Clinical Center of University of Sarajevo, Bosnia and Herzegovina[1]
Clinic for Pulmonary Diseases and Tuberculosis, Clinical center of University of Sarajevo, Bosnia and Herzegovina[2]
Academy of Medicial Sciences, Sarajevo, Bosnia and Herzegovina[3]

Aim: To assess efficacy of surgical and medical (conservative) treatment of acute exacerbation of chronic extremity ischemia by evaluating their early therapeutic outcomes in terms of mortality, extremity amputation and reamputation rate, limb salvage rate and length of hospitalization period. **Patients and methods**: Patients were divided into two groups based on method used for the treatment of critical ischemia. Group A consisted of 40 patients that were subjected to surgical treatment of critical extremity ischemia during period 2004-2009. All patients were subjected to thrombectomy in local anesthesia (2% lidocaine) as initial step of treatment protocol. Urgent Seldinger angiography was performed for all patients that have undergone thrombectomy regardless of successfulness of thrombectomy. Based on angiography findings decision was made about further definitive treatment. It consisted of either using antiaggregating drugs (acetyl salicylic acid; 150 mg/day) if no significant postthrombectomy stenotic lesion was found or subjecting patients to further surgical revascularization in the form of bypass were significant stenosis or occlusion was identified. Group B consisted of 40 patients; all of them received conventional heparin anticoagulation therapy supplemented with vasoactive infusion treatment (Pentoxyohylline 300 mg/day) during period 1998-2004. On the third day of hospitalization oral anticoagulation (Sintrom) was included in the therapy protocol using dosage 2-8mg/day in order to achieve INR 2-4, once therapeutic INR was obtained heparin was withdrawn. Study was clinical, designed as retrospective prospective and was conducted at the Clinic for vascular surgery in Sarajevo. **Results**: Mean age in group A was 66,5 years and in group B it was 65,78 years. Lenght of hospital stay in group A was 13,78 days while in group B it was 34,25 days (P value <0,001). Limb salvage rate was 70% in group A and 17,5% in group B (P value < 0,001). In group A , nine amputations were performed (22,5%) while in group B we had to perform 38 amputations (95%), P value <0,001. Only one reamputation was performed in group A (2,5% of patients) while in group B ten reamputations were performed (25% of patients). Mortality rate between groups was not statistically significant (P value <0,077). **Conclusion**: Surgical thrombectomy as introduction to definitive treatment of critical limb ischemia caused by atherothrombosis gives statistically superior results in comparison to conservative treatment. Key words:

Corresponding author: Nedzad Rustempasic, M.D. Clinic for Vascular Surgery, Clinical Center of University of Sarajevo, Cekalusa 88, Sarajevo. email: nrustempasic@yahoo.com

1. INTRODUCTION

Acute exacerbation of chronic extremity ischemia is caused by thrombus formation in the artery on its atherosclerotic plaque, the process also known as atherothrombosis. In 60% of cases it is responsible for acute limb ischemia. Clinically this phenomenon is recognizable as preterminal ischemia or critical limb ischemia which has been defined as degree of ischemia that would in the absence of timely provision of adequate revascularization lead to amputation of limb[1].Besides atherothrombosis, thromboembolism may also lead to acute limb ischemia and it is considered to be responsible factor in 30% of cases. Other causes of acute ischemia are trauma, thrombosis of arterial aneurysm, dissection of aorta etc. When thrombus occludes artery affected by atherosclerosis, vascular segment that is located distally from the site of arterial occlusion undergoes spasm, reaction that is deemed to have protective role in terms of prevention of thrombus propagation into distal arterial tree[2]. There is also retrograde deposition of thrombus in the artery with resultant complete covering or masking of potential culprit stenosis in the atherothrombosed artery. Distal arterial spasm persists about 8 hours and then it

is followed by relaxation of arterial wall with consequent deposition of thrombus in arterial segment located distally from the site of occlusion that in turn leads to occlusion of collateral vessels with exacerbation of ischemia[2].Skeletal muscles and nerves tolerate ischemia for about 8 hours without irreversible damage. Skin marmorization due to appearance of reticular cyanosis takes place. Skin can tolerate ischemia for about 24 hours. When period of ischemia tolerance is used up, irreversible phase of ischemia sets in[3]. Primary aim of treatment is prevention of mortality and limb loss. Five year mortality in patients with critical limb ischemia reaches up to 70%. Desirable outcome is survival without limb loss[4]. Treatment options are aimed at removal of thrombus by surgical or pharmacological means. Then angiographic mapping of affected artery and radiological insight into position, extent and degree of stenotic atherosclerotic lesion is done with subsequent planning of reconstructive procedure. The aim of this study was to assess efficacy of surgical and medical (conservative) treatment of acute exacerbation of chronic extremity ischemia by evaluating their early therapeutic outcomes on basis of following parameters:

- Length of hospitalization period
- Efficacy of limb salvage between analyzed groups
- Number of amputation procedures
- Number of reamputation procedures
- Mortality rate.

In addition primary, patency of revascularization procedure will be determined.

Current management of this condition is based on urgent thrombolytic treatment followed by additional endovascular or surgical revascularisation of arterial stenotic lesion. In our setting, instead of active thrombolysis we attempted to remove thrombus with Fogarty catheter and then based on angiographic findings we decided about further definitive treatment.

2. PATIENTS AND METHODS

Patients were divided into two groups based on method used for the treatment of critical ischemia. Inclusion criteria were: rest pain, confirmed positive history of previous intermittent claudication, positive risk factors for atherosclerosis. Exclusion criteria were: absolute arrhythmia, extremity rest pain after myocardial infarction, thromboangitis obliterans and thrombosis of arterial aneurysm.

APTT	HEPARIN
40-60 sec	10000 IU
60-80 sec	5000 IU
80-100 sec	-
Over 100 sec	Protamine suphate

Table 1 Bolus dosage according to APTT

Group A consisted of 40 patients that were subjected to surgical treatment of critical extremity ischemia during period 2004-2009. After confirming diagnosis of atherothrombosis, patients were subjected to urgent thrombectomy of affected artery. Thrombectomy was made in local anesthesia (2% lidocaine). Approach to occluded arterial segment was made via arteritomy on common femoral artery in case of lower extremity ischemia or through arteriotomy made on brachial or cubital artery in case of ischemia of upper extremity. Fogarty embolectomy catheters Ch 4 or 6 (depending on the size of artery) were used for extraction of thrombus from the artery exploiting technique of anterograde or retrograde Fogarty thrombectomy. Urgent Seldinger angiography was performed for all patients that have undergone thrombectomy regardless of successfulness of thrombectomy. Based on angiography findings that might have revealed the cause of atherothrombosis decision was made about definitive treatment. It consisted of further therapy using antiaggregating drugs (acetyl salicylic acid 150 mg/day) or subjecting patients to further surgical revascularization in the form of bypass.

Group B consisted of 40 patients; all of them received conventional heparin anticoagulation therapy supplemented with vasoactive infusion treatment (Pentoxyohylline 300 mg/day) during period 1998-2004. Heparin was used as part of a standard protocol for treatment of extremity atherothrombosis at our Clinic until year 2004. On admission, patient received heparin solution intravenously during 6 hour period (20000 IU in 500 ml of Normal Saline) and then every 6 hours bolus intravenous heparin supplementation was administered depending on APTT value according to the following scheme (see table 1).

On the third day of hospitalization oral anticoagulation (Sintrom) was included in the therapy protocol and once value of INR 2-4 was achieved, heparin was withdrawn. In case of favorable response patients continued to receive Sintrom, maintaining INR in therapeutical range (for maximum of 6 months when they would replace Sintrom with Aspirin-100 mg /day indefinitely). Concomitantly with heparin, pentoxyphilline infusion was administered to patients with favorable clinical response for 10 days in total. After that period patients would receive pentoxiphylline per os (400 mg, tid). Discrepancies in anticoagulation response are based on individual differences in heparin clearance as well as to the value of APTT on administered quantity of heparin.[5] Study

Analyzed group	Mean	T test	P value	Mean difference	Standard error difference
Group A	66,65				
Group B	65,78	0,368	<0,714	0,875	2,376

Table 2. Age difference between analyzed groups (in years) and statistical significance

Analyzed group	Mean	T test	P value	Mean difference	Standard error difference
Group A	13,78				
Group B	34,25	-7,488	<0,001	-20,478	2,734

Table 3. Length of hospital stay between analyzed groups (in days) and statistical significance

Analyzed group	Procenat	T test	P value	Mean difference	Standard error difference
Group A	70%	5,508	<0,001	0,525	0,095
Group B	17,5%				

Table 4. Percentage of limb salvage between analyzed groups and statistical significance

Analyzed group	Amputation	Chi square test	P value
Group A	9	43,378	<0,001
Group B	38		

Table 5. Number of patients with amputations and statistical significance

Analyzed group	Reamputated extremities	Chi square test	P value
Group A	1	8,538	<0,003
Group B	10		

Table 6. Number of patients with reamputations and statistical significance

Analyzed group	Mortality	Chi square test	P value
Group A	3	3,117	
Group B	0		<0,077

Table 7. Number of lethal outcomes and statistical significance

was clinical, designed as retrospective prospective and was conducted at the Clinic for vascular surgery in Sarajevo.

3. RESULTS

Mean age in group A was 66,5 years and in group B it was 65,78 years. (Table 2). Lenght of hospital stay in group A was 13,78 days while in group B it was 34,25 days, P value <0,001, (Table 3, Figure 1). Limb salvage rate in group A was 70% and in group B it was 17,5%, P value <0,001.(Table 4, Figure 2). In group A , nine amputations were performed (22,5%) while in group B we had to perform 38 amputations (95%), 33 major amputations and 5 minor amputations; major amputation stands for amputation performed above ankle joint and minor for amputations at the level of foot-below ankle joint. (Table 5 and Figure 3). Only one reamputation was performed in group A (2,5% of patients). In group B, 10 reamputations were performed (25% of patients), difference in reamputation rate was statistically significant (Table 6, Figure 4). Mortality rate between groups was not statistically significant , P value <0,077, though in group A we had three cases with death outcome. In group B mortality rate was zero. (Table 7)

4. DISCUSSION

Mean age for group A was 66.65 years while for the group B it was 65.78. Difference was not statistically significant and it was similar to the mean age in other relevant studies[6]. Age is important determinant of peripheral arterial disease (PAD) and with advancing age prevalence of PAD increases.

Length of hospital stay is expressed in days and it varies significantly between analyzed groups, (group A= 13,78 days, group B= 34,25; p<0,001). Mean patient hospital stay in surgical group is below mean hospital stay mentioned in Report of National Survey of Great Britain and Ireland[6]. 679 patients were included in that study and 70% of them received revascularization treatment; mean hospital stay in that study was 25 days. Length of hospital stay of patients in the group B was longer due to obviously ineffective therapeutical response in terms of failure to improve oxygen delivery to limb periphery and consequently it required higher rate of extremity amputation and reamputation treatments.

Limb salvage rate in group A was successful in 28 out of 40 patients. In group B it was significantly less, it was achieved only in case of 7 out of 40 patients (70 vs. 17,5 %; p<0,001). Although some studies[7,8] report certain therapuetical effect of pentoxifylline in the treatment of chronic critical ischemia in our study its effect was obviously inferior when compared to the results obtained by surgical intervention. Lapentalo et Matzke also noticed significant reduction of limb salvage percentage in the absence of reconstruction for the treatment of chronic critical limb ischemia[9].

In the group that received conservative treatment (group B), 33 amputations were done above ankle joint (major amputations), 5 patients had amputations of digits and 2 patients did not require amputation treatment at all. In summary, conservative therapy was effective in the case of 7 patients (2 patients did not required amputation treatment at all, while 5 patients after minor amputations of digits had successful wound healing and their walking function of foot was undisturbed)

In surgically treated group (group A) thrombectomy was successfully achieved in 29 out of 40 patients. In remaining 11 patients tip of Fogarty catheter came across hard intraluminal resistance that could not be traversed without danger of penetrating

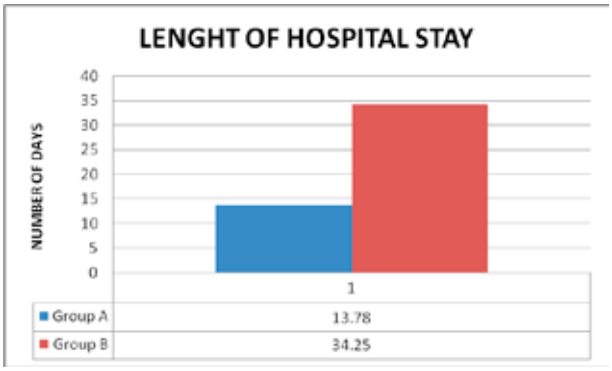


Figure 1. Lenght of hopsital stay in days

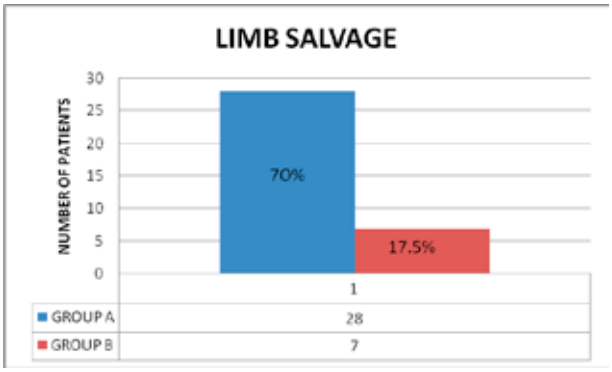


Figure 2. Percentage of limb salvage in analyzed groups

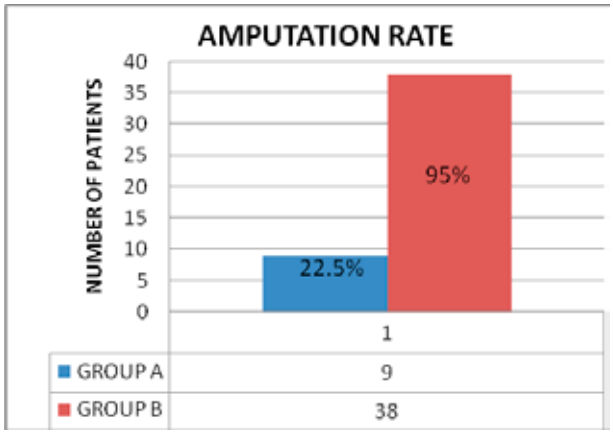


Figure 3. Amputation rate in analyzed groups

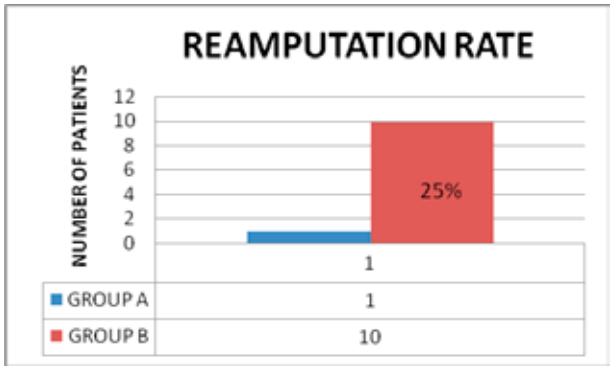


Figure 4. Reamputation rate in analyzed groups

arterial wall therefore thrombectomy procedure was abandoned. After urgent Seldinger angiography was performed, thrombectomy *per se* proved to be sufficient revascularization procedure in case of 20 patients since no haemodynamically significant stenosis was found in affected artery. All these cases coincided with intraopeartive finding of soft plaque and thrombus extraction from the artery with remaining denuded arterial wall that was devoid of presence of significant stenosis. Lifelong acetyl salicylic acid therapy -150 mg/day was administered to all those patients. 3 out of remaining 9 patients after thrombectomy procedure was performed ended up with amputation due to progression of irreversible leg ischemia while other 6 patients were subjected to additional revascularization procedure in the form of bypass with resulting successful limb salvage. Eleven patients that that did not receive successful thrombectomy due to hardness of intra-arterial obstructive lesion were nevertheless subjected to Seldinger angiography and they had the following outcome: 4 amputations (nonexistence of adequate recipient vessel on angiography), 4 bypass reconstructions (2 successful outcomes in 30 days follow up period while remaining 2 patients ended up with amputations due to progression of irreversible ischemia-insufficient outflow to the periphery) and 3 death cases.

Amputation rate in group B was 95% while amputation rate in group A was 22,5%. Difference is statistically significant; p<0,001. Increased need for amputation treatment should be also viewed in the light of possible belated referral of patients with critical ischemia to vascular surgery center as well as inadequate control of atherosclerotic risk factors. This problem is also noticed and reported in developed countries e.g. Great Britain[10]. In other words, timely referral of these patients to appropriate vascular centers will contribute to the decrease of number of amputation treatments[11]. In National Report of Great Britain and Ireland amputation percentage for the treatment of critical limb ischemia was 21,5%[1]. According to this study amputation treatment was directly related to longer intrahospital stay, higher mortality rate and more complex institutional support.

We report need for one reamputation (2,5%) in group A. On the other hand, in the group B due to wound dehiscence of amputation stump and ascending infection, 10 reamputations (25%) were performed. Difference in number of reamputation procedures between analyzed groups is significant; p<0,003.

There were no statistically significant difference in mortality rate between analyzed groups (p<0,077), the first patient died due to postprocedural myocardial infarction, second patient succumbed to massive pulmonary thromboembolism while third patient was lost because of aggravation of general status following stroke for which he was addmitted to the stroke unit prior to occurrence and treatment of acute atherothrombotic limb ischemia. Aune and Trippestad reported 14% operative mortality after 30 days[12]. Wolf and Wyatt reported 26% high mortality rate after one year of follow up period[13]. In National Survey of Great Britain and Ireland total mortality rate for the treatment of critical limb ischemia was 13,5%. Overall score of surgical treatment after 30 days of follow up period was: 28 successful limb salvages (70%), 3 dead cases (7,5%) and 9 patients with major amputations (22,5%). Results of limb salvage rate in our study did not significantly differ from limb salvage rate (75%) reported in National survey of Great Britain and Ireland regarding treatment of critical limb ischemia[1]. According to Baily and Saha after analyzing 130 patients in their one year prospective study, limb salvage rate was 61%[14]. Primary patency of revascularization treatment in the group A, after 30 days, was 70%. 50% (n=20) of revascularizations were in the form of thrombectomy while 20% (n=8) of them were bypass reconstructions. In British and Irish National survey for the treatment of critical limb ischemia, primary patency of performed revascularization procedures at the time of patient discharge from the hospital was 75%[1].

5. CONCLUSION

Surgical thrombectomy as introduction to definitive treatment of critical limb ischemia caused by atherothrombosis gives far superior results in comparison to conservative treatment in terms of higher limb salvage rate as well as lower rate of amputations and reamputations. Furthermore, patient hospital stay is significantly shorter in the group that received surgical treatment. Primary patency rate of revascularization procedures performed in this study was 70% and it positively correlates with published results of other European vascular centers.

REFERENCES

1. Critical limb ischemia: Management and outcome. Report of a National Survey. Vascular Surgical Society of Great Brit-

ain and Ireland. Eur J Vasc Endovasc Surg 1995; 10: 108-113.
2. Hobson R, Wilson S., Veith F, Vascular Surgery: Principles and Practice, Third Edition, 2004; 405-411.
3. Jivegard, L.; Holm, J.; Schersten, T. Acute Limb Ischemia Due to Arterial Embolism or Thrombosis:Influence of Limb Ischemia Versus Pre-existing Cardiac Disease on Postoperative Mortality Rate. J. Cardiovasc. Surg. 1988; 29- 32.
4. Norgen L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA and Fowkes FGR on behalf of TASC II working group, Inter Society consensus for the management of peripheral arterial disease (TASC II); Eur J Vasc Endovasc Surg, 2007; 33: 1-75.
5. Hirsh J, van Aken WG, Gallus AS, et al: Heparin kinetics in venous thrombosis and pulmonary embolism. Circulation 1976; 53: 691-695.
6. Vascular Surgical Society of Great Britain and Ireland. Critical limb ischemia: management and outcome. Report of national survey. Eur J Vasc Endovasc Surg. 1995; 10: 108–13
7. Intravenous pentoxifylline for the treatment of chronic critical limb ischaemia. The European Study Group, Eur J Vasc Endovasc Surg. 1995, 4: 426-36
8. Efficacy and clinical tolerance of parenteral pentoxifylline in the treatment of critical lower limb ischemia. A placebo controlled multicenter study. Norwegian Pentoxifylline Multicenter Trial Group, Int Angiol. 1996; 15(1):75-80.
9. Lepntalo M, Matzke S. Outcome of Unreconstructed Chronic Critical Leg Ischaemia, Eur J Vasc Endovasc Surg 1996; 11: 153-157.
10. The White Paper. The New NHS. Department of Health, 1998.
11. Henke P, Contemporary management of acute limb ischemia: factors associated with amputation and in-hospital mortality, Semin Vasc Surg. 2009; 22(1): 34-40
12. Aune S., Trippestad A: Operative and long term survival of patients operated on for acute lower limb ischemia. Eur J Endovasc Surg 1998; 15:143-146.
13. Wolfe J and Wyatt G.Critical and subcritical ischemia.Eur J Vasc Surg 1997; 13: 578-582
14. Bailey CMH, Saha S, Magee TR and Galland RB. A 1 year prospective study of management and outcome of patients presenting with critical lower limb ischemia. Eur J Vasc Surg 2003; 25: 131-134

ORIGINAL PAPER

Mediastinal Lymph Node Metastasis Pattern in Clinically N0 Non-small-cell Lung Cancer Patients Who Underwent Surgical Resection

Goran Krdzalic1, Dešo Mesic1, Ermina Iljazovic2, Selmira Brkic3, Alisa Krdzalic1, Nusret Ramic1, Zlatan Aljic1, Nermin Musanovic1
Clinic for Surgery, University Clinical Center Tuzla, Trnovac bb, 75000 Tuzla, Bosnia and Herzegovina1
Clinic for Pathology, University Clinical Center Tuzla, Trnovac bb, 75000 Tuzla, Bosnia and Herzegovina2
Department of Pathophysiology, Faculty of Medicine, University of Tuzla, Univerzitetska 1, 75 000 Tuzla, Bosnia and Herzegovina3
Clinic for of Anaesthesiology and Reanimatology, University Clinical Centre Tuzla, Trnovac bb, 75 000 Tuzla, Bosnia and Herzegovina4

The aim of this study was to evaluate the incidence, clinical data and patterns of mediastinal lymph node metastasis (pN2) in non-small-cell lung cancer patients who underwent systematic mediastinal lymph node dissection (SMLND). We retrospectively studied 140 consecutive patients [125 male and 15 female, mean ages 54.61±9.23 years (range, 21-75)], underwent SMLND and major lung resections due to non-small lung cancer (NSCLC), from January 2005 till December 2009. Preoperative clinical staging for mediastinal lymph node metastasis was negative (cN0) in all patients. SMLND was defined as a complete removal of mediastinal lymph nodes. Clinicalpathological data were compared according to the pN stage. Lymph node metastasis to the mediastinum was confirmed in 13(9.28%) patients. In squamous cell cancer pN2 were in 8(5.71%) cases out of 82 cases with cN0. On the other side in the adenocarcinomas pN2 were in 5(3.57%) cases out of 48 with cN0. Unvaried analysis revealed central tumor site as predictive factor for mediastinal lymph node involvement. The upper mediastinal compartment was infiltrated in 12(8.57%) cases, middle in 8(5.71%) and lower in 3(2.14%) cases. Pneumonectomy was the most performed surgical procedure in pN2 patients. We concluded that SMLND improves pTNM staging in lung cancer patients who underwent major lung resections with central location of the tumour. Key words: Mediastinal lymph node metastasis, clinically N0 non-small-cell lung cancer, undrewent surgical resection

*Corresponding author: Clinic for Surgery, University Clinical Centre Tuzla, Trnovac bb, 75 000 Tuzla, Bosnia and Herzegovina. Tel: +387 61644644; e-mail: goran.krdzalic@ukctuzla.ba

1. INTRODUCTION

Lung cancer is common cause of cancer mortality in the developed world. Despite advances in variety of therapies, surgery for NSCLC is still the most effective method of controlling the primary tumor provided it is resectable for cure. The treatment of NSCLC depends of the TNM stage and mediastinal N2 lymph nodes remain a critical part of staging lung cancer patients. For this reason many authors insist on the importance of SMLND for accurate staging (1). In this study we aimed to assess overall rate of pN2 for patients who underwent SMLNS based on our experience. We evaluated all consecutive SMLND and lung cancer resections performed on our department during 5 year period.

2. MATERIAL AND METHODS

We retrospectively studied clinical records of 140 consecutive patients with mean ages 54.61 ± 9.23 (range 21-75)] who underwent complete anatomical resection for histological proven NSCLC in five years, from January 2005 till December 2009. Among this group, 125 male patients with mean age 54.45±10.91 years and 15 female patients with mean age 53.16±11.34 years were enlisted. All patients had stage T1-3N0, assessed by preoperative computer tomography (CT) imaging of the chest, brain, abdomen, bone scan and abdominal and supraclavicular ultrasound scanning. Patients with proven N2 or N3 lymph node involvement were excluded from study. None of the patients in the study received preoperative chemotherapy or radiotherapy. Patients with previous or coexistent malignant disease were excluded from the study. Pulmonary and circulatory functions were required to be eligible for radical resections. Complete resection was defined as removal of primary tumor and all accessible hilar and mediastinal lymph nodes with

no residual tumor left behind. SMLND is defined as a radical and block mediastinal lymph node dissection. The major lung resections procedures were lobectomy and pneumonectomy with standard posterolateral thoracotomy. The three compartments included upper or superior mediastinal node (station 1-4), the middle or subcarinal and paraesophageal node (station 7-8) and lower compartment or pulmonary ligament node (station 9). Metastasis to these compartments including either to one or multiple node regarded as positive. All tissue samples were sent to department of pathology. Three major types of carcinoma, squamous cell carcinoma, adenocarcinoma and large cell carcinoma were diagnosed and selected to analyze lymph node pattern.

2.1. Statistical analysis

Statistical analysis was performed using χ^2 test (or the Fisher's exact test as required). Values were expressed as mean ± S.D. (ranges). Univariate analysis was performed to identify factors linked to the status of nodal involvement. P-value ≤ 0.05 was regarded as significant.

Stage	SCC[1]	AC[2]	Others[3]	Total (%)
I	26	18	2	46 (32.9)
II	41	24	6	71 (50.7)
IIIA	15	6	2	23 (16.4)
Total,%	82 (58.6)	48 (34.3)	10 (7.1)	140 (100)
1.Small-cell carcinoma, 2. Adenocarcinoma, 3. Large-cell carcinoma				

Table 1. Postoperative TNM and histological status

	N0	N1	N2*	Total (%)	
Patients	55	72	13	140(100)	
Male	51	63	11	125(89.3)	p>0.05
Female	4	9	2	15(10.7)	
Squamous cc	27	47	8	82(58.6)	p>0.05
Adeno cc	28	15	5	48(34.3)	
Central TS	11	31	10	59(42.1)	p=0.040
Peripheral TS	44	41	3	81(57.8)	
Pneumonectomy	7	32	12	51(36.4)	p=0.021
Lobectomy	48	40	1	89(63.6)	
*group of patients who underwent univariate analysis					

Table 2. Clinicopathological characteristics of patients according to the N status

	UC (n, %)	UMC*(n, %)	MC (n, %)	MLC*(n, %)	LC (n,%)
Total (n,%)	12(92.3)	6(46.1)	8(61.5)	2(15.4)	3(23.1)
Squamous cc[1]	6	3	4	1	2
Adeno cc	4	2	3	1	1
Large cc	2	1	1	0	0
1Cell-cancer; UC, single upper compartment metastasis; UMC*, Upper-middle multiple compartment metastasis; MC, single middle compartment metastasis; MLC* multiple middle-lower compartment metastasis, LC, single lower compartment metastasis;					

Table 3. Compartments pattern of N2 metastasis involvement based on tumor pathology

3. RESULTS

All patients were treated by lobectomy or pneumonectomy with standard posterolateral thoracotomy. There were 3 postoperative deaths or 2.1%. Atrial fibrillation was observed in 12 (8.5%) patients. Wound infections, athelectasis, prolonged air leak and thoracic empyema were observed in 10 (7.1%), 8 (5.7%) 3 (2.1%), and 5 (3.6%) patients. The extent of resection was lobectomy in 89 (63.6%) patients and pneumonectomy in 51 (36.4%). The pathologist revealed 82 (58.5%) squamous cell carcinoma, 48 (34.3%) adenocarcinoma and 10 (7.1%) large cell carcinoma. Postoperative TNM and histological status is shown in Table 1.

Patient's clinicopathological characteristics according to the N status are listed in Table 2. The pattern of lymph node status was N0 55 (39.3%), N1 72 (51.4%) and N2 13 (9.3%). Men were more likely to have lung cancer surgery than women (125/15). Lymph node metastasis to the mediastinum was confirmed in 13 (9.3%) patients. In squamous cell cancer pN2 were in 8 (5.7%) cases out of 82 cases with cN0. On the other side in the adenocarcinomas pN2 were in 5 (3.6%) cases out of 48 with cN0. Univariate analysis revealed central tumor site as predictive factors for mediastinal lymph node involvement. Pneumonectomy was performed in 12 (8.5%) pN2 patients and lobectomy in 1(0.7%). The feature of lymph node metastasis to the mediastinal compartment based on individual pattern is shown in Table 3.

Single or multiple compartments metastasis pattern of N2 involvement based on histology of the tumors are shown in Table 3. We had no significant statistical differences among all groups.

4. DISCUSSION

This study did not reveal an increased morbidity after SMLND in patients with NSCLC compared to the findings of other reports in this respect (2). Our results in general agree with the study reported by Izbicky and associates (3), which described 2001 patients and demonstrated no increase in the rate of broncho-pleural fistula due to interruption of blood supply to the bronchial stump, phrenic and recurrent laryngeal nerve injury, chylothorax and hemothorax. We reported only relatively high incidence of arterial fibrillation (8.5%) and athelectasis (5.7%) probably due to excess denervation after hilar dissection and inadequate controlling postoperative pain. Operative mortality in lung resections reported by Allen et al. (2) was 2.0% compared with 2.1% in current study. Therefore, the fear of increased complications by performing a SMLND is unfounded.

The results of our study confirmed lymph node metastasis to the mediastinum in 13 (9.3%) patients out of 140 patients with negative preoperative mediastinal lymph node staging (cN0). There was strong similarity in the percentage of patients (11.5%) reported by Sugi et al. (4). Sioris et al. (5) also demonstrated that SMLND is necessary for accurate pN2 staging. They found 17% pN2 patients who were preoperatively diagnosed as cN0. This highly accurate staging after SMLND might allow a more precise

selection of the patient chemotherapy protocols with possible benefit in overall survival (6). It also may allow to eradicate otherwise undetected micro metastasis which might result in better local control and improved overall outcome of the patients (7).

This study also analyzed clinicopathological factors that might be significant predictive for lymph nodal involvement in patients who underwent resections of the NSCLC. Univariate analysis revealed central tumor site as predictive factor for mediastinal lymph node involvement with p=0.04. Ketchedijan et al. also showed that central tumors have a higher incidence of lymph node metastasis (8). In their series the incidence for nodal involvement was 50% for central tumor of any size. The major contributors may be intrapulmonary lymphatic route, interlobar lymph node so-called lymph sump and tumor infiltration capability (9).

Considering our results, a lobectomy is acceptable for patients for N0-1 patients with peripheral tumor, and pneumonectomy for N1-2 patients with central tumors. The similar results are revealed by Takizawa et al. (10). In this study pneumonectomy is high correlated with pN2 involvement in patients underwent NSCLC surgery.

The distribution pattern of different N2 compartment metastasis was assessed. The most involved region of mediastinum was upper compartment. We have not recorded different lymphatic spreading pattern of N2 metastasis involvement according to the different histological type of tumor as Wu et al. revealed (11). Our results agree with those previously reported by Kotoulas et al. (12).

5. CONCLUSION

In conclusion, among our group of NSCLC patients who underwent SMLND, 9.3% of patients with preoperative negative mediastinal lymph node metastasis involvement had pN2 disease. Factors as central location of tumor and upper mediastinal metastasis compartment involvement were highly correlated with pN2 disease. SMLND is safe procedure, and improves pTNM staging in NSCLC patients. Results confirmed that SMLND should be performed in all patients who underwent pneumonectomy with central site of the tumor.

6. REFERENCES

1. Lardinois D., De Leyn P., Van Shill P., Rami Porta R., Waller D., Passlick B., Zielinski M., Lerut T., Weder W. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur. J. Cardiothorac. Surg. 2006; 30: 787-792.
2. Allen M.S., Darling G.E., Pechet T.T.V., Mitchell J.D., Herndon II J.E., Landreneau R.J., Inculet R.I., Jones D.R., Meyers B.F., Harpole D.H., Putnam Jr. J.B., Rusch V.W. The ACOSOG Z0030 Study Group. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 Trial. Ann. Thorac. Surg. 2006; 81: 1013-1020.
3. Izbicki J.R., Thetter O., Habekost M. Radical systematic mediastinal lymphadenectomy in non-small cell cancer: a randomized trial. Br. J. Surg. 1994; 81: 229-235.
4. Sugi K., Nawata K., Fujita N., Ueda K., Tanaka K., Maatsuoka T., Kaneda Y., Esato K. Systemic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2cm in diameter. World. J. Sur. 1998; 22: 190-294.
5. Sioris T. Jarvenpaa R., Kuukasjarvi P., Helin H., Saarelainen S., Tarkka M. Comparison of computed tomography and systematic lymph node dissection in determining TNM and stage in non-small-cell lung cancer. Eur. J. Cardiothorac. Surg. 2003; 23: 403-408.
6. Strauss GM., Herndon J., Maddaus MA., Green MR. Randomised clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small-cell (NSCLC): report of cancer and leukemia group B (CALGB) Protocol 9633. ASCO Annual meeting Summaries 2004; 53.
7. Coelo M.C., Luketic J.D., Litle V.R., Godfrey T.E. Prognostic significance of micro metastasis in non-small-cell lung cancer. Clin. Lung. Canc. 2004; 5: 214-225.
8. Ketchedjian A., Daly B. D.T., Fernando H.C., Florin L., Hunter C.J., Morelli D.M., Shemin R.J. Location as an important predictor of lymph node involvement for pulmonary carcinoma. J. Thorac. Cardiovasc. Surg. 2006; 3: 544-548.
9. Naruke T., Tsuchiya R., Kondo H., Nakayama H., Asamura H. Lymph node sampling in lung cancer: how should it be done? Eur. J. Cardiothorac. Surg. 1999; 16: 17-24.
10. Takizawa H., Kondo K., Matsuoka H., Uyama K., Toba H., Kenzaki K., Sakiyama S., Tangoku A., Miura K., Yoshizava K., Morita J. Effect of mediastinal lymph nodes sampling in patients with clinical stage I non-small-cell lung cancer. J. Med. Invest. 2008; 36: 897-906
11. Wu N., Lv C., Yan S., Duan H., Zheng Q., Wang J., Xiong H., Yang Y. Systemic mediastinal lymph node dissection of right lung cancer: surgical quality control and analysis of mediastinal lymph node metastatic patterns. Interact. Cardiovasc. Thorac. Surg. 2008; 7: 240-243.
12. Kotoulas S., Foroulis C.N., Kostika K. Involvement of lymphatic metastatic spread in non-small cell cancer accordingly to the primary cancer location. Lung Cancer 2004; 44: 183-191.

ORIGINAL PAPER

Correlation of Subglottic Laryngitis in Children and Meteorological Parameters

Merima Kasumovic
Clinic for Plastic and Maxillofacial Surgery, University Clinical Centre Tuzla

Considering hospitalization as an indicator of the severity of acute subglottic laryngitis (ASL), the aim of this study was to determine the correlation between meteorological parameters and the incidence of ASL in children from the Tuzla area. The study included fifty-nine boys and girls from the Tuzla area, which were referred and hospitalized due to the ASL at the Clinic for diseases of ear, nose, throat, cervical and maxillofacial Surgery, University Clinical Center in Tuzla, Bosnia and Herzegovina, during the period of March 21st 2006 until March 20th 2007. We formed two databases: 1. the database on each hospitalized child included data on Body Mass Index (BMI), sex and age. 2. Meteorology database which included information on humidity, air temperature, wind direction and atmospheric pressure, sorted by day, month and season. The results of this study indicate that the number of hospitalized boys due to ASL was significantly higher than girls (48 boys and 11 girls). Boys with an average BMI of 34.53 kg/m^2 and 6.77 years of age suffered more frequently from the ASL (81.35%) than girls (18.64%) with an average BMI of 21.59 kg/m^2 and the age of 3.8 years. The largest number of children with ASL was admitted during the period of lowest temperature (Fall-12.27˚C; Winter-0.50˚C), and the largest value of relative humidity (fall 77.33 mmHg–winter 82.50 mmHg). Therefore, this study indicates that meteorological factors (temperature, humidity, wind direction, atmospheric pressure) increase the risk of ASL with young children, primarily boys. Key words: Children, subglotic laryngitis, meteorological parameters.

Corresponding author: Mr.sc. Merima KASUMOVIĆ, MD. Clinic for Plastic and Maxillophacial surgery, University Clinical Center Tuzla, Tuzla, Trnovac 1., Bosnia and Herzegovina. E-mail:pluschel@hotmail.com

1. INTRODUCTION

Laryngismus stridulus–spasm closure of the glottis, which last for few seconds and is followed by a noisy inspiration, it is known under the name pseudo croup. Keyword, croup "comes from the Anglo-Saxon word CROUP which means, to cry out loud" (Cherry, 2004).

Subglottic laryngitis (pseudo croup, croup, laryngotracheobronchitis) is a form of viral infection of subglottic part of the upper respiratory tract, most often of the vocal cords and the structure of the larynx below the vocal cords, which causes acute inflammation and edema. Children are mostly affected by subglottic laryngitis, but it is not excluded also in adults (Bjornson and Johnson, 2004).

As a cause of croup were identified following the etiologic agents: parainfluenza virus type 1 and type 3, adenovirus, influenza A virus, parainfluenza virus type 2, respiratory syncytial virus, mycoplasma pneumoniae, staphylococcus, haemophylus influenzae type B, Klebs-Löffler bacillus, allergic reactions or insect bite in the area of pharynx or larynx, environmental pollution (cigarette smoke, air pollution in high concentrations).

Most common clinical manifestations are: slight fever, abrupt onset (often at night), distinctive ringing child cough, hoarseness, wheezing, island structures lining the larynx, contraction (spasm), the muscle below the vocal cords, narrowing of the airway.

Diagnosis: Radiography of the neck, blood tests, pulse oximetry, viral culture or rapid antigen tests, a clinical scoring system (Croup test table).

Westley Croup Score

LEVEL OF CONSCIOUSNESS	
Normal (including sleep)	0
Disorientation	5
CYANOSIS	
Without	0
Cyanosis with anxiety / agitation	4
Cyanosis at rest	5
STRIDOR	
None	0
Irritated / disturbed	1
At rest	2
AIRFLOW	
Normal	0
Decreased	1
Significantly reduced	2
RETRACTION	

None	0
Moderate (jugulum, epigastria)	1
Medium (jugulum, epigastria, sternal)	2
Severe (jugulum, sternal, intracostal, Epig.)	3

Westley Croup Score (Westley et al., 1978)

2. GOAL

The aim of this study was to determine the correlation between meteorological parameters and the incidence of ASL in children from the area of Tuzla, taking hospitalization as an indicator of the severity of clinical manifestations of acute subglottic laryngitis (ASL).

3. MATERIAL AND METHODOLOGY

The study included seventy-four children from the area of Tuzla aged 0-14 years that were referred and hospitalized due to ASL at the Clinic for ear, nose, throat disease, cervical and maxillofacial surgery, University Clinical Center in Tuzla, Bosnia and Herzegovina, in a period from March 21st 2006 until March 20th 2007. We formed two databases: 1. The database on each hospitalized child included data on Body Mass Index (BMI), sex and age. 2 The meteorological database which included information on humidity, air temperature, wind direction and atmospheric pressure, sorted by day, month and season in the area of Tuzla.

4. RESULTS

In the period of investigation at the Clinic for ear, nose, throat disease, cervical and maxillofacial surgery, University Clinical Centre Tuzla, due to acute subglottic laryngitis (ASL) were referred 74 patients, of whom 59 were hospitalized (79.2%).

Gender and age distribution of children hospitalized at the Clinic due to ASL in the examined period is shown in Table 1.

This study included 48 boys and 11 girls with mean age of 2.98 ± 0.376 years (aged from 2 months to 13 years). From the table we can see that in the period of investigation at the Clinic due to ASL were hospitalized more boys than girls (81.35%: 18.64%). The boys were a little older than the girls, the mean rate of 3.2 ± 0.3137 years.

In Table 2 shows the values of height and weight, and BMI values of hospitalized children.

Distribution of children referred and hospitalized for ASL by month during the same period is shown in Table 3 (Names of months in the Table marked initial letters, in chronological order from beginning to the end of the period of investigation).

The largest number of children hospitalized because of the ASL was during the fall, winter and early spring and lowest in summer. Months in which the largest number of hospitalizations of children due to ASL was: March, May, September, October, November, December, January, and months with the lowest number of hospitalized children were: July and August.

Majority of children hospitalized for ASL had only one episode of the disease (42), two episodes of disease had 12 children and more than two episodes of the disease is found in 5 children.

Table 4 shows the number of children hospitalized for ASL by the number of episodes of disease.

Seasonal distribution of episodes of acute subglottic laryngitis showed that the majority of cases occur during the colder time of year (from November to March) with a frequency that is nearly doubled compared to the warmer season (from May to October). Since the month of November the frequency of the frequency increases and reaches its maximum in March. Since March the number of children suffering from acute subglottic laryngitis gradually declines, reaching its minimum in August. From the table we can also see that the largest number of children hospitalized for ASL (with one or two episodes of disease) was in the colder seasons (winter-spring) and totaled 39 cases, and that children which are hospitalized more than two episodes of disease had no special seasonal representation (5 children).

Average monthly values of temperature and humidity during the same

Sex	No. Of hospitalized children	Average age (years)	Minimal age (years)	Maximum age (years)
Male	48	6.77	0.291	13.25
Female	11	3.8	0.5	7.1

Table 1. Sex and age distribution of patients hospitalized due to ASL

Sex	Average weight (kg)	Average height (cm)	Average Body Mass Index (kg/m^2)
Male	12.85	61.50	34.53
Female	12.74	77.00	21.59

Table 2 Body Mass Index of children hospitalized due to ASL by gender

YEAR	2006										2007		
Month	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb	Mar.
Season	Spring			Summer			Autumn			Winter			
Referred children (number)	8	2	10	2	1	1	3	3	13	9	8	2	12
Hospitalized children (number)	4	2	9	2	1	1	3	3	9	5	6	2	12

Table 3 Monthly distribution of children referred and hospitalized for ASL

No. Of episodes	Season					
	Autumn	Winter	F-W	Summer	Spring	S-S
1	5	17	22	3	17	20
2	4	4	8	3	1	4
3	0	0	0	1	1	2
4	0	1	1	0	2	2
Total	9	22	31	7	21	28

Table 4 Seasonal distribution of children hospitalized for ASL by the number of episodes of disease

YEAR	2006										2007		
Month	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb	Mar.
Season	Spring			Summer			Autumn		Winter				
Average air temperature (˚C)	5.2	11.7	15	18.2	21.4	18.7	16.9	12.9	7	3	5	6	8
Average humidity (mmHg)	74	73	72	76	70	78	78	77	77	84	75	76	71
Average value of atmospheric pressure (kPa)	9760	9796	9816	9843	9838	9772	9830	9833	9847	10949	9848	9788	9697

Table 5 The basic meteorological parameters in the region of Tuzla in the period of investigation

period in the municipality of Tuzla are shown in Table 5.

This table shows that the average monthly air temperature in the area of Tuzla in the period of investigation was the largest in months: June, July, August, September, October, and lowest in months: November, December, January, February, and March. The average atmospheric pressure of air during the same period in the municipality of Tuzla was the highest in the month of December (10949 kPa) and lowest in March 2007 (9607 kPa).

It is evident that the highest values of humidity for the period studied were in March, late April, in May, June, July and August 2006. Humidity has increased since the beginning of September 2006, and the highest was in December 2006 and January and February 2007. For the studied period were not recorded large fluctuations in the values of moisture. Minimum value of relative humidity was recorded in July 2006 and amounted to 43 mmHg, and the average humidity was 70 mmHg. The maximum value of humidity was in December 2007 and was 95 mmHg, and the average humidity was 84 mmHg.

Figure 2 shows daily fluctuations in air temperature during the same period in the municipality of Tuzla.

From Figure 2 it is concluded that the largest increase in air temperature during the day for the research period was the beginning of July 2006. The maximum temperature in July of 2006 was 28.7˚C, and the average value of air temperature was 21.4˚C. The largest drop in the value of air temperature was at the beginning of November (2.2˚C) and December (-0.2˚C) 2006. Average air temperature values were also in early November (7.0˚C) and December (3.2˚C) 2006. Temperature fluctuations during the episodes were changing to the amount of ± 5˚C.

Results of this study indicate that there is a significant seasonal distribution of disease. More cases in the autumn and winter (25 children). From November 2006 to March 2007, almost double the number of cases (44 children), than from May to October 2006 (27 children). Least number of cases was in the summer during the month of July and August 2006 (2 children).

5. DISCUSSION

Acute subglottic laryngitis is a common respiratory disease of children, much more serious than acute laryngitis in adults, which appears in the course of generalized viral infections of upper respiratory tract. Symptoms include slight fever, a rapid onset (often at night), dysphonia, cough like a barking dog, inspiratory stridor and dyspnea. Typical acute subglottic laryngitis in children is almost always viral, caused by influenza viruses, parainfluenza, rhinovirus and adenovirus.

In the fifth century BC, Hippocrates suggested that weather changes can affect physical health (Shutty et al., 1992).

Meteorological factors such as fluctuations in temperature, humidity and wind direction affect the incidence of respiratory diseases. Colds, asthma and croup are the most studied diseases. It is interesting that the temperature changes in Earth's crust affect the occurrence of colds. It was noted that the drop in temperature of 1˚F directly associated with increased morbidity from colds to 1% (Hope, 1958).

A highly significant correlation was found with an increased number of patients with croup and low daily temperatures, low absolute humidity and the rapid decline in mean monthly temperatures (Fielder et al., 1989).

Most authors agree that acute subglottic laryngitis (ASL) usually affect children in the second year of life, and then is the highest incidence of this disease (Denny et al., 1983; Save and Branica, 1993, Schwartz et al., 1991). Children with ASL are most often aged 6 months to 3 years (Ramos et al., 1990), and 90% of affected children are under 7 years of age (Save and Branica, 1993). Of course, the disease can affect children younger than 3 months, and those older than 15 years (Thomas and Friedland, 1998), although ASL is not recorded

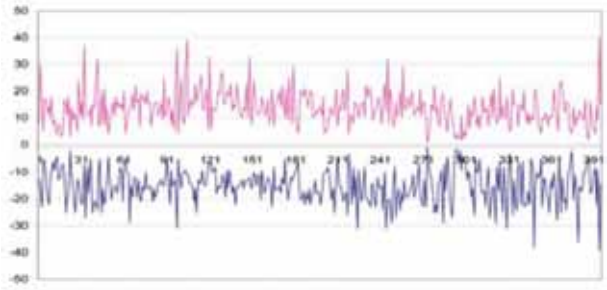


Figure 1. The greatest increase and greatest decrease in the value of moisture throughout the day during the same period

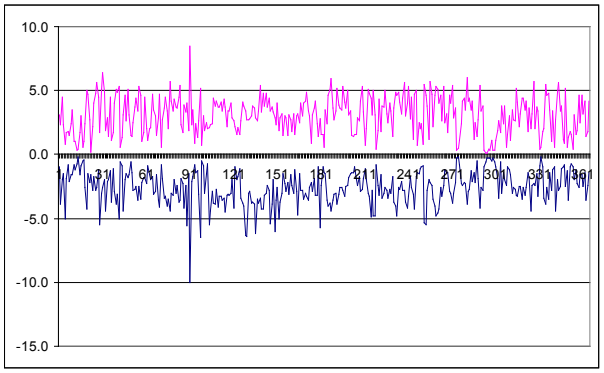


Figure 2. The greatest increase and greatest decrease in air temperature during the tested period

in the first month of life (Denny et al., 1983). Analyzing acute respiratory illnesses in children, it can be argued that ASL usually affect children in the second year of life, while obstructive bronchitis usually affect children in the first year of life (Schwartz et al., 1991). Our findings were correspondent with the results of these authors.

The boys are gender group which is more often affected by ASL, more than girls (Ramos Lizana J et al., 1990), and some authors the ratio of male to female ratio expressing in ratio of 1.43:1 (Denny et al., 1983) to 2.1:1 (Segal et al., 2005). The male to female ratio was 70:30% in a study conducted in Croatia during nineties of the twentieth century (Save and Branica, 1993). Our findings were correspondent with the results of previous researchers.

Most authors who dealt with the ASL testing in children came to the conclusion that the highest incidence of this disease is in the autumn and winter (Cohen and Dunt, 1988, Mars et al., 1997). If we are talking about months in which the highest incidence, it is October, a month with a minimum of admissions is February (Mars et al., 1997) and July (Save and Branica, 1993). Our findings regarding the seasonal occurrence of the ASL show that it occurs more often in late autumn and early winter. Months with the lowest number of hospitalizations were July and August 2006, while the highest incidence was in November 2006 and March 2007. Based on these facts, we conclude that our results are correspondent with the results of previous researchers.

Statistical analysis demonstrated that there was no significant difference in BMI and occurrence of ASL (Chmielk et al., 1984; Hide and Guyer, 1985). Our research has shown that children with higher BMI are more frequent occurrence of ASL (p < 0.05). Thus, our results are correspondent with the results of these authors.

6. CONCLUSION

Research conducted during the period from March 21st 2006 until March 20th 2007 at the Clinic for ear, nose, throat diseases, cervical and maxillofacial surgery, Clinical Center in Tuzla has shown that meteorological parameters affect the incidence of diseases such as acute subglottic laryngitis. The results of this research do not always prove a statistically significant effect of changing weather conditions and the incidence of diseases such as acute subglottic laryngitis. Therefore, we can confirm the assumption that the meteorological parameters are one of the major causes of morbidity in the pathogenesis of acute subglottic laryngitis.

Children's respiratory tract is smaller than in adults, so any inflammation leads to a reduction in the diameter of the respiratory tract. The highest incidence is between 6 months and three years, and the highest frequency in the second year of life. Croup was not recorded in the first month of life, but it is in children above fourteen years of age. Boys are more often affected than girls, at the percentage ratio of 70%:30%. In terms of season, more cases is recorded in late autumn and early winter, from November to March, twice as many cases than from May to October. The lowest incidence was in the summer, in July and August. Minimal changes in temperature or humidity changes have no impact on the occurrence of subglottic laryngitis. However, large and sudden changes in temperature and humidity results in a larger number of episodes, which have been proven by other researchers (Danielides et al., 2002).

Based on the foregoing, we consider useful for future researchers to suggest that besides the monitoring of meteorological parameters for the occurrence of subglottic laryngitis, research should be focused also on a concentration of air pollutants monitoring and air quality, in order to try correlated them with the appearance of subglottic laryngitis in children in municipality Tuzla.

REFERENCES

1. Ausejo M, Saenz A, Pham Ba', Kellner JD, Johnson DW, Moher D, Klassen TP. The effectivness of glucocorticoids in treating croup: meta-analysis. BMJ, 1999; 319: 595-600.
2. Bhende MS. End tidal carbon dioxide monitoring in pediatrics-clinical applications. J Postgrad Med; 2001;47:215.
3. Bjornson CL, Johnson DW. Pediatric Practice: That characteristic cough: When to treat croup and what to use. Patient Care, 2004; NP 27: 64-78.
4. Botelho C, Correia AL, da Silva AM, Macedo AG, Silva CO. Environmental factors and hospitalization of under five children with acute respiratory infection, Int J Pediatr Otorhinolaryngol, Jan 2001; 57 (1):41-3.
5. Cherry JD. The treatment of croup: continued due to failure of recognition of historic, ecologic, etiologic and clinical perspectives. J Pediatr, 1979; 94: 352.
6. Cherry JD. Croup (laryngitis, laryngotracheitis, spasmodic croup, laryngotracheobronchitis, bacterial tracheitis and laryngotracheobronchopneumonitis). Textbook of pediatric infectious diseases, (eds) Feigin RD, Cherry JD, Demmler GJ, Kaplan SL. Philladelphia: Saunders; 2004;252-65.
7. Chin R., et al. Effectivness of a croup clinical pathway in the managment of children with croup presenting to an emergancy department. J Paediatr Child Health, 2002; 38: 382-7.
8. Chmielik M, Debska M, Patryka M, Arcimowitz m, Chmielik LP, Jakubczyk I, Wachulski B. Body build-Is it factor in acute subglottic laryngitis? Int J Pediatr Otorhinolaryngol, 1997; Jun 20; 40(2-3): 147-53.
9. Danielides V, Nousia CS, Patrikakos G, Bartzokas A, Lolis CJ, Milionis HJ, Skevas. A. Effect of meteorological parameters on acute laryngitis in adults. Acta Otolaryngol, 2002; 122: 655-60.
10. Denny FW, Murphy TF, Clyde WA Jr, Collier AM, Handerson FW. Croup: an 11-year study in a pediatric practice. Pediatrics, 1983 Jun; 71(6): 871-6.
11. Fielder CP. Effect of weather conditions on acute laryngotracheitis. J Laryngol Otol, 1989; 103: 187-90.
12. Fielder CP. Effect of weather conditions on acute laryngotracheitis. Ann Emerg Med, 1993; 22(3): 523-9.
13. Hope, Simpson RE. Discussion of the common cold. Proc R Soc Med, 1958; 51: 267-71.
14. Jaklin RH, Bender SW, Becker F. Environmental factors in croup syndrome. Z Kinderheilkunde, 1971; 111: 85-94.
15. Peltola V, Heikkinen T, Ruskanen O. Clinical courses of croup caused by influenza and parainfluenza virus. The Pediatric Infectious Disease Journal, 2002; 21: 76-8.
16. Ramos Lizana J, Gonzales de Dios J, Lopez Lopez C. Epidemics of laryngitis (8983 cases of laryngotracheitis and croup). I. Epidemiologic Aspects. An Esp Pediatr, 1990; 32(3): 193-6.
17. Schweizer E, Weber G, Severien C, Mietents C. Effect of various weather parametars on the incidence of inpatient treated children with stenosis laryngotracheobronchitis (psudocroup) Clin Exp Allergy, Nov 2003; 33(11): 1526-30.
18. Shutty MS, Cundiff J, DeGood DE. Pain complaint and weather: weather sensitivity and simptom complaints in chronic pain patients. Pain, 1992; 49: 199-204.
19. Sprem N, Branica S. Effects of sulfur dioxide and smoke on the incidence of laryngotracheitis (croup). Int J Pediatr Otorhinologol, 1993 Apr;26(3): 245-50.
20. Thomas LP, Friedland LR. The cost-effectivive use of nabulizes recemic epinephrine in the treatment of croup. American Journal of Emergency Medicine, 1998; 16: 87-9.
21. Tibballs J, Shann FA, Landau LI. Placebo controlled trial of prednisole in children intubated for croup. Lancet, 1992;340:740-8.

ORIGINAL PAPER

Risk Factors for Development of Hip Disorder Among Newborn Babies in Tesanj Region

Seid Fazlagic [1] Predrag Grubor [2] Suad Fazlagic [3]
Department of surgery, General hospital Tesanj, Bosnia and Herzegovina1
Clinic for Traumatology, Clinical center of University of Banja Luka, Bosnia and Herzegovina2
Policlinic "Medicus", Tesanj, Bosnia and Herzegovina3

INTRODUCTION Development disorder of the hip is a congenital, dynamic and progressive disease where there is disorder in the development of all elements of hip that is clinically shows as functional disorders. **AIM** To determine clinical and statistical arthrosonographic representation of developmental disorders of the hip at newborn babies in Tesanj region, with or without risk factors. **MATERIAL AND METHODS** The subjects are 300 newborns born in Tesanj region, which are examined in the orthopedic clinics in the period from October 1st 2008 to May 1st 2009. **RESULTS** youngest child in the studied sample had an examination in the first nine and the oldest 42 days, an average of 33 days. In the studied sample representation of the firstborn children was 179, and second born children 97, third born 23. Only one child was born from the fourth pregnancy. Positive family history had 26 children and negative 274. Natural way was born four children, by Caesarean section 51 children. One child was born early but naturally. On time 244 children were born by normal natural way. Of firstborn children, the representation of female children was 80, and the male 99. 6 children were born as twins. Associated anomalies were found in two of the examined children; agenesis of fibula and pes equinovarus. One risk factor had 113 children, two 27 and three risk factors at one child. The remaining 159 children had no risk factor or a developmental disorder of the hip. **DISCUSSION D**evelopmental disorder of the hip is the most common developmental anomaly, which occurs in all races and ethnic groups, ranging from 0.4% to 6%. It is more common in female than male children in the ratio of 1:4 to 1:10. Mutual disorder appears more than one-sided reports. Sided phenomenon affecting more left than right hip. Developmental disorder of the hip is often associated with other developmental abnormalities. Early detection of initial disturbances in newborn is crucial, because of using of early traumatic therapy, which reduces the incidence of operative treatment and secondary complications. **CONCLUSION** Developmental hip disorders in children in Tesanj region, defined by hip sonography Graf, were found in 4.33% cases. If the borderline cases of type I by Graf included in the category of children with possible spontaneous evolution from type I to type II (no prevention measures), the incidence of RCC would be 10.66%. Almost half of children (139) of the investigated sample have a risk factor in the anamnesis. Remarkably high percentage of children born caesarean. The greatest correlation of risk factors, was determined in children with a positive family history, were born with abnormalities of the loco motor apparatus and natural way of born. **KEY WORDS** Developmental disorders of the hip, sonography

Corresponding author: Seid FazlagiĆ, MD. Ul. Novo naselje , Krndija-Tešanj, Broj telefona: 032 654 194 / Mo 061 260 496, e-mail : Fazlagics@ gmail. com

1. INTRODUCTION

Developmental hip dysplasia is a congenital, dynamic and progressive disease in which there is disorder in the development of all elements of the hip joint, resulting in complete dislocation of the joint parts with all the functional disorders. (1) The term "developmental disorder of the hip (DDH) encompasses all levels in the development of these anomalies: dysplastic, subluxated, and luxated hip (2).

The first descriptions of RPK gave Hippocrates. A significant contribution to the knowledge of the diagnosis is given by Ortolan and Palmen, Lorenz, in the treatment of with plaster, Hilgenreiner and Pavlik with their apparatus, and in prevention Roser (3). The significance of surgical treatment of DDH has given in his works Chiari 1955 introducing a pelvic osteotomy, Pemberton in 1959 by etabulum covering and Salter in 1961with innominate bone osteotomy and later with triradiat osteotomy (4). It is known for

certain that the DDH occurs in utero, and happens more frequent in children with positive family history, among the firstborn female children, twins, breech birth or Caesarean section, children who have other congenital anomalies, particularly of the locomotor apparatus (5,6). Identified are also other risk factors such as pelvic disproportion of mother and fetus, the lack of amniotic fluid (oligohydramnios), heavy and extended labor ... (5).

Radiographic hip examination is valid when the child reaches 3 months of life. This is because part of hip cartilage is replaced by bone mass and ossification core of the femoral head forms (7).

Sonography provides an absolutely safe intrauterine visualization of the hip or in the first days of life of a child. In this age most of the hip joints are made of cartilage, which provides a broad "ultrasonic window and display a large portion of the hip joint. In Europe, hip ultrasonography is used according to Graf (3).

For completely correct interpretation of the sonogram has to be shown seven anatomical structures: cartilage-bone border, head of the femur, the transitional groove, joint capsule, labrum acetabula, cartilage acetabula roof, bone acetabulum.

Drawing the base line which is tangential to the iliac bone wing and passing through the intersection and perichondria periosteal or through a place where the periosteal becomes perichondria (11). The second line is a line of the bony roof. It starts from the lower edge of the os ilium, the bottom of the acetabulum and passes tangentially through the bony acetabula roof angle creating alpha. The other line is drawn from the cartilage roof starts with bony bay windows and passes through the center of labrum acetabula making the angle beta. The angle beta indicates the state of the cartilage roof of the hip joint (11,12). According to the values of angles alpha and beta, there are four basic types of hips according to Graf (3,12).

2. GOAL

The goals of research are: to determine the clinical and arthrosonographic finding the hip in newborns in the hospital Tesanj, determine the prevalence and clinical and statistical significance of sonography findings in infants with risk factors and no risk factors, to propose recommendations for early detection of persons with increased risk for DDH.

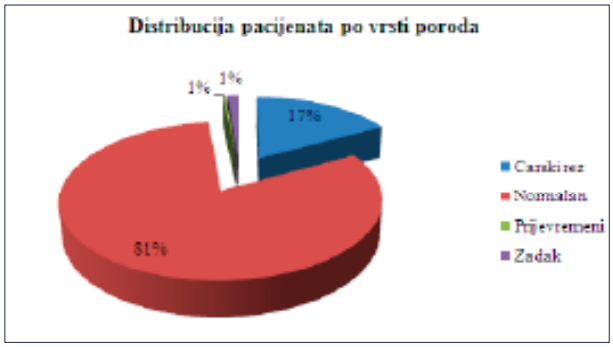


FIGURE 1.

3. MATERIAL AND METHODS

Subjects are 300 newborn infants in Tesanj region, which were examined in an orthopedic clinic in the period from October 1st 2008 to May 1st 2009. The first ultrasound examination was performed in infants who were not older than 45 days.

After taking the anamnesis data from the parent started clinical examination of the newborn. Formed is a questionnaire in which they entered the data used for statistical analysis. In addition to basic data such as general data, sex and age entered the data on the order of pregnancy, type of pregnancy (normal, twins). In the section on birth, entered the data on the type of delivery (normal, premature, by Caesarean section), followed by details on the fetus (head first, breech birth) and birth weight.

Entered are the data on the associated anomalies such as congenital pes equinovarus, pes. valgus and other anomalies and the occurrence of developmental anomalies of the hip in first degree relatives, and information on family history. In a special section were possible remarks.

Separate questionnaire was used for statistical analysis of the data about the DDH risk factors: positive family history, the firstborn female child, breech birth, birth by Caesarean section, twin pregnancy, premature birth, congenital anomalies of the musculoskeletal system, pes equinovarus, pes equinovalgus , various forms of dysplasia, and agenesis. The part of the questionnaire was designed for clinical examination of the hips collected are the data on asymmetry of gluteal, inguinal and femoral groove (Bade sign), the result of abduction test separately for each hip: Ortolani luxation and Palmen reposition sign. Clinical examination was performed by hip sonography. Used is ultrasound machine "Toshiba" with linear probe of 7.5 MHz. Method used is by Reinhardt Graf.

With tests of statistical significance determined is inferential statistics–tests of implicit (additional) and explicit (main) research hypotheses by nonparametric method,–χ^2 test (Chi-square test).

4. RESULTS

The youngest child in the sample had 9 and the oldest 42 days, an average of 33 days. In the baseline there was 179 (59.67%) first born, and the second born in 97 (32.33%), third-born 23 (7.66%)

Probability of true hypothesis about correlation between individual risk factors and research parameters (p) (tested sample)	Gender	Birth order	Pregnancy	Type of delivery	Family anamnesis	Bade sign	Abduction test	Ortolani sign	Palmen sign	Alpha angle (right)	Hip type according to alpha angle (right)	Alpha angle (left)	Hip type according to alpha angle (left)	Hip type according to beta angle (right)	Hip type according to beta angle (left)	Hip type by Graf (right)	Hip type by Graf (left)	Medical treatment
Probability (p)	0.4675	0.1599	NCFT	NCFT	NCFT	0.2228	0.7939	NCFT	NCFT	NCFT	NCFT	NCFT	NCFT	0.4897	0.1888	NCFT	NCFT	0.4064

TABLE 1.

cases. Only one child (0.33%) was born from the fourth pregnancy. Positive family history in the sample had 26 (8.67%) children, while with negative family history was 274 (91.33%). Breech birth was in case of 4 children (1.33%), born by Caesarean section were 51 (17%). (Figure 1) Premature, but naturally born is 1 (0.33%) child. Normal and natural way in the term was born 244 (81.33%) children. From the first-born children, in the sample were 80 (26.67%) female children and 99 (33.00%) male.

As the twins were born 6 (2%) children. Associated anomalies as a risk factor for DDH were found in two children. In one it was an agenesis of the fibula and lateral side of the foot, while in the second the congenital pes equinovarus. With only one risk factor for DDH was 113 (37.67%) children, with two risk factors for DDH 27 (9%) and three risk factors for DDH is born only 1 (0.33%) child. The remaining 159 (53%) children had no risk factor.

Testing of hypotheses about the significance of differences of research parameters (characteristics) in relation to individual risk factors in the sample is presented in Table 1

In the Table (1) NCFT is short: there are no conditions for the testing of hypotheses. NCFT label indicate the fact that at least one cell in the corresponding contingency table have frequencies of 5 or lower.

Based on the tables and rules of reasoning we conclude that for the studied sample:

- There is no correlation between individual risk factor and gender ($p = 0.4675$);
- There is no correlation between individual risk factors and the order of birth ($p = 0.1599$);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and pregnancy;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of birth;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and family history;
- There is no correlation between individual risk factors and positive Bade sign ($p = 0.2228$);
- There is no correlation between individual risk factors and positive Abduction test ($p = 0.7939$);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and positive Ortolani sign;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and positive Palmen sign;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and the angle alpha (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to angle alpha (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and the angle alpha (left);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to angle alpha (left);
- There is no correlation between individual risk factors and types of hip according to angle beta (right) ($p = 0.4897$);
- There is no correlation between individual risk factors and types of hip according to angle beta (left) ($p = 0.1888$);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to Graf (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to Graf (left);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and medical treatment.

Of 113 children with one risk factor in the sample was mostly female first-born children (19.67%), followed by those born by caesarean section (10.67%), with positive family history (5.33%) (Figure 2). The first clinical examination revealed some of the clinical signs of DDH in 59 (19.67%) children in the sample and without any clinical signs of DDH in 241 (80.33%) child. Asymmetry of skin furrows (Bade sign), was found in 49 (16.33%), abduction test positive in 17 (5.67%), and Ortolani Palmen sign was not verified. Positive two clinical signs (Bade sign and abduction test) were in case of 8 (2.67%) children. There were three children with positive clinical signs of DDH

Sonographic examination revealed DDH in 13 (4.33%) children from which 9 female and 4 male children. In case of 3 children it was a bilateral, and in 10 the unilateral DDH, which makes a total of 16 from which was 8 right and 8 left DDH. In our sample, 287 children had type I by Graf, 12 type II according to Graf, one child type III according to Graf. From a total of 16 altered hips 15 were type II and only one type III according to Graf. We did not found any hip of type IV according to Graf.

Clinical examination of 141 children in whom is determined the presence of risk factors, medical history, clinical signs were found DDH in 33 (23.40%), and of 159 children who have not any anamnestic risk factor was 26 (16.34%) children with clinical signs of DDH.

In 26 children who had a positive family history 21 had no other risk factors for DDH. In the remaining 5 (31.25%) children were found clinical signs of DDH and it was found in 4 cases Bade positive sign, and one child with a positive Ortolani Palmen sign.

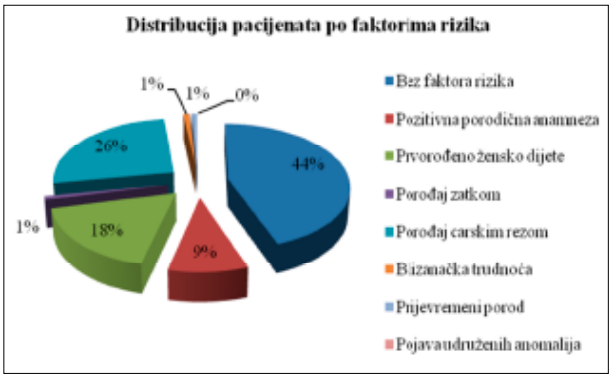


Figure 2.

Out of 80 first-born female children 59 had no other risk factors for DDH. From which 21 (30.50%) had clinical signs of DDH: 15 positive Bade sign, 5 abduction positive test and 1 positive for both these characters.

From 4 children who were breech born none had clinical signs of DDH.

From 51 children that were born by caesarean section 32 had no other risk factors for DDH. Clinical signs of DDH at birth by caesarean section had 2 (6.25%) children. In one was found positive Bade sign, and the abduction positive test in other.

For children from twin pregnancies, there were no clinical signs of DDH and with one child who is born prematurely. With congenital anomalies of the locomotor apparatus, there were two children. Neither of them have clinical signs of DDH.

Two risk factors for DDH had 27 children. In 19 there were no clinical signs of DDH and were found in 8. Clinical signs of DDH in 8 children are manifested: a positive Bade sign had a 4, a positive abduction test 2 and a positive sign for both of these 2 children.

Three risk factors had only 1 child in without clinical signs of DDH.

Without risk factors were 159 children. Clinical signs of DDH were found in 26 (16.35%) and a positive Bade sign in 19, abduction positive test in 2 and a positive sign of both in 5 children.

Analysis of 141 children with confirmed anamnestic, clinical risk factors, sonographic DDH was found in 9 (6.38%), and from 159 children without medical history or clinical risk factors for sonographic DDH was found in 4 (2.51%).

In relation to individual risk factors was found sonography of hips following conditions:

From 16 children with positive family history, and without other risk factors, by sonography DDH was found in 2 (12.50%).

Out of 59 first born girl child, and without other risk factors was found by sonography DDH in 4 (6 .77%).

From 32 children born by Caesarean section, and without other risk factors, only 1 (3.12%) had sonographic signs of DDH. One child from a twin pregnancy and one that is born premature, and without other risk factors had sonographic healthy hips (type I by Graf).

With congenital anomalies of the locomotor system in the sample were 2 children, both male. In one it was a congenital bilateral pes equinovarus, while in another the fibula and lateral agenesis of the right foot. In one was found sonographic DDH of the right hip.

From the 27 children with two clinical risk factors for DDH by sonography was diagnosed in 3 children (11.11%). In one child with three clinical risk factors there was no sonographic diagnosis of DDH. Out of 159 children from the tested sample at which it is not established in a single clinical risk factor, at 4 (2.51%) there was sonographic diagnosis of DDH.

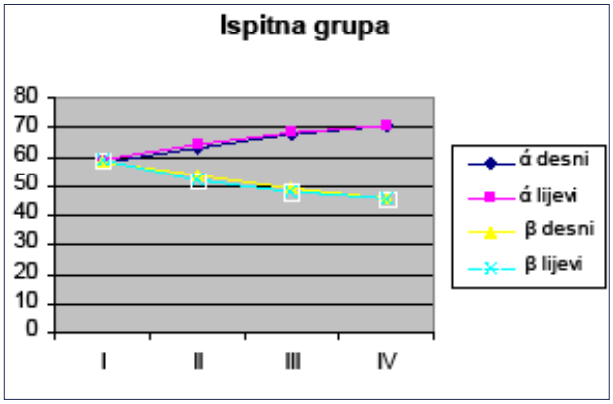


Figure 3.

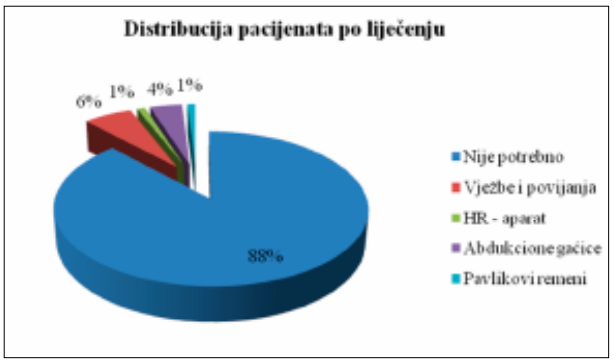


Figure 4.

In relation to individual risk factors by sonography of the hips was found the following conditions:

From 7 children with positive family history, and without other risk factors, DDH was verified by sonography in one case.

Out of 13 firstborn female children, and without other risk factors did not nor by a sonographic diagnosis of DDH,

Of 21 children who were born by caesarean section DDH was diagnosed by sonography in 2 children. Only one child was born from a twin pregnancy with sonography diagnosed DDH.

The maximum value of the angle alpha that was found on the right hip is 78^0, minimum 48^0, and the mean value of 70.44^0. The maximum value of angle alpha on left hip is 78^0, minimum 43^0, and the mean value of 70.40^0 degrees. (Figure 3)

The maximum value of the beta angle on the right hip was 82^0, minimum 39^0, and the mean value of 46.85^0 degrees. The maximum value of the angle beta on the left hip was 83^0, minimum 39^0, and the mean value of 47^0.

Most often value of angle alpha at the first examination of children in the sample was on the right hip 75^0 (41 times), 72^0 and 70^0 (37 times). The left hip angle commonly found value of alpha is 75^0 (43 times) 72^0 (35 times) and 70^0 (35 times).

Most frequent value of the angle beta in the right hip in the sample was 45^0 (30 times), 44^0 (29 times) and 48^0 (25 times). The most common value of left hip angle beta was 44^0 and 45^0 (29 times), and 46^0 (25 times).

Prevention, broadly folded, abduction exercises, treatment with Pavlik stripes and Hilgenrner tracks were involved from the first examination, diagnosis. (Figure 4)

Four weeks after the first clinical and sonographic examinations all children were reviewed for the second time. Clinical examination in neither one child from each sample was reported positive abduction test, and Palmen-Ortolani sign. All had asymmetric inguinal and femoral grooves, Bade positive sign, as at baseline. Any child who at the first examination had sonographic type I by Graf, had sonographic type I also at the second examination. From the 13 children who at baseline

had sonographic type II and type III by Graf, 10 patients (76.92%) were diagnosed with type I. Three children still had type II according to Graf.

At the third examination in the sample, by sonography were established DDH in two children, one male and one female. All children who at baseline had sonographic findings of DDH at the fourth review were healthy.

Measuring the angles alpha and beta in the second, third and fourth review is followed by maturation of acetabulum. The average value of angle alpha at baseline in healthy children in the sample was 71^0, second 73^0, third $73.5^0$and fourth 74^0, while the average value of the angle beta at baseline was 46.5^0, second 44^0, on third 43.2^0 and fourth 42.8^0. (Figure 3)

5. DISCUSSION

Developmental hip dysplasia is the most common developmental anomaly of the locomotor apparatus. It occurs in all races and ethnic groups, ranging from 0.4% to 6% (1,2). It is more common among the Slavic people, Navaho Native Americans... There are so called luxogenic zones such as the Valley of Zeta in Montenegro and Eastern Herzegovina, where the incidence of 9% is found (2). It is much more common in female than in male children and occurs at a ratio of 1:4 to 1:10 in favor of female children (12). More frequent is bilateral than unilateral. In cases of unilateral occurrence affected is more often the left hip than right. It is not rare that DDH is combined with other developmental anomalies (2).

Developmental hip dysplasia (DDH) is the most common disease of the joint. It is manifested as a dislocation in children and in adults as coxartrosis (9). Early detection of initial disorder in newborns and early atraumatic application of the therapy reduces the incidence of surgical treatment and secondary complications (10).

In our prospective study that was conducted in Tesanj from October 1st 2008 to May 1st 2009 we examined 300 children. The sample consisted of only those children who at the time of initial examination were not older than 45 days. The sample includes approximately one-half of children born in this region in time when the research was done. This data indicates that the method of early detection of DDH by sonography is not accepted method by the doctors who deal with this problem on Tesanj region. The incidence of DDH is different and varies in a range from 20-50 or even more per 1000 deliveries (2). For the big difference in the frequency the result is uneven terminology, the size of the study population, ethnic characteristics, and the child age during the examination, the experience of doctors, examination techniques and interpretation of results (5). The lowest incidence is in Hon Kong 0.01%, followed by Northern Ireland 0.14%, Sweden 0.17%, USA by 0.2% to 0.4%, in the UK about 1.5% (2.6,8,12). In Croatia, according to reports from several places DDH screening results show that the incidence is around 2%, although there are regions where it was 0.2% and even higher than 4% (Vrdoljak, Matasovic). The incidence of DDH in Serbia in recent years is around 2%. During 2002 and 2003 at the Department of Gynecology and Obstetrics in Novi Sad and the Institute of Orthopedic-Surgery "Banjica" clinically is examined 4016 newborns by ultrasound and found the incidence of DDH was 1.95% (12). Results of the first screening in Bosnia and Herzegovina, which was carried out in the Tuzla region at the sixties of last century, say that the incidence of DDH us 4.9%, followed by 6.3% (1,6). According to recent findings, the United Kingdom has the highest incidence of DDH in the whole Europe (6).

Data obtained by analysis of the sample indicate that the incidence of DDH in the Tesanj region is high (4.33%) and it is higher than in developed countries of Europe and neighboring countries in the region.

Breech birth was in 4 (1.33%) cases in the sample. The reports from Zagreb, Rijeka, Slavonski Brod in neighboring Croatia is that the breech birth is present in 2-3% of children (3).

Born by caesarean section in the sample are 51 (17%) children. The incidence of caesarean deliveries in the sample is as in developed European countries but lower than in the USA and Canada. According to WHO reports from 2002 and 2004 the incidence of caesarean birth in most developed countries is 10% to 15%, while it is slightly higher in the United States 20% and Canada 22.5%. These data, and data regarding the incidence of breech birth vary from region to region, and considering that a large number of deliveries by Caesarean started as breech birth and the birth by caesarean section has become a kind of trend, these data must be taken with a grain of salt.

The incidence of developmental dysplasia of the hip detected by clinical examination in the literature varies from 1.66% (Barlow), to 40% (Soc, Brecelj). These data do not depend only on the assessors, but also by region and time in which the research was done, and the age of children at the time of the hips examination. During sixties Soc and Brecelj SOC performed DDH research in Donja Zeta and found that the incidence of DDH is more than 40% (1). At the same time the data is completely contrary to Barlow and sets a very low incidence rate of DDH. He surveyed children at birth and then followed up to age 4 months and came to the conclusion that 60% of hips that are unstable at birth, stabilize in the first week and 88% in the next 2 months. The remaining 12% had residual instability. These data indicate that only a clinical examination is insufficient and unreliable method of screening of DDH but that it should be done within the inspection of children's hips.

Most investigators agree that heredity plays a significant role in the development of DDH, and that about 20% of children with DDH have a positive family history (6,8). In our sample 4 (30.76%) children with DDH have a positive family history, which is more than the specified data from the literature.

Of 59 first-born female children from the tested sample, only 2 (3.38%) has a developmental disorder of the hips. The incidence of DDH in first-born female children is even lower than in the whole sample, but higher than in children without risk factors, where the incidence is 2.51%.

Some say that more than 30% of children with DDH are firstborn female children (3). A number of authors have not point out to female first-born children, because they believe all the first-

born child, regardless of sex are at increased risk of DDH due to rigid walls of the uterus, and insufficient space for the development of the fetus. For female children the risk is increased because of greater amounts of estrogen that leads to looseness of the hip joint capsule (4).

In children with breech birth, twins and delivered prematurely within the tested sample has been no outbreak of DDH. In prematurely born children (one in each sample) was established DDH. Many authors believe that the lower risk of DDH is in these children because of better relations between the size of the fetus and the uterus. Data from this study speak in favor of it.

For breech born children in our sample, there was no occurrence of DDH, which is not consistent with data from the literature where it is stated that 20% of children with DDH had breech birth.

6. CONCLUSION

The incidence of DDH in children in the Tesanj region determined by sonography of the hips and using the Graf method was found in 4.33% of cases but is significantly higher than in developed European countries and USA.

If the borderline cases of type I by Graf are included in the category of children with possible spontaneous evolution from type I to type II (without prevention), the incidence of DDH would be 10.66% which is almost 2.5 times more than established.

Incidence of DDH in children with risk factors is 2.5 times more frequent than in children without risk factors.

Prevalence of risk factors in the sample is high. Nearly half of the children (141 or 47%) from baseline have at least one risk factor for DDH in anamnesis. Notably, a higher percentage of children are born by caesarean section.

The highest correlation between risk factors and DDH in the sample was found in children born with anomalies of the locomotor apparatus (50%) with positive family history (12.50%), and children with two risk factors (11.11%).

There was no significant correlation between DDH in first-born female children and birth by caesarean section, although it is slightly higher than in children without risk factors. Twin pregnancy, breech birth and preterm birth have no significance for the occurrence of DDH in our sample.

7th The curve of the value of angles alpha and beta indicates that the potential of acetabula bone maturation is very good in the first 6 weeks. From 6 until the late 12th week ossification potential of acetabulum is good, and after that period begins to weaken.

Clinical examination is not a reliable screening method of DDH. Significant differences in clinical and sonographic findings point to the possibility of diagnostic errors. Healthy children can be declared to be ill or sick to be healthy, which can have serious consequences. Clinical examination must not be omitted, and the first clinical examination should be carried out already at the maternity ward.

Sonography is a reliable method of detecting DDH in newborns. Method by Graf is practical and applicable. The possibility of error in estimating the type of hip by Graf is only in borderline cases. Therefore, the limiting case of type I and type II should be treated as type II, in order to avoid unwanted consequences.

Sonogram hip examination should be introduced as mandatory for all newborns and should be done in the first 6 weeks when ossification potential for maturation of acetabula is biggest, so the results of prevention and treatment of developmental dysplasia of the hip is the best.

REFERENCES

1. Alečković S, Zlatanović, Alaga M: Učestalost i liječenje kongenitalne anomalije kuka posljednjih 15 godina na terenu Tuzle, Skripta med., 10 143-149, 1975.
2. Ang KC, Lee EH, Lee PY, Tan KL: An epidemiological study of developmental dysplasia of the hip in infants in Singapore, Ann Acad Med Singapore, 1997 Jul; 26(4):456-8
3. Catteral , A.: What is congenital dislocation of the hip, J.Bone Joint Surg., 66-B, 469-471, 1984.
4. Committee on Quality Improvement, American Academy of Pediatrics (2000) Clinical practice guidelines: early detection of developmental dysplasia of the hip, Pediatrics 105:896–905
5. Čičak Nikola i suradnici: Ultrazvuk sustava za kretanje, Medicinska naklada – Zagreb, 2003.
6. Düppe H, Danielsson LG: Screening of neonatal instability and of developmental dislocation of the hip. A survey of 132,601 living newborn infants between 1956 and 1999. J Bone Joint Surg Br. 2002 Aug; 84(6): 878-85.
7. Gavrankapetanović Ismet, Talić Adnana, Gavrankapetanović Faris: Razvojni poremećaj dječijeg kuka, Sarajevo 2003. godine.
8. Gerscovich EO (1997) A radiologist's guide to the imaging in the diagnosis and treatment of developmental dysplasia of the hip. Skeletal Radiol 26:447–456
9. Graf R: Clasification of the hip joint dysplasia by means of sonography. Arch Orth. Trau. Surg. 1984, 102: 284-292.
10. Graf R: Fundamentals of sonografic diagnosis of infants hip dysplasia, J Pediatr. Orthop, 1984; 4:735-40.
11. Graf R, Wilson B: Sonography of the infant Hip and its Therapeutic Implications. Chapman-Hall, London, 1995
12. Graf R, Farkaš P, Lercher K, Tschauner C, Lojpur M; Priručnik iz sonografije kuka. Sonogram-dijagnoza-terapija., Stolzalpe 2001.

ORIGINAL PAPER

Relationship Between Anger, Alcoholism and Symptoms of Posttraumatic Stress Disorders in War Veterans

Avdo Šakušic[1], Esmina Avdibegovic[1], Zoran Zoricic[2], Slobodan Pavlovic[3], Vladimir Gašpar[2], Amra Delic[1]
[1]Department for Psychiatry, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina, [2]Department for Psychiatry, University Hospital „Sestre milosrdnice" Zagreb, Croatia, [3]Private agency «IQ&EQ», Tuzla, Bosnia and Herzegovina

Purpose: Studies among veterans indicate that veterans with posttraumatic stress disorder (PTSD) express anger, hostility and aggression as well as alcohol and substance abuse more then veterans without PTSD. The aim of this study was to analyze the relationship between anger, use of alcohol and symptoms of PTSD in war veterans in Bosnia and Herzegovina (B&H). **Method:** Comparing a group of veterans (n=54) with PTSD who use alcohol and a group of veterans (n=46) who do not use alcohol, the analyzed were dimensions of anger related to PTSD symptoms and alcohol usage. Medical records of patients treated at the Department for Psychiatry in Tuzla, B&H, Harvard Trauma Questionnaire (HTQ) – version for Bosnia and Herzegovina, State-Trait Anger Expression Inventory (STAXI), Structured Clinical Diagnostic Interview (SCID-I) were used in this study. The basic socio-demographic data were also collected**. Results:** A significant correlation is found between alcohol usage, and state and trait of anger (P<0.001), angry temperament (P = 0.001), anger-in expression (P<0.001), anger-out expression (P<0.001), and anger control (P<0.001). PTSD hyperarousal cluster symptoms were significantly correlated to state anger, anger-in expression (P<0.05), and use of alcohol (P = 0.010). **Conclusion:** The results indicate that there is a significant correlation between PTSD arousal symptom with anger dimensions, as well as between anger dimensions and use of alcohol in war veterans with PTSD. Key words: Alcohol Use, PTSD Symptoms, Anger

Corresponding author: Avdo Šakušic, Department of Psychiatry, University Clinical Centre of Tuzla, Rate Dugonjica bb, 75000, Tuzla, Bosnia and Herzegovina, Telephone number: +38761720242, E-mail: tuzlaavdosakusic@yahoo.com

1. INTRODUCTION

Posttraumatic stress disorder is frequently co-morbid with other psychiatric disorders (1, 2). Patients with PTSD often use alcohol or other psychoactive substances in order to cope with co-morbid problems such as anxiety or depression (3, 4), or as a way of reducing distress related to particular PTSD symptoms. Some studies point to the existence of high prevalence of aggression, and a connection of anger and aggression with PTSD symptoms (5). Symptoms of PTSD intermediate in the relation between trauma severity and the expression of both verbal and physical aggression (6). A significant number of studies have found a connection between PTSD symptoms in war veterans and aggressive behavior in partners' relationship (7, 8). War veterans' social functioning is considerably affected by relation between PTSD symptoms and the use of alcohol or psychoactive substances (9, 10). The alcohol use in war veterans with PTSD is interconnected with low quality of life (11). Recent study on U.S. soldiers returnees from Iraq in which demographic characteristics of the investigated groups of soldiers were very similar, point to a significantly high level of PTSD, depression and alcohol abuse, as well as to a significant presence of stigma linked to seeking help in mental health services (12,13). The incidence of aggressive and violent behavior in war veterans varies, while studies suggest that it is significantly higher in war veterans with PTSD. The predominant forms of aggressive behavior include auto-aggressive behavior and hetero-aggressive pattern with dominant verbal aggression and impulsive reactions. The level of education, low socio-economic status, childhood abuse, and prior violent behavior showed to be of importance for later occurrence of the aggressive behavior (14). Most studies show a high rate of PTSD symptoms, depression, and use of alcohol in war veterans (1, 3, 10), while difficulties related to anger in war veterans were much less analyzed (15). Chemtob et al. (16) report on a lack of empirical data on the relation between combat-related PTSD and increase in anger. Persons with PTSD symptoms have difficulties in anger control (17). Anger might be a very difficult emotion to deal with, and may

lead to a number of juridical and interpersonal problems (15). In DSM-IV TR (18) the anger is considered to be a possible symptom of PTSD. Angry ruminations and verbal expression contribute to PTSD symptoms maintenance. Several authors have recommended that treatment of PTSD should include anger management in certain groups of PTSD patients (19). The aim of this study is to determine the relationship between the anger and ways of anger expression, as well as the use of alcohol and PTSD symptoms in war veterans from Bosnia and Herzegovina.

2. SUBJECTS AND METHODS

The subjects enrolled in this study were male war veterans of the Army of Bosnia and Herzegovina, with the average age of 42.84±4.66 years, who did not use alcohol before the war and were hospitalized at the Department for Psychiatry in Tuzla during 2003, when diagnosed with combat-related PTSD according to DSM-IV criteria (18). This research is carried out in the period from September 2004 to February 2005. Data were collected from the admission protocols and medical records. Out of 1166 patients treated in 2003, the 130 (11.2%) were war veterans with PTSD. Their addresses were taken from the protocols and the letter about objectives of this research with a form of voluntary consent was sent via post office. The letter included the info about time schedule ascertained for each veteran as well as the place of investigation and travel costs to be covered. Psychometric tests and clinical assessment is done by clinical psychiatrist and psychologist who did not treat these patients previously. Out of 130 invited veterans, 113 responded among which 6 did not meet the inclusion criteria (4 used alcohol before the war, and 2 were older then 55). During the study procedure, 7 out of 107 war veterans dropped out for various reasons, and the investigated group of veterans with PTSD used some of psychotropic drugs in that period. All veterans used anxyolytics and sedatives, 49 used low dosages of atypical antipsychotics (Risperidon 1 to 2 mg a day), 70 used antidepressants (Paroxetin, Setralin, Fluoxetin). Veterans who use alcohol were taking psychotropic drugs on their own initiative out of recommended protocol, and temporarily taking anxyolytics with alcohol. After discharge 66 veterans were subject to a regular out-patient psychiatric treatment.

3. MEASURES

The State-Train Anger Expression Inventory (STAXI), which provides relatively brief and objectively scored measures of anger experience, expression and anger control, was used for the assessment of anger (20). The STAXI consists of 44 items administered in three parts and distributed across five main scales. In accordance with the above mentioned concept of anger, there exist three main aspects of the STAXI scales: State, Trait, and Anger Expression. Part 1 consists of 10 items to assess the State Anger. Part 2 contains 10 items to measure the Trait Anger. Trait contains two subscales to investigate different dispositions in trait anger–temperament and reaction. Part 3 consists of 24 items to measure Anger Expression. Anger Expression is an experimental composite of the three expression constructs In, Out, and Control. All items are rated on a four-point scale and assigned a score between 1 and 4. Trait-anger items are rated on 4-point scales from „almost never"–1 to „almost always"–4, and the state-anger items are rated on the intensity of feelings from „not at all"–1 to „very much so"–4. The coefficient of reliability for the trait-anger subscale was 0.91, for the state-anger subscale 0.82, and for the anger expression it was 0.79. The index of anger expression is being measured, which enables measuring the total anger expression, levels from 0-1.4 being low, 1.5–2.4 moderate, 2.5–3.4 high and 3.5–4.4 extremely high. Levels of anger expression were determined according to percentile range. Values of anger expression that fall to percentile 5 to 25 are considered to be low; values that fall to percentiles 50 to 75 are moderate; values to percentiles 75 to 90 are considered to be high, and values to percentiles 95 extremely high.

In order to determine alcohol consumption, the Structured clinical interview for DSM-IV, Axis I disorders (SCID-I), and application form for alcohol related disorder (21) were used. The interview format for the SCID includes an initial screen for evidence of any lifetime excessive drinking, followed by items for specific diagnoses of alcohol abuse and addiction. Each item is scored 1 – not present, 2 – mildly present or unclear or 3 – present. Every interview took about one hour. To evaluate traumatic events and the presence of PTSD, as well as the expressiveness of PTSD symptoms, a self-rating Harvard

Characteristics	No of war veterans (N=100)
Nationality	
Bosniaks	98
Serbs	2
Religion affiliation	
Islamic	96
Orthodox	2
Atheist	2
Marital status	
Married	82
Divorced	6
Widowed	4
Single	8
Education	
No education	10
Elementary	30
Secondary School	56
University degree	4
Employment status	
Employed	62
Unemployed	38
Alcoholism in family	
Present	40
Not present	60
Traumatic events	
Wounding	18
Death of the closest	22
Drawing a wounded and killed persons	94
Exposure to a heavy shelling	100
Being captured	10
Persecution	14
Witnessing death of other soldiers	92

Table 1. Socio-demographic characteristic of Bosnian and Herzegovina war veterans (N=100) with Posttraumatic Stress Disorders

Trauma Questionnaire (HTQ), Bosnia and Herzegovina Version (22) was used. For identified traumatic event, the respondents were asked: "How do you feel when you remember that?", rated on a 0-5 scale: 0 – No feeling, 1 – a bit upset, 2 – somewhat upset, 3 – moderately upset, 4 – seriously upset, and 5 – extremely seriously upset. Another part of the questionnaire contained a 16-item scale for measuring PTSD symptoms and the presence of PTSD. Stress level was defined as the frequency of each PTSD symptom in the last month, assessed on the 0 – 5 scale by determining its occurrence: 0 – not at all, 1 – almost never, 2 – sometimes, 3 – moderately, 4 – often and 5 – almost every day. To collect socio-demographic data, a questionnaire designed for this research was used; it contained questions related to general socio-demographic data and questions about family history of alcoholism.

4. DATA ANALYSES

A nonparametric Mann-Whitney test was used for the statistic analysis of differences between the groups in results of answers to questions about socio-demographic data (age, employment, education, marital status, employment of the partner, alcoholism in family). The difference between groups in stress levels, intensity of PTSD symptoms, number of traumatic events, and the score of index' of the subscale anger was analyzed by the factorial ANOVA model. The relation between dimensions of anger, use of alcohol, and PTSD symptoms was analyzed with the Pearson correlations. Collected data were statistically analyzed using the Windows Statistical Package for Social Sciences, version 10.0 (SPSS, Chicago, IL, USA).

5. RESULTS

Most subjects in this study were married, employed, of secondary school educational level, with no family history of alcoholism (Table 1). Average number of reported traumatic events was 4.8±1.75, where witnessing death or wounding of soldier mates prevail (Table 1). In total sample of the veteran group the mean of PTSD symptoms intensity was 3.37±0.41, the mean of stress level was 2.56±0.73, while the mean scores of clusters of intrusive symptoms was 2.78±0.57, avoidance symptoms 2.93±0.47, and arousal symptoms 2.46±0.76. According to SCID-I interview criteria, in the 12-month-period prior to this study, 54 veterans with PTSD used alcohol, and 46 did not use alcohol. There was no statistically significant difference related to age (43.56±4.94 vs. 42.00±42.84, F = 1.394, P = 0.244) between war veterans with PTSD who used alcohol and those who did not use alcohol. Using Mann-Whitney test, no significant difference is found between those two groups related to marital status (Z = -0.422, P = 0.673), level of education (Z = -1.199, P = 0.230), employment rate (Z = -0.729, P = 0.466), and family history on alcoholism (Z = -1.119, P = 0.263). No significant difference is found using Factorial ANOVA analysis in severity of PTSD symptoms (F = 0.268, P = 0.848), the intrusive symptoms (F = 1.404, P = 0.254), the avoidance symptoms (F = 1.625, P = 0.197), hyperarousal symptoms (F = 2.754, P = 0.053), and the number of traumatic events (F = 1.973, P = 0.131). Linear regression showed significant correlation between alcohol usage and the number of traumatic events (r = 0.334, P = 0.009), intrusive symptoms (r = 0.249, P = 0.041), avoidance symptoms (r = 0.309, P = 0.014), and hyperarousal symptoms (r = 0.384, P = 0.003). However, there was no significant relation between the number of traumatic events and intrusive symptoms (r = 0.039, P = 0.393), avoidance symptoms (r = 0.133, P = 0.178), and hyperarousal symptoms (P = 0.059, P = 0.342).

Out of total 100 war veterans with PTSD, a high and an extremely high level of trait anger was found in 18 veterans, a high level of anger-out expression was found in 24, anger-in expression a high in 20, and anger control a high to extremely high level in 46 war veterans (Table 2). Multivariate analy-

Anger Dimensions	No of war veterans related to level of anger expression*			
	Low (0-1.4)	Moderate (1.5-2.4)	High (2.5-3.4)	Extremely (3.5-4.4)
State anger	23	46	28	-
Trait anger	2	80	16	2
Angry temperament	6	66	28	-
Angry reaction	4	56	38	2
Anger expression	-	92	8	-
Anger-in	2	78	20	-
Anger-out	10	66	24	-
Anger controlž	8	42	40	6
* Levels of anger expression were determined according to percentile range; values of anger expression that fall to percentile 5 to 25 are considered to be low; values that fall to percentiles 50 to 75 are moderate; values to percentiles 75 to 90 are considered to be high, and values to percentiles 95 extremely high				

Table 2. Level of anger expression index measured by the State Trait Anger Expression Inventory (STAXI) in Bosnian war veterans with Posttraumatic Stress Disorder (N = 100)

Dimensions of anger	War veterans with PTSD (N=100)					
	Who use alcohol (n=54) M4SD	Who do not use alcohol(n=46) M4SD	Type III Sum of Squere	Mean Squere	F	P
State anger	2.1440.61	1.5640.37	5.33	1.77	6.08	0.001
Trait anger	2.3140.45	1.8640.41	3.41	1.13	6.41	0.001
Angry temperament	2.2940.55	1.8040.45	3.54	1.18	4.44	0.008
Angry reaction	2.3640.46	2.1140.57	2.25	0.75	3.03	0.038
Anger expression	2.2240.11	2.1540.14	0.13	4.52E-02	2.81	0.050
Anger-in	2.2940.26	2.0040.26	1.26	0.42	5.97	0.002
Anger-out	2.3240.42	1.7140.30	5.12	1.70	12.53	<0.001
Anger control	2.1040.67	2.7540.55	6.72	2.24	6.06	0.001
PTSD- Posttraumatic Stress Disorder, M-mean, SD–standard deviation, F value for factorial ANOVA						

Table 3. The mean of anger scores and differences in dimensions of anger measured by the State Trait Anger Expression Inventory (STAXI) in Bosnian war veterans with Posttraumatic Stress Disorder who use alcohol (n=54) and do not use alcohol (n=46)

sis used for fixed factors of alcohol usage found a significant difference in the dimensions of anger between war veterans with PTSD who use alcohol and those who not use alcohol (Table 3). In relation to cluster symptoms of PTSD and dimensions of anger, using linear regression it is found a significant correlation between hyperarousal symptoms and the state anger (r = 0.285, P = 0.022), and angry temperament (r = 0.270, P = 0.029), anger expression (r = 0.342, P = 0.008), and anger-out expression (r = 0.279, P = 0.025), while between intrusive symptoms, avoidance symptoms and dimensions of anger there was no significant correlation. A significant correlation is found by linear regression between the number of traumatic events and state anger (r = 0.267, P = 0.031), angry temperament (r = 0.266, P = 0.031), anger-out expression (r = 0.354, P = 0.006), and anger control (r = 0.281, P = 0.024). There was no significant correlation between the intensity of PTSD symptoms and state anger (r = 0.027, P = 0.425), trait anger (r = 0.023, P = 0.437), angry temperament (r = 0.021, P = 0.443), angry reaction (r = 0.009, P = 0.475), anger-in (r = 0.124, P = 0.195), anger-out (r = 0.142, P = 0.163, and anger control (r = 0.105, P = 0.235).

6. DISCUSSION

In this study most veterans with PTSD have had moderate to extremely high level of trait anger, angry reaction, and anger-in expression; moderate to high level of angry temperament, anger-out expression, and state anger. Moderate to high index of anger control was present in the largest number of veterans, which is opposite to expected results and results from other studies (16, 17). A significant correlation between the intensity of PTSD symptoms and score of anger dimensions is not found in this study, while a significant relation between symptoms of hyperarousal and state anger, angry temperament, anger expression and anger-out expression is found, which is similar to the results of Evans et al. (8). Also, a significant correlation is found between the number of traumatic events and state anger, angry temperament, anger-out expression and anger control. Possible explanation for the results obtained is that this study enrolled veterans who were taking one or more psychotropic drugs during the period of investigation, and most of them underwent treatment. It is also possible that veterans are afraid of their aggressive impulses and may lack self-efficacy with regard to anger control, and therefore, they are more likely to "stuff" their anger (23).

With regard to alcohol consumption, 54 veterans from Bosnia and Herzegovina enrolled in this study used alcohol, and a significant relationship is found between PTSD symptoms and use of alcohol, which does not differ from the results obtained in previous studies (4, 10, 12, 24). It is found that war veterans with PTSD who used alcohol have had significantly higher level of the trait anger, the state anger, the angry temperament, and higher expression of anger-in and anger-out, and a weaker control of anger compared to veterans suffering from PTSD who did not use alcohol. Studies indicate that hyperarousal symptoms of PTSD are related to alcohol usage too (25, 26). The studies conducted on war veterans in Croatia (24, 27), Bosnia and Herzegovina (28), Iraq and Afghanistan (19), and Vietnam war veterans (7, 15) showed a high level of aggression in veterans with PTSD who have alcohol-related disorders. Also, Lasko et al. (29) found in Vietnam veterans that those with PTSD had a higher aggression score compared to veterans without PTSD, and that aggression intensity was determined more as a part of PTSD. The association of PTSD symptoms with aggressive behavior and directing aggression outwardly was also found in studies related to violent behavior of war veterans against their partners (8, 15), and interpersonal violence (30). However, a relationship between anger, PTSD symptoms and alcohol consumption in veterans is being analyzed in only several studies (31). No statistically significant difference is found in socio-demographic variables, number of traumatic events, stress level, and severity of PTSD symptoms between veterans with PTSD who use alcohol and those who do not use alcohol. But a significant correlation of hyperarousal symptoms and state anger, angry temperament, anger expression and anger-out expression was found. As a symptom of PTSD, hyperarousal appears as a predictor of anger and alcoholism. It is found by Taft et al. (32) that hyperarousal symptoms were directly associated with aggression and indirectly with alcohol related-problems. Also, Savarese et al. (33) report that there is a complex interaction between hyperarousal and alcohol consumption in predicting violence. Some explanations for the connection of hyperarousal symptoms and aggressions may relate to changes in the activity of areas of the brain such as nucleus accumbens in the dominant hemisphere (34).

Based on the results obtained in this study, it can be concluded that there is a significant relationship between anger, alcohol consumption and PTSD symptoms where the cluster of hyperarousal symptoms is significantly correlated with anger dimensions and use of alcohol. It can also be concluded that exposure to a larger number of combat-related traumatic events is directly connected with alcohol usage and anger dimensions.

There were several methodological limitations in this study. Firstly, the factor related to duration and methods of treatment was not included. The study is carried out in the group of veterans who underwent in-patients treatment only with psychotropic drugs, while investigation took place one to two years after the hospitalization. Secondly, this study did not include other psychological factors such as depression and anxiety where the emotion of anger is present; and the occurrence of aggressive behavior in war veterans with PTSD who have a high index of anger and who use alcohol is not analyzed. This study indicates the need for exploring the anger related to the above mentioned factors. Also, the results of this study show that in the treatment of war veterans with PTSD it is necessary to explore the emotions of anger as important factor to managing therapeutic interventions.

REFERENCES:

1. Kozaric-Kovacic D, Hercigonja DK, Grubisic-Ilic M. Posttraumatic stress disorder and depression in soldiers with combat experiences. Croat Med J 2001;

42: 165–170.
2. Spivak B, Segal M, Laufer N, Mester R, Weizman A. Lifetime psychiatric comorbidity rate in Israeli non-help-seeking patients with combat-related posttraumatic stress disorder. J Affect Disord 2000; 185-188.
3. Prorokovic A, Cavka M, Cubela Adoric V. Psychosomatic and depressive symptoms in civilians, refugees, and soldiers: 1993-2004 longitudinal study in Croatia. Croat Med J 2005; 46: 275–281.
4. Kozaric-Kovacic D, Kocijan-Hercigonja D. Assessment of post-traumatic stress disorder and comorbidity. Mil Med 2001; 166: 677–80.
5. Yehuda R. Managing anger and aggression in patients with posttraumatic stress disorder. J Clin Psychiatry 1999; 60(Suppl 15): 33–37.
6. O'Donnell C, Cook JM, Thompson R, Riley K, Neria Y. Verbal and physical aggression in World War II former prisoners of war: role of posttraumatic stress disorder and depression. J Trauma Stress 2006; 19(6): 859-866.
7. Byrne CA, Riggs DS. The cycle of trauma; relationship of aggression in male Vietnam veterans with symptoms of posttraumatic stress disorder. Violence Vict 1996; 11(3): 213-225.
8. Evans L, McHugh T, Hopwood M, Wat C. Chronic posttraumatic stress disorder and family functioning of Vietnam veterans and their partners. Aust N Z J Psychiatry 2003; 37(6): 765-772.
9. McFall MF, Mackay PW, Donovan DM. Combat-related PTSD and psychosocial adjustment problems among substance abusing veterans. J Nerv Ment Dis 1991; 179(1): 33-38.
10. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA 2007; 298(18): 2141-2148.
11. Erbes C, Westermeyer J, Engdahl B, Johnsen E. Posttraumatic stress disorder and service utilization in a sample of service members from Iraq and Afganistan. Mil Med 2007; 172(4): 359-363.
12. Friedman M J. Posttraumatic stress disorder among military returnees from Afganistan and Iraq. Am J Psychiatry 2006; 163: 586-593.
13. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afganistan, mental health problems and barriers to care. N Engl J Med 2004; 351(1): 13-22.
14. Begic D, Jokic-Begic N. Aggressive behavior in combat veterans with posttraumatic stress disorder. Mil Med 2001; 166(8): 671-676.
15. Taft CT, Vogt DS, Marshall AD, Panuzio J, Niles BL. Aggression among combat veterans: relationship with combat exposure and symptoms of posttraumatic stress disorder, dysphoria and anxiety. J Trauma Stress 2007; 20(2): 135-145.
16. Chemtob CM, Hamada RS, Roitblat HL, Muraoka MY. Anger, impulsivity, and anger control in combat-related posttraumatic disorder. J Consult Clin Psychol 1994; 62(4): 827-832.
17. Laor N, Wolmer L, Wiener Z, Weizman R, Toren P, Ron S. Image control and symptom expression in posttraumatic stress disorder. J Nerv Ment Dis 1999; 187(11): 673-679.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-IV-TR (Fourth ed.). Washington D.C.: American Psychiatric Association; 2000
19. Jakupcak M, Conybeare D, Phelps L, Hunt S, Holmes HA, Felker B, Klevens M, McFall ME. Anger, Hostility, and Aggression among Iraq and Afganistan war veterans reporting PTSD and sub-threshold PTSD. J Trauma Stress 2007; 20(6); 945-954.
20. Spielberger C. State-Trait Anger Expression Inventory, Research Edition. Professional Manual. Psychological Assessment Resources: Odessa, Florida; 1988.
21. First MB, Spitzer RL, Gibbon M, Williams JBV. Structured Clinical Interview for DSM-IV AXIS I Disorders (Clinician Version) SCID-I Administration Booklet, Washington, DC: American Psychiatric Association; 1997.
22. Allden K, Ceric I, Kapetanovic A, Lavelle J, Loga S, Mathias M, et al. Harvard Trauma Manual: Bosnia-Herzegovina version. Cambridge (MA): Harvard Program in Refugee Trauma; 1998.
23. Jakupcak M, Tull MT. Effects of trauma exposure on anger, aggression, and violence in a nonclinical sample of men. Violence and Victims 2005; 20(5): 589-598.
24. Zoričic Z, Karlovic D, Buljan D, Marušic S. Comorbid alcohol addiction increases aggression level in soldiers with combat-related posttraumatic stress disorder. Nord J Psychiatry 2003; 57(3): 199-202.
25. McFall ME, Mackay PW, Donovan DM. Combat-related posttraumatic stress disorder and severity of substance abuse in Vietnam veterans. J Stud Alcohol 1992; 53(4): 357-363.
26. Bremner JD, Southwick SM, Darnell A, Charney DS. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. Am J Psychitary 1996; 153(3): 369-375.
27. Zoričic Z, Buljan D, Thaller V, Karlovic D. Aggression in posttraumatic stress disorder comorbid with alcohol dependence. Eur J Psychiatry 2003; 17 (4): 243-247.
28. Babic D, Martinac M, bjelanovic V, Babic R, Sutovic A, Sinanovic O. Aggression in war veterans suffering from posttraumatic stress disorder with co-morbid alcoholism. Coll Antropol 2010; 34(Suppl 1): 23-28.
29. Lasko NB, Gurvits TV, Kuhne AA, Orr SP, Pitman RK. Aggression and its correlates in Vietnam veterans with and without chronic posttraumatic stress disorder. Compr Psychiatry 1994; 35(5): 373-381.
30. Beckham JC, Feldman ME, Kirby AC, Hertzberg MA, Moore SD. Interpersonal violence and its correlates in Vietnam veterans with chronic posttraumatic stress disorder. J Clin Psychol 1997; 53(8): 859-869.
31. Orth U, Wieland E. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. J Consult Clin Psychol 2006; 74(4): 698-706.
32. Taft CT, Kaloupek DG, Schumm JA, Marshall AD, Panuzio J, King DW, et al. Posttraumatic stress disorder symptoms, physiological reactivity, alcohol problems, and aggression among military veterans. J Abnorm Psychol 2007; 116(3):498-507.
33. Savarese VW, Suvak MK, King La, King DW. Relationships among alcohol use, hyperarousal and marital abuse and violence in Vietnam veterans. J Trauma Stress 2001: 14(4): 717-732.
34. Pavic L. Alterations in brain activation in posttraumatic stress disorder patients with severe hyperarousal symptom and impulsive aggressiveness. Eur Arch Pscyhiatry Clin Neurosci 2003; 253 82): 80-83.

ORIGINAL PAPER

Application of Botulinum Toxin in Treatment of Spasticity and Functional Improvements for Children Suffering from Cerebral Palsy

Ajsa Meholjic, Dijana Madjar
Pediatric Clinic, Clinical Centre of Sarajevo University, Patriotske Lige 81, 71000 Sarajevo, Bosnia and Herzegovina

Application of Botulin toxin type A in children with cerebral palsy is represent targeted antispasm treatment for relaxation of spastic muscles. **Goal:** The goal of this study was to determine the significance of the application of Botulin toxin in the treatment of spasticity and functional progress of children suffering from cerebral palsy. **Material and methods:** At the Department of Developmental diagnosis, habilitation and rehabilitation of children in the Pediatric Clinic, Clinical Center of Sarajevo University study included 20 patients aged 4-18 years. Data were obtained by examining the patient's records. Selected patients are diagnosed with cerebral palsy and were treated with Botulin toxin. The study was retrospective, and data are presented in tables and charts using descriptive statistics. As a measurement scale, we used the "gross motor function measurement"–GMFM, based on which the children were scored by the " Gross Motor Function Classification System"–the GMFCS. **Results:** Of 20 children, 11 or 55% were boys and 9 or 45% of girls. The largest number of children in the sample had 9 ± 4.03 years (5 or 25%), with an average age of 9 years (range: 4-18 years). 80% of children suffering from cerebral palsy for the first time received botulin toxin at the age of 2-6 years, 40% of children had 2 applications of Botulin toxin, and for 45% of children the time interval between repeated applications was from 3-6 months. Measuring gross motor function before and after botulin toxin application registered significant functional improvement. **Conclusion:** Botulin toxin is beneficial in the treatment of spasticity in children suffering from cerebral palsy. **Key words:** spasticity, Botulin toxin, Gross Motor Function Classification Systemž

Pediatric Clinic, Clinical Centre of Sarajevo University, Patriotske Lige 81, 71000 Sarajevo, BiH

1. INTRODUCTION

Cerebral palsy is a set of symptoms that arise as a result of abnormal brain development or brain damage at an early age. These symptoms are motor deficits, non-physiological increase or decrease and the distribution of muscle tone, sensory and sensitivity disturbance, mental deficit, speech disturbances, neurovegetative disturbances, etc. As a result of damage to the pyramidal path develops muscle spasticity (1,2).

To decrease the muscle spasm, as one aspect of treatment is the application Botulin toxin (BT), which is best applied to children suffering from cerebral palsy at the age of 2-6 years, which have dynamic contractures that affect the function of the limbs (3)? Clinical signs of improvement are visible within the first two weeks after the injection of botulin toxin into the muscles. The dose may be repeated before the symptoms completely disappear prior injection, but not more frequently than every 2 months (4,5). Contraindications for the application are: hypersensitivity to some component of the product, the generalized disturbance of muscle activity (e.g. myasthenia gravis), concomitant administration of aminoglycoside antibiotics, the presence of infection at the site or around the injection site, and bleeding disorder (6,7).

The main criterion for inclusion of Botulin toxin is localized hypertonic muscles and the absence of static contracture, and indications are: on the feet–dynamic equinus, equinovarus, equinovalgus, dynamic restriction of movement in the knees, adduction position of the hips, scissors like position of the legs or the hands–permanent position of thumb in the palm of the hand, the dominant palmar flexion with ulnar deviation or only the dominant palmar flexion (8,9).

2. GOAL

The goal of this study was to determine the efficacy of the treatment of spasticity in children suffering from cerebral palsy by application of botulin toxin in spastic muscles of the lower limbs.

3. MATERIAL AND METHODOLOGY

The study included children who were diagnosed with cerebral palsy treated at the Department of Developmental diagnosis, habilitation and rehabilitation of children at the Pediatric Clinic of Clinical Center, Sarajevo University who had received botulin toxin in spastic muscles of the lower extremities. Research data were obtained by examining the history of the disease of observed groups of patients. The total number of observed is a group of 20 patients. Patients were aged 4-18 years. The study was retrospective and all the data are presented in tables and charts using descriptive statistics and through the absolute number of cases, percentage and arithmetic mean with standard deviation.

4. RESULTS

The largest number of children in the sample had 9±4.03 years (5 or 25%),

Age (in years)	N	%
4	2	10.0
5	2	10.0
6	1	5.0
7	3	15.0
8	2	10.0
9	5	25.0
10	1	5.0
15	2	10.0
16	1	5.0
18	1	5.0
Total	20	100.0

Mean	9.00
Standard deviation	4.026
Minimum	4
Maximum	18

Table 1. The age of children suffering from cerebral palsy who had received Botulin toxin

	N	%
Male	11	55.0
Female	9	45.0
Total	20	100.0

Table 2. The gender representation

Cerebral palsy type	N	%
Diaparesis spastica	7	35.0
Hemipresis cer. lat. dex.	2	10.0
Tetraparesis spastica pp Diaparesis spastica	10	50.0
Triparesis spastica pp Diaparesis spastica	1	5.0
Total	20	100.0

Table 3 Clinical type of cerebral palsy

Age	N	%
2- 6 years	16	80.0
7- 15 years	4	20.0
Total	20	100.0

Mean	5.75
Std. deviation	3.626
Minimum	2
Maximum	15

Table 4. Age when the child first received Botulin toxin

with an average age of 9 years (range: 4-18 years). In 10 children (50%) is registered a spastic tetraparesis. 80% of children suffering from cerebral palsy has received Botulin toxin for the first time at the age of 2-6 years.

Number of BT applications	N	%
1	6	30.0
2	8	40.0
3	3	15.0
4	2	10.0
5	1	5.0
Total	20	100.0

Table 5. Number of Botulin toxin applications

The largest number of children (40%) had 2 applications of botulin toxin into the muscles of the lower limbs.

GMFCS before BT application	N	%
II	4	20.0
III	3	15.0
IV	10	50.0
V	3	15.0
Total	20	100.0

Table 6. Gross Motor Function Classification System (GMFCS) before application of Botulin toxin

Before application of the Botulin toxin 50% of children suffering from cerebral palsy was classified as stage IV in GMFCS.

GMFCS after BT application	N	%
I	4	20.0
II	3	15.0
III	10	50.0
IV	2	10.0
V	1	5.0
Total	20	100.0

Table 7. Gross Motor Function Classification System (GMFCS) following application of Botulin toxin

After application of Botulin toxin noticed is improvement or change to a lower level of GMFCS in 50%, of children suffering from cerebral palsy.

After application of BT is evident that the measurement of gross muscle forces all respondents, except one change from high to lower levels of GMFCS. The correlation coefficient of GMFCS before and after application of Botulin toxin shows a high statistical significance, Rho=-0.981, p<0.01.

5. DISCUSSION

Using Botulin toxin, which leads to local haemodenervation, achieved is reduction in tome of spastic muscles in children with cerebral palsy. It is of great importance for the course of treatment because it allows better mobility of joints, prevents contracture, facilitates the work of physiotherapists in the implementation of the development of medical gymnastics and postpones or even makes unnecessary the corrective surgical procedures.

At the Department of Developmental diagnosis, habilitation and rehabilitation of children at the Pediatric Clinic of the Clinical Center, University of Sarajevo, the total number of children with spastic cerebral palsy who received in the period since 2006 until 2010 botulin were 20, of which 9 (45%) were girls and 11 (55%) boys. In 20 children, aged 4-18 years Botulin toxin was injected intramuscularly into the muscles of the lower limbs, as follows: mm. adductores Magni, longi et brevi and mm. gastrocnemio.

Analyzing the distribution of CP in studied children, we can see that 10 or 50% had spastic tetraparesis with dominant diaparesis, 7 children or 35% had spastic diaparesis, 2 children or 10% hemiparesis and 1 child or 5% triparesis with dominant spasmodic diaparesis.

16 or 80% of children for the first time received botulin toxin at the age of 2-6 years, and the remaining 4 or 20%, at age 7-15 years, mean age 5.75 years. Reference literature favors early treatment with botulin toxin before the age of 4 years if we want to improve and facilitate walking, or a child can be treated by the same in any age, for better care and spastic pain relief.

Analyzing the application of botulin toxin, we found that 6 or 30% of children

			GMFCS after application					Total
			I	II	III	IV	V	
GMFCS before application	II	N	4	0	0	0	0	4
		%	100.0	0.0	0.0	0.0	0.0	20,0
	III	N	0	3	0	0	0	3
		%	0.0	100.0	0.0	0.0	0.0	15,0
	IV	N	0	0	10	0	0	10
		%	0.0	0.0	100.0	0.0	0.0	50,0
	V	N	0	0	0	2	1	3
		%	0.0	0.0	0.0	100.0	100.0	15,0
Total		N	4	3	10	2	1	20
		%	100,0	100.0	100.0	100.0	100.0	100.0

Table 8. The correlation coefficient of GMFCS before and after Botulin toxin application. Pearson Rho = -0.981, p = 0.0001

had 1 application, 8 or 40% of children 2 applications of BT, 3 or 15% of children 3 applications of BT, 2 or 10% of children 4 BT applications and one child or 5% had 5 applications of Botulin toxin. The literature does not indicate that the maximum number of applications of BT that patient can receive, but is recommended for each subsequent application of BT to be administered 3 months after the previous. The dose may be repeated even before the symptoms of prior injection completely disappear, but not more frequently than every 2 months.

To estimate the severity of cerebral palsy used is five degrees classification system for gross motor function in cerebral palsy (Gross Motor Function Classification System GMFCS I-V). Before the BT application, for the treated children was determined a GMFCS level, and found that 10 or 50% of children belong to stage IV, 4 or 20% of children belonging to stage II, 3 or 15% of children to stage III and 3 or 15% of children belongs to the GMFCS stage V. After the application Botulin toxin, children suffering from cerebral palsy were clinically re-examined with Gross Motor Function Measure-GMFM and re-determined a degree of GMFCS. These results indicate that 10 or 50% of children now belonged to the third stage, 4 or 20% of children belonging to stage I, 3 or 15% of children belonging to stage II, 2 or 10% in stage IV and 1 or 5% of children belonging to GMFCS stage V. Noted is the decrease in GMFCS level after application of botulin toxin and all the children, except one child moved into a lower category. Only one child remained in the stage V. Statistical analysis of the correlation coefficient of GMFCS before and after application of Botulin toxin shows a high statistical significance (Rho=-0.981, p<0.01). Lack of response to the application of botulin toxin rarely occurs but may occur as a result of wrong BT injection, lower applied doses, achievement of the maximum effect only after the second or third application, present static contractions or due to the development of antibodies.

Camargo and colleagues investigated the safety and efficacy of botulin toxin in treating spasticity in 20 children with spasmodic diplegia as a form of cerebral palsy. All patients received injections into the muscles of the lower limbs, and 15 patients in the adductors of the thighs. The total dose ranges 70-140 U (99.75 +/- 16.26 U), or 7.45 +/-2.06 U/ Kg per patient. After the applications have been recognized significant improvements in gait in patients with a significant increase in ankle flexibility. They concluded that botulin toxin is safe and effective in the treatment of spasticity in children suffering from cerebral paralysis, but that the functional changes are temporary (10). Pena-Segura and colleagues investigated the effect of botulin toxin in 702 children with cerebral palsy with positive results in reducing muscle spasms in the limbs in 70% of children (11). Based on our research and investigations of numerous authors, it is evident that botulin toxin significantly reduces muscle spasm in children with cerebral palsy.

6. CONCLUSION

Botulin toxin is effective in the conservative treatment of spasticity in children suffering from cerebral palsy and improve the their mobility, provide better position the individual parts of the body in the supine, sitting or standing position, allowing the possibility of learning new and better pattern of movement, extend the time until surgery and reduces pain in spastic muscle.

REFERENCES

1. Rameckers EA, Duysens J, Speth LA, Vles HJ, Smits-Engelsman BC.Effect of addition of botulin toxin-A to standardized therapy for dynamic manual skills measured with kinematic aiming tasks in children with spastic hemiplegia. J Rehabil Med. 2010 Apr;42(4):332-8.
2. Kaishou Xu, Tiebin Yan, Jianning Mai.A randomized controlled trial to compare two botulin toxin injection techniques on the functional improvement of the leg of children with cerebral palsy.Clin Rehabil. 2009 Sep;23(9):800-11.
3. Hu GC, Chuang YC, Liu JP, Chien KL, Chen YM, Chen YF. Botulinu toxin (Dysport) treatment of the spastic gastrocnemius muscle in children with cerebral palsy: a randomized trial comparing two injection volumes.Clin Rehabil. 2009 Jan;23(1):64-71.
4. Rameckers EA, Speth LA, Duysens J, Vles JS, Smits-Engelsman BC. Botulin toxin-a in children with congenital spastic hemiplegia does not improve upper extremity motor-related function over rehabilitation alone: a randomized controlled trial.
5. Neurorehabil Neural Repair. 2009 Mar-Apr;23(3):218-25. Epub 2008 Dec 23.
6. Bach-Rojecky L, Relja M, Filipović B, Lacković Z. Botulin toxin type A and cholinergic system. Lijec Vjesn. 2007 Dec;129(12):407-14.
7. Sławek J. Botulin toxin type A in the treatment of spasticity in cerebral palsy: theoretical and practical foundations of effective therapy. Ortop Traumatol Rehabil. 2001;3(4):541-6.
8. Rameckers EA, Speth LA, Duysens J, Vles JS, Smits-Engelsman BC. Kinematic aiming task: measuring functional changes in hand and arm movements after botulin toxin-A injections in children with spastic hemiplegia. Am J Phys Med Rehabil. 2007 Jul;86(7):538-47.
9. Singhi P, Ray M. Botulin toxin in children with cerebral palsy. Indian J Pediatr. 2004 Dec;71(12):1087-91.
10. Hurvitz EA, Conti GE, Brown SH. Changes in movement characteristics of the spastic upper extremity after botulin toxin injection. Arch Phys Med Rehabil. 2003 Mar;84(3):444-54.
11. Camargo CH, Teive HA, Zonta M, Silva GC, Oliveira MR, Roriz MM, Brandi IV, Becker N, Scola RH, Werneck LC. Botulin toxin type A in the treatment of lower-limb spasticity in children with cerebral palsy. Arq Neuropsiquiatr. 2009 Mar;67(1):62-8.
12. Peña-Segura JL, Marco-Olloqui M, Cabrerizo de Diago R, Pérez-Delgado R, García-Oguiza A, Lafuente-Hidalgo M, Sebastián-Torres B, Rebage V, López-Pisón J. Early care and botulin toxin. Our experience in the 21 st century. Rev Neurol. 2008;47 Suppl 1:S25-33.

PROFESSIONAL PAPER

Echocardiographic Measurements of Normal Fetal Pulmonary Artery and Pulmonary Branches and Comparison on Fetuses with Congenital Diaphragmatic Hernia

Ramush A.Bejiqi1, Ragip Retkoceri1, Hana Bejiqi2
1University Clinical Centre of Kosova, Pediatric Clinic, Rrethi i spitalit, PN, 10 000 Prishtina, Kosova
2University Clinical Centre of Kosova, Clinic for Obstetric and Gynecology, Rrethi i Spitalit, PN, 10 000, Prishtina, Kosova

Objective: Congenital diaphragmatic hernia is one of the severe congenital pulmonary anomaly (PA) associated with pulmonary hypoplasia, pulmonary sequestration and severe respiratory distress. The aim of this study was to present difference between measurements of the size of fetal pulmonary artery and pulmonary branches (PB) in normal growth fetuses and comparison with the same in fetuses with congenital diaphragmatic hernia (CHD). Measurements were done by echocardiography. Methodology: During the period March 2007 to March 2009 measurements were performed on a total of 115 normal fetuses, at 20–38 weeks gestation. By cross-sectional echocardiography were measured fetal PA and PB diameters. Retrospectively were reviewed 6 fetuses with left-sided CHD from 2005 to 2009. Measurements were done at level of the three vessel view (superior vena cava, ascending aorta and main PA). Results: Diameter of main PA and both branches were found to correlate with the advanced gestational age ($r = 0.74$, $p < 0.01$). There was calculated diameter of the left PB to main pulmonary artery ratio (LPB/MPA) and right PB to main pulmonary artery (RPB/MPA) ratio. These two parameters were almost constant throughout gestation. In all fetuses with CDH, LPB was normal or smaller than in normal fetuses. Both PB in compare with PMA were within the normal range in all normal fetuses. Conclusion: Echocardiographic measurement of PB is an important method to establish the normal range of diameters of the PA branches and it appears to be useful to compare results on normal fetuses and fetuses with CDH and pulmonary hypoplasia. Key words: Antenatal echocardiography, pulmonary branch, congenital diaphragmatic hernia, lung hypoplasia, respiratory distress

Ramush Bejiqi, MD, Pediatrics cardiologist, Head of Intensive Care Unit, Pediatric Clinic, University Clinical Centre of Kosova, Prishtina, Kosova. Mobile: 00377 44 120 129, Phone: 00381 38 553 217. E-mail address: rbejiqi@hotmail.com

1. INTRODUCTION

Pulmonary hypoplasia (PH) is the result of retardation in pulmonary development associated after birth with high level of early respiratory distress, severe respiratory insufficiency, pneumothorax, pulmonary interstitial emphysema persistent pulmonary hypertension, and high rate of mortality, ranging from 50 to 90 %. PH may be appear bilateral or often, unilateral, caused by more different factors. Unilateral congenital diaphragmatic hernia (CDH) associated with displacement of abdominal viscera in the thoracic cavity, through a defect in the diaphragm, results in intestinal obstruction and severe respiratory compromise. It occurs often as 1: 2200 live births. The severity of CDH and respiratory insufficiency may be very mild or as severe as to be incompatible with life and are related to the time and degree of prenatal visceral herniation. PH is defined as a wet lung/body weight ratio of < 0.015 before 28 weeks gestation or < 0.012 at 28 weeks or later. The classical diagnosis has only been demonstrated by autopsy. Advances in antenatal ultrasound technique, the prenatal diagnosis of CDH is possible as early 16 weeks gestation. Despite the lethal outcome, there have been no reliable prenatal diagnostic methods and parameters for indicating the severity of pulmonary hypoplasia.

By echocardiography, two-dimensional measurement of main pulmonary artery (MPA) and pulmonary artery branch (PAB) diameters and Doppler waveform of PA have provided as

CASE	Maternal a. years	Hernia side	Herniated viscera	Poly-hydramnions	Body w. at delivery, g	Outcome
1	25	left	Intestine	-	3.238	Survived
2	25	left	Intestine	-	2.744	Survived
3	40	left	Intestine	+	2.904	Survived
4	34	left	Intestine, lien	-	2.820	Survived
5	29	left	Intestine	+	2.520	Died
6	24	left	Intestine, lien	+	3.150	Survived

Table 1. Basic inputs and outcomes of the fetuses with congenital diaphragmatic hernia

CASE	Hernia side	Herniated viscera	MPA mm	RPB mm	LBP mm	RPB/MPA	LBP/MPA	Body w. at delivery, g	Outcome
1	left	Intestine	9.80	6.80	6.60	0.69	0.67	3.238	Survived
2	left	Intestine	8.70	5.80	5.70	0.67	0.66	2.744	Survived
3	left	Intestine	9.10	5.90	5.70	0.65	0.63	2.904	Survived
4	left	Intestine + lien	9.05	6.10	5.40	0.67	0.60	2.820	Survived
5	left	Intestine	9.50	4.80	4.50	0.51	0.47	9.50	Died
6	left	Intestine + lien	11.00	7.50	7.40	0.68	0.67	3.150	Survived

Table 2. Achieved measurements in fetuses with congenital diaphragmatic hernia

an effective methods to determine degree of pulmonary hypoplasia. Sokol et al. have proposed that fetal branch PA diameters correlated strongly with lung weights measured at autopsy.

In this presentation we measured the normal range of the diameter of the main pulmonary artery (MPA), left pulmonary branch (LPB), right pulmonary branch in the normal fetus. This allowed calculation of the LPB/MPA ratio and RPB/MPA ratio independent of gestation. These branch PA diameters were compared with diameters measured in fetuses with CDH and poor prognosis caused by pulmonary hypoplasia.

2. METHODS

In a 115 pregnant women, gestational age 20 – 38 weeks, with singleton uncomplicated pregnancies were performed measurement of internal diameter of MPA, LPB and RPB, including measurements of parameters of fetal growth. Diameters were measured from a cross-sectional view at the level of the three-vessel view (main pulmonary artery, ascending aorta and vena cava superior). We visualized the long axis of pulmonary branches when possible. Measurements were done from frozen real-time images, in the absence of fetal movement. All measurements were done from one obstetrician (H.B) and two pediatrics cardiologists (R.B and R.R). Measurements were done by using an Acuson Aspen Advanced and Acuson Sequoia 216, and a convex probe 3 and 4 MHz and pediatric cardiologic probe 7 MHz. Data are presented in millimeters (mm).

Retrospectively we investigated 6 fetuses with CDH, born in different regional hospitals in Kosova, during the period March 2005 and March 2009. Since they manifested severe respiratory distress, they were admitted in Center for Neonatology and Preterm born children in Pristina. One baby was delivered by elective cesarean section and other four children were delivered by vaginal delivery. Despite minimum two antenatal ultrasonography examination none of them were diagnosed CDH or any other malformation. All babies had left CDH. 4 neonates (case 1–4) after surgical treatment survived, the fifth died before surgical intervention.

3. RESULTS

In our study both pulmonary branches diameter were significantly correlated with gestational age ($r = 0.74$, $p < 0.01$). We calculated diameter of MPA, LPB and RPB and calculated ratio LPB/MPA and RPB/MPA and we confirmed that the data were in correlation with gestation (LPB/MPA: 0.48 ± 0.08, RPB/MPA: 0.49 ± 0.08). Also we correlated data LPB/MPA and RPB/MPA with diameters of pulmonary branches of 6 patients with CDH. Data are presented on the diagram (Table.2). There was statistically significant correlation between LPB/MPA and RPB/MPA ratios and the gestational age. In all babies with CDH, RPB diameter immediately preceding delivery was within the normal range in the 5 babies surviving surgical intervention. In case that died, diameter of RPB was under lower limit of the norm. LPB diameter was below

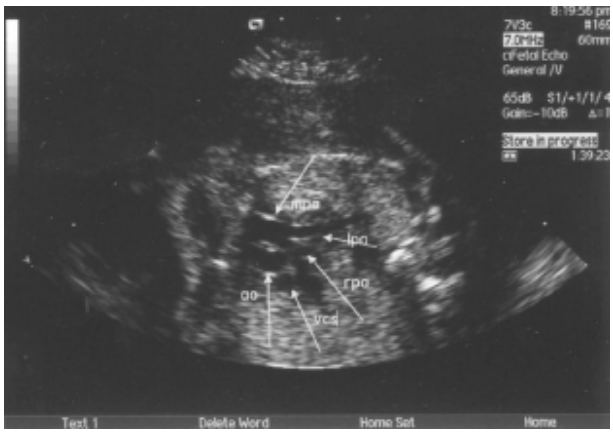


Figure 1. Two dimensional image cross.sectional view with three vessel view in normal fetus; Ao - aorta, MPA - main pulmonary artery, LPA - main pulmonary artery; RPA - main pulmonary artery, VCS - vena cava superior

Figure 2. Cross-sectional ultrasound image with a three vessel view in normal fetus RV - right ventricle, Ao - aorta, MPA - main pulmonary artery, LPA - main pulmonary artery; RPA - main pulmonary artery, VCS - vena cava superior

the normal range in all children with CDH. Four surviving patients in CDH (1 – 5), were bellow the normal range in PB/MPA and within the normal range in RPB/MPA. In one case, that died was within the normal range for both LPB/MPA and RPB/MPA.

4. DISCUSSION AND CONCLUSION

The survival rates of babies with severe CDH have increased dramatically, particularly over the past two decades as a result of early prenatal ultrasonography diagnosis and organization of these high-risk deliveries to tertiary centers so that optimal ventilatory care and surgical expertise are available. Important prognostic predictors (for survival of congenital diaphragmatic hernia) include the degree of fetal liver herniation into the chest and the presence or absence of other anomalies. Prenatal evaluation of congenital diaphragmatic hernias consists of a Level II ultrasound, an ultrafast fetal MRI, fetal chromosome studies, and a fetal echocardiogram. Ultrasonography can be a non-invasive method to predict prenatal clinical pulmonary hypoplasia caused by CDH. Among the other basic ultrasonography measurements in fetuses (lung-thoracic transverse area ratio, lung-head ratio, thoracic circumference/abdominal circumference ratio), in diagnosis and prognosis of pulmonary hypolasia recent investigations and reports shows that diameter of MPA and pulmonary branches are related to the pulmonary hypoplasia. It is so difficult to measure PA at a particular interrogation angle. There is also low reproducibility when using this method. Fetal PA and PAB diameter measurement are a potential method for pulmonary hypolasia evaluation. In this study we concluded that the diameter of the left and right PB and the ratio PB and main PA in normal fetuses, were increased linearly with advancing gestation. In fetuses with CDH the LPB diameter was significantly below the normal range during the second half of pregnancy, whereas the RPB diameter was around the lower limit of normal pregnancy.

In this study the MPA, LPB and RPB diameter was measured and the LPB/MPA and RPB/MPA ratios were calculated. In all normal fetuses these ratios were constant during the gestation. MPA diameters, as good as RPB and LPB diameters in the babies with CDH were smaller than those in normal fetuses but much smaller than those in baby who died. The explanation of those changes is that the blood flow in the LPB decreased due to pressure from the herniated viscera and was distributed through the ductus arteriosus to RPB, in fetuses with CDH. Recent investigations showed that increasing blood flow per unit area would cause injury to the pulmonary arterial wall, especially RPB, which would lose elasticity and those neonate would have persistent pulmonary hypertension after birth.

After 38 weeks gestation in fetuses with left CDH, in both sided, the

distal pulmonary arterial wall becomes thicker. Also, the weight of the right lungs in left CDH is significantly smaller than in normal fetuses. This indicates that function would be affected by both pulmonary sides, despite left CDH at third trimester of pregnancy which are in agreement with the measurements in our study. Also, the branch of PA diameters might become smaller in the case of prolonged preterm premature rupture of membrane or in Potter syndrome, which are leading to pulmonary hypoplasia.

REFERENCES

1. Sokol J, Bohn D, Lacro RV, Rayan G. Stephens D, Rabinovitch M, Smallhorn J, Hornberger LK: Fetal pulmonary artery diameters and their association with lung hypolasia and postnatal outcome in congenital diaphragmatic hernia. Am. J Obstet Gynecol 2002; 186: 1085 – 1090.
2. Sokol J, Shimziu N, Bohn D, Doherty D, Rayan G, Hornberger LK: Fetal pulmonary artery diameter measurements as a predictor of morbidity in antenatally diagnosed congenital diaphragmatic hernia: a prospevtive study. Am J Obstet Gynecol 2006; 195: 470 – 477.
3. Bargy F, beaudoin S, barbet P: Fetal growth in congenital diaphragmatic hernia, fetal Diagn Ther 2006; 21: 39 – 44.
4. Fuke S, Kanzaki T, Mu J, Wasada K, takemura M, Mitsuda N, Murata Y: Antenatal prediction of pulmonary hypoplasia by acceleration time/ejection time ratio of fetal pulmonary arteries by Doppler blood flow velocimetry. Am J Obstet Gynecol 2002; 188: 228 – 233.
5. Dillon PW, Cilley RF, Mauger D, Zachary C, Meier A: The relationship of pulmonary artery pressure and survival in congenital diaphragmatic hernia . J Pediatr Surg. 2004; 39; 307 – 312.
6. Yoshimura S, Masuzaki H, Hiraki K, Miura K, Nakayama D, IshimaruT: Congenital diaphragmatic hernia: an evaluation of the prognostic value of the lung-to-head ratio. J Med Ultrasonics 2005; 32: 115 – 119.
7. Harmath A. Hajdu J. Hauzman E, Pete B, Rona Z, Papp Z: Experiences in the prenatal management of congenital diaphragmatic hernia during the last 15 years in a tertiary referral institute. Fetal Daign Ther 2007; 22: 209 – 216.
8. Bosenberg AT, Brown RA; Management of congenital diaphragmatic hernia. Cur Opin Anaesthesiol. 2008 Jun; 21(3):323-31
9. Migliazza L, Bellan C, Alberti D, Auriemma A, Burgio G, Locatelli G, Colombo A. (September 2007). "Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization". Journal of Pediatric Surgery 42 (9): 1526–32.
10. Avroy A. Famaroff, Richard JM. Neonatal – perinatal medicine: diseases of the fetus and infant 6th ed. 1997 Vol.2 Mosby

PROFESSIONAL PAPER

Concurrent Chemoradiation for Cervical Cancer: Results of Five Randomized Trials

Nermina Kantardzic

Background: Cervical cancer is the second most common cancer among women's in Bosnia and Herzegovina. Most of these women's in the time of diagnosis are with advanced disease. In the 1999 NCI issued a clinical alert, recommending that chemo radiation should be implemented as new treatment for these patients. Aim: To determine a survival, loco regional control and toxicity in patients with cervical carcinoma treated in Institute o Oncology from 2000-2006. Patients and methods: This is retrospective study. Data of five hundred and fourteen patients diagnosed as cervical cancer FIGO stage Ib, -IVb and presented in our institute, were analyzed. We treated 345 with combined chemo radiotherapy, 162 with radiotherapy alone and 7 patients with symptomatic therapy. In the follow up 134 patients were lost, so 373 patients were analyzed for survival, loco regional control and toxicity. Subgroup of 148 patients with advanced disease and grade of tumor unknown and 136 patients with known grade of tumor were compared for time to local progression, time to distant metastasis and time to death. Results: Median age in this group of patients was 52 (27-85). Of 514 patients 492 were treated with curative intentions and 15 got palliative treatment. All treated patients finished their planed therapy. Follow up was from 6-78 months, median 28 months. From 373 patients who were analyzed 65 died, progressions were observed in 77 patients. Acute toxicity G3/G4 experienced 109 patients, and late toxicity G3/G4 8 patients. Patients with advanced disease and unknown grade of tumor cells had significantly shorter time to local progression, distant metastasis and death. Conclusion: The combined therapy for cervical cancer is the safe and good tolerated treatment. In the group of patients with advanced disease we observed 81% overall survival, 55.9% disease free survival for median follow up of 28 months. . In the group of patients with early disease we observed 90% overall survival, and 78.8% disease free survival for median follow up of 28 months. There were no deaths caused by treatment. Key words: cervical cancer, chemotherapy, radiotherapy

Corresponding author:

1. INTRODUCTION

In the United States alone, 11150 women this year will be diagnosed with invasive cervical cancer. That is roughly 30 females a day, every day, for a year, in America alone. About 3,870 women will die from cervical cancer in the United States during 2008. In the UK, over 2,700 women are diagnosed with cervical cancer, and cause around 950 deaths each year in the UK. In the whole Europe around 50000 women will be diagnosed with cervical cancer, 25000 will die, and more important 175000 living with cervical cancer in some stage of disease. [1]

Cervical cancer was once one of the most common causes of cancer death for American women. The cervical cancer death rate declined by 74% between 1955 and 1992. The main reason for this change is the increased use of the Pap test. This screening procedure can find changes in the cervix before cancer develops. It can also find early cervical cancer in its most curable stage. The death rate from cervical cancer continues to decline by nearly 4% a year.

The burden of cervical cancer is particularly high across the whole of Eastern Europe. The systematic screening for cervical cancer is not jet established in the most of Eastern Europe countries. The dramatic contrast between West and East European states merits particular attention from the health authorities of the countries concerned and the EU as a whole. [2]

The prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. The current death rate is far higher than it should be and reflects that, even today, Pap smears are not done on approximately 33% of eligible women. Among the major factors that influence prognosis are stage, volume and grade of tumor, histological type, lymphatic spread, and vascular invasion. The 5-year relative survival rate for the earliest stage of invasive cervical cancer is 92%. The overall (all stages com-

bined) 5-year survival rate for cervical cancer is about 72%. [3]

Cervical cancer is still very high in incidence among women's in Bosnia and Herzegovina. Around 65% of patients in the time of diagnosis are with advanced disease. All of them who reach doctor are treated in Institute of Oncology in Sarajevo as the only institution with radiotherapy department in the whole country. [4]

Improvement of survival in patients with advanced cervical cancer was evident from year 2000. New standard therapy including concomitant chemotherapy and radiotherapy proposed by NCI in 1999 was main factor for this development. [5]

2. PATIENTS AND METHODS

This is retrospective study. We analyzed records of all patients treated in Institute of oncology in Sarajevo from the year 2000 to 2006, diagnosed as invasive cervical cancer. There were 514 patients with histological diagnosis of cervical cancer.

Early disease- FIGO stage Ib and IIa had 114 patients and 400 were with advanced stage of disease.

Surgery with adjuvant radiotherapy had 110 patients, 345 were treated with combined chemotherapy and radiotherapy concomitantly, 52 with radiotherapy alone and 7 with symptomatic therapy.

Radiation therapy

Radiation therapy was delivered with high-energy linear accelerator (Philips) from 2000 to 2005 and (Siemens Primus plus) after, using 18 MV photons at 2Gy/d, 5days/wk with no planned breaks. All patients were treated with using two–dimensional treatment planning (render plan). Brachitherapy was delivered with Selctron-Nucletron LDR, and NTP planning or Gama Med plus-Varian HDR and ABACUS planning. We used four field box techniques with AP+PA fields and two lateral fields, no central shielding, to TD 45-50Gy. Brachytherapy was given on Selectron LDR after completing of external radiotherapy with two fractions of 15 Gy one week break, or on Gama Med plus HDR weekly one fraction of 5 Gy to TD of 25 to 30 Gy, during and after external radiotherapy.

Age	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Patients	2	61	170	152	85	40	4
Percent	0.3	11.8	33	29.5	16.5	7.7	0.7

Table 1. Patients due to age.

Stage-FIGO	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb
Patients	109	5	264	1	124	8	3
Percent %	21.2	0.9	51.3	0.1	24.1	1.5	0.5

Table 2. Stage of disease.

PHD	Squamous cell	Adenocarcinoma	Adenosquamous cell	Other
Patients	461	37	9	7
Percent %	89.6	7.2	1.7	1.3

Table 3. Histology of patients

Grade	G1	G2	G3	Gx
Patients	44	144	90	236
Percent %	8.5	28	17.5	45.9

Table 4. Distribution of patients due to grade of tumor

Chemotherapy

Chemotherapy was delivered as monochemotherapy weekly, during radio therapy, for five or six cycles, or polyhchemotherapy platinum based. Every week prior to cycle of chemotherapy we check standard laboratory tests.

Majority of patients got cis-diamminedichloroplatinum 40 mg/m², and small group got cis-diamminedichloroplatinum, gemcitabine, or 5 fluorouracil or taxanes.

From the year 2000 to 2006 we accepted 514 patients with diagnosis of cervical cancer. The most of patients were between 40 to 60 years, median 52. The most of patients were with advanced disease. The most of patients had squamous cell carcinoma.

The most of patients had G2 grade of tumor cells, but almost 50% of patients had no G of tumor cells. The most of patients had some kind of combined treatment (88.5%). The most of patients were treated with curative intentions.

The most of patients got standard monochemotherapy concomitantly with radiotherapy.

3. RESULTS

Follow up was from 6 to 78 months, median 28 months. In the first 2 years patients were looked at every 4 months, to fifth year every 6 months and to 10 years once a year. We check standard laboratory analysis, gynecological exam and CT scan every year. We lost 134 patients in follow up mostly due to geographic distance and due to health care autonomy in different regions of Bosnia and Herzegovina. From 514 patients 7 refused specific oncology therapy, so we analyzed 373 patients.

Most of patients had good response to treatment. Subgroup of patients with known G of tumor cells had better time of response in all categories.

Local progression (l.p.) had 19, distant (d.p.) 31 and both (l.p.+d.p.) 27 patients. Death occurred in 63 patients, 61

Treatment	Surgery and radiotherapy	Combined chemo-radiotherapy	Radiotherapy alone	Symptomatic therapy
Patients	110	345	52	7
Percent %	21.4	67.1	10.1	1.3

Table 5. Distribution of patients due to treatment

Radiotherapy	Curative	Palliative
Patients	492	15
Percent %	95.7	4.3

Table 6 Distribution of patients due to radiotherapy course

Response	Complete response	Stabile disease	Progression
Number	234	62	77
Percent %	62.8	16.6	20.6

Table 7 Distribution of patients due to response

Year	I	II	III	IV	V	VI
Number	25	20	7	6	3	2
Percent %	39.6	31.7	11.1	9.5	4.7	3.1

Table 9. Distribution of deaths thru years

Metastasis	Pulmo	Liver	Bones	Other
Number	14	13	21	16

Table 10. Distribution of distant metastasis

Metastases in two organs were found in 4 patients and 1 patient with metastasis in 3 organs.

Metastases were treated with radiotherapy in 26 patients and chemotherapy in 32 patients. In 6 patients we performed just symptomatic therapy due to poor ECOG status.

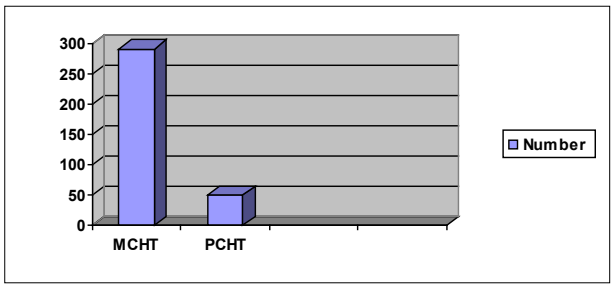
Toxicity

Acute toxicity mostly neutropenia G3/G4 experienced 109 patients, and they had pause in treatment for one to two weeks.

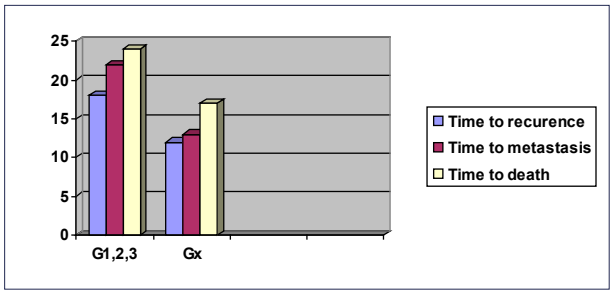
Late toxicity experienced 14 patients (2.6%)

Necrosis of small bowls had 3 patients, recto–vaginal or urethra–vaginal fistulas in 4 patients and palliative surgeries were performed for all of them.

Seven patients had edema in both legs, and symptomatic therapy was performed.



Graficon 1. Distribution of patients due to scheme of chemotherapy



Graficon 2. Comparison of response of patients due to grade of tumor cells (G)

4. DISCUSSION

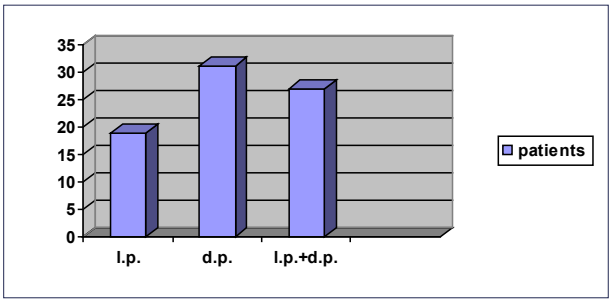
To evaluate results of our Institute and to compare with results of similar studies in literature is very important for us. In this way we can check our standard treatments and its efficacy.

With number of total population nia and Herzegovina (500) shows that we had fewer patients then can be expected. In this study we treated about 20 % of patients annually from the number we can expect.

This can be connected with poor organization of the oncology in the country, poverty of population, no organized screening for cervical cancer and still present shame of disease.

Peak of disease is between 40 to 60 years of age which is consistent with other countries in the world. Distribution of stage and histology of our patients are the same as in the other countries.

Presented data of grade of tumors cells shows us that around 50% of patient's grade was not known in the time of decision of treatment. There are medical centers in the country where pathology is poor and not adequate to fulfill all requirements of modern oncology practice. This is one of important points witch have to be discussed among executives in the planning of health care. Pathological diagnosis is one of the main prognostic factors in gynecological oncology and has to be further improved.



Graficon 3. Distribution of patients due to progression type

The most of our patients were treated with combined concomitant chemo radiation treatments, and with curative intentions, according to standard in the world.

Results of this study are consistent with reported results of other institutions. Survival with no signs of disease was 62.7% for follow up of 28 months. (6, 7, 8)

Acute and late toxicity were as expected, and as reported in the most of literature. (9, 10, 11)

The most of deaths occurred in the first two years after the treatment, and none of it was caused by therapy.

5. CONCLUSIONS

- In our Institute we treated 514 patients with invasive cervical cancer thru years 2000- 2006.
- Median age of patients was 52 years.
- In 45, 9 % patient's histological grade of tumors cells was not known.
- Optimal standard therapy received 88, 5 % patients.
- Median follow up was 28 months.
- Survival with no signs of disease was comparable with other similar studies in literature for this period of time.
- Time to recurrence, time to metastasis and time to death was better in the group of patients with known grade of tumor cells.
- Late toxicity G3/4 was observed in 2.6% of patients, for this follow up time.
- No deaths occurred due to therapy.

LITERATURE

1. American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American Cancer Society, 2008. Also available online. Last accessed July 24, 2008.
2. M Arbyn, AO Raifu, P Autier, J Ferlay Burden of cervical cancer in Europe:
3. Estimates for 2004. Annals of Oncology.

2007; March16
4. © 2007 European Society for Medical Oncology
5. P. Boyle, J. Ferlay. Cancer incidence and mortality in Europe, 2004 Annals of Oncology 2005; 16(3):481-488; doi:10.1093/annonc/mdi098
6. N. Obralic, F. Gavrankapetanovic, Z. Dizdarevic, O.Duric, F.Sisic, I Selak, S. Balta, B. Nakas. Regional comparison of cancer incidence. Radiol.Oncol 2004; 38(2):145-51
7. National Cancer Institute: Concurrent chemo radiation for cervical cancer: February 1999. NCI Cancer Trials Resource Page Available at: http://cancertrials.nci.nih.gov/NCI CANCER TRIALS/zones/TrialInfo/News/cervcan/clinann.html. Accessed 2/22
8. Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, Insalaco S; Gynecologic Oncology Group. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007; Jul 1;25(19):2804-10.
9. Long-Term Data Support Cisplatin-Based Chemoradiation for Cervical Cancer Comment in: Nat Clin Pract Oncol. 2008; Mar; 5(3):128-9.
10. H. Ikushima, K. Osaki, S. Furutani, K. Yamashita, T. Kawanaka, Y. Kishida, S. Iwamoto, Y. Takegawa, T. Kudoh, H. Nishitani. Chemoradiation therapy for cervical cancer: toxicity of concurrent weekly cisplatin; radiation Medidine; 2006; Vol.24 No.2,115-121
11. L. C. Wong, H. Y.S. Ngan, A. N.Y. Cheung, D. K.L. Cheng, T. Y. Ng, D. T.K. Choy. Chemoradiation and Adjuvant Chemotherapy in Cervical Cancer. Journal of Clinical Oncology, 1999; Vol 17, Issue 7 (July), 2055
12. L Cetina, A Garcia-Arias, M de Jesus Uribe, A Astorga, M Candelaria, A Mota, R Guadarrama, L Rivera, J Hinojosa, ADueñas-Gonzalez. Concurrent chemoradiation with carboplatin for locally advanced cervical cancer at high-risk for developing cisplatin-induced renal dysfunction. BMC Cancer. 2007; 7(Suppl 1): A17.
13. L Cetina , L Rivera , M Candelaria , J de la Garza , A Dueñas-González. Chemoradiation with gemcitabine for cervical cancer in patients with renal failure. Anticancer Drugs. 2004; Sep;15(8):761-6.

CASE REPORT

Sequelae of Neonatal Septic Arthritis of Hip

Hasime Qorraj[1], Cen Bytyçi[2], Lul Raka[3]
[1]Orthopaedic Hospital, University Clinical Center of Kosova, Prishtina,Kosova
[2]Institute of Pharmacology, Univerisity Clinical Center of Kosova, Prishtina,Kosova
[3]National Institute for Public Health of Kosova, Prishtina-Kosova

The aim of the study was evaluation of residual deformity after neonatal septic arthritis of the hip. The patient was operatively treated by intetertrochanteric osteotomy of valgisation of 35^0 with anterotation of 10^0 and extension 25^0 at age of nine years because of leg length discrepancy, changes in the femoral neck, coxa vara, plana and breva. It was delay in diagnosis and failure to begin treatment promptly in the neonatal period. Delay in the diagnosis and the treatment of septic arthritis can result in disastrous complication like in this case report. **Key words**: Septic arthritis of the hip, residual deformity and late treatment, intertrochanteric osteotomy

1. INTRODUCTION

The most serious complication of the septic arthritis of the hip in childhood and especially in newborns is the avascular necrosis of the femoral head which can lead to partial or complete destruction of the capital femoral epiphysis, the growth plate or both. The sequelae of infantile septic arthritis and osteomyelitis of the hip are diverse and can include[1]:

- Necrosis of the articular cartilage Premature closure of the triradiate cartilage
- Premature or asymmetrical closure of the capital femoral physis
- Acetabular dysplasia
- Lower-extremity length discrepancy
- Osteonecrosis
- Pseudoarthrosis of the femoral neck, and
- Complete destruction of the femoral head and neck

The aim of the treatment of sequelae of neonatal septic arthritis of the hip is to preserve good relation between the femoral head and acetabulum. We are presenting a case of a boy aged twelve years, with coxa vara, plana et breve treated with corrective osteotomy of valgisation with anterotation. The intertrochanteric osteotomy results also in local hyperemia, improved venous drainage, and remodeling of internal architecture.

2. CASE REPORT

On clinical examination, there was muscle wasting et the hip and thigh region. The patient has Duchenne-Trendelenburg limp and the Trendelenburg sign with flexion, rotational and adduction contracture of the left hip. Abduction and adduction was tested with patient supine. The Thomas test was positive and flexion deformity was 25^0, abduction 20^0, adduction deformity of 25^0. Internal and external rotation was determined with the patient prone. Internal rotation was limited of 20^0. Determination of leg length discrepancy was done with patient laying and standing, and the shortening was 3.8 cm. Magnetic Resonance Imaging (MRI) was not done because our hospital lacks the equipments. The residual deformity was classified with a radiological classification system suggested by Choi at al.[2]. Our patient was grouped under Choi's Type IIIA, with severe coxa vara angular deformity with retroversion but no pseudoarthrosis of the femoral neck. A boy aged ten years complained of painless limp on the left hip. He had suffered septic arthritis of the left hip in the neonatal period. Intertrochanteric osteotomy was done with lateral approach to change the loading of the hip and to place the epiphyseal plate at right angle to the resultant of the compressive forces. With this intertrochanteric osteotomy of valgisation of 35^0 with anterotation of 10^0 and extension 25^0 we achieved transferring the greater trochanter distally and laterally so it is level with the center of the femoral head, restoring normal tension to the pelvitrochanteric muscles and improving their mechanical efficiency. With this procedure we placed the superior end of the femur against the lateral aspect of the pelvis and also increased the distance between the tip of the trochanter and the center of the hip rotation, years old after op treatment.

3. DISCUSSION

Delay in diagnosis, failure to begin treatment promptly, and patient age less than 1 year are the most common reason for late complication[3,4]. Early diagnosis and iniatiating immediate treatment is vital for the therapeutic outcome and long-term good prognosis. Septic arthritis of the hip is a common and rapidly destructive pyogenic infection in children and continues to be a

challenge despite improved antibiotic therapy because of the devastingely poor results when treatment fails or is begun late[5,6]. Acute septic arthritis represent e surgical emergency which demands early and vigorous treatment in order to preserve normal joint function[7,8]. Septic arthritis of the hip frequently is associated with osteomyelitis of the metaphysis of the proximal femur, since the capsule in the hip joint encompasses the metaphysis. In our case intetrochanteric femoral osteotomy increased the stability of the hip due to correction of the neck-shaft angle. In this type of osteotomy the operation is extracapsular so the hip joint is not directly approached. A good understanding of natural history of sequelae of septic arthritis of the hip is essential to plan the best treatment. Our patient was grouped under Choi's Type IIIA. The intertrochanteric osteotomy of valgisation of 35^0 with anterotation of 10^0 and extension 25^0 in our case has given a satisfactory result, improving the lower-extremity length discrepancy from 3.8 cm preoperatively to 1, 2 cm. and anatomic and functional relations. Postoperatively the pelvic drop (Trendelenburg gait) was reduce.

REFERENCES:

Rozbruch SR, Paley D, Bhave A, Herzenberg JE. Ilizarov Hip reconstruction for late sequelae of infantile hip. J Bone Joint Surg Am. 2005; 1007-1018

Choi IH, et al. Sequelae and reconstruction after septic arthritis of the hip in infants. J Bone Joint Surg Am: 1990: 1150.

Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. J Bone Joint Surg Am. 2004; 86 (8):1629-1635.

Goldenberge DL. And Reed JI. Bacterial arthritis. N.Engl. J. Med. 1985; 312:764-771.

Bonhoeffer J, Haeberle B, Shaad U, Heininger U. Diagnosis of acute haematogenous osteomyelitis and septic arthritis: 20 years experience at the University children's hospital Basel. Swiss Med WKLY 2001; 131:575-581.

Vidigal EC, Jacomo AD. Early diagnosis of septic arthritis of the hip in neonates. Int Orthop. 1994; 18:189-192.

Eich GF, Superi-Furga A, Umbricht FS, Willi UV. The painful hip: evaluation of criteria for clinical decision –making. Eur J Pediatr. 1999; 158: 923-928.

McCarthy JJ, Dormans JP, Kozin SH, Pizzuillo PD. Musculoskeletal infections in children. Basic treatment principles and recent advancements. J Bone Joint Surg Am. 2004; 86 (4): 850-863.

CASE REPORT

Ecthyma Gangrenosum In a Patient With Acute Leukemia

Emrush Kryeziu*, K. Kryeziu, G. Bajraktari, M.Abazi, B.Zylfiu, I.Rudhani, Sh.Sadiku, A.Ukimeri, A.Brovina, Sh.Dreshaj, S.Telaku
University Clinical Centre of Kosova, Department of Hematology, 10000, Prishtina, R. of Kosova

Ecthymagangrenosum (EG)is a rare condition with characteristic clinical appearance of red maculae that progresses to a central area of necrosis surrounded by an erythematous halo. The most frequently it is caused by*Pseudomonas bacteriaemia* in neutropenic patient. The authors presents a patient with acute myloblastic leukemia M_4 type in whom in relapse EG caused by*Pseudomonas aeruginosa* was found. The patient was treated with antibiotics and surgical debridement.The author wants to point out on clinical significance this condition with high mortality rate. **Key words:** Ecthyma gangrenosum, acute myeloid leukemia

Corresponding author: Emrush Kryeziu Assistant professor of Internal Medicine*, University Clinical Centre of Kosova, Department of Hematology, 10000, Prishtina, R. of Kosova,

1. INTRODUCTION

Ecthymagangrenosum (EG) is a rare cutaneous disease that is characterized with appearance of hemorrhagicbullaes that fastly evaluate into gangrenous ulcerations and they most commonly occur inimmunocompromised very often neutropenic patients. It is oftenly caused by bacteriaemia with *Pseudomonas aeruginosa* and it may be a first sign of *Pseudomonas* bacteriemia[1, 2]. Apart from *P.aeruginosa* EG can be caused even by other types of these bacteria[3, 4] or other bacteria like Staphylococcus aureus, Seratiamarcenses, Escherichia colli andother [5-10]. Very rarely EG can appear even without bacteriaemia and extremely rarely it can be a complication of antibiotic therapy. This cutaneous disease appears mostly in hematologic, especially leukemic patients andothers who receive immunosuppressive drugs [11]. The risk of this complication is enlarged in immunocompromised or neutropenic patients and patients who receive corticosteroid therapy [1].

2. CASE REPORT

A 31-year old male presented in September 2006 with fatigue and malaise. On physical examination he had petechial bleeding, splenomegaly 170x65 mm and hepatomegaly 160 mm. Laboratory data showed reduced hemoglobin Hb70 g/l, platelet count $18x10^9$/l, on days 1,2,3), WBC $100x10^9$/l (differential formula myeloblasts 67%, myelocytes 3%, monocytes 18%, lymphocytes 12%).ESR 120 mm, prothrombin time 105%, partial thromboplastin time 21,7 sec, fibrinogen 4,45 g/l. Biochemical analyses of the blood were within normal limits. Bone marrow aspirate showed hypercellularity. As regards the blast cell morphology, the type I (<15 acidophilic granules in the cytoplasm) and type II (>15 acidophilic granules in the cytoplasm) blasts comprised 32% of the mononuclear cells, some with Auer rods. Some 20% of the blasts were of monoblastic morphology. The MPO stain was positive in 40% of blast cells. The immunophenotype of the blasts corresponded to AML-M4 (HLA DR+, CD34+, CD33+, CD13+, CD11b+, CD14+, CD15+, MPO+) and glycophorin A-.Cytogenetic analysis showed normal karyotype 46XY. Induction chemotherapy was initiated with daunorubicin and cytosine-arabinoside. A complete remission was achieved and consolidation therapy according to MRC AML 10 protocol was administered. Four months later, the patient developed speech difficultie and relpse of acute leukemia with signs of central nervous system involvement(cephalea, nausea, visual disturbances, synkopa) was diagnosed. Physical examination showed again hepatosplenomegaly and dysphasia. Laboratory date: Hemoglobin was normal 13 g/l, WBC $2,1x10^9$/l, platelets $34x10^9$/l (9% of blasts in DLF). Bone marrow aspirate showed hypercelullarity with 70% of myelomonoblasts, some of which were myeloperoxidase positive. Cytogenetic examination revealed again a normal male karyotype, 46XY. In cerebrospinal fluid there was a number myeloblast (109/mm^3). Ophtalmologic examination of fundus oculi showed papilla stagnans with massive haemorrhages. As it had been shown that it was the relapse of leukemia in bone marrow and CNS he was treated according to Archimbaud protocol for relapse with cytosinarabinoside 1000mg i.v. in conitinuosly infusion from day 1 to day 3 and days 8 to 10, novantrone 20 mg from day 1 to 3. and etoposide 400 mg i.v. in conitinuous infusion from 8 to 10 days. He was treated with intratechal application of citosine arabinoside and depo-medrool (12 injections). After this he developed

Fig. 1. Ulcer necrotic lesion in left inguinal region that has eroded through the top layer of skin (dermis).

aplasia, high temperature in which period he was treated with antibiotics and G-CSF. His condition improved but in ingiunal region appeared deep necroses (Fig. 1.). From the necrotic surfaces taken material in cultures *Pseudomonas aeruginosa* was isolated. He was treted with imipenem, ciprofloxacin and surgical debridement with signs of local improvement. Unfortunately he he is still in partial remission with signs of CNS leukemia.

3. DISCUSSION

It is known that patients with long hospitalization and the ones who receive antibiotics have more *Pseudomonas aeruginosa* on their skin comparing to the healthy persons in general population. In the states of diminished immunity and eventual neutropenia microorganisms enter the body in the spots of microerrosions especially over intravenous and urinary catheters, decubital ulcerations and thermic damages[1].

EG appears in up to 30% patients with septicemia caused by *Pseudomonas aeruginosa*[12]. Appearance of skin lesions often precede high temperature, chill and fever, erythematousmaculaes, fast evaluate into big bullaes and pustules and after that appears the necrosis of epiderm and derm. EG also can be accompanied by systemic vasculitis. It is assumed that necrosis of the skin is caused with *Pseudomonas* elastase which destroys elastic lamina of the blood vessels which allows for liberationof the bacilli into the subcutaneous tissues[11]. The proliferation and multiplication of the bacteria in the tissue cause liberation of exotoxinA and proteases leads to theulcerative lesions which is characterized by hemorrhage, encircled by a rim of reactive erythema.Epiderm sometimes separates from the dermis, dermis become indurate, gains grey metal colorand become indurat-edulcurs around which the skin is red. Ulcerations are usually sensitive on palpation [1, 4].

The commonest site of involvement is the gluteal or perineal region, in axillas, and sometimes on the lips and tongue[1, 5]. Gluteal and perineal region are involved in more then 50% of patients[12]. Solitary skin lesion has better prognosis then multiple ones.

The diagnosis of EG is easy. It is most important to think about this dermatological disease when these symptoms appear in immunocompromised or hematologic patient, other patients that have received cytotoxic drugs that made them neutropenic what was the case in our patient. The microorganism can be proved and diagnosed either by hemoculture and/or by culture of the tissue taken from the wall of the ulceration or ulceration itself [1, 8].

The result of bacteria culture is not to be waited for but should immediately be started with antibiotic therapy efficacious to *Pseudomonasaeruginosa* as the most frequent cause and the ulcerations should be surgically treated (surgical debridement should be done). Antibiotic should be changed after the result of antibiogram if the antibiogram shows some other microorganism. Very useful is the nutrition support of the patient[4].

In the case of failure of antibiotic therapy in the literature the authors have used the granulocyte colony-stimulating factor (Neupogen). EG should be understood as a very serious and life-threatening systemic infection. The poor prognosis is caused by delay of the diagnosis and treatment, which results in delay of application adequate antibiotic therapy.

Clinicians should be aware of the skin manifestations of EG to avoid fatal septicemia in neutropenic patients[15].

REFERENCES

1. Fitzpatrick Th B, Johnson RA, Polano MK, Suurmond D, Wolf K. Color atlas and Synopsis of Clinical Dermatology. Common and Serious Diseases. Second ed. Mc Graw-Hill, Inc.1994;352-3.
2. Duman M, Ozdemir D, Yis U, Koroglu TF. Oren O, Berktas S.Multiple erythematous nodules and ecthyma gangrenosum as a manifestation of Pseudomonas aeruginosa sepsis in previously healthy infant. Pediatr Dermatol 2006;23:243-6.
3. Puzenat E, Chirouze C, Khayat N, Aubin F, Estavoyer JM, Humbert P, Hoen B.Ecthyma gangrenosum avec septicémie à Pseudomonas stutzeri s'accompagnant d'une vascularite systémique. Rev Med Interne 2004;25:315-8.
4. Singh TN, Devi KM, Devi KS. Ecthyma gangrenosum: a rare cutaneous manifestation caused by pseudomonas aeruginosa without bacteriaemia in a leukaemic patient-a case report. Indian J Med Microbiol 2005;23:262-3.
5. Solowski NL, Yao FB, Agarwal A, Nagorsky M. Ecthyma gangrenosum: a rare cutaneous manifestation of a potentially fatal disease. Ann Otol Rhinol Laryngol 2004;113:462-4.
6. Brown KL, Stein A, Morrell DS. Ecthyma gangrenosum and septic shock syndrome secondary to Chromobacterium violaceum. J Am Dermatol 2006;54:S224-8.
7. Reich HL, Williams Fadeyi D, Naik NS, Honig PJ, Yan AC. Nonpseudomonal ecthyma gangrenosum. J Am Acad Dermatol 2004;50:S114-7.
8. Levy I, Stein J, Ashkenazi S, Samra Z, Livni G, Yaniv I.Ecthyma gangrenosum caused by disseminated Exserohilum in a child with leukemia:a case report and review of the literature. Pediatr Dermatol 2003;20:495-7.
9. Song WK, Kim YC, Park HJ, Cinn YW.Ecthyma gangrenosum without bacteraemia in a leukaemic patient. Clin Exp Dermatol 2001;26:395-7.
10. Ishikawa T, Sakurai Y, Tanaka M, Daikoku N, Ishihara T, Nakajima M, Miyagawa S, Yoshioka A.Ecthyma gangrenosum-like lesions in a healthy child after infection treated with antibiotics. Pediatr Dermatol 2005;22:453-6.
11. Mull JD, Callahan WS. The role of the elastase of Pseudomonas aeruginosa in experimental infection. Exp Mol Pathol 1995;4:567-75.
12. Almeida JFL, Sztajnbok J, Troster EJ, Vaz FA. Pseudomonas aeruginosa septic shock associated with ecthyma gangrenosum in an infant with agammaglobulinemia. Rev Inst Med Trop S Paulo 2002;44:167-9.
13. Versapuech J, Leaute-Labreze C, Thedenat B, Taieb A, Ragnaud JM.Ecthyma gangréneux à Pseudomonas aeruginosa sans septicémie chez une patiente neutropénique.Rev Med Interne 2001;22(9):877-80.
14. Obara Y, Nagai T, Mori M, Ohmine K, Toshima M, Komatsu N, Ozawa K. [Pseudomonas sepsis with ecthyma gangrenosum in an acute myeloid leukemia patient]. Rinsho Ketsueki 2004;45:1138-40.
15. Singh N, Devi M, Devi S. Ecthymagangrenosum: A rare cutaneous manifestation caused by Pseudomonas aeruginosa without bacteremia in a leukemic patient. Indian J DermatolVenereolLeprol 2005; 71:128-9

PROFESSIONAL PAPER

Treatment of Anterior Encephaloceles Over 24 Years in Kosova

Arsim Morina[1], Fatos Kelmendi[1], Qamile Morina[2], Shefki Dragusha[1], Feti Ahmeti[1], Dukagjin Morina[3]
University Clinical Center of Kosova, Clinic of Neurosurgery, Prishtina, Kosova[1]
University Clinical Center of Kosova, Clinic of Anesthesiology, Prishtina, Kosova[2]
Stadtische Kliniken Duisburg, Klinikum Kalkweg – Neurochirurgische Klinik, Duisburg, Germany[3]

Introduction: In the present study we report 36 cases of anterior encephaloceles treated at Clinic of Neurosurgery in the University Clinical Center of Kosova over a 24 year period. Materials and methods: All 36 children were included in this retrospective study (1986 through 2009). Their ages ranged from 1 day to 10 years (mean 13 months); 20 were boys and 16 were girls. The commonest type of anomaly seen was nasofrontal 17 patients, 12 nasoethmoidal , and 7 nasoorbital. The size of the lesion varied from 2.5cm to 28 cm. Hypertelorism occurred in 12 patients. Hydrocephalus was present in 11 patients and in 8 of them was progressive. Results: 1 patient died on 10th postoperative day due to fulminant meningitis. Cosmetic results were judged from parents as excellent in 16 patients, good in 12 patients, average in 6 patients and poor in 2 patients. None of patients were lost to follow-up. Discussion: Histologic examination of the herniated tissue can vary between normal brain to fibrous atrophic nonviable tissue (4). No familial cases have been reported in the literature , we also have similar experience. In our study we have found that the prevalence is higher among patients coming from rural parts of our country with pore living conditions, malnutrition and so on . We have avoided surgery in very young children until body weight is around 5-6 kg because of complication from blood lose and hypothermia. Conclusion: The aim of treatment is early removal of the meningoencephalocele to allow normal growth forces to be re-established. In patients with hypertelorism, correction surgery is done in the same session. If hydrocephalus is not treated before corrective surgery for encephalocele, the risk of postoperative CSF is very high. With one stage surgery excellent results can be achieved. **Key words: Anterior encephaloceles, craniofacial malformations, pediatric neurosurgery, sincipital encephalocele.**

Corresponding author: prof Arsim Morina,MD, PhD. University Clinical Center of Kosova, Clinic of Neurosurgery, Rruga e spitalit p.n., 10 000 Prishtina, Kosova

1. INTRODUCTION

Anterior encephaloceles are congenital herniations of cranial contents through a defect in the skull (1,2,3,4,5,6,7,8,9,10). Encephaloceles commonly are present in the midline sagittal axis of the cranium from the nasofrontal region to the occiput (11,12,13,14,15,16,17,18,19,20). Anterior encephalocele is classified according to its location as sincipital and basal and according to its content in meningoencephalocele and meningocele. Sincipital encephalocele are again subdivided into 3 types : nasofrontal, nasoethmoidal, and nasoorbital (21). The size of the lesion may vary from a barely noticeable mass to lesions larger than the patient's head (1). Although now rare in Europe and North America, this malformation continuous to be seen frequently in southeast Asia (15,17) and its cause are still debated (15,17,22). In the present study we report 36 cases of anterior encephaloceles treated at Clinic of Neurosurgery in the University Clinical Center of Kosova over a 24 year period.

2. MATERIAL AND METHODS

2.1. Clinical feature

All 36 children were included in this retrospective study (1986 through 2009). Their ages ranged from 1 day to 10 years (mean 13 months) ; 20 were boys and 16 were girls, with no significant difference by gender (X^2-test =0.44, P>0.05), (Table 1). For testing of the data we have used X^2-test with significant level P<0.05 or P<0.01.

2.2. Radiology

CT scans were obtained in all cases. In 27 of them it was performed 3D reconstruction of the skull. Hydrocephalus was present in 11 patients in 7 of them cerebral index was less than 2.2cm. 2 patients had corpus callosum agenesis.

2.3. Operative procedure

	N (%)	P-value
Gender		
Male	20 (55.6%)	P= 0.505
Female	16 (44.4%)	X^2-test=0.44
Age		
Mean 4 SD	13 month (4 7 month)	
Rank	1 day to 10 years	

Table 1. Main characteristic of patients

Figure 1. Clinical photograph of an one month boy with gigantic meningoencephalocele.

Figure 2. Cranial CT, axial cut of same child.

Figure 3. Intraoperative picture from extracranial part of surgery.

Figure 4. Two months after surgery.

One patient was precluded from surgery because of severe mental retardation. 35 patients underwent surgical reconstruction, 8 patients underwent ventriculo peritoneal shunt medium pressure before corrective surgery. 5 cases underwent extracranial repair alone. Transcranial approach was done in 31 patient. Surgical incisions include a bicoronal scalp flap, giving wide exposure of the craniofascial skeleton . Bilateral frontal craniotomy was performed were bone was removed as a free graft. After the elevation of frontal lobe the herniated brain was clearly seen. The dura was opened and the cerebral herniation inspected. Herniated brain in majority of cases consists of gliotic nonfunctional neural tissue and was apirated. Bone defect was closed with bone graft that was taken from cranium. In 12 patients osteotomies are performed to translocate the orbit medially.

3. RESULTS

The commonest type of anomaly seen was nasofrontal 17 patients, 12 nasoethmoidal, and 7 nasoorbital, with no significant difference by localization (X^2-test =4.167, P>0.05). The size of the lesion varied from 2.5cm to 28 cm. In 9 patients the contents were cystic in 7 of them when baby cried pulsation was felt over the swelling, 27 cases the contents were a mixture of solid and cystic mass with significant difference by content (X^2-test =9, P<0.01) (Table 2). Hypertelorism occurred in 12 patients. Hydrocephalus was present in 11 patients and in 8 of them was progressive. In 32 patients the skin coverage was complete and in 4 cases thin layer of epidermis was covering the lesion. In 1 case the lesion was extremely large and trampled on the nose and eyes, causing severe difficulties with breathing and vision because of this required urgent operative treatment. The average paternal age was 28,2 years. Consanguinity was reported in 1 family. There was no family history of other encephaloceles or any neural tube defect. In 3 cases epileptic seizures were present. From 36 children 3 of them were going to school before the surgery and 2 of them reported teasing from other children. Other congenital anomalies like cleft palate, cleft clip, absence of nostril, microphtalmia, syndactyly were noted in 1 patient each. 34 patients who underwent correction survived the operation. Immediate postoperative CSF leak through the skin was observed in 1 patient which required tighter skin closure and a tight head bandage. In 1 patient bone flap osteomyelitis was observed she underwent repeated surgery and received antibiotic therapy until the infection heald completely dhe cause was: Pseudomonas aeuroginosa. 1 patient died on 10th postoperative day due to fulminant meningitis. In spite of anticonvulsant therapy 1 children continue to seize even after 8 years following surgery. Nasolacrimal dysfunction usually persisted postoperatively. Cosmetic results were judged from parents as excellent in 16 patients, good in 12 patients, average in 6 patients and poor in 2 patients. None of patients were lost to follow-up.

	N (%)	P-value
Type of anomaly		
Nasofrontal	17 (47.2%)	P=0.124 X^2-test = 4.167
Nasoethmoidal	12 (33.3%)	
Nasoorbital	7 (19.4%)	
Size of lezion	2.5 cm–28 cm	
Content		
Cystic	9 (25.0%)	P= 0.002 X^2-test= 9
Mixture (solid and cystic)	27 (75.0%)	

Table 2. Characteristics of Anterior Encephaloceles

4. DISCCUSION

Anterior encephaloceles are common in many southeast Asian countries such as Burma (19,23), Thailand (14,18), Cambodia (11), Malaysia (13), and Indonesia (12). In Thailand, it has been shown that frontoethmoidal MECs occur in one of 5000 to 6000 live births (14,18). A few authors have described these deformities in Australian aboriginal people (13), and in some patients in African countries (3), and in India and Pakistan (9,10). This lesion are rare in North America, Japan and Wester Europe. Till date, the exact etiology is not known, although various hypotheses have been proposed (5,6). Currently, two schools of thought exist regarding the origin of these lesions. The first concept involves the point of weakness in the facial skeleton. The frontal bone is a membranous bone that forms from the underlying dura, whereas the ethmoid bone developes from endochondral bone formation. The function of the membranous and endochondral bone (foramen cecum is thought to result in a week area through which the neural elements can hernaite (2,7). A second

hypothesis states that a delayed closure of the neural tube ultimately prevents normal union of the facial bone (8). Findings of a trapped meningocele and peripheral nerve elements, as well as isolated neural tissue remnants along the original tract appear to substantiate this second theory. However, the fact that most anterior encephaloceles are covered with normal skin indicates that these defects are not simply a failure of neuraltion. Thus, the precise etiology of these lesions remains speculative. Histologic examination of the herniated tissue can vary between normal brain to fibrous atrophic nonviable tissue (4). No familial cases have been reported in the literature, we also have similar experience. Suwanwela (16) described a pair of identical twins where 1 twin was not affected, concluding that a genetic mechanism was not the primary cause. Other theories have included a simple vitamin deficiency however, Kyu and Thu (18), in a large series in Burma, revealed that over half of the mothers of (16); affected children were on vitamins during their pregnancy. In our study we have found that the prevalence is higher among patients coming from rural parts of our country with pore living conditions, malnutrition and so on . We have avoided surgery in very young children until body weight is around 5-6 kg because of complication from blood lose and hypothermia.

5. CONCLUSIONS

In a country such as Kosova, the treatment of specific disease processes must be adapted to fit current local conditions. The development of low-cost procedures is very important. Three-dimensional CT scan has been a major improvement in investigation of defects in craniofacial skeleton. The aim of treatment is early removal of the meningoencephalocele to allow normal growth forces to be re-established. In patients with hypertelorism, correction surgery is done in the same session. If hydrocephalus is not treated before corrective surgery for encephalocele, the risk of postoperative CSF is very high. With one stage surgery excellent results can be achieved.

REFERENCES

1. Albright AL, Pollack IF, Adelson PD. Principles and Practise of Pediatric Neurosurgery Second Edition Thieme, 2008.
2. Chapman PH, Swearingen B, Caviness VS. Subtorcularoccipital encephaloceles. J Neurosurg, 1989; 71: 375-81.
3. De Klerk DJ, De Villiers JC. Frontal encephaloceles. S Afr Med J, 1973; 47: 1350-5.
4. Gallo AE Jr. Repair of giant occipital encephaloceles with microcephaly secondary to massive brain herniation. Child Nerv Syst, 1992; 8: 229-30.
5. Hoving EW, Vermeij-Keers C. Frontoethmoidal encephaloceles, a study of their pathogenesis. Pediatr Neurosurg, 1997; 27: 246-56.
6. Hoving EW, Vermeij-Keers C, Mommaas-Kienhuis AM, Hartwig NG. Separation of neural and surface ectoderm after closure of the rostral neuropore. Anat Embryol (Berl), 1990; 182: 455-63.
7. Lorber J, Schofield JK. The prognosis of occipital encephalocele. Z Kinderchir, 1979; 28: 347-51.
8. Padget DH. Neuroschisis and human embryonic maldevelopment: new evidence on anencephaly spina bifida and diverse mammalian defects. J Neuropath Exp Neurol, 1970; 29; 192-216.
9. Rahman NU. Nasal encephalocoele: treatment by trans-cranial operation. J Neurol Sci, 1979; 42: 73-85.
10. Rapport RL II, Dunn RC Jr, Alhady F. Anterior encephalocele. J Neurosurg, 1981; 54: 213-9.
11. Richards CG. Fronto-ethmoidal meningoencephalocele: a common and severe congenital abnormality in South East Asia. Arch Dis Child, 1992; 67: 717-9.
12. Rojvachiranonda N, David DJ, Moore MH, Cole J. Frontoethmoidal encephalomeningocele: new morphological findings and a new classification. J Craniofac Surg, 2003; 14: 847-58.
13. Simpson DA, David DJ, White J. Cephaloceles: treatment, outcome and antenatal diagnosis. Neurosurgery, 1984; 15: 14-21.
14. Suwanwela C, Sukabote C, Suwanwela N. Frontoethmoidal encephalomeningocele. Surgery, 1971; 69: 617-25.
15. Suwanwela C, Sukabote C, Suwanwela N. Frontoethmoidal encephalomeningocele.
16. Suwanwela, C. Geographical distribution of fronto-ethmoidal encephaloceles.Br J Preventative Med, 1972; 26: 193.
17. Suwanwela C, Suwanwela N. A morphological classification of sincipital encephalomeningoceles. J Neurosurg, 1972; 36: 201-11.
18. Thu A, Kyu H. Epidemiology of frontoethmoidal encephalomeningocoele in Burma. J Epidemiol Community Health, 1984; 38: 89-98.
19. Von Meyer E. Uber eine basale Heirnhernie in der Gegend der lamina cribrosa. Virhows Arch, 1890; 120: 309-320.
20. Whatmore WJ. Sincipital encephalomeningoceles. Br J Surg, 1973; 60:261-270.

CASE REPORT

Epiphrenic Diverticulum as a Rare Cause of Dysphagia

Jovan Culum, Dragan Kostic, Bozo Krivokuca, Ozren Kordic, Dragan Tomic, Jugoslav Djeri
Clinic for General and Abdominal Surgery, Clinical Center Banjaluka, Banja Luka, Bosnia and Herzegovina

Epiphrenic diverticulum is a rare condition which produces disphagic problems. It occurs in one fifth of the total number of patients with esophageal diverticula. It is often associated with motility disorders such as hypertensive lower esophageal sphincter, achalasia and diffuse esophageal spasm. Increased intraluminal pressure is responsible for the prolapse of mucosa and submucosa through the muscle layer, and the consequently formation bag extensions (diverticula). We presented 55 year old female patient who had dysphagia, regurgitation and chest pain caused by retrosternal epiphrenic diverticulum who has successfully operated in our clinic. We performed open approach (left thoracotomy), and complex surgery: diverticulectomy, long esophagomyotomy and antireflux procedure (Belsey Mark IV). After 4 years patient is without symptoms of disphagia and in a good nuitrition. Key words: Epiphrenic diverticulum, surgical treatment

Coresponding author: Culum Jovan, brace Cubrilovic 16a Banja Luka, Bosnia and Herzegovina tel.051 430 410 mob. 065 580 088

1. INTRODUCTION

Epiphrenic diverticula are acquired protrusion of mucosa through the muscular wall of the distal esophagus. Most of them are associated with underlying esophageal motility disorders. The cause of their is motor dysfunction of the esophagus (diffuse spasm or achalasia). Elevated intraluminal pressure is responsible for the prolapse of mucosa and submucosa through the muscle layer and the consequent formation bag extensions (diverticula) (1,2).

The predominant symptoms is the dysphagia and regurgitation, and may occur retrosternal pain, if it is accompanied by spasm of the esophagus. Halitosis (foetor ex ore) due to undigested food is expressed in a lesser degree than Zenker's diverticulum. In some patients disease is asymptomatic and discovered as incidental findings on chest radiography. Simptoms is sometimes difficult to distinguish from other functional esophageal disorders (diffuse esophageal spasm, achalasia, hiatal hernia or reflux esophagitis), and can sometimes mask a picture of esophageal neoplasms. Size varies from small ones who empted spontaneously and does not constitute a big problem, to big ones that its size can be to perform compression on the esophagus and cause dysphagia (1,2,3).

Diagnosis is possible to set by contrast radiography, endoscopy and esophageal manometry.

Asymptomatic patients with a small diverticulum and a wide communications with the lumen of the esophagus, empted spontaneously and does not require any treatment. Progressive dysphagia, chest pain, increasing the diverticulum which is not empted spontaneously, is indication for surgical therapy. Complexity of the surgical procedure is that it consists from 3 phases: diverticulectomy long esophagomyotomy and transthoracic antireflux procedure (modified Belsey Mark IV) (4,5,7,8,9).

2. CASE REPORT

In our clinic since 2002 a total of 30 patients with benign causes of dysphagia had syrgery (functional disorders and diverticula). Only in one case the cause of dysphagia was epiphrenic diverticulum.

Patient, 55 year old female had dysphagia, regurgitation and chest pain caused by retrosternalni epiphrenic diverticula. Our patient had a diverticulum, which led to the development of progressive dysphagia, regurgitation, night cough due to retention of undigested food and aspiration. Dysphagia developed slowly and led to loss of body weight and avoid eating. The diagnosis was establish a year ago when the size by the X ray examination, radiography and

FIGURE 1.

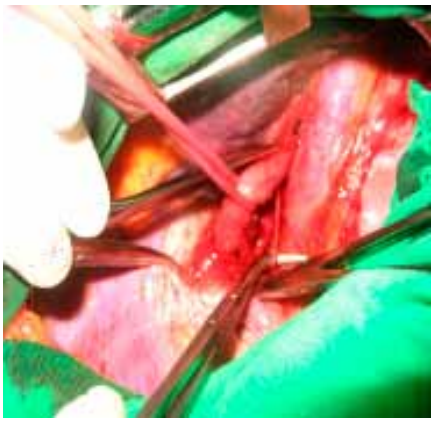


FIGURE 2.

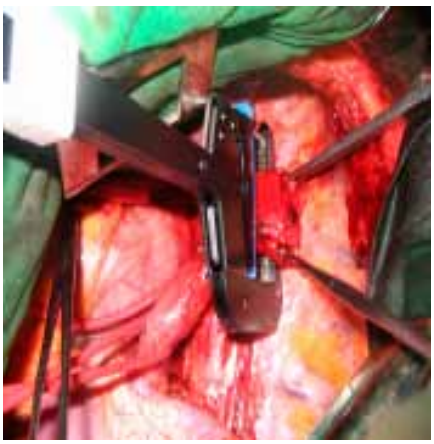


Figure 3.

Figure 4.

CT scan was approximately 7 cm, but the patient has not adopted for surgical treatment. The pains were intensified, so that the size of the diverticulum in the surgery time was 9 cm in diameter (Figure 1). Left thoracotomy approaches for the distal thoracic esophagus is apply who mobilisises and with preservation vagal nerv branches (Figure 2).

After the preparation and presentation of diverticular sack, the same preparated carefully, making sure not to break the parietal pleura, than diverticulum is removed by mechanical sewing (TA-60, 4.8 mm stapling device), performed a long infraaortal myotomy on the contralateral side of the mouth of the diverticulum, and added antireflux procedure (modified Belsey Mark IV) (Figure 3 and 4).

Early postoperative course was satisfied. Contrast radiography after 6 and 12 months showed normal findings, and the patient has no symptoms, with normal body weight (Figure 5).

Histopathologic analysis confirmed the presence of leyomioma in the diverticular sack.

3. DISCUSSION

Functional obstruction due to motility disorders resulting intraesophageal increasing pressure, and this is the impetus for the development pulsion diverticula. Epiphrenic diverticulum is generally associated with supporting a motor disorder that is considered the cause of diverticula (1,2,3). More than 30-40% of epiphrenic diverticula are asymptomatic. The main symptoms are dysphagia, regurgitation or vomiting, chest pain and weight loss. Night cough, pneumonia and laryngitis may develop secondarily due to aspiration of undigested food (4,5).

Diagnosis of diverticula is establish by chest radiography with barium, upper gastrointestinal endoscopy, manometry and computerized tomography (CT scan). However, most epiphrenic diverticula were incidentally diagnosed. The native chest radiography shows the level of shading in the middle part of the posterior mediastinum. Barium radiography was the primary modality in the diagnosis epiphrenic diverticula. Endoscopy helps to exclude other abnormalities of the esophagus. Stationary manometric examination of the esophagus is usually indicated regarding diagnostic motility disorders that may affect the decision on the modality of treatment. Clinical manifestations are unpredictable and not correlated with the size of the diverticula, but are correlated with primary motility disorders (6,7). Dysphagia and regurgitation are the dominant symptoms, and respiratory symptoms, when present, indicate complicated disease. CT indicates the differentiation of diverticula from mediastinal abscess, tumor or even a hiatus hernia. Epiphrenic diverticulum usually appears on CT as a structure with thin walls, filled with air or air-fluid collection in communication with the lumen of the esophagus. However, diverticula are associated with distal esophageal obstruction may remain in a state of contraction and may therefore be invisible to CT (7.8). Asymptomatic patients should be treated conservatively. Symptomatic patients should undergo surgical treatment. Surgical options include diverticulectomy, long myotomy and antireflux procedure (according to the results of manometry) (8). More recently, thoracoscopy, minimally invasive procedure and endoscopic procedures are become popular in the treatment of diverticular disease, but open approach only provides to handle all aspects of the disease (9,10).

Figure 5.

REFERNCES

1. Deschamps C and Trastek VF. Esophageal diverticula. In: Shields TW, LoCicero J, Ponn RB, ed. General Thoracic Surgery, fifth edition. Lippincott Williams & Wilkins, 2000:1839-49.
2. Benacci JC, Deschamps C, Trastek VF, Allen MS, Daly RC, Pairolero PC. Epiphrenic diverticulum: Results of surgical treatment. Ann Thorac Surg, 1993;55:1109-14.
3. Allen MS. Treatment of epiphrenic diverticula. Semin Thorac Cardiovasc Surg 1999;11:358-62.
4. Hamilton S. Esophageal leiomyoma arising in an epiphrenic diverticulum. Eur J Radiol,1988;8:118-9
5. Tescado P, Fisichella PM, Way LW, Patti MG. Cause and treatment of epiphrenic diverticula. Am J Surg, 2005;190:891-4.
6. Hudspeth DA, Thorne MT, Conroy R, Pennell TC. Management of epiphrenic esophageal diverticula. A fifteen-year experience. Am Surg, 1993;59:40-42.
7. Costantini M, Zaninotto G, Rizzetto G, Narne S, Ancona E.esophageal diverticula. Best Pract Res Clin Gastroenterol, 2004; 18: 3-17.
8. Tedesco P, Fisichella PM, Way LW, Patti MG. Cause and treatment of epiphrenic diverticula. Am J Surg, 2005; 190 : 891-4.
9. Klaus A, Hinder RA, Swain J, Achem SR. Management of epiphrenic diverticula. J Gastrointest Surg, 2003; 7: 906-11.
10. Jordan PH Jr, Kinner BM. New look at epiphrenic diverticula.World J Surg, 1999; 23: 147-52.
11. Fernando HC, Luketich JD, Samphire J, Alvelo-Rivera M, Christie NA, Buenaventura PO, Landreneau RJ. Minimally Invasive Operation for Esophageal Diverticula. Ann Thor Surg, 2005;80:2076-81.

CASE REPORT

Pericardial Tamponade Due to Synergistic Effects of Tuberculosis and Myxedema

Ahmet Karabulut MD, Mahmut Cakmak MD
Department of Cardiology, Istanbul Medicine Hospital, Istanbul, Turkey

Tuberculosis is a leading cause of massive pericardial effusion and tamponade especially in underdeveloped and developing countries. Hypothyroidism is also associated with pericardial effusion with rare progression to tamponade. We present a case of pericardial tamponade who diagnosed as both tuberculosis and myxedema at admission. Urgent pericardiocentesis performed as an initial therapy and four-agents antituberculous and thyroxine replacement therapy started immediately as long term management. Coexistance of tuberculosis and myxedema is a rare condition and they can cause tamponade formation with synergistic effect. Such a additive etiologies of pericardial tamponade have not been reported.
Key words: Tuberculosis; Myxedema; Cardiac Tamponade

Address for Correspondence: Ahmet Karabulut, MD. Istanbul Medicine Hospital Department of Cardiology. Hoca Ahmet Yesevi Cad. No: 149, 34203, Istanbul, Turkey . Phone:+90 212 489 08 00 Fax:+90 212 474 36 94 E-mail: drkarabulut@yahoo.com

1. INTRODUCTION

Cardiac tamponade i a life-threatening condition that may occur after any cause of pericardial effusions with variable incidence. Malignant diseases are the most frequent causes of pericardial tamponade. Especially in developing countries, tuberculosis (tbc) is still primary cause of massive pericardial effusion and tamponade (1) . Here, we presented a case of pericardial effusion and tamponade due to tbc and myxedema. Tbc and myxedema both was contributed to development of effusion and progression to tamponade. Such a case has never reported before in the literature.

2. CASE REPORT

A 45-year-old woman was admitted to emergency service with a complaints of shortness of breath, wekness and malaise. She defined progressive dyspnea for 2 years. There was prominent deteriotion of symptoms within last 2 weeks. 2 day before presentation, she applicated to another emergency service of public hospital. Anemia and cardiomegaly on chest x-ray was obtained. She was directed to outpatient clinic for further investigation. On admission, she was looked pale and lethargic; tachypnea and tachcardia was present. Her blood pressure was 60/40 mmHg. Heart rate was 130/minute and pulses was filiform. There was bilateral crackles in the bottom of lungs. Heart sounds heard deeply on chest auscultation. There was 2+ bilateral pretibial edema. Hemogram showed a mild anemia (hb-9.5 g/dl, hct:27.1 %) in normochrome nature. Sedimantation rate was 70/ a hour and creatine level vas 0.9 mg/dl. Electrocardiography showed sinusal tachycardia and low QRS voltage. İmmediate transthoracic echocardiography revealed pericardial effusions with tamponade physiology. Effusions was surrounding all around the heart and its thickness reaching 3.3 posteriorly and 2.5 cm from apical segment. Fibrinoid structure was observed in the discrete part of fluids. There was marked compression to the whole heart and collapses of both right atrium and right ventricle. Ejection fraction of left ventricle was normal. Then pericardiocentesis was performed. 850 cc hemorrhagic fluid was aspirated. Samples from the pericardial fluid were prepared for biochemical, microbiologic, and pathologic examinations. After pericardiocentesis, signs of respiratory distress resolved, arterial blood pressure and heart beats came back to normal levels. İndomethacin 3*25 mg was begun as a first treatment. Biochemical analysis of fluid show exudative pericardial effusion. Although there was not any proliferation of mycobacterium tuberculosis on culture, adenosine deaminase (ADA) level found as 59.4 u/l. Biochemical analysis of pericardial fluids also show higher levels of cholesterol (total cholesterol: 189 mg/dl; normal range:<60 mg/dl) Thyroid function test showed deep hypothroidism. Serum free T4was lower than 0.30 ng/dl (normal range:0.8-2.0 ng/dl), and TSH was 0.693 IU/ml (normal range:0.3-4.5 IU/ml). On anamnesis, patient also described menstrual irregularity for 2 years. LH and FSH levels also checked

for hypophyseal insuffiency. Serum LH was 0.562 mIU/ml and FSH was 0.882 mIU/ml; both was decreased (normal ranges for LH:1.1-14.7 and FSH:1.2-9 mIU/ml). Cranial MRI showed partial empty sella with thinning of hypopyhsis. Hypothyroidism tought to had developed secondary to hypophyseal insufficiency. Thyroxine was begun for hypothyroidism. 24 hours later, patient dicharged from hospital with a treatment of 4 agent-combination antituberculous, tyroxine and indomethacine. 7-day control echocardiography showed minimal pericardial effusion.

3. DISCUSSION

Massive pericardial effusions most commonly associated with neoplastic diseases, tbc, renal failure and myxedema. Up to one-third of patients with asymptomatic large pericardial effusions develop unexpected cardiac tamponate (2) . Tbc induced pericardial effusions mostly seen in developing countries and immune-compromised patient. Progression to tamponade can be seen up to two-third of patient and mortality approaches 85 % without treatment. Tbc pericarditis and pericardial effusions may be seen in 1-8 % of pulmonary tbc cases (3). Exact diagnosis of tuberculous pericarditis can be made with identification of mycobacterium tuberculosis from the pericardial tissue or fluid cultures or histopathologic demonstration of granulomas or acid-fast bacilli in the pericardial tissue. It is difficult to isolate mycobacterium species from pericardial fluid samples and only one-third of them are diagnostic. ADA is a white blood cell-mediated enzyme and increases of its level in the pericardial fluid enhance the diagnostic accuracy. In a prospective study, it was reported that ADA levels higher than 40 U/l had a sensitivity of 93%, and specificity of 97% for the diagnosis of tbc (3). If ADA levels are found to be higher than 70 u/l, tbc diagnosis can be made with 100 % sensitivity and 97 % specificity. Therefore, in case of any suspicion, pericardial fluid levels of ADA must be determined. In our case, fluid culture result was negative. Tbc diagnosis made according to higher ADA level. It was 59.4 u/l which prominently higher than cut-off level.

In hypothyroidism, large effusions can occur in 5-30 % of patient. But, proggression to tamponade occurs rarely (4). Fluids accumulates slowly and also with treatment effusions decreases in a longer time period. Mechanism for accumulation of pericardial fluids proposed as increased capillary permeability and subsequent leakage of fluid high in protein into the interstitial space, impaired lymphatic drainage, and a greater retention of salt and water (5). Cholesterol levels are typically higher in the hypothyroidism induced pericardial effusion fluids. Higher cholesterol level in the aspirated fluids also indicate the role of hypothroidism in presented patient.

In our case, hypothyroidism seem to be first triggering factor for development of pericardial effusion. Patients complaint date back to 2 years ago. İt indicate that patient had undiagnosed hypothyroidism up to 2 years. Such a time period is sufficient for slow proggression of massive pericardial effusion. Most probably advancement of tbc turned up the clinical picture to tamponade suddenly.

4. CONCLUSION

Myxedema can cause pericardial effusions up to 30% of patients. Although cardiac tamponade is a rare condition, with occurance of comorbid diseases, such as tbc; tamponade can ocur in a rapid manner. Mortality rate is higher in such concominant etiology induced pericardial tamponade. İmmediate pericardiocentesis save up the patient life and longer and close follow up of patient can prevent reoccurance of pericarial effusions and tamponade.

Acknowledgement:

The authors do not report any conflict of interest regarding this manuscript.

REFERENCES:

1. Cornily JC, Pennec PY, Castellant P, Bezon E, Le Gal G, Gilard M et al. Cardiac tamponade in medical patients: a 10-year follow-up survey. Cardiology. 2008;111:197-201.
2. Maisch B, Soler JS, Hatle L, Ristic AD. Pericardial diseases. In: Camm AJ, Lüscher TF, Serruys PW, editors. The ESC textbook of cardiovascular medicine. Sophia antipolis: blackwell publishing; 2006. p.517-33.
3. Avşar A, Günay NK, Celik A, Melek M. A case of cardiac tamponade caused by tuberculous pericarditis. Turk Kardiyol Dern Ars. 2008 Oct;36:482-4.
4. Akdemir R, Karasu BB, Balcı MM, Özbek M, Aksoy M, Akdemir N. Cardiac Tamponade, as Initial Manifestation of Empty Sella Syndrome: Case Report. Turkiye Klinikleri J Cardiovasc Sci 2008;20:206-9.
5. Lin CT, Liu CJ, Lin TK, Chen CW, Chen BC, Lin CL. Myxedema associated with cardiac tamponade. Jpn Heart J. 2003 May;44:447-50.

CASE REPORT

Succcessful Laparoscopic Treatment of Cholecystoduodenal Fistula

Azra Latic[1], Ferid Latic[2], Mirela Delibegovic[3], Josip Samardzic[2], Darko Kraljik[2], Samir Delibegovic[4].
Department of radiology, County hospital Slavonski Brod[1], Department of surgery, County hospital Slavonski Brod, Croatia[2], Department of radiology, University Clinic Center Tuzla[3], Department of surgery, University Clinic Center Tuzla, Bosnia and Herzegovina[4]

Background: Cholecystoduodenal fistula (CD) is a rare complication of gallstone disease. Laparoscopic stapling techniques have been reported as feasible methods for treating this fistula, however these procedures are not always performed successfully. We have reported five cases of CD diagnosed intraoperatively, managed successfully by laparoscopic approach. Materials and methods During the 3-year period, from 2007 to 2009, 1500 patients underwent LC for gallstone desease, five of them (3.3%), who presented with classic symptoms of symptomatic chole-lithiasis, intraoperatively CD were found. Data were collected on patients' age, sex, pre-operative diagnoses, operative methods, morbidity and management. Laparoscopic surgery was performed using the standard three trocars technique. Results All patients were females, 67 years old on average. They had gallstones detected by abdo-minal ultrasound, but CD's were found during operative treatment of gallstones. In three cases CD was completely mobilized with a combination of blunt and sharp dissection and divided using the endoscopic linear stapling device. In the other two cases after division of the cystic duct and artery the gallbladder was dissected from the liver bed, leaving just the fistulous connection to the duodenum. Then division of the fistula was completed using the same stapling device. All five patients had uneventful postoperative course. The hospital stay of five patients ranged from 5 do 10 days (median 6 days). Conclusion CD does not preclude a laparoscopic approach. With more experience and improved techniques, most of these cases could be performed laparoscopically, with all of the advan-tages of minimally invasive surgery. Key words: Cholecystoduodenal fistula, laparoscopic treatment.

Corresponding author: Azra Latic, MD. Department of radiology, County hospital Slavonski brod, Croatia.
E-mail: delibegovic.samir@gmail.com

1. INTRODUCTION

Enterobiliary fistulae are a rare complication of biliary tract disease. Cholecystoduodenal fistulae (CD) are most frequently encountered, comprising 75-80% of all such fistulae (1). In 90% of cases CD is a complication of gallstone disease, but it can be related to peptic ulcer or neoplasia (2). The symptoms of CD are nonspecific, and often resemble those due to sympto-matic cholelithiasis, unless a gallstone ileus is encountered. Laparoscopic stapling techniques have been reported as feasible and safe methods for treating this fistula (2,3). However, these procedures are not always performed successfully. We have reported five cases of CD diagnosed intraoperatively, managed successfully by laparoscopic approach due to experienced laparoscopic surgeons.

2. MATERIALS AND METHODS

From January 2007 to December 2009, 1500 patients underwent LC for gallstone desease at the Department of surgery, County hospital Slavonski Brod, Croatia. Five (0,1%) of them, who presented with classic symptoms of symptomatic cholelithiasis, intraoperatively CD were found. CD was defined as an abnormal communication between gallbladder and duodenum. This study retrospectively reviewed the medical records of these five patients. Data were collected on patients' age, sex, preoperative diagnoses, operative methods, morbidity and management.

Surgery was performed under general anesthesia using the standard three trocars technique.

In one patient ultrasound revealed dilated intrahepatic and extrahepatic ducts with gallbladder calculi. She also had elevated hepatic transaminases. She underwent a laparoscopy and a chole-cystoduodenal fistula was revealed. The closure of the fistula was performed with the use of an endoscopic linear stapling device (ELC 35, blue firing, ETHICON), but because of the unclear anatomy in Calot's triangle and a very dilated common bile duct (CBD) it had to be converted to laparot-

omy. Exploration of CBD showed a large stone which was extracted and cholecystectomy was performed. The postoperative course was uneventful and a normal T-tube cholangiogram was demonstrated on postoperative day 10.

In the other four patients, ultrasound revealed contracted gallbladder with stones. In each case laboratory findings were normal. Laparoscopy revealed a cholecystoduodenal fistula in each case. In two cases, cholecystoduodenal fistula was completely mobilized with a combination of blunt and sharp dissection. The fistula was divided using the endoscopic linear stapling device (Figure 1). After fistula occlusion the cholecystectomy was completed in the usual manner.

In the other two cases after division of the cystic duct and artery the gallbladder was dissected from the liver bed, leaving just the fistulous connection to the duodenum (Figure 2). The division of the fistula was then completed using the same stapling device.

3. RESULTS

All patients were females, 67 years old on average. They had gallstones detected by abdo-minal ultrasound, and one petient had dilated intrahepatic and extrahepatic ducts with gallstones. CD was found during operative treatment of gallstones. In three cases CD was completely mobilized with a combination of blunt and sharp dissection and divided using the endoscopic linear stapling device. After that, laparoscopic cholecystectomy was performed. In the other two cases after division of the cystic duct and artery the gallbladder was dissected from the liver bed, leaving just the fistulous connection to the duodenum. The division of the fistula was then completed using the same stapling device.

None of the patients needed to be converted to open cholecystectomy and all five patients had uneventful postoperative course. The hospital stay of five patients ranged from 5 do 10 days (median 6 days), length of follow up was 6 months.

4. DISCUSSION

The development of a fisulous tract from gallbladder is associated with gallstones in 90% of cases (4). As seen in this study, patients with CD are commonly presented with signs and symptoms of chronic cholecystitis. There were no specific symptoms which suggested CD and each fistula was diagnosed intraoperatively. Preoperative findings such as pneumobilia can be suggestive of internal biliary fistula (5), but we had no this sign. ERCP and MRCP are reliable diagnostic tools to clearly demonstrate the abnormal communication (4), but it was possible to use only US. That is the reason why we diagnosed CDs exclusevely intra-operatively.

Treatment advocated for CD is cholecystectomy and closure of fistula communication (4,6). Prompt recognition is crucial in the treatment of these cases along with meticulous prepa-ration of the fistula site. Laparoscopic suturing is time-consuming and can not secure fistula closure (4). For the fistula repair, the linear stapling device appears to be an useful instrument (1,7). If it is feasible to perform the cholecystectomy first, then the exposure and repair of the fistula is easier and safer. After careful dissection, the occlusion of the fistula can be performed first, enabling easier cholecystectomy.

CD does not preclude a laparoscopic approach. With more experience and improved techniques, most of these cases could be performed laparoscopically, with all of the advan-tages that minimally invasive surgery offers.

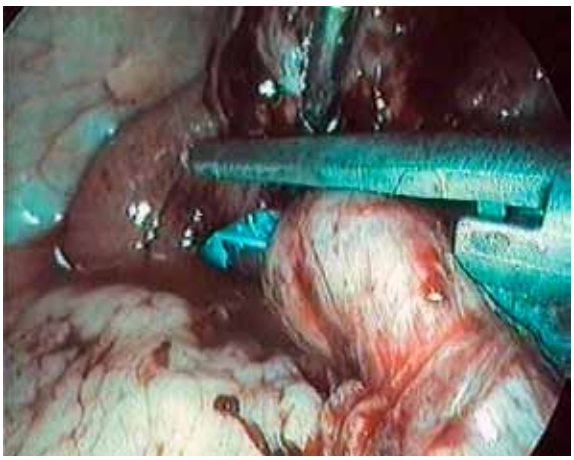


Figure 1. The cholecystoduodenal fistula was mobilized and divided using the endoscopic linear stapling device.

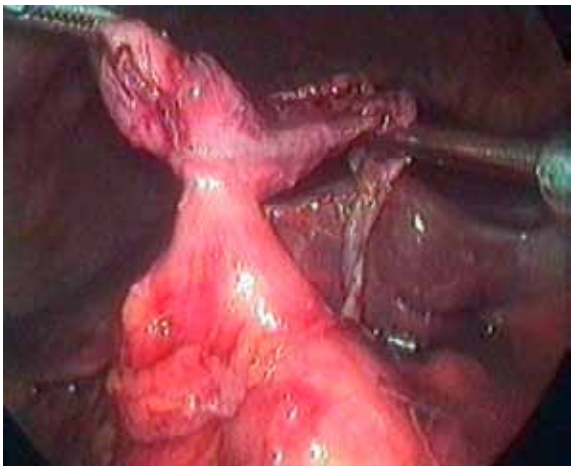
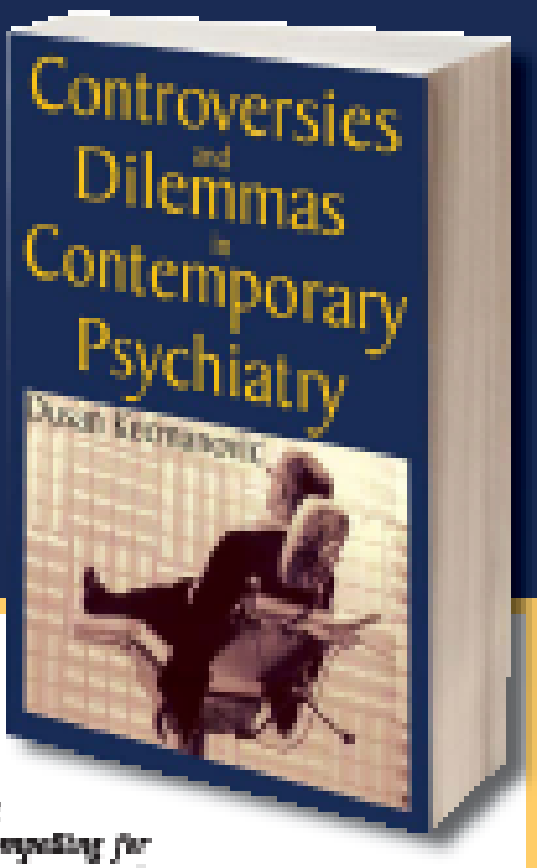


Figure 2. The fistulous connection of gallbladder with the duodenum.

REFERENCES

1. Sharma A, Sullivan M, English H, Foley R. Laparoscopic repair of cholecystoduodenal fistulae. Surg Laparosc Endosc,1994;4:433-5.
2. Gentileschi P, Forlini A, Rossi P, Zoffoli M, Gentileschi E. Laparoscopic approach to cholecystocolic fistula: report of a case. J Laparoendosc Surg, 1995;5:413-7.
3. Ibrahim M, Wolodiger F, Saber AA, Dennery B. Treatment of cholecystocolic fistula by laparoscopy. Surg Endosc, 1995; 9:728-9.
4. Wang WK, Yeh CN, Jan YY. Successful laparoscopic management for cholecystoenteric fistula. World J Gastroenterol, 2006;7:772-5.
5. Macintyre IM, Wilson RG. Laparoscopic cholecystectomy. Br J Surg, 1993;80:552-9.
6. Correria MFS, Amonkar DP, Nayak SV, Menezes JLAS. Cholecystocolic fistula. A diagnostic engma. The Saudi Journal of Gastroenterology, 2009;15:42-4.
7. Angrisani L, Corcione F, Tartaglia A, Tricarico A, Rendano F, Vincenti R et al. Cholecys-toenteric fistula (CF) is not a contraindication for laparoscopic surgery. Surg Endosc, 2001;15:1038-41.

Controversies and Dilemmas in Contemporary Psychiatry



"Always an erudite and clear thinker, Professor Kecmanovic with this book addresses the most difficult issue in psychiatry."

—Professor Norman Sartorius, M.D., Geneva University, formerly the president of the World Psychiatric Association

"Professor Kecmanovic confronts and explains the fundamental controversies in psychiatry in a manner that is engaging and compelling for professionals and lay readers. . . His approach is honest, realistic and constructive."

—Professor Derrick Silove, M.D., University of NSW, Sydney

Learning about the origin, nature and effects of the psychiatric controversies and dilemmas is beneficial for several reasons. First, it is of help to psychiatrists since a great many of them are unaware of how many controversies and dilemmas are contained in their day-to-day practice or else, fearing that they will undermine psychiatry's reputation, they minimize them in defense. Second, it is beneficial to those who are interested in psychiatry for whatever reason, enabling them to gain insight into important aspects of psychiatric theory and practice. Third, it shows that the contradictions and dilemmas in contemporary psychiatry are not the dark side of psychiatry. They are both the dark and the bright side of psychiatry, just the same as other laws contentions in one related to psychiatry. Kecmanovic undertakes a major effort of showing which contradictions might be resolved and which are there to stay or they are embedded in mental disorder.

ISBN: 978-1-4128-1460-7 (cloth) 278 pp. $49.95/£44.95/$C59.95

Dusan Kecmanovic is former professor of psychiatry and political psychology at Sarajevo University, and now is a private psychiatrist in Sydney, Australia. He has written numerous pieces in the fields of social psychiatry, social pathology, and the psychology of ethnonationalism. He is the author of *Ethnic Times: Exploring Ethnonationalism in the Former Yugoslavia* and *The Mass Psychology of Ethnonationalism*.

TRANSACTION PUBLISHERS

OSTEOPOROZA

Kako se život može promijeniti u 6 mjeseci?

Actonel®
(risedronat natrij)

- smanjen rizik od prijeloma kičme
- smanjen rizik od prijeloma kuka
- dobra gastrointestinalna podnošljivost

sanofi aventis
Jer zdravlje je najvažnije

Detaljnije informacije zatražite od:
sanofi-aventis groupe
Predstavništvo u BiH
Fra Anđela Zvizdovića 1/8
71 000 Sarajevo, BiH
Tel: 033-295-519; Fax: 033-270-030

BA-RIS.09.06.02

Pravi izbor, zadatak izvršen!

Pobijedimo infekcije:

- disajnih puteva
- urinarnog trakta
- kože i mekih tkiva