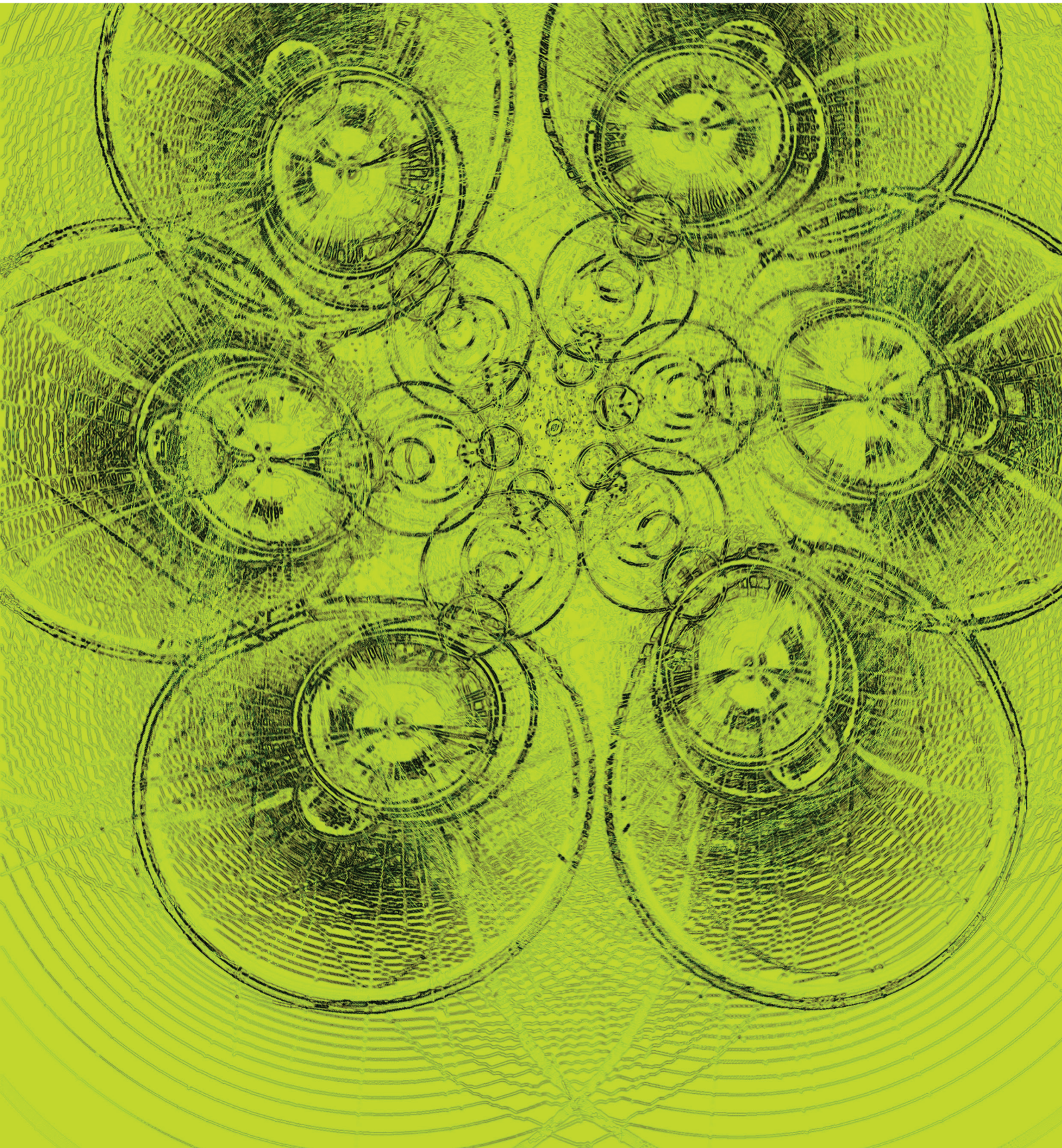
Volume 9 / Number 3 / 2015 ISSN 1840-2291

HealthMED

Journal of Society for development in new net environment in B&H



Volume 9 / Number 3 / 2015

HealthMED

Journal of Society for development in new net environment in B&H

Address Bolnicka bb, 71 000 Sarajevo,
Bosnia and Herzegovina.
Editorial Board e-mail: healthmedjournal@gmail.com web page: http://www.healthmed.ba
Published by DRUNPP, Sarajevo
Volume 9 Number 3, 2015
ISSN 1840-2291 e-ISSN 1986-8103

HealthMED journal is indexed in:

- EBSCO Academic Search Complete
- EBSCO Academic Search Premier,
- EMBASE,
- SJR Scopus,
- Index Copernicus,
- Universal Impact Factor: Impact Factor is 1.0312 (UIF 2012)
- Electronic Social and Science Citation Index (ESSCI),
- Direct Science,
- ISI - institute of science index,
- SCImago Journal and Country Rank,
- ISC Master Journal List,
- Genamics Journal Seek,
- World Cat,
- Research Gate,
- CIRRIE,
- getCITED and etc.

Sadržaj / Table of Contents

Therapeutic management of Visceral Leishmaniasis in children: a systematic review 87
Claudio Gleidiston Lima da Silva, Ana Carolina Lima Pinheiro Sobreira, Filipe Bezerra Macedo, Antonio Gilvan Teixeira Junior, Victor Hugo Goncalves Lopes, Maria do Socorro Vieira dos Santos, Modesto Leite Rolim-Neto, Bianca Bianco

Serum Calcium, Magnesium and Iron Levels and Their Relation to Bone Mineral Density in Postmenopausal Women from Kosovo 100
Elton Bahtiri, Hilmi Islami, Rexhep Hoxha, Hasime Qorraj-Bytyqi

Application of p-value from statistical normality tests in RR intervals for short recordings 106
Vitor E. Valenti, Marco A. Cardoso, Letícia S. de Oliveira, Patricia S. G. Moreira, Joice A. T. Amaral, Celso Ferreira, Rodrigo D. Raimundo, Rayana L. Gomes, Luiz Carlos de Abreu

Evaluation of the competence of residents at department of anesthesiology in the assesment of difficult airways and in the recognition and use of difficult airway devices 114
Elmas Kara, Ismail Aydin Erden, Banu Ayhan, Sennur Uzun, Ulku Aypar

Depression and physical disability, their influence in quality of life in patients with multiple sclerosis - which factor has greater influence? 120
Nexhat Shatri, Nazim Dakaj, Petrit Bara, Kamber Zeqiraj

Intubation with flexible bronchoscope and surgical resection of a post-tracheostomy stenosis 127
Amina Selimovi[c], Walter Klepetko, Thomas Schweiger, Konrad Hoetzenecker, Ermina Mujicic, Senka Mesihovic Dinarevic, Safet Guska, Alen Pilav, Amir Rekic, Hilmi Kacamakovic, Mahir Moro, Azra Kudumovic, Mensura Kudumovic, Ahmed Katica

Impact of Inhaled Corticosteroids on Emergency Department visits and hospitalization Rates of Children with Persistent Asthma 131
Fatemeh Behmanesh, Sepideh Bagheri, Fatemeh Ghane Sharbaf, Farid Reza Edjlali, Mohammad Hadi Fooladi

Instructions for the authors 134

Therapeutic management of *Visceral Leishmaniasis* in children: a systematic review

Claudio Gleidiston Lima da Silva[1,2], Ana Carolina Lima Pinheiro Sobreira[1], Filipe Bezerra Macedo[1], Antonio Gilvan Teixeira Junior[1,3], Victor Hugo Goncalves Lopes[1,3], Maria do Socorro Vieira dos Santos[1,2], Modesto Leite Rolim-Neto[1], Bianca Bianco[2]

[1] Faculty of Medicine, Federal University of Cariri, Barbalha, Ceara, Brazil,
[2] Faculty of Medicine of ABC, Santo Andre, Sao Paulo, Brazil,
[3] Institutional Program for Scientific Initiation (PIBIC) / National Council for Scientific and Technological Development (CNPq) fellow at Faculty of Medicine, Federal University of Cariri, Barbalha, Ceara, Brazil.

Abstract

The Visceral Leishmaniasis (VL) is a public health problem present in several regions of the world. We aim to relate the main drugs used for the VL treatment in children, as well as knowing its adverse effects. With regard to the treatment regimen, the use of more than one drug for this disease treatment is a subject not discussed, because this therapy appears to be effective for curing without generating resistance to treatment.

Key words: Visceral Leishmaniasis; Children, Treatment; Safety; effectiveness.

Introduction

Visceral leishmaniasis (VL) is a systemic infection caused by an intracellular protozoan belonging to the *Leishmania donovani* complex: *Leishmania donovani, L. infantum, and L. chagasi* (1) that manifests with irregular bouts of fever, substantial weight loss, hepatosplenomegaly, pancytopenia, and increased susceptibility to bacterial infection (2). It's transmitted by an insect vector, the *Phlebotomus sandfly* (3). It is endemic in 62 countries (4)**,** with an estimated 500,000 new cases occurring every year world-wide (5)**.** Visceral leishmaniasis (kala-azar) affects large, rural, resource-poor populations in South Asia, Africa, and Brazil (6). India, Bangladesh and Nepal (Asia), Sudan (Africa) and Brazil (Americas), are responsible for about 90% of cases reported in the world (7).

It is considered an underreported disease, and some studies have demonstrated a high frequency of relapses during follow-up (8). With effective drug treatment, clinical cure is relatively rapidly obtained, suppressing (but not eliminating) the parasite load to undetectable levels. However, some VL patients relapse with clinical VL, usually months after the end of treatment. HIV infections increase the risk of developing VL by 100- to 2,320- fold in endemic areas. This relapse is common in HIV co-infected patients but also occurs in immunocompetent individuals (9).

Early diagnosis and treatment is one of the major pillars of the ongoing elimination programme (10). Pentavalent antimonials are the most common treatment worldwide (11). VL treatment options in East Africa are primarily limited to the antimonial sodium stibogluconate, which is efficacious, but requires 4 weeks of hospitalization for daily intramuscular injections and has been associated with serious adverse events such as cardiotoxicity (12). Liposomal amphotericine B appears to be an effective therapy for VL in children and could be used as a first line treatment (13). Visceral leishmaniasis is a major public health problem in Bihar, accounting for 90% of all cases in India, where about 100,000-300,000 new cases occur every year (14). Pentavalent antimonials are now ineffective because of the development resistance (11). Miltefosine, the only oral drug for visceral leishmaniasis, is currently the first-line therapy in the VL elimination program of the Indian subcontinent (15).

American visceral leishmaniasis is a major health problem in many parts of Brazil (4). In Brazil, during the past 10 years, an average of 3600 new cases per year of VL were registered, and the children younger than 10 years were more frequently affected, representing 48.9% of the cohort (16). The World Health Organization Expert Com-

mittee recommended that meglumine antimoniate (Glucantime) be administered in doses of 20 mg/kg per day up to a maximum of 850 mg for 28–30 days (5). The effectiveness of the medication in the first course of treatment was 93.2%. The patients were retreated with amphotericin B, with good clinical response (7). Given this global context, we aim to answer the question: are the major drugs used for treatment of visceral leishmaniasis in children truly effective and lead to the cure of patients? This study is a systematic review of articles published in the last ten years on the subject.

Methods

A qualitative systematic review of articles on treatment of visceral leishmaniasis in children, published in the database of the SCOPUS (Elsevier) online data and was limited to articles published from July 1, 2004 to July 31, 2014 order was made to set a parameter to limit the age range covered by this review, the definition of "child" used in this study was in accordance with the limits set by the organization of the United Nations (UN), where a child means every human being below the age of 18, unless under the law applicable to him, reaches maturity earlier (17). Therefore in accordance with the Statute of Children and Adolescents (Law No. 8069 from July 13, 1990) of Brazil, it is considered child as a person until 12 years old (18), which was the limit used in this review. The choice for this age group was due to the fact that children, along with the elderly are the most susceptible individuals develop visceral leishmaniasis, as well as progress to complications and death. Over the past decade, despite intensive care resources and routines established for the specific treatment of VL, there was an increase in the lethality of the disease in different regions of Brazil. The mortality rate increased from 3.4% in 1994 to 5.7% in 2009, representing an increase of 67.6%. Observed for Brazil, in the years 2001 to 2008, the fatality rate primarily affects patients with lower age of 1 year old and 50 or more years of age (19). Early identification of patients susceptible to higher risk of death is a great important factor to initiation of therapy and implementation of protective measures to reduce the lethality of the disease.

Initially, the search terms used in the database SCOPUS data were:

1. "Child" (term Medical Subject Headings [MeSH],
2. "Treatment" (keyword);
3. "Visceral Leishmaniasis" (keyword).

The analysis of articles followed a predetermined eligibility criteria. We adopt the following inclusion criteria:

1. The articles that included in the title a combination of the terms described in the search strategy (1 AND 2 AND 3);
2. Articles written in Portuguese, English or Spanish;
3. Studies on the treatment of visceral leishmaniasis in pediatric patients;
4. Original articles with full text available on-line available at CAPES (Coordination Agency for Higher Education), a virtual library linked to the Ministry of Education of Brazil and submitted to content subscription.

The exclusion criteria were: (1) reports, case series, literature review and comments; (2) The non-original studies, including editorials, prefaces, short communications and letters to the editor.

Results

Initially, 312 articles were found in the SCOPUS database using search strategies described above. After reading the titles of the articles and their abstracts and selected application of eligibility criteria, 227 articles were excluded and 85 articles were reviewed in detail, and then excluded 45 articles, resulting in a final sample of 40 articles (Figure 1).

Table 1 provides an overview of all studies included in the final sample and of all data elements used during the data analysis process. The 40 studies were distributed into the previously determined three categories as follows: MAJOR DRUGS [3, 5, 6, 9, 10, 12, 14, 15, 16, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 (32 studies)]; DRUGS INTERACTIONS [6, 11, 12, 42, 43 (5 studies)] and ADVERSE EVENTS [6, 10, 11, 12, 14, 23, 29, 30, 36, 44, 45, 46 (12 studies)]. Among the 40 studies, some studies were referenced in more than one category. The categorization of studies aims to a better organizational quality systematic review and it is not compulsory that each article must be referenced only in their respective category.

Table 1. Studies and main findings

Author and Year	Journal	Sample	Main findings
Nateghian et al. (2011)[29]	Iran J Clinic Infect Dis	58 cases with final diagnosis of VL,2months to 12 years who were discharged from Ali Asghar children hospital from 1976 to 2010	Glucantime still has good effect for VL in Iran and it's lower doses might also be effective for treatment although follow up studies are needed.
Sundar et al. (2011)[11]	Lancet	634 patients between 5 and 60 years (26.9% of patients aged 5 to 18 years)	Combination treatments for visceral leishmaniasis are efficacious and safe, and decrease the duration of therapy, thereby encouraging adherence and reducing emergence of drug-resistant parasites.
Sinha et al. (2011)[40]	J Trop Med	phase 4 study with 506 adult and pediatric patients	This study confirms the safety and efficacy of paromomycin to treat VL in an outpatient setting
Kajaia et al. (2011) [28]	Trop Med Int Health	300 cases of visceral leishmaniasis in Georgia between 2002 and 2004 (73.3% of children under 5 years)	Factors significantly associated with VL relapse were delay in diagnosis for >90 days and age <1 year . Physician and public education is needed to reduce delays in diagnosis. Prolonging treatment for 30 days or implementing new regimens may reduce the number of relapses.
Sinha et al. (2010)[37]	Am J Trop Med Hyg	251 patients in Bihar, India (54.18% patients under 16 years)	The 20 mg/kg body weight treatment dosage is effective and safe under routine program conditions. Given that the exorbitant cost of liposomal amphotericin B is a barrier to its widespread use, we recommend further study to monitor and evaluate a lowered dosage and a shorter treatment course.
Hailu et al. (2010)[42]	PLoS Negl Trop Dis	135 patients per arm, to compare three treatment regimens for VL in East Africa: paromomycin sulphate at 15 mg/kg/day for 21 days versus sodium stibogluconate at 20 mg/kg/day for 30 days; and the combination of both dose regimens for 17 day	The efficacy of PM at 15 mg/kg/day for 21 days was inadequate, particularly in Sudan. The efficacy of higher doses and the combination treatment warrant further studies.
Petrela et al. (2010)[20]	PLoS Negl Trop Dis	1,210 children age range 0–14 years, with a median of 4 years	Despite recent reports on decreased responses to antimonial drugs of patients with Mediterranean VL, meglumine antimoniate treatment appears to be still highly effective in Albania
Sundar et al. (2010)[32]	N Engl J Med	412 patients in a 3: 1 ratio to receive either liposomal amphotericin B or amphotericin B deoxycholate	A single infusion of liposomal amphotericin B was not inferior to and was less expensive than conventional therapy with amphotericin B deoxycholate.
Brustoloni et al. (2010)[27]	Infection	A total of 116 children were treated for Visceral Leishmaniasis	Antimoniate ofN-methylglucamine remains highly efficient and well tolerated in pediatric patients, which allows its utilization as a first-line therapy in Brazilian children until a better drug for widespread use becomes available

Zanoni et al. (2009)[45]	Biol Trace Elem Res	Weekly ECGs analysis of 87 children treated with antimoniate N-methyl glucamine	In total, ECG abnormalities were detected in 34.4% of treatment courses, while in adults they were reported in 53.8%. Antimony therapy needs ECG monitoring of the cardiac function in order to prevent complications.
Mueller et al. (2009)[46]	Trop Med Int Health	3483 clinically suspect patients, 53% were confirmed with primary VL. Sixty-two per cent were children <16 years.	Subgroups of VL patients at higher risk of death during treatment with drugs currently available in Uganda were identified. Less toxic drugs should be evaluated and used in these patients.
Sundar et al. (2009)[41]	Clin Infect Dis	assess the efficacy and safety of 2 regimens of paromomycin administered intramuscularly. Group A received 11 mg/kg/day for 14 days (n=217) and group B received 11 mg/kg/day for 21 days (n=112) for the treatment of VL in India	Although the cure rate in the group of patients who received the 14-day regimen was not optimal, the results with respect to initial cure were encouraging. Further studies that combine a short course of paromomycin with treatment with another antileishmanial agent are warranted
Arık Yılmaz et al. (2009)[22]	Turkiye Parazitol Derg	13 children with Visceral leishmaniasis	All the children were finally cured. Meglumine antimonate still seems to be the first choice inthe treatment of pediatric VL in Turkey
Canatan et al. (2009)[23]	J Pediatr Inf	22 children with visceral leishmaniasis	The findings highlight liposomal amphotericin B as an effective therapy for visceral leishmaniasis in children. Early detection and appropriate management of complications may reduce morbidity and mortality in childhood visceral leishmaniasis.
Xavier-Gomes et al. (2009)[26]	Rev bras epidemiol	51 children with Visceral Leishmaniasis	Suggest a more effective monitoring by health professionals, aiming at early recognition and proper treatment of the disease and its complications.
Rey et al. (2005)[25]	J Pediatr	450 children with American visceral leishmaniasis	Cases of American visceral leishmaniasis spiked with a 5-year interval, and affected most under-five urban children. Mortality was related to low age, signs of severe disease and concomitant infection.
Sundar et al. (2006)[31]	Clin Infect Dis	Evaluated the efficacy and safety of a 6-day course of Amphotericin B colloidal dispersion in 3 different dose groups, each of which included a cohort of 135 patients.	Although the cost of ABCD is prohibitive, the high level of efficacy associated with short-term treatment with low-dose ABCD provides another alternative for the treatment of VL, especially in regions where VL is antimony refractory
Caldas et al. (2006)[24]	Acta Trop	23 patients with American visceral leishmaniasis (VL), comparing clinical and laboratory parameters of 14 children to nine adults	Difference in clinical or laboratory parameters between children and adults did not indicate the need for different clinical or therapeutic approaches
Singh et al. (2006)[39]	Indian J Pediatr	125 children randomized into four groups. Group 1 and 2 receive Miltefosine and Group 3 and 4 receive Amphotericin B	Miltefosine is safe , well tolerable, and highly effective and has same efficacy as amphotericin B in newly diagnosed and SAG resistant children with Visceral Leishmaniasis

Tanir et al. (2006)[21]	Pediatr Int	records of 19 children with VL were retrospectively reviewed	Lipid formulations of amphotericin B may be useful in cases of treatment failure with antimonials or signifi cant adverse effects of the drug.
Sinha et al. (2006)[33]	J Infect	737 patients with visceral leishmaniasis (VL)	The increasing unresponsiveness of VL patients to conventional anti-leishmanial drugs, e.g. sodium antimony gluconate (SAG) and pentamidine, has definitely posed a major therapeutic challenge in combating the disease. Amphotericin B, though costly, is highly effective. Miltefosine is a highly promising new oral drug for VL.
Rocha et al. (2013)[16]	Pediatr Infect Dis J	432 patients, the pediatric population comprised 44.7% of the total and 29,1% younger than 2 years.	Patients were treated with intravenous injections of pentavalent antimonial (glucantime), unless clinical indications for amphotericin use was present. In cases of treatment failure, patients received amphotericin B. Acute kidney injury is prevalent in both groups. In the pediatric population, the presence of secondary infections, such as pneumonia, was found to be an independent risk factor for acute kidney injury.
Apa et al. (2013)[43]	Turk J Pediatr	17 cases of visceral leishmaniasis admitted to Behçet Uz Children's	While pentavalent antimony salts were found to increase biochemical and hematological findings, liposomal amphotericin B was responsible for rapid recovery in fever and shorter hospital stay. The study shows the advantages of both medications independent of their costs.
Dorlo et al. (2012)[38]	Antimicrob Agents Chemother	Indian children, Indian adults, and European adults. Linear and allometric scaling of PK parameters by either body weight or fat-free mass was evaluated for body size models. Based on the developed PK model, a dosing algorithm for miltefosine in children and adults was proposed and evaluated	The use of a new allometric dosing algorithm for miltefosine in VL patients results in optimal exposure to miltefosine in both adults and children and might improve clinical outcome in children
Musa et al. (2012)[12]	PLoS Negl Trop Dis	359 patients per arm. More than 65% of patients were under the age of 18 years.	The 17 day SSG & PM combination treatment had a good safety profile and was similar in efficacy to the standard 30 day SSG treatment, suggesting suitability for VL treatment in East Africa.
Uranw et al. (2013)[10]	Trop Med Int Health	171 patients	Patient adherence to miltefosine was 83%. Gastrointestinal side effects and negligence after the resolution of clinical symptoms of VL were the main reasons for poor adherence. Poor adherence was associated (though not statistically significant) with future relapse.

Rijal et al. (2013)[15]	Clin Infect Dis	120 VL patients treated with MIL in Nepal.	The initial cure rate was 95.8% and the relapse rate at 6 and 12 months was 10.8% and 20.0%, respectively. No significant clinical risk factors of relapse apart from age <12 years were found. Although more tolerant strains were observed, parasite resistance, as currently measured, is thus not likely involved in MIL treatment failure.
Verma et al. (2013)[44]	Biomed Res Int	Pediatric VL patients aged between 2 and 14. Altogether, 40 subjects were selected.	Amphotericin B nephrotoxicity in children is a known complication. Glomerular involvement is the main renal injury in pediatric VL patients. The eGFR, MA, and microscopic examination maybe helpful in prediction of early renal damage.
Mondal et al. (2014)[36]	Lancet Glob Health	300 participants, with 175 children aged < 18 years.	treatment of visceral leishmaniasis with singledose liposomal amphotericin B in a rural hospital in Bangladesh was feasible, acceptable, safe, and effi cacious. The present recommendation of WHO for its use as a fi rst-line drug for visceral leishmaniasis in southeast Asia is supported by these results.
Ostyn et al. (2014)[9]	PLoS One	1016 patients	Young age and male gender were associated with increased risk of VL relapse after miltefosine. The observed decrease in efficacy of miltefosine may be explained by the inclusion of younger patients compared to the earlier clinical trials, rather than by a decreased susceptibility of the parasite to miltefosine
Salih et al. (2014)[3]	Trop Med Int Health	382 patients eligible for AmBisome treatment, the median age was 11 years, with 59% children (<15 years).	AmBisome appears to be effective for initial cure of VL and the drug seems safe, but is expensive (400 USD/treatment). Sustained mechanisms to allow improved access of this expensive drug particularly in East Africa are urgently needed
Sundar et al. (2007)[6]	N Engl J Med	667 patients between 5 and 55 years of age who were negative for the human immunodeficiency virus and had parasitologically confirmed visceral leishmaniasis	Paromomycin was shown to be noninferior to amphotericin B (final cure rate, 94.6% vs. 98.8%; difference, 4.2 percentage points; upper bound of the 97.5% confidence interval, 6.9; P<0.001). Mortality rates in the two groups were less than 1%.
Bhattacharya et al. (2007)[14]	J Infect Dis	1132 adult and pediatric patients between 2 and 65 years of age, 428 being under the age of 12 years	The oral administration of miltefosine, a safe and effective treatment shown in previous studies including adults and children, has led to new perspectives in the treatment of kala azar. This study supports the use of miltefosine in an outpatient setting in an area where VL is endemic

Mueller et al. (2008)[30]	Ann Trop Med Parasitol	210 patients treated with Ambisome and 161 patients treated with Stibogluconate of sodium.	Conventional AmB is an effective and reasonably safe drug for the treatment of VL in Uganda. Liposomal AmB would probably be even better tolerated and a more practical option, reducing the duration of the hospital stay.
Silva et al. (2008)[7]	Rev Soc Bras Med Trop	299 casos autóctones, sendo 83,6% em menores de 9 anos e 54,1% do sexo masculino. Distribuídos em: 10,3% entre 0 e 4 anos; 9,9% entre 5 e 9 anos; 24,3% entre 10 e 19 anos.	O tratamento de escolha foi à base de N-metilglucamina (glucantime), na dose de 20mg/kg/dia, durante 20 dias, em injeção endovenosa ou intramuscular, com percentual de cura de 96,1%. Houve 12 pacientes resistentes ao tratamento, sendo cinco co-infectados com HIV. Estes 12 pacientes foram retratados com anfotericina-B, com boa resposta clínica. A letalidade média foi de 3,7%.
Melaku et al. (2007)[2]	Am J Trop Med Hyg	4,263 patients: zero to five years (21.9%), between 6 and 14 years (24.9%) and above 15 years (53, 1%).	17 days of SSG combined with PM gives better survival and initial cure rates than 30 days of SSG monotherapy.
Albuquerque et al. (2014)[8]	Rev Soc Bras Med Trop	1,779 new patients with VL, 33 of whom were also infected with HIV	The incidence of VL/HIV coinfection increased in 2010. VL and VL/HIV infections have been emerging with increased frequency in Brazil.
Lemos et al. (2007)[4]	Clin Vaccine Immunol	21 patients, ranged from 6 months to 10 years old, were enrolled at Minas Gerais, Brazil.	Data demonstrated the potential of flow cytometry as a tool for noninvasive assessment of the success of visceral leishmaniasis treatment. Treatment of patients was carried out with 1.0 mg/kg of body weight/day of amphotericin B during 14 days, and no parasites were detected in bone marrow aspirate collected after the end of treatment. All patients enrolled were successfully treated and none of them relapsed
Cascio et al. (2004)[35]	J Antimicrob Chemother	A total of 164 HIV-negative children treated with six intravenous doses of 3 mg/kg L-AmB	This study highlights the efficacy (>95%) and safety of the six dose L-AmB regimen and validates it as a first-line treatment for Mediterranean VL in children.
Thakur et al. (2004)[34]	Indian J Med Res	282 patients with Visceral Leishmaniasis. Parasites isolated from patients were tested in vitro to assess their response to sodium antimony gluconate	Antimony resistant strains of L. donovaniwere wide spread over different geographical areas in Bihar. SAG cured lesser percentage of VL cases clinically compared to AMB and should be replaced by AMB as a first line drug

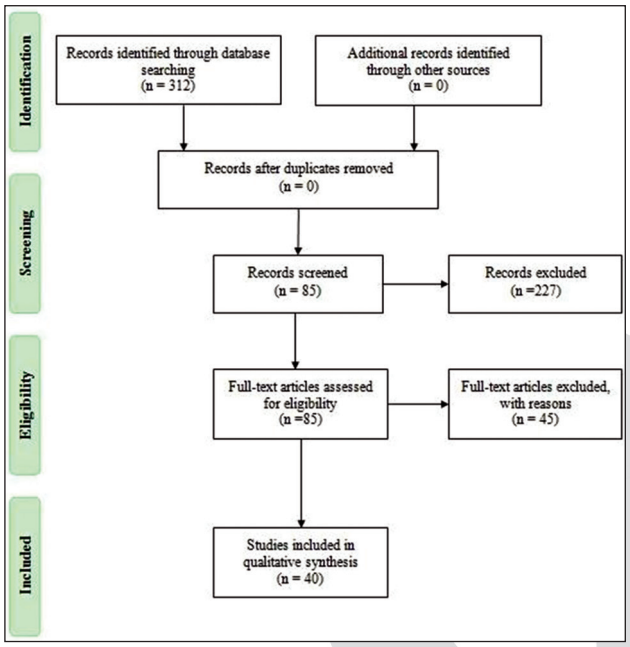


Figure 1. Flow chart showing study selection for the review

Discussion

Major Drugs

Pentavalent antimonials

Sodium stibogluconate and meglumine antimoniate have been standard first-line medicines in most parts of the world (> 90% overall cure rate) (5). A cohort study evaluated the data regarding 1,210 children with Visceral Leishmaniasis in Albania in the 1995–2009 period showed a very high therapeutic efficacy of pentavalent antimony exhibited (99.3% cure rate). Furthermore, it appears that the drug was well tolerated in children. There were no cases of primary unresponsiveness and the relapse rate was low (0.7%) (20). That treatment of VL with antimonials in pediatric patients is a relatively inexpensive (21,22,23) safe and effective treatment with low relapse rates (21, 22, 23, 24, 25, 26, 27). Liposomal amphotericin-B may be useful in cases of treatment failure or relapse with antimonials or significant adverse effects of the drug (22, 16) factors associated with relapse were age <1 year, diagnosis delay >90 days and haemoglobin level <60 g/l (28). Initial treatment of visceral leishmaniasis should be based on a daily injection of 20 mg/kg body weight of Sb5+ (no upper limit of 850 mg). Injections are usually given for 28–30 days (5). However multicentric prospective studies are needed to detect potential resistance to Antimony and the need for changing therapeutic strategies (29).

Amphotericin B

Amphotericin B deoxycholate given daily or on alternate days by intravenous infusion in 5% dextrose for 4h at a dose of 0.75–1.0 mg/kg per day for 15–20 doses was 99% effective (5). The initial cure rates with amphotericin B deoxycolate variate of 92.4% and 96.3% (30, 31, 32, 33). That liposomal amphotericin B was noninferior to amphotericin B deoxycholate (31) and appears as effective and safe as meglumine antimoniate. The relatively good tolerance of Amphotericin B deoxycholate is probably related to the long infusion time, the maintenance of adequate hydration and the supplementation of electrolytes (30). A small amount of hydrocortisone and paracetamol was also given with infusion to ward off phlebitis and infusion related shivering or rigor (34).

The total dose of Lipid formulations of amphotericin B requirements for treatment of visceral leishmaniasis varies by region (5). The efficacy and safety a total dose of 18 mg/kg for 6 days of L-AmB in Mediterranean in children with Visceral Leishmaniasis, is at least as effective as conventional antimonial therapy (35). Liposomal amphotericin B cure rate variate of 96%-98,8% (36, 31, 15) is safe and effective for children and adults (15, 3). Regimens that contain amphotericin B are the most effective therapeutic options available for the treatment of VL in areas where there is widespread resistance to pentavalent antimonials (31) and treatment of complicated VL (3). In developing countries, the high cost of lipid formulations of amphotericin B hampers its use on a large scale (27).

Miltefosine

Miltefosine at a dose of 2.5 mg/kg per day for 28 days to children aged 2–11 years and for people aged 12 years and above at a dose of 50 mg/day for those weighting < 25 kg, 100 mg/day for 25–50 kg body weight (5). Cure rate at 6 months after treatment varies if 82.5% for 93.6% (9, 15, 37, 14). In Nepal adherence to MIL treatment not reached in at least 17% of the enrolled patients. Adherence was better in patients who were informed on treatment duration and side effects compared to tho-

se who were not. Effective counselling is the best way to prevent poor adherence (10). Relapse was two times more common amongst men, and 2 to 3 times more frequent in the age groups below 15 years. The higher relapse rate in children after miltefosine treatment might also have a pharmacological cause (9). In Nepal, we observed relapse in one-fifth of the MIL-treated patients (15). The currently applied dose of 2,5 mg/kg/day results in a substantially lower exposure to miltefosine in children than in adults. We recommend employment of an allometric dosing table for miltefosine in the treatment of VL patients, the use of which results in similar levels of exposure to miltefosine for adults and children and might improve clinical outcome in children (38). In India, Miltefosine was well tolerated, and outpatient treatment in the vast majority of patients was safe (14). Miltefosine was well tolerated, safe and effective in children (14, 39).

Paramomycin

Paromomycin (aminosidine) has been shown to be effective in Indian visceral leishmaniasis (5). Paromomycin (administered intramuscularly at a dose of 11 mg per kilogram daily for 21 days) demonstrated final cure rates 6 months after the end of treatment of 95% (6). Paromomycin was shown to be efficacious when used in an outpatient setting. Paromomycin has a reasonable safety profile, including demonstrated safety and efficacy in pediatric patients(6, 40). The advantages associated with the use of paromomycin are low cost, easy availability, and indigenous production (6, 40, 41).

In some regions in East Africa was shown negative efficacy results of PM monotherapy (cure was only 63.8%) (42) and significantly lower than Stibogluconate of sodium (12, 42). Pharmacological differences in the East African and Indian populations that may explain these results were explored and will be reported separately (12).

Drug Interactions

All combinations were non-inferior to the standard treatment, in both the intention-to-treat and per-protocol populations, and the patients in the combination groups had fewer adverse events than did those assigned standard treatment (11). The conventional treatment of kala-azar consists of pentavalent antimony salts – sodium stibogluconate and meglumine antimoniate. However due to the development of resistance to previous drugs and side effects, amphotericin B deoxycholate and liposomal amphotericin B have been recommended for treatment of VL (43).

The duration of treatment with paromomycin (daily for 21 days) is shorter than with amphotericin (every other day for 30 days), sodium stibogluconate (daily for 30 days), or miltefosine (daily for 28 days), though the visit burden may be higher. Use of concomitant medication was less common in the paromomycin group than in the amphotericin group (6). While pentavalent antimony salts were found to increase biochemical and hematological findings, liposomal amphotericin B was responsible for rapid recovery in fever and shorter hospital stay. As a result, our study shows the advantages of both medications independent of their costs (43)

Sodium stibogluconate and Paromomycin combination treatment, by 17 days, has comparable efficacy and safety profiles to conventional Sodium stibogluconate monotherapy, by 30 days, in a Phase III setting, and support its introduction for treatment of primary visceral leishmaniasis in East Africa (12). Combination treatments for visceral leishmaniasis are efficacious and safe, and have the advantage of shortening treatment duration from 21–28 days for monotherapy with paromomycin or miltefosine to 8–11 days with combinations, thereby encouraging adherence and reducing emergence of drug-resistant parasites (11). Treatment with both SSG and PM resulted in an increase of liver enzymes, amylase and alkaline phosphatase, which abated spontaneously whilst on treatment. Less than 1% of patients receiving either SSG or PM developed ECG abnormalities and no clinically significant abnormal audiometry readings were detected by the final assessment. Primary cure with Paromomycin was significantly inferior to that with SSG standard treatment (63.8% versus 92.2%) (42).

Adverse Events

Amphotericin B deoxycholate adverse effects requiring interruption of treatment - vomiting, itching or an anaphylactic reaction - occurred in 1.9% patients. The main reported adverse effects were fever (52,7%), sweating (40%), abdominal

pain (38.9%), headache (37.0%), diarrhea (22.2%), itching (14.8%), and/or shivering (14.5%). All these adverse effects were considered as mild to moderate, and none required an interruption of treatment. The intensity of all the adverse effects recorded decreased during the course of the treatment (30). Conventional amphotericin B is associated with a high risk of renal toxicity in addition to other side effects: rigor, fever, malaise, anorexia, thrombophlebitis, and bone marrow suppression (44). Adverse events that were most frequently reported among patients receiving amphotericin were infusion reactions of fever, rigors, and vomiting (57%, 24%, and 10%, respectively) (6).

Liposomal amphotericin B, although effective, is prohibitively costly (14). Liposomal formulations of amphotericin B, which require a shorter treatment course and have fewer side effects, remain unaffordable at nearly 30 times the cost of conventional formulations (6). The most common adverse event during trial medication was fever, vomiting, and fever with rigor. Within 2 h of medication, the most common adverse event was fever with rigor followed by fever and hypotension, which responded well to oral rehydration therapy only. On the day after infusion, all patients were afebrile and all adverse events had resolved (36). In India, liposomal amphotericin B showed lower rates of toxicity than conventional amphotericin B. Amphotericin B nephrotoxicity in children is a known complication (44).

The antimony methylmeglumine is the first line drug in therapy in Brazil (45), and the resistance have become a major problems in some countries (29). Side-effects of therapy are dosage and duration dependent and may include painful injection, arthralgia, fever, rash, elevation of hepatic enzymes, gastrointestinal irritation, pancreatitis, renal failure, and particularly cardiac toxicity (23). Post-kala-azar dermal Leishmaniasis was recorded actively as an adverse event during patient follow-up or reported directly by 12.7% of the patients in the SSG arm (12). Electrocardiographic tracing is recommended to monitor the cardiac function in order to prevent complications of antimonial therapy (45). The only adverse effect that required interruption of meglumine antimoniate treatment was clinical pancreatitis (30). Adverse effects during treatment with Pentavalent antimonials, were associated with higher mortality. They should be promptly interrupted in presence of ominous adverse effects (46).

Miltefosine is expensive and has significant gastrointestinal side effects (6). The drug is contraindicated in pregnancy, because its potential teratogenicity, and caution must be taken in women of childbearing age, restricts its use in large-scale programmes (36). Gastrointestinal symptoms (diarrhea and vomiting were the predominant symptoms) have to be recognized as the most common adverse effect due to miltefosine therapy and may limit drug tolerability in some patients. Adverse events were higher during the first week of treatment and progressively diminished by 4 weeks of treatment (14). Treatment related adverse events including rise in aspertate amino transferase, alanine amino transferase, or serum creatinine levels, similar to previous clinical experience. It is contraindicated in pregnancy because its potential teratogenicity, and caution must be taken in women of childbearing age, restricts its use in large-scale programmes (36). This side effects and the negligence after the resolution of clinical symptoms of VL were the main reasons for poor adherence (10).

Injection-site pain was the most frequently reported adverse event among patients receiving paromomycin (55%). Adverse events, which were more common among patients receiving paromomycin than among those receiving amphotericin B, included transient elevation of aspartate aminotransferase levels; transient reversible ototoxicity. Only 1% of the patients in the paromomycin group had renal dysfunction (6). These adverse events were mild or moderate in severity. Vomiting was most common in patients receiving amphotericin B. Pain at the injection site (mild and moderate) was reported with paromomycin; chills and rigor were reported during infusion, mostly with amphotericin B and some with liposomal amphotericin B, but there were no reports in the group that did not have amphotericin B or liposomal amphotericin B (11).

Conclusion

In the last 10 years few studies on adverse effects, risk of relapse and death in children related to the treatment of visceral leishmaniasis were

performed. With regard to the treatment regimen, the use of more than one drug for the treatment of visceral leishmaniasis is a subject not discussed in order that this therapy appears to be effective for curing without generating resistance to treatment. The drugs currently used for treatment of visceral leishmaniasis appear to be effective and safe in children. Nevertheless, further studies focused on the effects of these medications in children are needed.

Acknowledgments

We are grateful to the Faculty of Medicine of ABC. We would also like to the Scientific Writing Lab (LABESCI) of the Federal University of Cariri (UFCA).

References

1. *Lainson R, Shaw JJ. Evolution, classification and geographical distribution, In W. Peters and R. Killick-Kendric (ed.), The leishmaniases in biology and medicine. Academic Press, London, England, 1987; 1-120.*

2. *Melaku Y, Collin SM, Keus K, et al. Treatment of Kala-Azar in Southern Sudan using a 17-day regimen of Sodium stibogluconate combined with Paromomycin: a retrospective comparison with 30-day Sodium stibogluconate monotherapy. American Journal Med Hyg 2007; 77(1): 89-94.*

3. *Salih NA, Griensven JV, Chappuis F, et al. Liposomal amphotericin B for complicated visceral leishmaniasis (kala-azar) in eastern Sudan: how effective is treatment for this neglected disease? Tropical Medicine and International Health 2014; (19)2: 146–152.*

4. *Lemos EM, Gomes IT, Carvalho SFG, et al. Detection of Anti-Leishmania (Leishmania) chagasi Immunoglobulin G by Flow Cytometry for Cure Assessment following Chemotherapeutic Treatment of American Visceral Leishmaniasis. Clinical and Vaccine Immunology 2007; 14(5): 569.*

5. *WHO, 2010. Control of the leishmaniasis. Proceedings of a meeting of the WHO Expert Committee on the Control of Leishmaniases, March 22–26, 2010, Geneva, Switzerland.*

6. *Sundar S, Jha TK, Thakur CP, et al. Injectable Paromomycin for Visceral Leishmaniasis in India. The New England journal of medicine 2007; 356: 2571-81.*

7. *Silva RA, Tauil PL, Cavalcante MNS, et al. Situação epidemiológica da leishmaniose visceral, na Ilha de São Luís, Estado do Maranhão. Revista da Sociedade Brasileira de Medicina Tropical 2008; 41(4): 358-364.*

8. *Albuquerque LCP, Mendonça IR, Cardoso PN, et al. HIV/AIDS-related visceral leishmaniasis a clinical and epidemiological description of visceral leishmaniasis in northern Brazil. Revista da Sociedade Brasileira de Medicina Tropical 2014; 47(1): 38-46.*

9. *Ostyn B, Hasker E, Dorlo TPC, et al. Failure of Miltefosine Treatment for Visceral Leishmaniasis in Children and Men in South-East Asia. PLoS ONE 2014; 9(6): e100^{22}0.*

10. *Uranw S, Ostyn B, Dorlo TPC, et al. Adherence to miltefosine in visceral leishmaniasis under routine conditions in Nepal. Tropical Medicine and International Health 2013; 18(2): 179–187.*

11. *Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet 2011; 377(9764): 477-486.*

12. *Musa A, Khalil E, Hailu A, et al. Sodium Stibogluconate (SSG) & Paromomycin Combination Compared to SSG for Visceral Leishmaniasis in East Africa: A Randomised Controlled Trial. PLoS Negl Trop Dis. 2012; 6(6): e1674.*

13. *Bhattacharya SK, Sur D, Karbwang J, et al. Childhood visceral leishmaniasis. Indian J Med Res 2006; 123(3): 353-6.*

14. *Bhattacharya SK, Sinha PK, Sundar S, et al. Phase 4 Trial of Miltefosine for the Treatment of Indian Visceral Leishmaniasis. The Journal of Infectious Diseases 2007; 196: 591-8.*

15. *Rijal S, Ostyn B, Uranw S, et al. Increasing Failure of Miltefosine in the Treatment of Kala-azar in Nepal and the Potential Role of Parasite Drug Resistance, Reinfection, or Noncompliance. Clinical Infectious Diseases 2013; 56(11): 1530-8.*

16. *Rocha NA, Oliveira MJC, Franco LFLG, et al. Comparative Analysis of Pediatric and Adult Visceral Leishmaniasis in Brazil. The Pediatric Infectious Disease Journal 2013; 32(5).*

17. *Convenção sobre os Direitos da Criança, adotada pela Resolução nº L 44 (XLIV) da Assembléia Geral das Nações Unidas em 20.11.1989, ratificada pelo Brasil em 24.9.1990 (Aprovado no Brasil pelo Decreto Legislativo nº 28, de 14.09.1990, e promulgado pelo Decreto nº 99.710, de 22.11.1990).*

18. *Brasil. Lei 8.069, de 13 de Julho de 1990. Estatuto da Criança e do Adolescente. Brasília: Ministério da Justiça, 1990.*

19. *Ministério da Saúde (BR). Leishmaniose visceral: recomendações clínicas para redução da letalidade. Brasília: Ministério da Saúde; 2011.*

20. *Petrela R, Kuneshka L, Foto E, et al. Pediatric Visceral Leishmaniasis in Albania: A Retrospective Analysis of 1,210 Consecutive Hospitalized Patients (1995–2009). PLoS Negl Trop Dis 2010; 4(9): e814.*

21. *Tanir G, Özkan AT, and Daglar E. Pediatric visceral Leishmaniasis in Turkey. Pediatrics International 2006; 48: 66–69.*

22. *Arık Yılmaz E, Tanir G, Tuygun N, et al. Visceral Leishmaniasis in 13 Pediatric Patients in Turkey: Treatment Experience. Turkiye Parazitol Derg 2009; 33(4): 259-262.*

23. *Canatan D, Çomak E, and Kuybulu AE. Visceral Leishmaniasis of Childhood. J Pediatr Inf 2009; 3: 109-11.*

24. *Caldas AJM, Costa J, Aquino D, et al. Are there differences in clinical and laboratory parameters between children and adults with American visceral leishmaniasis? Acta Tropica 2006; 97: 252–258.*

25. *Rey LC, Martins CV, Ribeiro HB, et al. Leishmaniose visceral americana (calazar) em crianças hospitalizadas de área endêmica. Jornal de Pediatria 2005; 81(1): 73-8.*

26. *Xavier-Gomes LM, Costa WB, Prado PF, et al. Características clínicas e epidemiológicas da leishmaniose visceral em crianças internadas em um hospital universitário de referência no norte de Minas Gerais, Brasil. Revista Brasileira de Epidemiologia 2009; 12(4): 549-55.*

27. *Brustoloni YM, Cunha RV, Cônsolo LZ, et al. Treatment of visceral leishmaniasis in children in the Central-West Region of Brazil. Infection 2010; 38: 261–267.*

28. *Kajaia M, Morse DL, Kamkamidze G, et al. Risk factors for relapse of visceral leishmaniasis in Georgia. Tropical Medicine and International Health 2011; 16(2): 186–192.*

29. *Nateghian A, and Mousavi H. Clinical findings and initial treatment response of patients with visceral Leishmaniasis admitted in Ali asghar children hospital from 1976 to 2010 in Tehran, Iran. Iran J Clin Infect Dis 2011: 6(3).*

30. *Mueller Y, Nguimfack A, Cavailler P, et al. Safety and effectiveness of amphotericin B deoxycholate for the treatment of visceral leishmaniasis in Uganda. Annals of Tropical Medicine e Parasitology 2008; 102(1): 11-19.*

31. *Sundar S, Mehta H, Chhabra A, et al. Amphotericin B Colloidal Dispersion for the Treatment of Indian Visceral Leishmaniasis. Clinical Infectious Diseases 2006; 42(5): 608–13.*

32. *Sundar S, Chakravarty J, Agarwal D, et al. Single-Dose Liposomal Amphotericin B for Visceral Leishmaniasis in India. New England Journal of Medicine 2010; 362: 504-12.*

33. *Sinha PK, Ranjan A, Singh VP, et al. Visceral leishmaniasis (kala-azar) - the Bihar (India) perspective. Journal of Infection 2006; 53(1): 60–64.*

34. *Thakur CP, Narayan S, and Ranjan A. Epidemiological, clinical & pharmacological study of antimonyresistant visceral leishmaniasis in Bihar, India. Indian J Med Res 2004; 120(3): 166-72.*

35. *Cascio A, di Martino L, Occorsio P, et al. A 6 day course of liposomal amphotericin B in the treatment of infantile visceral leishmaniasis: the Italian experience. Journal of Antimicrobial Chemotherapy 2004; 54: 217–220.*

36. *Mondal D, Alvar J, Hasnain G, et al. Efficacy and safety of single-dose liposomal amphotericin B for visceral leishmaniasis in a rural public hospital in Bangladesh: a feasibility study. Lancet Glob Health 2014; 2: 51-57.*

37. *Sinha PK, Roddy P, Palma PP, et al. Effectiveness and Safety of Liposomal Amphotericin B for Visceral Leishmaniasis under Routine Program Conditions in Bihar, India. Am J Trop Med Hyg 2010; 83(2): 357–364.*

38. *Dorlo TP, Huitema AD, Beijnen JH, et al. Optimal Dosing of Miltefosine in Children and Adults with Visceral Leishmaniasis Antimicrob Agents Chemother 2012; 56(7): 3864-72.*

39. *Singh UK, Prasad R, Mishra OP, et al. Miltefosine in Children with Visceral Leishmaniasis: A Prospective, Multicentric, Cross-Sectional Study. Indian Journal of Pediatrics 2006; 73(12): 1077-1080.*

40. *Sinha PK, Jhuma TK, et al. Phase 4 Pharmacovigilance Trial of Paromomycin Injection for the Treatment of Visceral Leishmaniasis in India. Journal of Tropical Medicine 2011; (2011): ID645203.*

41. *Sundar S, Agrawal N, Arora R, et al. Short-Course Paromomycin Treatment of Visceral Leishmaniasis in India: 14-Day vs 21 Day Treatment. Clinical Infectious Diseases 2009; 49(6): 914–8.*

42. *Hailu A, Musa A, Wasunna M, et al. Geographical Variation in the Response of Visceral Leishmaniasis to Paromomycin in East Africa: A Multicentre, Open-Label, Randomized Trial. PLoS Negl Trop Dis 2010; 4(10): e709.*

43. *Apa H, Devrim İ, Bayram N. Liposomal amphotericin B versus pentavalent antimony salts for visceral Leishmania in children. The Turkish Journal of Pediatrics. 2013; 55: 378-383.*

44. *Verma N, Lal CS, Rabidas V, et al. Microalbuminuria and Glomerular filtration rat in paediatr ic visceral leishmaniasiionals. BioMed Research International. 2013; ID498918.*

45. *Zanoni LZ, Brustoloni YM, Melnikov P, et. al.; Antimony Containing Drug and ECG Abnormalities in Children with Visceral Leishmaniasis. Biol Trace Elem Res 2009; 132: 35–40.*

46. *Mueller Y, Mbulamberi DB, Odermatt P, et al. Risk factors for in-hospital mortality of visceral leishmaniasis patients in eastern Uganda. Tropical Medicine and International Health 2009; 14(8): 910–917.*

Corresponding Author
Maria do Socorro Vieira dos Santos,
Faculty of Medicine,
Federal University of Cariri,
Barbalha,
Ceara,
Faculty of Medicine of ABC,
Santo Andre,
Sao Paulo,
Brazil
E-mail: socorro.vieira@ufca.edu.br

Serum Calcium, Magnesium and Iron Levels and Their Relation to Bone Mineral Density in Postmenopausal Women from Kosovo

Elton Bahtiri[1,2], Hilmi Islami[1], Rexhep Hoxha[1], Hasime Qorraj-Bytyqi[1]

[1] Department of Pharmacology, Faculty of Medicine, University of Prishtina, Republic of Kosova,
[2] The Endocrinology Clinic, University Clinical Center of Kosovo, Prishtina, Republic of Kosova.

Abstract

Objective: Recent studies revealed conflicting results regarding relationship between calcium, magnesium and iron serum levels and bone mineral density. This study aimed to investigate correlation between serum levels of these elements and bone mineral density in postmenopausal women.

Methods: A total of 140 postmenopausal women divided into three groups according to lumbar vertebrae bone mineral density (Total T-score) were included in the study. Data on subjects' age, body mass index (BMI), duration of menopause, bone mineral density (BMD) in lumbar vertebrae, femur neck and hip, as well as serum levels of calcium, magnesium and iron were collected. Dual-energy X-ray absorptiometry (DXA) was done to estimate BMD. One-way ANOVA was performed to compare characteristics of the groups and Person's correlation test was performed to test correlation between variables.

Results: Comparison between groups by one-way ANOVA showed no significant difference in elements contents, while Pearson's correlation analysis failed to demonstrate statistically significant correlation between BMD and element contents.

Conclusion: Lack of significant correlation between serum element contents analyzed in this study and BMD urges further studies before magnesium or iron supplements are advised in cases other than deficiencies.

Key words: postmenopausal women, calcium, magnesium, iron

Introduction

Osteoporosis, a systemic skeletal abnormality characterized by reduction of bone mineral content and changes of bone microarchitecture, is associated with higher fracture risk (1, 2). It is a widely prevalent health problem in the world as elderly population increases with hundreds of millions of people assumed to be affected worldwide (3). According to a report prepared in collaboration with the International Osteoporosis Foundation in 2010, it was estimated that twenty-two million women and 5.5 million men have osteoporosis in the European Union (4).

Although there are many identified risk factors that contribute to bone strength, definite pathophysiology of osteoporosis remains to be clarified (5). The elements such as calcium (Ca), magnesium (Mg) and Iron (Fe) are important for essential bone tissue processes. They play a role in growth and development and maintenance of bone mass due to their functions in bone matrix synthesis (5-7). Ca is a major bone-forming mineral and its supplementation is important part of any preventive or treatment regimen for osteoporosis (8). Mg also plays important role in bone mineralization, having mitogenic effect on osteoblasts (9-13). Fe is another important element having beneficial effect on bone mass (14-16).

Of particular consideration in present study was determination of calcium (Ca), magnesium (Mg) and Iron (Fe) status in postmenopausal normal, osteopenic and osteoporotic women, as well as investigation of correlation between serum levels of these elements and bone mineral density (BMD) in these subjects. To our best knowledge, this is the first study performed in Kosovo focusing in this particular issue. Cross-sectional data used for this study are baseline data of a bigger study aiming to evaluate safety of long term use of Proton Pump Inhibitor drugs.

Material and methods

Study population

The study population of this research consisted of 140 women who had been in natural menopause for at least one year. Research subjects were divided into three groups according to lumbar vertebrae BMD (Total T-score): Normal Bone Health group (n=42), Osteopenia group (n=48) and Osteoporosis group (n=50). Subjects were excluded if they had taken calcium, magnesium or iron supplements up to 6 months and bisphosphonates and glucocorticoids up to 12 months prior to investigation. Subjects that suffered from diseases that might affect bone metabolism or had severe chronic diseases were also excluded. The study protocol was approved by Ethical Committee of the Faculty of Medicine, University of Prishtina (decision no:1699, date: 11.05.2012), and the research was conducted in accordance to guidelines in Declaration of Helsinki. Written informed consent was obtained from all study participants before inclusion in the study. Height (m) and weight (kg) were measured by standard methodology and body mass index (BMI) was calculated as subjects' weight divided by height squared (kg/m2).

Bone mineral density measurements

Bone mineral density (BMD) was measured in lumbar vertebrae (L1-L4), femoral neck and total hip in all study participants by dual-energy X-ray absorptiometry (DXA; Hologic QDR-4500, USA). The precision error of DEXA measurements was 1%. According to WHO T-score criteria from 1994, subjects with lumbar spine BMD 2.5 SD below reference range (T-score ≤ -2.5 SD) were considered osteoporotic, subjects with T-score between -2.5 SD and -1 SD were considered osteopenic, and subjects with T-score > -1SD were considered of normal bone mineral density.

Determination of elements in serum

Blood samples were obtained from antecubital veins in the morning after overnight fasting. Samples were allowed to clot in the tubes, then centrifuged at 3000 rpm for 10 min and isolated serums were stored -20˚C until analysis.

The serum concentrations of total Ca (mmol/l), Mg (mmol/l) and Fe (μmol/l) were measured using COBAS Integra 400 Plus System (Roche Diagnostics Ltd., Switzerland).

Statistical analysis

Statistical analyses were performed using SPSS statistical package version 16.0 (SPSS Inc., Chicago, IL, USA). All continuous variables are expressed as the means ± standard deviations (SD) and as range (minimum-maximum). Characteristics of the three groups were compared using one-way analysis of variance (ANOVA), and Tukey test was applied for Post Hoc Multiple Comparisons. Correlation between variables was done using Person's correlation test. In all analyses, a value of $p < 0.05$ was taken as statistically significant.

Results

Study population consisted of 140 post-menopausal women aged between 37 and 65 years with a mean age of 56.39±6.05 and with mean duration of menopause of 8.69±6.23, while BMI overall mean was 29.96±4.89. Characteristics of the entire study population are summarized in Table 1.

Total T-score of the lumbar vertebrae revealed that 42 subjects had T-scores within normal range (Normal Bone Health group, n=42), 48 subjects had T-scores in osteopenic range (Osteopenia group, n=48), and 50 subjects had T-scores in osteoporosis range (Osteoporosis group, n=50). There were significant differences between 3 groups in lumbar vertebrae BMD (Total T-score), femur neck BMD (T-score) and Hip BMD (Total T-score) ($p<0.05$), while taking into account BMI and duration of menopause, Osteoporosis group was significantly different from Normal Bone Health group ($p<0.05$), and from Normal Bone Health group and Osteopenia group, respectively ($p<0.05$). There were no significant differences between groups in Ca, Mg or Fe serum levels ($p>0.05$) (Table 2).

Pearson's correlation analysis shown in Table 3 shows a significant positive correlation between serum elements contents ($p<0.01$), as well as a significant positive correlation between BMI and lumbar vertebrae BMD (Total T-score), femur neck BMD (T-score) and Hip BMD (Total T-score) ($p<0.01$). No statistically significant correlation was shown between serum elements and BMD of postmenopausal women, though there was a posi-

Table 1. Characteristics of the study population

	N	Mean ± SD	Range (Min-Max)
Age (years)	140	56.39±6.05	28 (37-65)
BMI (kg/m^2)	140	29.96±4.89	29.04 (16.23-45.7)
Duration of menopause (years)	140	8.69±6.23	30.0 (1.0-31.0)
Lumbar vertebrae BMD (Total T-score)	140	-1.73±1.54	10.07 (-5.40-4.7)
Femur Neck BMD (T-score)	140	-0.95±1.14	7.80 (-4.50-3.30)
Hip BMD (Total T-score)	140	-0.67±1.15	8.20 (-4.50-3.70)
Ca (mmol/l)	140	2.41±0.25	1.28 (1.52-2.80)
Mg (mmol/l)	140	0.81±0.09	0.40 (0.60-1.0)
Fe (µmol/l)	140	18.23±4.51	23.20 (8.50-31.70)

Table 2. Clinical and biochemical characteristics of the study population (n=140), divided into 3 groups on the basis of total T-score of the lumbar vertebrae

	Normal Bone Health Group (n=42)	Osteopenia Group (n=48)	Osteoporosis Group (n=50)	p values
Age (years)	56.74±5.74 (21.0)	55.46±6.65 (26.0)	57.00±5.71 (28.0)	$p > 0.05$
BMI (kg/m^2)	31.57±4.42 (22.31)	30.01±5.02 (18.91)	28.57±4.81 (21.86)	$p < 0.05$
Duration of menopause (years)	7.12±5.25 (19.0)	7.79±5.73 (29.0)	10.88±6.89 (30.0)	$p < 0.05$
Lumbar vertebrae BMD (Total T-score)	0.12±0.99 (5.60)	-1.82±0.47 (1.40)	-3.22±0.71 (2.90)	$p < 0.05$
Femur Neck BMD (T-score)	-0.95±1.16 (6.50)	-0.94±0.89 (3.60)	-1.67±0.78 (4.70)	$p < 0.05$
Hip BMD (Total T-score)	0.23±1.08 (5.20)	-0.76±0.78 (3.20)	-1.33±1.01 (5.50)	$p < 0.05$
Ca (mmol/l)	2.47±0.21 (1.03)	2.40±0.28 (1.23)	2.37±0.24 (0.92)	$p > 0.05$
Mg (mmol/l)	0.84±0.96 (0.40)	0.80±0.087 (0.30)	0.81±0.10 (0.30)	$p > 0.05$
Fe (µmol/l)	19.34±4.33 (17.10)	17.43±4.50 (15.70)	18.06±4.57 (23.20)	$p > 0.05$

All parameters are given in mean± standard deviation; () in the brackets indicates range

Table 3. Pearson's correlation analysis between serum elements, BMI and BMD (r)

	Total Ca (mmol/l)	Mg (mmol/l)	Fe (µmol/l)	Body mass index (BMI)
Lumbar vertebrae BMD (Total T-score)	0.125	0.44	0.081	0.316**
Femur Neck BMD (T-score)	0.066	0.034	0.052	0.455**
Hip BMD (Total T-score)	0.067	0.027	0.089	0.538**
Ca (mmol/l)	-	0.594**	0.246**	-0.034
Mg (mmol/l)	0.594**	-	0.218**	-0.049
Fe (µmol/l)	0.246**	0.594**	-	-0.030
*p <0.05; **p<0.01				

tive correlation tendency of calcium, magnesium and iron with BMD of lumbar vertebrae, femur neck and hip (p>0.05). BMI showed a negative correlation tendency with serum elements, but this tendency had no statistic significance (p>0.05).

Discussion

Osteoporosis is a global health concern of the aged people and health care utilization of patients with osteoporosis is increasing (17). Minerals are among the factors that have vital role in bone tissue structure and function, that's why focus of prevention and treatment strategies of osteoporosis during recent years is in minerals other than Ca, like Mg, Fe and other trace elements (6). Several studies demonstrated their role in bone metabolism (18-20). In this study we investigated the correlation between serum levels of Ca, Mg and Fe and BMD in postmenopausal women. The main finding of this study is that there were no significant differences regarding Ca, Mg and Fe se-

rum levels between 3 groups created on the basis of BMD. Correlation analysis showed that there was no significant correlation between elements and BMD, but there was significant correlation between serum elements contents.

Being crucial constituent of bone mineral hydroxyapatite, calcium is directly related to bone health, that's why calcium supplementation in daily doses of at least 1200 mg with vitamin D is an important component in any drug prescription regimen for osteoporosis (8, 21). Studies analyzing correlation between Ca serum levels and osteoporosis or osteopenia have revealed conflicting results; some of them found no correlation at all (18, 20, 22).

Ahmed S *et al*. reported a significant difference in calcium levels between 3 groups, but there was no significant correlation between serum levels of calcium and severity of osteoporosis as measured by T-score (22). Similarly, Liu *et al*. reported no significant correlation of Ca serum levels with BMD, but no significant differences in Ca levels between osteoporosis group, osteopenia and healthy group, however (20). Results from current study are fully consistent with those of Li *et al*., as far as there were no significant differences between groups in Ca serum levels and no correlation of Ca serum levels with values of BMD for all sites.

Magnesium plays an essential role in a wide range of body functions; it exerts direct as well as indirect effects on skeleton (13, 23). About 60% of total body Mg stored in the bone, mainly on cortical bone, and plays a vital role in bone formation, bone differentiation and matrix calcification (12, 13). Several studies have studied correlation between Mg status and bone mineral density, but the evidence is still inconclusive. Razmandeh R *et al*. reported significant differences in terms of Mg levels between osteoporotic patients and healthy subjects (19). In another study, Okyay E *et al*. observed a significant correlation between Mg levels and BMD values and reported that low serum levels of magnesium are independent risk factor for osteoporosis (7). Similarly, two other studies by Mutlu M *et al*. and Gur A *et al*. reported that Mg levels in serum were significantly lower among patients with osteoporosis than the controls (11, 18). Contrary to these reports, Liu *et al*. reported no significant differences in Mg levels between osteoporosis group and healthy groups and no significant correlation of Mg levels with BMD (20). Findings from our study were similar to this study and to a previous report by Odabasi E *et al*. that reported no significant difference in Mg serum concentrations between patient and control groups (10).

Iron is a trace element that has direct effects on bone metabolism (24). Animal studies suggested that severe iron deficiency decreases bone formation and affects bone mineral density (15, 16). Maurer *et al*. suggested that dietary iron positively influences bone mineral density in postmenopausal women (25). Studies in patients with hematologic disorders associated with iron-overload support negative impact of excess iron on BMD through increased oxidative stress and bone resorption (26). In present study there was no significant difference in iron levels between three groups, and no significant correlation between serum levels of iron and bone mineral density, also. These results support those of Liu *et al*. (20), but they contrast to results reported by Okyay E *et al*., who observed significantly lower mean serum levels of iron in osteoporosis group compared with non-osteoporosis group (7).

Relatively small sample of 140 postmenopausal women that were not selected randomly from the general population, may have limited the ability to detect significant relationships between serum elements contents and BMD, thus making it difficult to refer the results to the general population.

Conclusion

In conclusion, results of this study showed that there were no significant correlation between serum contents of calcium, magnesium and iron neither with BMD of lumbar vertebrae nor with BMD of femur in 140 postmenopausal women, and also no significant difference regarding Ca, Mg and Fe serum levels between osteoporosis, osteopenia and normal bone health group. In this context, this study recommends that further studies are needed before magnesium or iron supplements are advised in cases other than deficiencies.

Acknowledgements

This study was partially supported by a grant from Ministry of Education, Science and Technology (MEST) of Republic of Kosova (grant no:

2-4447). Conclusions or recommendations expressed in this article do not necessarily reflect the views or policies of MEST.

We would like to thank all the study participants.

References

1. *WHO. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO study group, vol. 843. Geneva: World Health Organization Technical Report Series; 1994; P.1-129.*

2. *Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008; 42: 467-475.*

3. *Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006; 17: 1726-1733.*

4. *Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in the collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013; 8(1-2): 136.*

5. *Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements-An overview. J Trace Elem Med Biol. 2012; 26: 149-152.*

6. *Nieves JW. Skeletal effects of nutrients and nutraceuticals, beyond calcium and vitamin D. Osteoporos Int. 2013; 24(3): 771-86.*

7. *Okyay E, Ertugrul C, Acar B, Sisman AR, Onvural B, Ozaksoy D. Comparative evaluation of serum levels of main minerals and postmenopausal osteoporosis. Maturitas. 2013; 76(4): 320-325.*

8. *[No authors listed] Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. 2010; 17(1): 25-54.*

9. *Rude RK, Gruber HE. Magnesium deficiency and osteoporosis: animal and human observations. J Nutr Biochem. 2004; 15(12): 710-716.*

10. *Odabasi E, Turan M, Aydin A, Akay C, Kutlu M. Magnesium, Zinc, Copper, Manganese, and Selenium Levels in Postmenopausal Women With Osteoporosis. Can Magnesium Play a Key Role in Osteoporosis? Ann Acad Med Singapore. 2008; 37: 564-567.*

11. *Mutlu M, Argun M, Kilic E, Saraymen R, Yazar S. Magnesium, Zinc and Copper Status in Osteoporotic, Osteopenic and Normal Post-menopausal Women. J Int Med Res. 2007; 35: 692-695.*

12. *Leidi M, Dellera F, Mariotti M, Banfi G, Crapanzano C, Albisetti W, et al. Nitric oxide mediates low magnesium inhibition of osteoblast-like cell proliferation. J. Nutr. Biochem. 2012; 23: 1224-1229*

13. *Castiglioni S, Cazzaniga A, Albisetti W, Maier JA. Magnesium and osteoporosis: current state of knowledge and future research directions. Nutrients. 2013; 5(8): 3022-33.*

14. *D'Amelio P, Cristofaro MA, Tamone C, Morra E, Di Bella S, Isaia G, et al. Role of iron metabolism and oxidative damage in postmenopausal bone loss. Bone. 2008; 43(6): 1010-1015.*

15. *Katsumata S, Tsuboi R, Uehara M, Suzuki K. Dietary iron deficiency decreases serum osteocalcin concentration and bone mineral density in rats. Biosci Biotechnol Biochem. 2006; 70(10): 2547-50*

16. *Katsumata S, Katsumata-Tsuboi R, Uehara M, Suzuki K. Severe iron deficiency decreases both bone formation and bone resorption in rats. J Nutr. 2009; 139(2): 238-43.*

17. *Lee YK, Yoon BH, Koo KH. Epidemiology of Osteoporosis and Osteoporotic Fractures in South Korea. Endocrinol Metab. 2013; 28(2): 90-93.*

18. *Gür A, Colpan L, Nas K, Cevik R, Saraç J, Erdoğan F, et al. The role of trace minerals in the pathogenesis of postmenopausal osteoporosis and a new effect of calcitonin. J Bone Miner Metab. 2002; 20(1): 39-43.*

19. *Razmandeh R, Nasli-Esfahani E, Heydarpour R, Faridbod F, Ganjali MR, Norouzi P, et al. Association of Zinc, Copper and Magnesium with bone mineral density in Iranian postmenopausal women - a case control study. J Diabetes Metab Disord. 2014; 13(1): 43*

20. *Liu SZ, Yan H, Xu P, Li JP, Zhuang GH, Zhu BF, et al. Correlation Analysis Between Bone Mineral Density and Serum Element Contents of Postmenopausal Women in Xi'an Urban Area. Biol Trace Elem Res. 2009; 131: 205-214.*

21. *Aloia JF, Dhaliwal R, Shieh A, Mikhail M, Islam S, Yeh JK. Calcium and vitamin d supplementation in postmenopausal women. J Clin Endocrinol Metab. 2013; 98(11): E1702-9.*

22. *Ahmed SF1, Fouda N, Abbas AA. Serum dickkopf-1 level in postmenopausal females: correlation with bone mineral density and serum biochemical markers. J Osteoporos. 2013: 460210.*

23. *Belluci MM, Giro G, del Barrio RA, Pereira RM, Marcantonio E Jr, Orrico SR. Effects of magnesium intake deficiency on bone metabolism and bone tissue arround osseointegrated implants. Clin Oral Implants Res. 2011; 22(7): 716-21*

24. *Li GF, Pan YZ, Sirois P, Li K, Xu YJ. Iron homeostasis in osteoporosis and its clinical implications. Osteoporos Int. 2012; 23: 2403–2408*

25. *Maurer J, Harris MM, Stanford VA, Lohman TG, Cussler E, Going SB, et al. Dietary iron positively influences bone mineral density in postmenopausal women on hormone replacement therapy. J Nutr. 2005; 135(4): 863-9.*

26. *Kim BJ, Lee SH, Koh JM, Kim GS. The association between higher serum ferritin level and lower bone mineral density is prominent in women ≥45 years of age (KNHANES 2008-2010). Osteoporos Int. 2013; 24(10): 2627-37.*

Corresponding Author
Rexhep Hoxha,
Department of Pharmacology,
Faculty of Medicine, University of Prishtina,
Prishtina,
Republic of Kosova,
Email: rexhephoxha@gmail.com

Application of p-value from statistical normality tests in RR intervals for short recordings

Vitor E. Valenti[1,2], Marco A. Cardoso[2], Leticia S. de Oliveira[3], Patricia S. G. Moreira[3], Joice A. T. Amaral[3], Celso Ferreira[4], Rodrigo D. Raimundo[4], Rayana L. Gomes[2], Luiz Carlos de Abreu[4]

[1] Center for Autonomic Nervous System Studies (CESNA), Department of Speech Pathology, Faculty of Philosophy and Science, UNESP, Marilia, SP, Brazil,
[2] Graduate Program in Physical Therapy, Faculty of Science and Technology, Sao Paulo State University, UNESP, Presidente Prudente, SP, Brazil,
[3] Department of Physical Therapy and Occupational Therapy, School of Philosophy and Sciences, UNESP, Marilia, SP, Brazil,
[4] Department of Morphology and Physiology, Faculty of Medicine of ABC, Santo Andre, SP, Brazil.

Abstract

Introduction: It was previously indicated a novel technique to analysis heart rate variability (HRV) by modeling RR intervals as a linear combination of Gaussians. In this study we investigated the association of the p-value for statistical normality tests with HRV indices for short period in women.

Methods: We evaluated 36 healthy women between 18 and 30 years old. HRV was analyzed with a minimal number of 256 RR intervals in the time (SDNN, RMSSD, NN50 and pNN50) and frequency (LF, HF and LF/HF ratio) domains, the geometric indices were also analyzed (triangular index-RRtri, triangular interpolation of RR intervalsTINN and Poincaré plot-SD1, SD2 and SD1/SD2) as well as short and long-term fractal exponents (alpha-1 and alpha-2) of the detrended fluctuation analysis (DFA) and correlation dimension. It was applied the normality testes in all RR intervals and the p-value was obtained. We performed correlation between the p-value for statistical normality tests with HRV indices.

Results: The p-value for the Shapiro-Wilk test presented significant correlation with RMSSD, pNN50, SDNN, RRTri, TINN, LF and HF in absolute units, LF/HF ratio and SD1. However, the p-value for the Kolmorogov-Smirnov did not present significant correlation with any HRV index.

Conclusion: Application of Shapiro-Wilk statistical normality test in RR intervals presented strong association with parasympathetic and global indices of HRV in women.

Key words: Autonomic nervous system; Cardiovascular system; Gaussian Distribution.

Introduction

Heart rate variability (HRV) is a conventionally well-accepted term that describes the fluctuations in the intervals between consecutive heartbeats (RR intervals). This method is related to influences of the autonomic nervous system on the sinus node. Alterations in HRV provide a sensitive and early indicator of health impairments. High HRV indicates good adaptation, featured by a healthy individual with efficient autonomic mechanisms. On the other hand, low HRV is often a marker of abnormal and inadequate adaptation of the ANS [1, 2].

The statistical behavior of the heart rate can be investigated by substituting the complex waveform of a heartbeat recorded from a subject with the time occurrence of the contraction, which is a single number. Mathematically, the heartbeat sequence is modeled by an unmarked point process that decreases the computational complexity of the problem and allows its analysis by well known methods [3]. In great part of studies HRV has been analyzed by considering spectral analysis of an array of R{R intervals (frequency domain analysis) or statistics of RR intervals (time domain analysis) or by [4].

The non-Gaussian behavior of HRV in healthy humans was presented through multiscale probability density function analysis [4-6]. In this circumstance, we raised the hypothesis that the analysis of RR intervals distribution could be considered as an indicator of HRV. In addition, establishment of new indices that represents cardiac autonomic regulation is of substantial practical value. Thus, our investigation was undertaken to evaluate the asso-

ciation of the p-value for normality tests applied in RR intervals with HRV indices.

Method

Study Population

We analyzed 36 healthy men aged between 18 and 30 years old. All volunteers were informed about the procedures and objectives of the study and, after agreeing, have signed a term of informed consent. All study procedures were approved by the Ethics Committee in Research of the Faculty of Sciences of the Universidade Estadual Paulista, Campus of Marilia (Protocol No. 554/2012) and followed the resolution 196/96 Council National Health 10/10/1996.

Non-inclusion criteria

We did not include subjects under the following conditions: body mass index (BMI) >35 kg/m^2; systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg (at rest); cardiorespiratory, neurological and endocrine reported disorders, smoking, treatment with drugs that influence cardiac autonomic regulation, i.e. beta adrenergic, beta-blockers, angiotensin agonists and antagonists and women between 10-15 and 20-25 days after the first day of menstrual cycle.

Initial Evaluation

Before the experimental procedure, volunteers were identified by collecting the following information: age, gender, weight, height and body mass index (BMI). Weight was determined by using a digital scale (W 200/5, Welmy, Brasil) with a precision of 0.1kg. Height was determined by using a stadiometer (ES 2020, Sanny, Brasil) with a precision of 0.1 cm and 2.20 m of extension. Body mass index (BMI) was calculated using the following formula: weight (kg)/height (m^2). We also measured systolic and diastolic blood pressure and heart rate.

Experimental protocol

Data were collected in our laboratory under controlled temperature (21° C–25° C) and humidity (50%–60%), and volunteers were instructed to avoid consuming alcohol, caffeine and substances that influence the autonomic nervous system for 24 hours before evaluation. Data were collected between 6 p.m. and 9 p.m. All procedures necessary for the data collection were explained to the individuals, and the subjects were instructed to remain at rest and to avoid talking during the data collection.

After the initial evaluation the heart monitor strap was placed on each subject's thorax over the distal third of the sternum. The HR receiver (Polar RS800CX monitor, Polar Electro OY, Kempele, Finland) was placed on the wrist. The subject remained 10 minutes seated at rest with spontaneous breathing.

HRV analysis

The R-R intervals recorded by the portable HR monitor (with a sampling rate of 1000 Hz) were downloaded to the Polar Precision Performance program (v. 3.0, Polar Electro, Finland). The software enabled the visualization of HR and the extraction of a cardiac period (R-R interval) file in "txt" format. Following digital filtering complemented with manual filtering for the elimination of premature ectopic beats and artifacts, at least 256 R–R intervals were used for the data analysis. Only series with more than 95% sinus rhythm was included in the study [1, 2]. For calculation of the indices we used the HRV Analysis software (Kubios HRV v.1.1 for Windows, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) [7].

Time and frequency domain indices of HRV

To analyze HRV in the frequency domain, the low frequency (LF =0.04 to 0.15 Hz) and high frequency (HF = 0.15 to 0.40 Hz) spectral components were used in ms^2 and normalized units (nu), which represents a value relative to each spectral component in relation to the total power minus the very low frequency (VLF) components, and the ratio between these components (LF/HF). The spectral analysis was calculated using the Fast Fourier Transform algorithm.

The analysis in time domain was performed by means of SDNN (standard deviation of normal-to-normal R-R intervals), the percentage of adjacent RR intervals with a difference of duration greater than 50ms (pNN50) and RMSSD (root-mean square of differences between adjacent normal RR intervals in a time interval) [1, 2].

Geometric indices of HRV

The HRV analysis was performed using the following geometrical methods: RRtri, TINN and Poincaré plot (SD1, SD2 and SD1/SD2 ratio). The RRtri was calculated from the construction of a density histogram of RR intervals, which contains the horizontal axis of all possible RR intervals measured on a discrete scale with 7.8125 ms boxes (1/128 seconds) and on the vertical axis, the frequency with which each occurred. The union of points of the histogram columns forms a triangle-like shape. The RRtri was obtained by dividing the number of RR intervals used to construct the histogram by their modal frequency (i.e., the RR interval that most frequently appeared on RR).

The TINN consists of the measure of the base of a triangle. The method of least squares is used to determine the triangle. The RRtri and the TINN express the overall variability of RR intervals.

The Poincaré plot is a map of points in Cartesian coordinates that is constructed from the values of RR intervals. Each point is represented on the x-axis by the previous normal RR interval and on the y-axis by the following RR interval.

For the quantitative analysis of the plot, an ellipse was fitted to the points of the chart, with the center determined by the average RR interval. The SD1 indices were calculated to measure the standard deviation of the distances of the points from the diagonal y=x, and SD2 measures the standard deviation of the distances of points from the line y=-x+RRm, where RRm is the average RR interval. The SD1 is an index of the instantaneous recording of the variability of beat-to-beat and represents the parasympathetic activity, whereas the SD2 index represents the long-term HRV and reflects the overall variability. The SD1/SD2 shows the ratio between the short- and long-term variation among RR intervals.

The plot was qualitatively analyzed using HRV analysis software based on the figures formed by its attractor. The expected shapes were described by Tulppo et al. [8]:

1. Figures in which an increase in the dispersion of RR intervals is observed with increased intervals, characteristic of a normal plot.
2. Small figures with beat-to-beat global dispersion without increased long-term dispersion of RR intervals.

Fractal analysis of HRV

For the analysis of the fractal properties of the heart rate, detrended fluctuation analysis (DFA) was applied to a time series of the R–R intervals obtained from the participants. The procedure for the calculation of DFA is made up of the following steps [9]:

The R–R series obtained experimentally is integrated using the expression:

$$Y(k) = \sum_{i=1}^{k} [RR(i) - RR_{ave}]$$

in which Y(k) is the k-th term of the integrated series (k = 1, 2,..., N); R–R(i) is the i-th value of the R–R intervals; and $R–R_{ave}$ is the mean of the R–R intervals of the original series, with N length:

$$RRave = \frac{1}{N} \sum_{i=1}^{N} RR(i)$$

The integrated time series is then divided into intervals with a length of n, (n = 1, 2,..., N). In each of these intervals, the local trend of the series is calculated by a straight line of minimum squares adjusted to the data. The y-coordinate of this straight line was denominated Yn(k). The integrated series was then detrended [Y(k)], subtracting the local tendency Yn(k) in each interval. For a given interval of size n, the size characteristic of the fluctuation for the integrated and detrended series is calculated by:

$$F(n) = \sqrt{\frac{1}{N} \sum_{K=1}^{N} [Y(k) - Yn(k)]^2}$$

This procedure is repeated for all intervals of size *n*, thereby obtaining a relation between the mean of the fluctuations [*F*(*n*)] and the size of the intervals (*n*). A linear relation on a log–log graph indicates a scale exponent law, based on the following formula:

$$F(n) \approx n\alpha$$

in which α is the scale exponent, which can be calculated by linear regression on a log–log graph.

The following were calculated: short-term fractal exponent (alpha-1), corresponding to a period of 4 to 11 beats; long-term fractal exponent (alpha-2), corresponding to periods longer than 11 beats; and the alpha-1/alpha-2 ratio.

Normality of distribution of RR intervals

The RR intervals recorded by the portable HR monitor (with a sampling rate of 1000 Hz) were downloaded to the Polar Precision Performance program (v. 3.0, Polar Electro, Finland). The software enabled the visualization of HR and the extraction of a cardiac period (R-R interval) file in "txt" format. Following digital filtering complemented with manual filtering for the elimination of premature ectopic beats and artifacts, at least 256 R–R intervals were used for the data analysis. Only series with more than 95% sinus rhythm was included in the study. In order to determine if the data set of each RR interval is well-modeled by a normal distribution and to compute how likely it is for a random variable underlying the data set to be normally distributed we applied two normality tests (Kolmorogov-Smirnov and Shapiro-Wilk) in all RR interval stationary samples and considered the p-value for each volunteer [10]. For calculation of the p-value of the normality tests we used the Software Biostat version 5.8.4 for Windows.

In order to perform qualitative analysis of RR intervals distribution we used ARTiiFACT Version 2.05.

Statistical Analysis

Normal Gaussian distribution of the data was verified by the Shapiro-Wilk goodness-of-fit test (z value >1.0). For parametric distributions we applied the Pearson correlation test. For non-parametric distributions we used the Spearman correlation test. We performed correlation of the alpha-1 and alpha-2 exponents with the time and frequency domain and geometric indices of HRV. We considered weak correlation for $r < 0.3$, moderate correlation for r between 0.31 and 0.49 and strong correlation for $r>0.5$. We performed correlation between the p-values of the normality tests and the HRV indices. Differences were considered significant when the probability of a Type I error was less than 5% ($p < 0.05$). We used the Software Biostat version 5.8.4 for Windows.

Results

We observe in Table 1 the values regarding basal diastolic (DAP) and systolic arterial pressure (SAP), heart rate (HR), mean RR, weight, height and body mass index (BMI) of the volunteers.

Table 1. Baseline diastolic (DAP) and systolic arterial pressure (SAP), heart rate (HR), mean RR interval, weight, height and body mass index (BMI) of the volunteers.

Variable	Value
Height (m)	1.64 ±0.06
Weight (kg)	58.68 ±9.48
BMI (kg/m^2)	21.95 ±3.69
HR (bpm)	83.40 ±13.09
Mean RR (ms)	742 ±131.3
SAP (mmHg)	109.37 ±7.87
DAP (mmHg)	69.31 ±2.49

Mean+standard-deviation. m: meters; kg: kilograms; bpm: beats per minut; mmHg: millimeters of mercury.

According to Table 2 we note that p-value for the Kolmorogov-Smirnov normality test did not present significant correlation with the time (SDNN, RMSSD and pNN50) and frequency (LF, HF and LF/HF ratio) domain indices of HRV, as well as the geometric indices (RRTri, TINN, SD1, SD2 and SD1/SD2 ratio), fractal exponents (alpha-1, alpha-2 and alpha-1/alpha-2 ratio) and correlation dimension. We also investigated the correlation of the p-value for the Shapiro-Wilk normality test with the HRV indices and we reported positive correlation. We noted significant correlation of the p-value with SDNN, RMSSD, pNN50, RRTri, TINN, LF and HF in absolute units, SD1, SD2 and SD1/SD2 ratio (Table 3).

Figure 1 shows an example of distribution of RR intervals of a subject with high HRV (A) and a subject with reduced HRV (B).

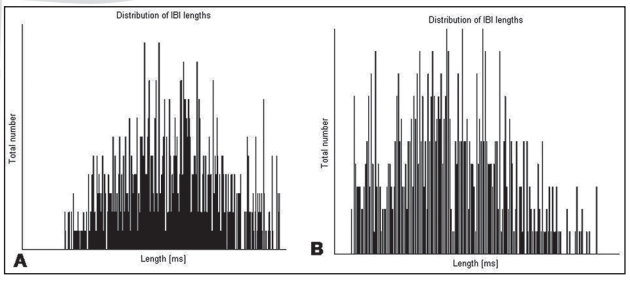


Figure 1. Visual pattern of RR intervals distribution of a subject with high HRV (A) and a subject with reduced HRV (B).

IBI: Inter beat intervals; ms: milliseconds.

Table 2. Correlation between the p value for the Kolmorogov-Smirnov test and the HRV indices.

Index	r	p
Mean RR	-0.29	0.08
SDNN	-0.25	0.14
Mean HR	0.29	0.09
RMSSD	-0.28	0.10
SDNN/RMSSD	0.24	0.16
pNN50	-0.25	0.13
RR triangular index	-0.20	0.24
TINN	-0.25	0.14
LF (ms²)	-0.15	0.37
LF (nu)	0.32	0.06
HF (ms²)	-0.25	0.15
HF (nu)	-0.31	0.07
LF/HF	0.27	0.11
SD1	-0.24	0.15
SD2	-0.21	0.21
SD1/SD2	-0.21	0.22
α1	0.23	0.18
α2	-0.21	0.22
α1/α2	0.31	0.06
Correlation Dimension	0.01	0.95

Mean RR: Mean RR intervals;
Mean HR: mean heart rate;
SDNN: standard deviation of normal-to-normal R-R intervals;
pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50ms;
RMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval. ms: millisecond.
LF: low frequency;
HF: high frequency;
LF/HF: low frequency/high frequency ratio;
RRtri – Triangular index;
TINN – triangular interpolation of RR intervals;
SD1 – standard deviation of the instantaneous variability of the beat-to beat heart rate;
SD2 – standard deviation of long-term continuous RR interval variability;
SD1/SD2 ratio – ratio between the short - and long - term variations of RR intervals. ms: milliseconds; nu: normalized units.

Table 3. Correlation between the p value for the Shapiro-Wilk test and the HRV indices.

Index	r	p
Mean RR	0.11	0.51
SDNN	0.83	p<0.0001
Mean HR	-0.10	0.56
RMSSD	0.37	0.03
SDNN/RMSSD	0.08	0.64
pNN50	0.51	0.01
RR triangular index	0.76	p<0.0001
TINN	0.76	p<0.0001
LF (ms²)	0.86	p<0.0001
LF (nu)	0.04	0.84
HF (ms²)	0.55	0.01
HF (nu)	-0.04	0.83
LF/HF	0.03	0.87
SD1	0.52	0.01
SD2	0.88	0.02
SD1/SD2	0.4	0.1
α1	-0.02	0.89
α2	-0.05	0.78
α1/α2	-0.01	0.94
Correlation Dimension	0.28	0.10

Mean RR: Mean RR intervals;
Mean HR: mean heart rate;
SDNN: standard deviation of normal-to-normal R-R intervals;
pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50ms;
RMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval. ms: millisecond.
LF: low frequency;
HF: high frequency;
LF/HF: low frequency/high frequency ratio;
RRtri – Triangular index;
TINN – triangular interpolation of RR intervals;
SD1 – standard deviation of the instantaneous variability of the beat-to beat heart rate;
SD2 – standard deviation of long-term continuous RR interval variability;
SD1/SD2 ratio – ratio between the short - and long - term variations of RR intervals. ms: milliseconds; nu: normalized units.

Discussion

In relation to HRV analysis, it was stated that normalized units are more likely to obey parametric assumptions [12]. In line with this investigation, a previous study proposed a new method to analysis HRV that was based on modelling it as a linear combination of Gaussians [11]. In this sen-

se, we evaluated the p-value of two normality tests (Shapiro-Wilk and Kolmorogov-Smirnov) applied in RR intervals in a stationary period, i.e. the stable activation of a single control mechanism and a well-controlled experimental setting. The p-value of the Kolmorogov-Smirnov normality test did not present significant association with the HRV indices, although it tended to correlate with LF (0.06) and HF (0.07) indices in normalized units. Conversely, the p-value of the Shapiro-Wilk test applied in RR intervals presented significant association with great part of the linear HRV indices. Our findings support the p-value of the Shapiro-Wilk normality test applied in RR intervals as possible indicator of cardiac autonomic regulation function.

The TINN and RRTri indices are calculated according to the construction of a histogram of the density of normal RR intervals that contains the length of RR intervals in the x-axis and the frequency that they occur in the y-axis. The RRtri index has a close association with the standard deviation of all RR intervals and is not influenced by ectopic beats and artifacts because ectopic beats and artifacts are located outside the triangle [13]. The RRTri and TINN indices correspond to the overall modulation of the heart and reduction of the both indices are found in cardiac disorders and during exercise or physiological stress [13]. The SDNN index represents the global modulation of the heart [4]. Based on our study, the SDNN, RRTri and TINN indices presented strong and positive correlation with the p-value of the Shapiro-Wilk test applied in RR intervals. The normality test evaluates if the distribution of the sample fits in the Gauss curve [14]. A previous investigation reported that chronic heart failure patients with non-Gaussian HRV presented increased mortality compared to patients with reduced and less complex variability of heart rate [15]. The non-Gaussian HRV was analyzed through the non-Gaussian index proposed by the authors. This index aims to characterize an increased distribution of sudden alterations in heart period [5]. On the other hand, the authors investigated non-stationary periods, i.e. 24 hours, while we investigated healthy men under stationary condition. Our data supports the p-value of the Shapiro-Wilk test applied in RR intervals as an indicator of the global variability of heart rate, the higher the p-value for short term analysis, i.e. closer to non-parametric distribution, the higher the global modulation of the heart.

Regarding the Komorogov-Smirnov normality test applied in RR intervals, we also observed significant correlation with RMSSD, pNN50, HF in absolute and normalized units and SD1 indices. The pNN50 is the percentage of adjacent RR intervals with a difference of duration greater than 50ms while the RMSSD is root-mean square of differences between adjacent normal RR intervals in a time interval [2]. The SD1 index represents the transverse axis of the Poincaré plot and indicates the standard deviation of the instantaneous variability of the beat-to-beat heart rate and represents the parasympathetic activity influence on the sinoatrial node [1]. The four indices mentioned above correspond to vagal tone on the heart. It was previously reported that HRV in healthy subjects does not present gradual and slow convergence to a Gaussian distribution [15], an important condition of the multiplicative cascade model. Conversely, previous studies [4, 5] indicated that HRV frequency domain indices (LF and VLF ranges) of chronic heart failure patients, especially non-survivors, are more compatible with the multiplicative cascade model.

Our data also suggests that the HRV indices do not support gradual and slow convergence to a Gaussian distribution, because the higher the p-value of the normality test, the lower the probability of a Gaussian distribution and the higher the HRV indices values. In this sense, our results indicate that the higher the p-value of Komorogov-Smirnov normality test the higher the parasympathetic tone on the heart.

Considering only the Kolmorogov-Smirnov test applied in RR intervals, our data supports the idea that increased parasympathetic tone on the heart is closer to non-normal distribution of RR intervals. Normal distribution is a usually occurring continuous probability distribution, a function that indicates the likelihood that an observation in some context will fall between any two real numbers [10]. In this case we may surmise that a high probability of a RR interval fall between any two RR intervals is an indicator of reduced HRV.

As mentioned above, significant correlation was found between Kolmorogov-Smirnov normality test applied in RR intervals and HRV indices,

whereas no significant correlation was reported for the Shapiro-Wilk normality test. Conversely, the literature has indicated that Shapiro-Wilk normality test is the most powerful test for all types of distribution and sample sizes while Kolmorogov-Smirnov test is the least powerful test [10. However, Shapiro-Wilk normality test is not suitable for small sample. In our study we used at least 256 RR intervals. The number of RR intervals analyzed in our study helps to explain the absence of significance for the Kolmorogov-Smirnov normality test. Our findings support previous studies [16, 17] that reported Shapiro-Wilk as the most powerful normality test between three tests (Kolmorogov-Smirnov, Anderson-Dawling and Liliefors normality tests).

We investigated only women in order to avoid sex-dependent effects on cardiac autonomic regulation. The literature reported conflicting data regarding cardiovascular and physiological responses between men and women. Several studies have reported on gender-related differences regarding sympathetic and parasympathetic tone [18, 19] obtaining variable results, while other studies have failed to show significant differences whatsoever [20, 21]. Moreover, the menstrual cycle was also indicated to affect baseline nonlinear properties of HRV [22]. In order to exclude the interference of the follicular and luteal phases of the menstrual cycle on cardiac autonomic regulation we did not evaluate volunteers on 10-15 days and 20-25 days after the first day of the menstrual cycle.

Conclusion

The p-value of Shapiro-Wilk normality test applied in RR intervals presented strong association with parasympathetic and global indices of HRV in women. We suggest that this index can be useful for future HRV analysis.

Acknowledgements

This manuscript received financial support from FAPESP. The funding body provided financial support to make all procedures and in the decision to submit the manuscript for publication.

References

1. *Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996; 93:1043-65.*

2. *Vanderlei LC, Pastre CM, Hoshi RA, Carvalho TD, Godoy MF. Basic notions of heart rate variability and its clinical applicability. Rev Bras Cir Cardiovasc. 2009; 24: 205-17.*

3. *Costa T, Boccignone G, Ferraro M. Gaussian mixture model of heart rate variability. PLoS One. 2012; 7: e37731.*

4. *Abreu LC.). Heart rate variability as a functional marker of development. Journal of Human Growth and Development. 2012; 22: 279-281.*

5. *Kiyono K, Hayano J, Watanabe E, Struzik ZR, Yamamoto Y. Non-Gaussian heart rate as an independent predictor of mortality in patients with chronic heart failure. Heart Rhythm. 2008; 5: 261-8.*

6. *Kiyono K, Hayano J, Kwak S, Watanabe E, Yamamoto Y. Non-gaussianity of low frequency heart rate variability and sympathetic activation: lack of increases in multiple system atrophy and Parkinson disease. Front Physiol. 2012; 3: 34.*

7. *Mainardi LT, Sassi R. Analysis of scaling behavior of ECG signal during atrial fibrillation. Comput Cardiol. 2005; 32: 627–630.*

8. *Tulppo MP, Kiviniemi AM, Hautala AJ, Kallio M, Seppänen T, Mäkikallio TH. Physiological background of the loss of fractal heart rate dynamics. Circulation. 2005; 112: 314-9.*

9. *Makikallio TH, Hober S, Kober L, Torp-Pedersen C, Peng CK, Goldberger AL. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. Am J Cardiol. 1999; 83: 836-9.*

10. *Razali N, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. J Stat Model Anal. 2011; 2: 21–33.*

11. *Kobayashi H, Park BJ, Miyazaki Y. Normative references of heart rate variability and salivary alpha-amylase in a healthy young male population. J Physiol Anthropol. 2012; 31: 9.*

12. *Costa T, Boccignone G, Ferraro M. Gaussian mixture model of heart rate variability. PLoS One. 2012; 7: e37731.*

13. *Acharya UR, Joseph KP, Kannathal N, Lim C.M. Suri J.S. Heart rate variability: a review. Med Bio Eng Comput. 2006; 44: 1031-51.*

14. *Razali N, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. J Stat Model Anal. 2011; 2: 21–33.*

15. *Kiyono K, Struzik ZR, Aoyagi N, Sakata S, Hayano J, Yamamoto Y. Critical scale-invariance in healthy human heart rate. Phys Rev Lett 2004; 93: 178103.*

16. *Mendes M, Pala A. Type I error rate and power of three normality tests. Pak j Inform Techn. 2003; 2: 135-9.*

17. *Keskin S. Comparison of several univariate normality tests regarding type I error rate and power of the test in simulation based small samples. J Appl Science Res. 2006; 2: 296-300.*

18. *Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, Stein PK. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease acute myocardial infarction. Circulation. 1995; 91: 1936-1943.*

19. *Hogarth AJ, Mackintosh AF, Mary DA. Gender-related differences in the sympathetic vasoconstrictor drive of normal subjects. Clin Sci (Lond). 2007; 112: 353-361.*

20. *Fu Q, Witkowski S, Okazaki K, Levine BD. Effects of gender and hypovolemia on sympathetic neural responses to orthostatic stress. Am J Physiol Regul Integr Comp Physiol. 2005; 289: R109-R116.*

21. *Ng AV, Callister R, Johnson DG, Seals DR. Sympathetic neural reactivity to stress does not increase with age in healthy humans. Am J Physiol. 1994; 267: H344-H353.*

22. *Bai X, Li J, Zhou L, Li X. Influence of the menstrual cycle on nonlinear properties of heart rate variability in young women. Am J Physiol Heart Circ Physiol. 2009; 297: H765-74.*

Corresponding Author
Vitor Valenti,
Center for Autonomic Nervous System Studies (CESNA),
Department of Speech Pathology,
Faculty of Philosophy and Science,
UNESP,
Marilia, SP,
Brazil,
E-mail: vitor.valenti@marilia.unesp.br

Evaluation of the competence of residents at department of anesthesiology in the assesment of difficult airways and in the recognition and use of difficult airway devices

Elmas Kara[1], Ismail Aydin Erden[2], Banu Ayhan[2], Sennur Uzun[2], Ulku Aypar[2]

[1] Sincan State Hospital Ankara, Turkey,
[2] Hacettepe University Department of Anesthesiology And Reanimation Ankara, Turkey.

Abstract

Objective: The topic of 'Difficult airway management' represents a major part of training in Anesthesiology. The aim of this study is to determine the level of competence of residents in anesthesiology training in the assessment of difficult airways and recoginition and use of difficult airway devices, and whether residents feel confident in managing difficult airways and using difficult airway devices.

Materials and Methods: A survey composed of six sections was created for this purpose. After approval of the Hacettepe University Ethics Committee , twenty-nine (29) residents in the Anesthesiology training program at Hacettepe University were included in the study. The questions were asked to residents such as the training of difficult airway and their opinion on this topic, preoperative evaluation methods and experiences during the daily practice of anesthesia and their practice in a variety of difficult airway situations.

Results: Residents answered 93-100% of the questions aimed at evaluating theoretical knowledge. The most common methods used for evaluating airways were Mallampati score at 100%, oral aperture at 93%and the state and position of the teeth at 72%. Experience with fiberotic intubation ranged from 65-100% whereas percutaneous tracheotomy and Trans-tracheal jet ventilation experience remained at only 0-6%.

Conclusion: The results of the study revealed that residents were sufficient in assessing difficult airway and recognizing difficult airway devices. Residents believe that they are good enough about the ability to use most of the difficult airway devices and specified that practical training about the devices they are insufficient and apply the algorithm for the management of difficult airway should be extended. They notified that they achieved to this positive result through difficult airway management courses and practice studies, teaching the alternative airway techniques extensively and accessibility of the devices on difficut airway carts.

Key Words: preoperative assessment, difficult airway management, difficult airway devices, difficult airway algorithms.

Introduction

It is known that the problems associated with airway management during anesthesia application is an important cause of morbidity and mortality (1). Developed countries have performed studies evaluating their institutions and doctors in terms of equipment, training and implementation and used these data as guides in order to further improve the difficult airway management in their countries (2-4). In recent years, while the number of different airway devices that can be used in airway management has gradually increased, at the same time, organizations such as the American Society of Anesthesiologists (ASA) and Difficult Airway Society (DAS) have developed algorithms that can be used for the situations of difficult airway and whose clinical use has been proposed (5,6).

The topic of 'Difficult airway management' represents a major part of the educational process of Anesthesiology residents. Nevertheless, the stiuations such as whether the education is adequate, the levels of recognition and being able to use of the difficult airway devices by residents

and to feel adequate in this issue are matters of debate. The aim of this study is to determine the level of competence of residents of Department of Anesthesiology and Reanimation in terms of the assessment of difficult airways, recoginition and use of difficult airway devices and feel confident in managing difficult airways.

Materials and methods

This study was conducted at Hacettepe University Faculty of Medicine Adult Hospital between March 2013 and April 2013. After the approval of Hacettepe University Non-Interventional Clinical Research Ethics Committee was obtained, the study was started. Twenty-nine (29) research assistant physicians, who were undergoing training in Hacettepe University, Department of Anesthesiology and Reanimation, were included in the study.

A survey composed of six sections were prepared. Among twenty nine residents who volunteered to participate in the study; while those who were in the first two years of training were included in the 'Junior' group; those who were in the third, fourth and fifth years of training were included in the 'Senior' group. The questions were posed to residents related to training that they have received on difficult airway and their opinions on this subject, preoperative assessment methods and their experiences during daily practices of anesthesia and applications in the situations of a variety of difficult airway. Two questions were asked questioning their thoughts and experiences related to airway devices; LMA, Fastrach, Ctrach, Videolaryngoscopy, Fiberoptic Bronchoscopy, Exchange Catheter of Intubation Tubes (Tube Exchanger), Percutaneous Tracheostomy Kit, Transtracheal Jet Ventilator (TTJV) and devices. It has been aimed to form a judgment on the level of knowledge of researchers in this issue with theoretical questions.Thus, a total of thirty-three questions were asked to answer from twenty-nine residents who participated in this study.

Statistical methods

Student's t test was used for the analysis of demographic data. $P > 0.05$ was considered statistically significant. The data in the second, third, fourth, fifth ans sixth parts were expressed as percent.

Results

Fifteen (15) residents were included in the 'Junior' group, and the other fourteen (14) were included in the 'Senior' group. It has been determined that, practical training on difficult airway equipment and their use were taken a rate of 92.8%, in the senior group and 26.6% in the junior group. Eighty-two.seven % of residents have stated that the training on algorithm, devices and application of difficult airway that they have received was not enough; 58.6% and 41.3% of them have thought that the training should be repeated once and twice a year, respectively. Eight questions aimed at measuring the theoretical knowledge about airway and difficult airway were directed to the residents. Five, one and two of eight questions were answered by the residents as a rate of 100%, 96.5% and 93.1%, respectively. All senior and junior group (100%) have stated that; they have routinely saved the preoperative airway evaluation in the anesthesia assessment form.

The most commonly used parameters when evaluating the difficult airway preoperatively were determined as; Mallampati score (100%), mouth opening (interinsisor gap) (93.1%) and language - tooth structure (72.4%). When the materials and methods most commonly used when a patient, who was considered as a difficult airway, was extubated were asked; the most commonly preferred materials and methods were; awake extubation (45.4%) and endotracheal tube exchanger (24.2%). One hundred % of senior and 80% of junior groups have stated that they have informed their patients assessed as difficult airway on this subject and asked them to warn their doctor about future potential anesthetic experience.

In order to assess the thoughts and experiences of residents about airway devices, we have asked them to state whether they have used airway devices such as LMA Fastrach, Ctrach, Videolaringoscopy, Fiberoptic Bronchoscopy, Tube Exchanger, Percutaneous Tracheostomy Kit and TTJV and devices, if they used, how many times and whether they felt theirselves sufficient in the use of airway devices. The data obtained are shown in Table 1 by dividing into groups.

Table 1. Airway devices and use

Airway devices	Asisstant doctor (1.-2. year) (n=15)				Asisstant doctor (3.-4. year) (n=14)			
	Use	Not use	Ability to use enough	Ability to use not enough	Use	Not use	Ability to use enough	Ability to use not enough
Laryngeal mask	%100	%0	%86.6	%13.3	%100	%0	%100	%0
Fastrach	%60	%40	%0	%100	%78.5	%21.4	%50	%50
C trach	%33.3	%66.6	%0	%100	%92.8	%7.1	%42.8	%57.1
Fiberoptic bronchoscopy	%33.3	%66.6	%0	%100	%100	%0	%28.5	%71.4
Video laryngoscope	%6.6	%93.3	%6.6	%93.3	%28.5	%71.4	%7.1	%92.8
Tube exchanger	%40	%60	%13.3	%86.6	%92.8	%7.1	%57.1	%42.8
Percutaneous tracheostomy	%0	%100	%0	%100	%0	%100	%0	%100
TTJV and devices	%0	%100	%0	%100	%14.2	%85.7	%0	%100

The question of after how many interventions you need to call for help when you have encountered a difficult intubation in an unpredictable patient was answered as two and three attempts by 44.8% and 27.5% of all residents, respectively.

They were asked to write the first three steps in parallel with situations mentioned that they will apply when they have faced with a patient who they could not predict as difficult airway . The first situation mentioned was: patients with difficult intubation and easy mask ventilation. The most commonly preferred methods were; 1. Fiberoptic Intubation (58.6%) 2. Continue to mask ventilation (41.3%) 3. LMA (37.9%). Intubation with Fiberoptic Bronchoscopy (55.1%), LMA (48.2%), and to call for help (31.0%) were identified as the most preferred method in patients with difficult intubation and mask ventilation.

Discussion

Preoperative evaluation is the first step which lead us to predict the patients who may be with difficult airways. It has been identified in a study conducted by Gurkan et al. (7) that; Mallampati test, mouth opening, neck mobility and temporomandibular joint were evaluated in the preoperative evaluation as a rate of 98%, 93%, 93% and 70%, respectively. In our study, in a similar manner; Mallampaty score, mouth opening and tongue and tooth structure were the first three parameters evaluated most commonly as a rate 100%, 93.1% and 72.4%, respectively. These findings were consistent with the preoperative tests proposed for difficult intubation in the TARS Preoperative Preparation Guide (8).

In cases where the physicians who evaluated the patient and who will perform the anesthesia are different, recording the information in the anesthesia assessment form is gaining more importance as the preoperative evaluation. It has been determined in a study conducted by Gürkan et al. (7) that while 93% of the preoperative evaluation was recored in the anesthesia assessment form, this rate was expressed as 100% in our study.

TARS suggest the documentation of the tips which can help the patient's subsequent possible initiatives in the postoperative follow-up of the patient with difficult airway in difficult airway management practice guidelines and preparation of epicrisis for this purpose (9). Our study; in parallel to this information, it was detected that the patients evaluated as difficult airway were informed at a rate of 89.6% and the necesity of warning the doctor for the subsequent anesthesia experience was told. We have reached the conclusion that here in our clinic, the issue of informing the patients and their relatives when faced with difficult airways had a great importance.

In difficult airway algorithm of ASA; it is proposed in the case of failed intubation attempts that: using the non-invasive airway techniques with elective alternative approach to if mask ventilation can be provided; providing ventilation with LMA, Fastrach, LMA ProSeal if ventilation with mask is unsuccessful. If ventilation is possible with this tools; alternative non-invasive difficult airway techniques are recommended to use, if ventilation is

not possible; combitube, rigid bronchoscopy and transtracheal jet ventilation which are emergency noninvasive ventilation techniques are recommended to use (5).

While in the study conducted by Ezri et al. (10), the first preferences in the case of an unexpected failed intubation and adequate mask ventilation were; fiberoptic intubation by waking the patient 29% and intubation LMA 22%, fiberoptic intubation and LMA were preferred at rates of 58.6% and 37.9%, respectively in our study. In the same study (10), the first three airway techniques preferred when mask ventilation was difficult or impossible after unexpected failed intubation were LMA 85%, combitube 48% and TTJV (transtracheal jet ventilation) 42%. In our study, the first three preferences in a similar situation were; emergency fiberoptic intubation (55.1%), LMA (48.2%) and to call for help (31%). In the study conducted by Ezri et al. (10), LMA was selected as the first choice to maintain the ventilation . In our study, fiberoptic intubation was the most preferred method in both cases; the supraglottic airway tools have been proposed in the difficult airway algorithm of ASA as the first choice in cases of unexpected failed intubation if mask ventilation is not possible (5, 10). Residents need more training in the application of difficult airway algorithm.

Burkle et al. (11) were investigated failed intubation in 37482 patients who were planned intubation using a laryngoscope. In 161 patients (0.4%) whose intubation was failed by direct laryngoscopy; only 5 of them were canceled due to failed intubation, 1 patient underwent regional anesthesia mortality was not observed. It has been reported that this positive conclusion has been reached by teaching widely the alternative airway techniques as a result of the difficult airway course and implementation studies and the equipment were in the difficult airway cars. However, it has been stated that the use of alternative techniques in the early period without insisnting on unsuccessful attempts was important in terms of airway trauma and so there was no non-intubated-ventilated patient. ASA suggests that standard laryngoscopic intubation attempts should be limited with 3 attempts and it should be passed to alternative techniques in the case of being unsuccesful. The conclusion was reached that the repeated intubation experience in case of failure resulted more in mortality and brain damage (12). In our study, the question of after how many attemts you call help when you encounter with in an unpredictable patients was aswered by all residents as two attempts and three attempts at rates of 44.8% and 27.5%, respectively and a result supporting this conclusion has been reached.

It has been reported in a study conducted by Gurkan et. al (7) including 44 clinics, residents have performed fiberoptic intubation in only three institutions. In continuation of the study conducted by Ezri et al. (10), the fiberoptic intubation experience was determined as 59%. In our study, this rate was in the senior and junior groups were 100% and 65.5%, respectively.

Fiberoptic intubation is a method that is being proposed in difficult airway algorithm of ASA, in the cases that both awake intubation and direct laryngoscopy are failed; in the the elective approach to airway that ventilation is possible and in difficult airway algorithm of DAS, in secondary intubation plan when direct laryngoscopy is failed (11, 13). Intubation with fiberoptic bronchoscopy is an airway technique emphasized theoretical and practically in every period of our clinic assistant training; providing the opportunity to earn experience by residents practically especially in the second two-year period of training

When it is thought that extubation is being condidered as safe in difficult airway extubation strategy of DAS; the intubation tube exchange catheter (tube exchanger) is recommended as one of the advanced techniques that can be applied (14). In a study conducte by Ezri et al. (10), the experience with intubation tube exchange catheter was reported to be as 28%; in our study, this rate is 65.5%. In addition, tube exchanger was determined as the the second preference of residents with a rate of 24.2% when the airway techniques that they use most often during difficult airway extubation were asked.

In our study, the responding rate of the questions aiming to measure theoretical knowledge about difficult airway was determined as 93.1to 100%; the answers to theoretical questions responded by residents in the senior and junior goups were evaluated as similar. It has been conculuded that the differences in the application of airway devices may have caused that the practical trai-

ning of some of airway devices was given in the first two years (LMA, LMA Fastrach) or in the secont two years (Fiberoptic bronchoscopy, Videolaringoskop, Ctrach).

The use of clinical practice guidelines or algorithms is believed to provide benefits in terms of the reduction of complications in clinical practice and raising the standards (6). When the patients between the years 1993-1999 that ASA difficult airway algorithm was published and the patients between the years of 1985-1992, it has been seen that the mortality rate related to airway problems decreased from 67% to 35% (12). The study conducted by Gurkan et al. (15) has showed that 58% of the residents in our country have believed that the education they received about the management of difficult airway was not sufficient, 42% - 50% of them did not know how oxygenation would provide from the cricothyroid membrane. It has been shown in a study conducted by Dunn et al. (16) that the two months of difficult airway rotation during the specialized training has contributed to the recoginition on the different techniques and the development of the skills in this respect dramatically. In our study, 82.7% of the residents do not think that training they received about difficult airway algorithm, difficult airway equipments and their applications is enough. Fifty-eight.six % of the residents think that the difficult airway training should be repeated twice a year. As is apparent from these findings, although difficult airway issue is a vital issue, residents see themselves and their education in this matter are inadequate. Although the experiences of residents about difficult airway equipments were close or similar to the rates found in in previous studies, the experiences about some airway techniques (TTJV, Percutaneous tracheotomy, Videolaringoskopy) were observed to be inadequate. After the knowledge and skills of residents in airway management were found to be insufficient in a study conducted in Denmark, the three-day mandatory airway course including al residents that, theoretical training, workshops and simulation training were applied, has been implemented (57). It has been concluded in a study conducted by Gurkan et al. (15) in Turkish Anaesthesiology and Reanimation Society (TARS) 2004 Congress that close to 40% of participants including the specialists, have found their education about the difficult airway management as insufficient. In parallel with this information; the results may be achieved that the difficult airway management training should include not only residency period also after specialization period and it would be useful to repeat from period to period.

This study; has created the idea that to create a rotation standardized on a national scale for difficult airway management in each anesthesia residency program would provide that the residents gain sufficient knowledge and skills about the routine and difficult airway management. Until this rotation is organized; the clinics should prepare training programs repated and renewed periodically about difficult airway management and devices for residents and other allied health professionals in the context of their own circumstances. It should be aimed to the reduce of the complications associated with airway management with widespread use of difficult airway algorithm and increasing the training on this issue and to raise standards with the use of modern airway devices in an approach to the difficult airway. The wider studies which will be done about this issue including allied health professionals in the field of anesthesiology are needed.

References

1. *Domino KB, Posner KL, Caplan RA, Cheney FW. Airway injury during anesthesia: a Closed Claims Analysis. Anesthesiology 1999; 91: 1703-1711.*

2. *Rosenblatt WH, Wagner PJ, Ovassapian A, Kain ZN. Practice patterns in managing the difficult airway by anesthesiologists in the United States. Anesth Analg 1998; 87: 153-157.*

3. *Jenkins K, Wong DT, Correa R. Managemen choices fort he difficult airway by anesthesiologists in Canada. Can J Anesth 2002; 49:850-856.*

4. *Mellado PF, Thunedborg LP, Swiatek F, Kristensen MS. Anaesthesiological airway management in Denmark: Assesment, equipment and documentation. Acta Anaesthesiol Scand 2004; 48: 350-354.*

5. *The American Society of Anesthesiologists Task Force on Management of the Difficult Airways. Practice guidelines for management of the difficult airways. Anesthesiology 2003; 98: 1269-1277.*

6. *Difficult Airway Society Guidelines for Management of the Unanticipated Difficult İntubation Henderson*

JJ, Popat MT, Latto IP, Pearce AC; Difficult Airway Society Anaesthesia. 2004 Jul; 59(7): 675-694.

7. *Gürkan Y, Toker K, Solak M. Türkiye'de Eğitim Kurumlarinda Hava Yolu Yönetimi: Değerlendirme, Ekipman ve Dökümantasyon. TARD Dergisi, 2007; 2: 35*

8. *Türk Anesteziyoloji ve Reanimasyon Dernegi (TARD). Anestezi Uygulama Kilavuzlari. Preoperatif Hazirlik. Kasim 2005; 1: 1-9.*

9. *Türk Anesteziyoloji ve Reanimasyon Dernegi (TARD). Anestezi Uygulama Kilavuzlari. Zor Hava Yolu. Kasim 2005: 1; 1-9.*

10. *Tiberiu Ezri, Peter Szmuk, MD, R. David Warters, Jeffrey Katz, Carin A. Hagberg. Difficult Airway Management Practice Patterns Among Anesthesiologists Practicing in the United States: Have We Made Any Progress? Journal of Clinical Anesthesia 2003; 15: 418-422.*

11. *Burkle CM, Walsh MT, Harrison BA, Curry TB, Rose SH. Airway management after failure to intubate by direct laryngoskopy: outcomes in a large teaching hospital. Can J Anesth 2005; 52: 634-640.*

12. *Peterson GN, Domino KB, Caplan RA, et al. Management of the Difficult Airway:: a Closed Claims Analysis. Anesthesiology 2005; 103: 33-39.*

13. *Benumof JL: Management of the difficult airway – with special emphasis on awake tracheal intubation. Anesthesiology 1991; 75: 1087-1110.*

14. *DAS Extubation Guidelines - ''At risk'' Algorithm / Difficult Airway Society Guidelines http://www.das.uk.com/guidelines/ddl.html*

15. *Gürkan Y, Toker K. Türkiye'de Anestezistlerin Hava Yolu İdaresine İlişkin Klinik Uygulamalari, Ekipman Durumu ve Eğitimi. TARDD- 2006; 34: 241- 248.*

16. *Dunn S, Connelly NR, Robbins L. Resident training in advanced airway management. J Clin Anesth 2004; 16: 472-476.*

17. *Rosenstock C, Qstergaard D, Kristensen MS, et al. Residents lack knowledge and practical skills in handling the difficult airway. Acta Anesthesiol Scand 2004; 48: 1014-1018.*

Corresponding Author:
Elmas Kara,
Sincan State Hospital Ankara,
Turkey,
E-mail: elmas_eyk@hotmail.com

Depression and physical disability, their influence in quality of life in patients with multiple sclerosis - which factor has greater influence?

Nexhat Shatri[1], Nazim Dakaj[1], Petrit Bara[2], Kamber Zeqiraj[1]

[1] University Clinical Center of Kovova, Prishtine, Republic of Kosova,
[2] University Hospital Center "Mother Theresa" Tirana, Albania.

Abstract

Introduction: Depression and physical disability are among other factors influencing quality of life (QoL) in multiple sclerosis (MS) patients. Interferons, particularly interferon beta-1b (IFNβ-1b) may have depressive effect in MS patients.

The study purpose was to test two hypotheses:

1. Depression affects more QoL than physical disability in multiple sclerosis patients.
2. Depression is more pronounced in MS patients treated with IFNβ-1b compared with untreated patients.

Study Design and Setting: Prospective study in a Clinic of Neurology in University Clinical Center of Kosova.

Material and methods: Study included 50 patients with definite MS, according to McDonald's criteria, observed as out-patient/admitted in the clinic of Neurology between January 2012 and January 2014. Depression was diagnosed using the Diagnostic and statistical manual of mental disorders criteria (DSM-IV), and its severity was assessed using the Beck's depression inventory (BDI). Physical disability was evaluated with Kurtzke expanded disability status scale (EDSS). The QoL was assessed using the Medical Outcomes Study Short Form 36-item Questionnaire (SF-36).

Results: The mean age of patients was 36.7 ±8.993 years. The mean EDSS score was 3.3 (range 1 to 8). The mean BDI score was 14.9. The prevalence of depression in MS patients was 62% (31/50). Depression and physical disability influence QoL. No difference ($P > 0.05$) was found in the level of depression between MS patients treated with IFNβ-1b and untreated.

Conclusion: In cases where depression is negligible, the role of physical disability in quality of life is highlighted. The particular concern regarding depressive effect of IFNβ-1b is not clearly established.

Key words: Multiple Sclerosis, EDSS, Depression, QOL SF-36, BDI, IFNβ-1b

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, demyelinating neurologic disease of unknown etiology. Physical disability and depression is very frequent symptom seen in MS patient, negatively affecting quality of life of these patients.

Neuropsychiatric disorders in general and particularly depression are encountered for the main causes of disability world-wide (1). The presence of psychiatric symptoms in patients with multiple sclerosis has been known since the nineteenth century, when Charcot, in his lectures in Salpetriere hospital introduced for the first time the clinical-pathological description for "disseminated sclerosis" (2). These symptoms are attributed both to the psychosocial impact of a disabling illness and to cerebral demyelination (3).

Depression is a symptom that is very often seen in multiple sclerosis patients. Most comparative studies have reported higher rates of depression among groups of patients with MS compared with groups of patients with other chronic diseases, including other neurological diseases (4,5,6). During the life span of patients with MS, the risk of manifesting depressive spectrum disorders is very high (7). Many studies have shown that the frequency of appearance of depression in patients with multiple sclerosis ranges from 40-60% (8). The point prevalence of major depressive syndrome in people with MS is around 14% but can be even higher (9).

In terms of early detection as well as the successful treatment of it, depression is a big challenge (10). Management of depression in a dis-

order like MS is very important. Except that depression is very common clinical manifestation in patients with MS, it is also one of the main determinants of the quality of life of these patients (11). Depression can further compromise cognitive functions in patients with MS and may lead to suicidal attempt (12,13). If not treated, the social relationship between patients with MS and their environment can be disturbing (14). In another hand, treating depression improves adherence to therapy with interferon beta-1b for the treatment of MS (15). Numerous studies show that depression is often overlooked and, even if detected, is not adequately treated (16).

Physical disability is another important clinical factor that impacts QoL of MS patients. Results from several studies indicate a strong correlation between disability and QoL (17,18).

There are some findings that disease modifying drugs, especially interferon beta- 1b (IFNβ-1b), may have depressogenic effects. Some studies report severe depression and suicide attempts among MS patients treated with interferon β who had no prior psychiatric history while other studies have found no evidence to support interferon-β alone causing or exacerbating depression (19,20).

Material and Methods

During the study, 50 patients with multiple sclerosis were evaluated. These patients visited out-patient facility or were admitted in the Clinic of Neurology at the University Clinical Centre of Kosova in Pristina from January 2012 to January 2014.

All patients included in the study met the McDonald et al. (2010) criteria for definite multiple sclerosis. The diagnosis of depression is made based on the criteria of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) and depression rate is determined based on the Back Depression Inventory-BDI. This questionnaire contains 21 groups of statements that describe the way the patients have been feeling during the past two weeks, including the examining day as well. All patients underwent complete clinical neurological examination and the level of disability was evaluated using the Expanded Disability Status Scale (Kurtzke et al. 1983). Patients' quality of life (QOL) is evaluated using special questionnaire SF - 36 (Medical Outcomes Study Short Form 36 item Questionnaire). Through this questionnaire there were assessed 8 domains of life: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. The results of the study are analyzed using the SPSS program, version 16. Correlation between EDSS and depression (BDI), EDSS and quality of life (QOL), EDSS and age as well as correlation between depression (BDI) and quality of life (QOL) was evaluated using Spearman's rank correlation test. Statistical significance is calculated by the Student test, while p-values < 0.05 are considered statistically significant.

Results

From 50 MS patients included in the 31 (62 %) were female and 19 (38 %) were male.

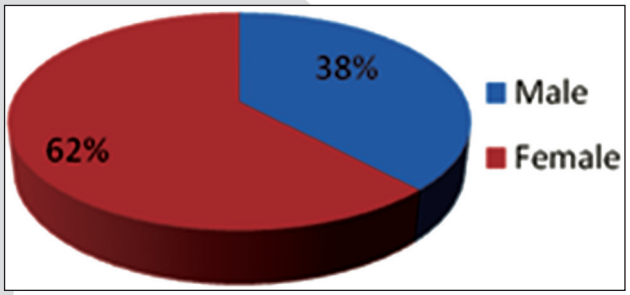


Chart 1. Gender distribution of patients with MS

The average age of patients at the time of study was 36.7 years (SD 8.993). The average age of male patients was 35.8 years (SD 8.657), whereas for women it was 37.2 years (SD 9.290). When analyzing the course of the disease, 86% of patients were with relapsing–remitting and 14% with secondary progressive form of multiple sclerosis. None of the patients were with the primary progressive form of the disease. The average value of the EDSS score was 3.3 (range 1 to 8). In male patients the average value of EDSS score was slightly lower than in females (3.1 to 3.4 respectively), but there was no statistically significant difference of EDSS between gender ($t = 0.469$; $P = 0.641$, for $p< 0.05$). The average score of BDI was 14.9 (minimum 0, max 45 points). The average BDI score of male patients was slightly higher (15.05), compared to females (14.83) (Chart 2).

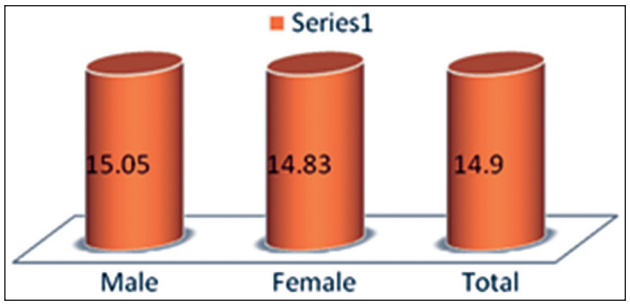


Chart 2. Mean BDI sore of patients according to the gender

However there was no statistically significant difference of average BDI scores between gender (t = 0.067, P = 0.946, for the p <0.05 level). Out of the 50 patients included in the study, 20 (40%) have manifested symptoms of depression of varying degrees (BDI score ≥17). Eleven (22%) patient had mild mood disturbance (BDI score 11-16), and 19 (38%) patients had manifested ups and downs within normal range (BDI score 1-10) (Table 1).

Results of our study show that the rate of depression, evaluated with Beck Depression Inventory, is positively correlated with the level of disability (EDSS) (rho = 0.740, P < 0.05) and negatively correlated with quality of life (QOL) (rho= -0.691, P < 0.05) (Table 2and 3).

Out of 19 (38%) patients with ups and downs within normal range of depression, 13 (68%) had **EDSS < 2.5** and mean **QoL 83.13%,** while 6 (32%) had **EDSS ≥ 2.5** and mean **QoL 60.92%.**

From 11 (22%) patients with mild mood disturbance, 4 (36%) with **EDSS < 2.5** and mean **QoL 64.96%,** while 7 (64%) were with **EDSS ≥ 2.5** and mean **QoL 64.19%.** From other 11 (22%)

Table 1. The level of depression in MS patients distributed according to the gender

Level of depression	Gender					
	Male		Female		Total	
	N	%	N	%	N	%
Ups and downs within normal range (1-10 score)	5	26	14	74	19	38
Mild mood disturbance (11-16 score)	4	56	7	44	11	22
Borderline clinical depression (17-20 score)	6	55	5	45	11	22
Moderate depression (21-30 score)	3	50	3	50	6	12
Severe depression (31-40 score)	1	50	1	50	2	4
Extreme depression (>40 score)	0	0	1	100	1	2
Total	**19**	**38**	**31**	**62**	**50**	**100**

Table 2. Correlation between Expanded Disability Status Scale (EDSS) and Depression (BDI)

Correlations			EDSS	BDI
Spearman's rho	EDSS	Correlation Coefficient	1.000	**.740****
		Sig. (2-tailed)	.	**.000**
		N	50	50
	BDI	Correlation Coefficient	.740**	1.000
		Sig. (2-tailed)	.000	.
		N	50	50

***. Correlation is significant at the 0.01 level (2-tailed).*

Table 3. Correlation between depression (BDI) and quality of life (QOL)

Correlations			BDI	QoL
Spearman's rho	BDI	Correlation Coefficient	1.000	-.691**
		Sig. (2-tailed)	.	.000
		N	50	50
	QoL	Correlation Coefficient	-.691**	1.000
		Sig. (2-tailed)	.000	.
		N	50	50

***. Correlation is significant at the 0.01 level (2-tailed).*

MS patients, with borderline clinical depression, in 2 (18%) **EDSS < 2.5 and mean QoL 51.56%** and in 9 (82%) with **EDSS ≥ 2.5 and mean QoL 53.69%.** Moderate depression had 6 (12%) patients and all of them had **EDSS ≥ 2.5.** Mean **QoL in these patients was 37.37%.** Other 3 (6%) patients manifested severe depression, they had **EDSS ≥ 2.5 and t**he mean **QoL** was **46.17%** (Table 4).

Table 4. EDSS and QoL in MS patients with depression (BDI score >=17)

	No.(%)	QoL
EDSS <2.5	2 (10%)	51.6%
EDSS >=2.5	18 (90%)	45.75%

EDSS – Expanded Disability Status Scale
QoL- Quality of Life
BDI – Back Depression Inventory
No – Number of patient

Patients with higher rates of depression (BDI score ≥ 17) had a significantly lower percentage of quality of life, 40.7%, compared with those with lower rates of depression (BDI score 11-16) 73.7%, and those without signs of depression (BDI score 1-10) 81.3%. A significant negative correlation is found between EDSS and quality of life, showing that higher levels of EDSS score are associated with significant reduction in the percentage of the total quality of life (rho= - 0.718, P < 0.05) (Table 5).

Results of the study showed that there is **positive correlation** between the level of disability (EDSS) and age, indicating that older patients with multiple sclerosis have higher values of EDSS (greater disability) (**rho=0.757; P < 0.05)**.

Although the mean percentage of QoL in patients treated with interferon beta-1b was higher compared to the mean percentage of **QoL** in patients not treated, **Student test** did not show statistically significant difference in the average percentage of QoL between treated and untreated patients (**t = -0.783; p = 0.454, at p < 0.05**). The Student test did not show also statistically significant difference in the average scores of BDI between patients treated and those not treated with **interferon beta-1b** (**t = -0.573, p = 0.581, at p < 0.05**).(Table 6).

Table 5. Correlation between Expanded Disability Status Scale and quality of life (QOL)

Correlations			EDSS	QoL
Spearman's rho	EDSS	Correlation Coefficient	1.000	**-.718****
		Sig. (2-tailed)	.	**.000**
		N	50	50
	QoL	Correlation Coefficient	-.718**	1.000
		Sig. (2-tailed)	.000	.
		N	50	50

***. Correlation is significant at the 0.01 level (2-tailed).*

Table 6. Clinical and demographic characteristics of patients treated and those untreated with interferon beta-1b.

Classification of patients	No (%)	Gender		The mean age (SD)	The mean disease duration (SD)	The mean EDSS (SD)	The mean QoL (SD)	The mean BDI (SD)
		M (%)	F (%)					
Patients treated with interferon beta-1b	30 (60)	11 (38)	19 (62)	37.25 (± 9.03)	9.89 (± 4.96)	3.23 (± 1.92)	**63.6% (± 20.13)**	**14.7 (±7.44)**
Patients not treated with interferon beta-1b	20 (40)	4 (20)	16 (80)	35.8 (±9.28)	7.9 (± 6.94)	3.05 (± 1.77)	**54.6 (± 17.94)**	**13.1 (±5.74)**
Total	**50**	**15**	**35**					

No – Number
M – Male
F – Female
SD – Standard Deviation
EDSS – Expanded Disability Status Scale
QoL – Quality of Life
BDI – Back Depression Inventory

Discussion

Numerous studies have shown that depression is a very common disorder that is encountered in patients with multiple sclerosis. For the diagnosis of depression among five symptoms must be included: sadness, depressed mood, and loss of interest and pleasure in usual activities of life (21). Review of affective disorders in patients with multiple sclerosis, in 1990, has revealed that the majority of studies have reported that depressive symptoms have higher incidence and prevalence in patients with multiple sclerosis compared with patients with other neurological diseases (22). Studies have also shown that the prevalence of depression in multiple sclerosis is higher compared with groups of patients with other chronic diseases (23).

Prevalence of depressive disorders ranges 27% -75%, while in patients with MS it is between 47% and 54% (24,25). The presence of depression among our MS patients was 36%, which is lower than that reported in the studies cited above. According to the results of our study out of 18 (36%) patients with multiple sclerosis who manifested symptoms of clinical depression, 4 (22.2%) have manifested severe and extreme depression. The average value of BDI scores of patients in our study was 14.9, which is within the current gold standards for the diagnosis of depressive disorders in people with multiple sclerosis according to the Goldman consensus group (cut-off score 13 in Beck inventory) (26). In our study a positive correlation resulted between EDSS and depression (rho= 0.740, $P < 0.05$). A positive correlation between depression and EDSS is also found in a study in Serbia (27), while in another study conducted in Bosnia and Herzegovina there was no correlation obtained between EDSS and depression (28). The results of our study show that people with higher values of depression (BDI score ≥ 17) have significantly lower average of quality of life (40.7%) compared with those with lower values of depression and those without symptoms for depression (79.1%).

Many studies have explored the relationship between EDSS and quality of life in patients with multiple sclerosis. Results from several studies indicate a strong correlation between disability and QOL (29,30). Our results show that the overall quality of life was significantly lower in patients with high EDSS score. The Spearman's rank correlation test in our patients showed that EDSS is in a significant negative correlation with QOL (rho= - 0.718, $P < 0.05$). Approximately, same results, regarding correlation of EDSS and QOL were obtained in a study conducted in Serbia (26). Our study revealed a negative correlation between BDI and QOL as well (rho= -0.691, $P < 0.05$). Positive correlation was found between EDSS and age (rho = 0.757, $P < 0.05$) and that correlation is evident in many other studies in the world and the region.

The leaflets accompanying interferon β 1b include warnings about their use in depression and/ or previous psychiatric history. There are studies that support severe depression among MS patients treated with interferon-β who had no prior psychiatric history while other studies have found no evidence to support interferon-β alone causing or exacerbating depression (19,20). The result of our study could not establish clear evidence that treatment with interferon beta-1b causes depression. The Student test did not show statistically significant difference in BDI mean scores between the patients treated and those not treated with **interferon beta-1b** (**t= -0.573, P > 0.05**).

There are conflicting data in the literature regarding influence of treatment with interferon beta-1b in QoL in MS patients. Some data report that treatment with interferon beta-1b patients treated with interferon beta-1b improves quality of life in MS (31), while other shows no effect (32). The results of our study show higher mean percentage of QoL in patients treated with interferon beta-1b compared to the mean percentage of **QoL** in patients not treated (63.6% ± 20.13 vs 54.6% ± 17.94 respectively). However the **Student test** did not show statistically significant difference in the QoL between treated and untreated patients (**t = -0.783; P > 0.05)**.

Conclusions

The results of our study support the first hypothesis **Depression affects more QoL than physical disability.** We concluded that depression and physical disability represent the main factors that determine impaired quality of life in patients with MS. Our results show that depression has greater influence in QoL of MS patients than physical disability. With the increasing level of depression the

impact of disability on QoL minimizes. In cases where depression is negligible, the role of physical disability in the quality of life is highlighted.

Regarding the second hypothesis tested in this study **Depression is more pronounced in patients treated with IFNβ-1b compared with untreated patients**, results of our study do not support it. The particular concern regarding depressive effect of IFNβ-1b is not clearly established in our study.

References

1. *World Health Report. Mental Health, New Understanding, New Hope, Chapter 2. Geneva: World Health Organization, 2001; 20_/45.*
2. *Charcot JM. Lectures on the diseases of the nervous system. Philadelphia: Henry C Lea, 1879.*
3. *Goeb JL, Even C, Nicolas G, Gohier B, Dubas F, Garré JB. Psychiatric side effects of interferon-beta in multiple sclerosis. Eur Psychiatry. 2006 Apr; 21(3): 186-93. Epub 2005 Dec 28.*
4. *Minden SL, Orav J, Reich P. Depression in Multiple Sclerosis. General Hospital Psychiatry 1987; 9: 426_/34.*
5. *Schiffer R, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis: An epidemiologic study. Archives of Neurology 1984; 41: 1067_/69.*
6. *Papucæ E, Stelmasiak Z. Factors predicting quality of life in a group of Polish subjects with multiple sclerosis: Accounting for functional state, sociodemographic and clinical factors. ClinNeurolNeurosurg. 2012; 114: 341–6.*
7. *Minden SL, Schiffer RB. Affective disorders in multiple sclerosis: Review and recommendations for clinical research. Archives of Neurology 1990; 47: 98_/104.*
8. *Bakshi R, Shaikh ZA, Miletich RS, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000; 6(3): 181-5.*
9. *Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. Am J Psychiatry 2002; 159: 1862_/68. Goldman Consensus statement on depression in MS Goldman Consensus Group 332 Multiple Sclerosis.*
10. *Schiffer RB, Rao SM, Fogel BS. Neuropsychiatry, 2nd edition. Baltimore: Lippincott Williams and Wilkins, 2003.*
11. *D'Alisa S, Miscio G, Baudo S, Simone A, Tesio L and Mauro A.: a classification-regression (CART) study. DisabilRehabil 2006; 28: 307–314.*
12. *Arnett PA, Higginson CI, Voss WD, Wright B, Bender WI, Wurst JM, et al. Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. Neuropsychology 1999; 13: 434–446.*
13. *Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology 2002; 59: 674–678.*
14. *Maybury CP and Brewin CR. Social relationships, knowledge and adjustment to multiple sclerosis. J NeurolNeurosurg Psychiatry 1984; 47: 372–376.*
15. *Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA and Rudick RA. Treatment of depression improves adherence to interferon Beta-1b therapy for multiple sclerosis. Arch Neurol 1997; 54: 531–533.*
16. *Mohr DC, Hart SL, Fonareva I and Tasch ES. Treatment of depression for patients with multiple sclerosis in neurology clinics. MultScler 2006; 12: 204–208.*
17. *Hansen H., Henriksen N., Stenager E Trends in survival and cause of death in Danish patients with multiple sclerosis. DOI: 10.1093/brain/awh104. Brain 2004; 127: 844±850.*
18. *Janardhan V., Bakshi R. Quality of Life and its Relationship to Brain Lesions and Atrophy on Magnetic Resonance Images in 60 Patients with Multiple Sclerosis. Arch Neurol. 2000; 57: 1485-1491.*
19. *Fragoso YD, Frota ERC, Lopes JS, et al. Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. Clin Neuropharmacol 2010; 33: 312–16.*
20. *Borras C, Rio J, Porcel J, et al. Emotional state of patients with relapsing–remitting MS treated with interferon beta-1b. Neurology 1999; 52: 1636–9*
21. *American Psychiatric Association. Diagnostic and statistical manual of mental disorders - DSM-IV-TR. Arlington, VA: American Psychiatric Publishing, Inc, 2000.*
22. *Schiffer RB. Disturbances of affect. In: Rao SM, ed. Neurobehavioral aspects of multiple sclerosis. New York: Oxford University Press, 1990.*

23. *Siegert R J, Abernethy D A. Depression in multiple sclerosis: a review; J NeurolNeurosurg Psychiatry 2005; 76: 469–475. doi: 10.1136/jnnp.2004.054635*

24. *Fisher JS, Foley FW, Aihens JE, Ericson GD, Rao SM. What do we really know about cognitive dysfunction, affective disorders and stress in multiple sclerosis? A practitioner's guide . J Neurol Rehab 1994; 8: 151-64.*

25. *Arnett PA. Randolph JJ. Longitudinal course of depression symptoms in multiple sclerosis. J Neurol-Neurosurg Psychiatry 2006; 77: 606-10.*

26. *The Goldman Consensus statement on depression in multiple sclerosis. Multiple Sclerosis 2005; 11: 328_/337*

27. *Miletic S., Toncev G., Jevdjic J., Jovanovic B., Canovic D. Fatigue and Depression in Multiple Sclerosis: Correlation with Quality of Life. Arch. Biol. Sci., Belgrade, 63(3), 617-622, 201.*

28. *Alajbegovic A., Loga N., Tiro N., Alajbegovic S., Cindro V., Hozo I. Cognitive and Depressive Disorders in Multiple Sclerosis. ActaClin Croat 2009; 48: 3-8.*

29. *Hansen H., Henriksen N., Stenager E Trends in survival and cause of death in Danish patients with multiple sclerosis. DOI: 10.1093/brain/awh104. Brain 2004; 127: 844-850.*

30. *Janardhan V., Bakshi R. Quality of Life and its Relationship to Brain Lesions and Atrophy on Magnetic Resonance Images in 60 Patients with Multiple Sclerosis. Arch Neurol. 2000; 57: 1485-1491.*

31. *G.P. Rice, J. Oger, P. Duquette, G.S. Francis, M. Bélanger, S. Laplante, J.F. Grenier. Treatment with Interferon Beta-1b Improves Quality of Life in Multiple Sclerosis. Can. J. Neurol. Sci. 1999; 26: 276-282.*

32. *Schwartz CE, Coulthard-Morris L, Cole B, Vollmer T. The quality of- life effects of interferon beta-1b in multiple sclerosis. Arch Neurol 1997; 54: 1475-1480.*

Corresponding Author
Nexhat Shatri,
University Clinical Center of Kovova,
Prishtine,
Kosovo,
E-mail: drshatri@gmail.com

Intubation with flexible bronchoscope and surgical resection of a post-tracheostomy stenosis

Amina Selimovic[1], Walter Klepetko[2], Thomas Schweiger[2], Konrad Hoetzenecker[2], Ermina Mujicic[3], Senka Mesihovic Dinarevic[1], Safet Guska[4], Alen Pilav[4], Amir Rekic[5], Hilmi Kacamakovic[6], Mahir Moro[7], Azra Kudumovic[8], Mensura Kudumovic[9], Ahmed Katica[10]

[1] Medical University Sarajevo, Pediatric Clinic, Sarajevo, Bosnia and Herzegovina,
[2] Medical University of Vienna, Division of thoracic surgery,
[3] Medical University Sarajevo (cardio anesthesia), Sarajevo, Bosnia and Herzegovina,
[4] Medical University Sarajevo, Division of thoracic surgery, Sarajevo, Bosnia and Herzegovina,
[5] Cantonal hospital Bihac Division of ORL surgery, Bihac, Bosnia and Herzegovina,
[6] Medical University Sarajevo, General and thoracic anesthesia, Sarajevo, Bosnia and Herzegovina,
[7] State Hospital – orthopedic surgery, Sarajevo, Bosnia and Herzegovina,
[8] Medica Sarajevo, Sarajevo, Bosnia and Herzegovina,
[9] Medical University Sarajevo, Sarajevo, Bosnia and Herzegovina,
[10] Primary ORL division Sarajevo, Sarajevo, Bosnia and Herzegovina.

Abstract

An 11-year-old tracheostomized boy was admitted to the emergency department with respiratory failure due to an accidentally removed cannula. The patient underwent tracheostomy three years before after a car accident. A re-insertion of the cannula failed due to a severe tracheal stenosis distal of the stoma. An orotracheal tube was placed under bronchoscopic guidance bridging the stenotic segment and the tracheostoma. After stabilization of the patient, he was transferred to the Division of Thoracic Surgery, Medical University of Vienna, Austria (Head: Prof. Walter Klepetko). The stenotic segment was resected and an end-to-end anastomosis was performed. A follow-up examination three months after surgery revealed a well-healed anastomosis and a sufficient lumen of the trachea. The multidisciplinary and transnational cooperation was a prerequisite for the successful treatment of this patient.

Key words: fiberbronchoscopy, tracheal stenosis, tracheal resection

1. Introduction

The trachea reaches from the cricoid cartilage (*lat. cartilago cricoidea*) of the larnyx and ending at the level of the 5th thoracic vertebra with the tracheal bifurcation. The anterior and lateral walls of the trachea are comprised from C-shaped cartilaginous rings (*lat. cartilagines tracheales*). The membranous portion (*lat. pars membranacea*) represents the posterior border dividing the airway from the esophagus. Tracheotomy is most commonly performed at the level of 2-3 tracheal rings (about 2-4 cm above the jugulum) (2).

Benign tracheal stenosis is a rare condition based on excessive scar formation leading to a gradual narrowing of the trachea. The first surgical correction of an airway stenosis in children was described by Fearon and Cotton in 1972 using the technique of a double-stage laryngotracheoplasty for a subglottic stenosis. This technique was improved in 1988 by Prescot, who performed a single-stage surgery. Segmental cricotracheal resection in subglottic cricoid stenosis with the incision of larynx mucus membrane high up to the vocal cords today gives better results, especially in children. (1,3) In contrast to glotto-subglottic stenosis, which is nearly always the sequel of prolonged orotracheal intubation, tracheostomy-related stenosis are most of the time limited to the cervical trachea not involving the subglottis. Thus, surgical correction is easier by a mere resection of the affected tracheal segment with an end-to-end anastomosis (Figure 1).

Tracheostomy is an artificially created opening in the frontal cervical region of the trachea.

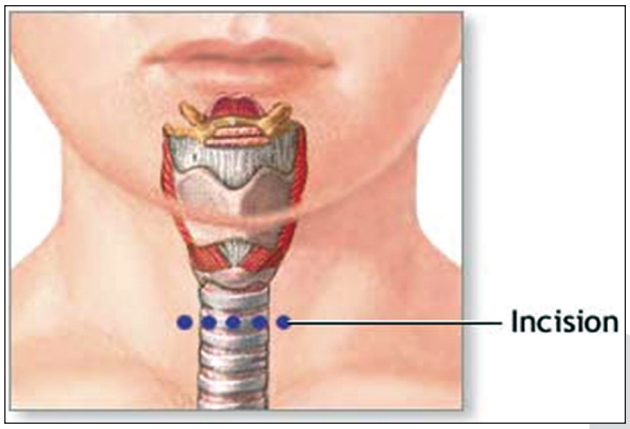


Figure 1. Place for surgical correction

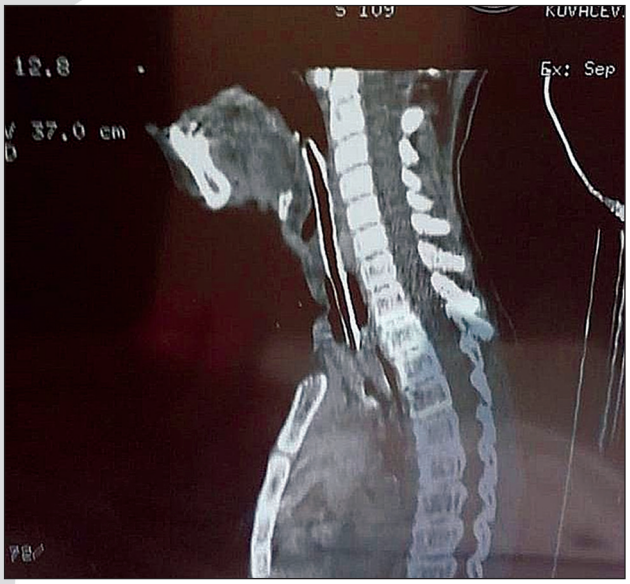
2. Objective

Herein we present a case of a 11-year-old boy presenting with acute dyspnea after accidental decannulation. The airway was temporarily saved by re-inserting a tube under bronchoscopic guidance. The tracheal stenosis (length 4.5cm) was surgically resected at the Division of Thoracic Surgery, Medical University of Vienna (Head: Prof. Walter Klepetko).

3. Case study

A 11-year-old tracheostomized boy was admitted to our institution with an accidentally removed cannula. The patient was brought to our emergency department from the Cantonal Hospital in Bihać by a rescue helicopter. Three years ago the boy underwent tracheotomy after severe trauma due to a car accident. The boy was directly transferred to the pediatric intensive care unit with agonal respiration and respiratory acidosis (pCO2 9.5 kPa) despite oxygen insufflation into the tracheostoma via tube. The attempt to re-insert a cannula directly to the tracheostoma failed.

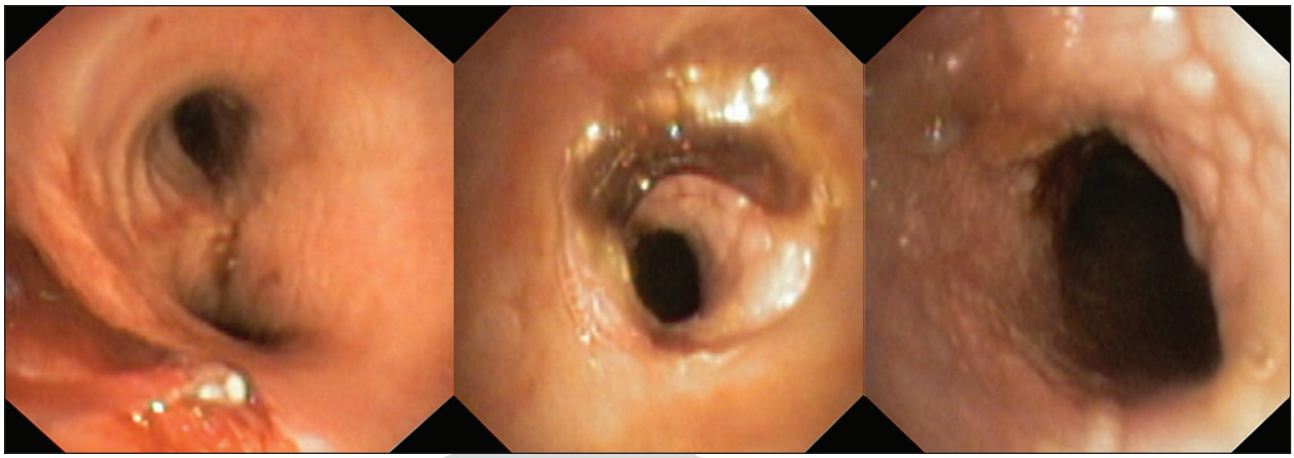
The child was transferred to the operating room of the Division of Pediatric Surgery, where a tube (diameter 6 mm) was inserted orotracheally under guidance of a flexible bronchoscope by a team consisting of an anesthesiologist and a pediatrician pulmonologist. A severe long-segment stenosis was seen distally of the insertion site of the tracheostomy. The inserted tube could not be fully passed through the stenotic segment of the trachea, but the patient's condition could be stabilized. A CT scan of the neck and the chest confirmed the stenosis (length: approximately 3 cm) starting distally from the tracheostoma. The patient was moved to the pediatric intensive care unit, where he was further stabilized until the next day when the trachea was again explored with a smaller fiberoptic bronchoscope (diameter 2.8 mm). A tracheal tube could be placed beyond the stenotic segment with the tip of the tube placed above the carina. The child was then moved to the Department of Pulmonology where he was prepared for the transfer to the Division of Thoracic Surgery, Medical University of Vienna, Austria (Head: Prof. Walter Klepetko) for surgical resection of the stenotic segment.



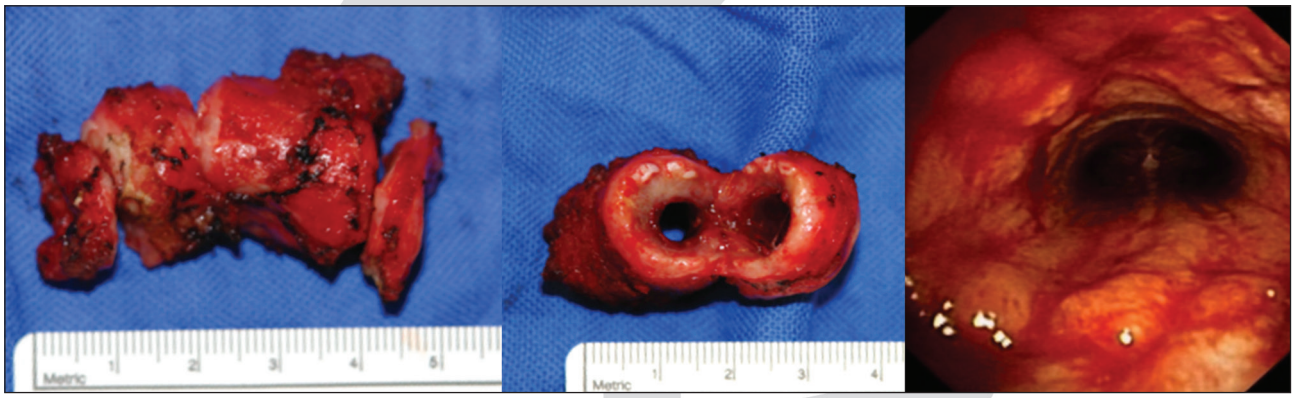
Picture 1. The preoperative CT scan shows a tracheal tube placed bridging the stenotic tracheal segment.

Surgical report

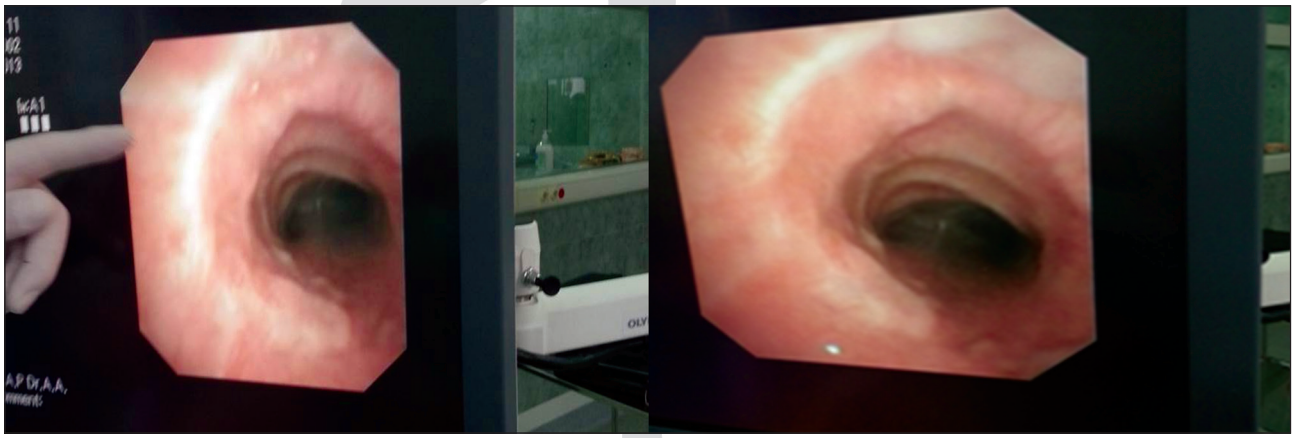
After induction of general anesthesia, the patient was ventilated with a laryngeal mask in place. Through a vertical skin incision, the complete glottis, subglottis and cervical trachea was exposed, releasing any fixation by scar tissue. The stenotic tracheal segment was exposed by preparation stringent laterally to the trachea in order to prevent any damage to the recurrent nerves. The trachea was dissected distally of the stenosis and cross-table ventilation was initiated. The upper end of the stenosis was located and the diseased segment was removed together with the tracheostoma insertion site (total resection length of 4.5cm). After mobilization of the distal ending of the trachea a tensionless end-to-end anastomosis was performed



Picture 2. Endoscopic images of the entrance into both principal bronchi and stenotic trachea (mid).



Picture 3. A segment of 4.5 cm total length has been resected. The concentric narrowing of the tracheal lumen can be seen after dividing the stenotic segment. An intra-operatively performed bronchoscopy showed a tensionless end-to-end anastomosis.



Picture 4. Follow-up bronchoscopy revealed a well-healed anastomosis and a sufficient lumen of the trachea.

under intermittent cross-table ventilation using a running 5-0 PDS suture for the membranous portion and single 4-0 PDS stiches for the cartilaginous parts. After examination of the tightness of the anastomosis by a water submersion test, the suture line was covered with strap muscles. A intra-operative bronchoscopy revealed a well-adapted anastomosis and no swelling of the glottis. Thus, the laryngeal mask could be removed after wound closure in the operation theatre. The further postoperative course was uneventful. Oral nutrition could be started after satisfactory FEES (fiberoptic

endoscopic evaluation of swallowing). Recurrent nerve function after surgery was inconspicuous. After three months, a follow-up fiber bronchoscopy was performed in Sarajevo at the Division of Thoracic Surgery showing a well- healed anastomosis without any narrowing of the trachea.

4. Discussion

Tracheal stenosis is a well-known complication after long-term intubation or tracheostomy. An initial ischemic lesion of tracheal mucosa leads to chronic inflammatory process and self-maintaining scarring. This results in a gradual narrowing of the airway months to years after the initial damage (4,5,6,7,8). The surgical resection of stenotic tracheal segments is a definite treatment option, whereas dilation, stenting or laser resection leads often only lead to temporary relief with a high rate of re-stenosis. An appropriate diagnostic work-up and planning before surgery is crucial for a successful surgical intervention. The pre-operative work-up should include a bronchoscopy performed in a spontaneously breathing patient, a CT scan, lung function testing and voice and swallowing functioning. The length of the stenosis in relation to the total length of the trachea determines the extent of the surgical procedure. A one-step approach with end-to-end anastomosis described by Grillo and colleagues is the standard surgical approach for correction of most tracheal stenosis. In experienced hands this technique results in excellent long-term results. A thorough preoperative work-up and interdisciplinary perioperative patient care by thoracic surgeons, phoniatricians and speech therapists is prerequisite for an optimal patient treatment.

5. Conclusion

The herein presented case illustrates that an interdisciplinary collaboration, even transnationally, can lead to a successful treatment of patients with complex and challenging conditions.

References

1. *Preciado D, Cotton RT, Rutter MJ. Single-stage tracheal resection for severe tracheal stenosis in older children. Int J Pediatr Otorhinolaryngol. 2004 Jan; 68(1): 1-6.*

2. *George M, Lang F, Pasche P, Monnier P. Surgical management of laryngotracheal stenosis in adults. Eur Arch Otorhinolaryngol. 2005; 262: 609-615. http: // dx.doi.org/10.1007/s00405-004-0887-9*

3. *Marques P, Leal L, Spratley J, Cardoso E, Santos M. Tracheal resection with primary anastomosis: 10 years experience. American Journal of Otolaryngology-Head and Neck Medicine and Surgery. 2009; 30: 415-418. http: //dx.doi.org/10.1016/j.amjoto.2008.08.008*

4. *Wain JC. Post intubation tracheal stenosis. Chest Surg Clin N Am. 2003 May; 13(2): 231-46.*

5. *Nouraei SA, Ma E, Patel A, Howard DJ, Sandhu GS. Estimating the population incidence of adult post-intubation laryngotracheal stenosis. Clin Otolaryngol. 2007 Oct; 32(5): 411-412.*

6. *Zias N, Chroneou A, Tabba MK, Gonzalez AV, Gray AW, Lamb CR, et al. Post tracheostomy and post intubation tracheal stenosis: Report of 31 cases and review of the literature. BMC Pulmonary Medicine. 2008; 8: 18. http: //dx.doi.org/10.1186/1471-2466-8-18*

7. *D'Andrilli A, Ciccone AM, Venuta F, Ibrahim M, Andreetti C, Massullo D, et al. Long-term Results of Laryngotracheal Resection for Benign Stenosis. Eur J Cardiothorac Surg. 2008; 33: 440-43. http: //dx.doi.org/10.1016/j.ejcts.2007.12.014*

8. *Rea F, Callegaro D, Loy M, Zuin A, Narne S, Gobbi T, et al. Benign tracheal and laryngotracheal stenosis: surgical treatment and results. Eur J Cardiothorac Surg. 2002; 22: 352-56. http: //dx.doi.org/10.1016/S1010-7940(02)00342-1*

Corresponding Author
Amina Selimovic,
Medical University Sarajevo,
Pediatric Clinic,
Sarajevo,
Bosnia and Herzegovina,
E-mail: amina.selimovic@hotmail.com

Impact of Inhaled Corticosteroids on Emergency Department visits and hospitalization Rates of Children with Persistent Asthma

Fatemeh Behmanesh[1], Sepideh Bagheri[1], Fatemeh Ghane Sharbaf[1], Farid Reza Edjlali[2], Mohammad Hadi Fooladi[2]

[1] Department of Pediatrics, Mashhad University of Medical Sciences, School of Medicine, Mashhad, Iran,
[2] Mashhad Azad University of Medical Sciences, School of Medicine, Mashhad, Iran.

Abstract

Objective: to determine if inhaled corticosteroid treatment of asthmatic children reduces their risk of hospitalization or emergency department (ED) visit for asthma.

Methods: 50 children (3-12 years of age) with the diagnosis of asthma who had not received inhaled corticosteroids (ICS) before were selected. ICS was initiated and rate of hospitalization and ED visits before and after the initiation of ICS was compared.

Results: over a six month period after ICS initiation, readmission to hospital and ED visits for asthma was significantly lowered in children receiving this therapy.

Conclusion: inhaled corticosteroid therapy is associated with a significant reduction in hospitalization and ED visits in children with asthma.

Key Words: Asthma, hospitalization, Inhaled corticosteroid, emergency department

Introduction

Asthma is one of the most common chronic diseases, which is increasing in prevalence especially among children[1]. Current international asthma guidelines recommend daily inhaled corticosteroids (ICS) as the mainstay of therapy in children with mild to moderate persistent asthma.[2-4]

Inhaled corticosteroids have shown to improve airway obstruction, severity of asthma symptoms, frequency of asthma exacerbations and quality of life in asthmatic patients[5, 6].

The purpose of the present study was to examine the effect of inhaled corticosteroid therapy on hospitalization and emergency department admission by children 3 to 12 years old for asthma.

Materials and methods

This study was conducted between February to July 2013 in the pediatric asthma and Allergy department of Mashhad University of Medical Sciences.

Illegible patients were asthmatic children between 3- 12 years old who had persistent asthma (step 2, 3, 4) and had not received inhaled corticosteroids (ICS) before.

Hospitalization and emergency department admission rates in the past 6 months before the initiation of inhaled corticosteroids was investigated and recorded. Then the patients received inhaled corticosteroids so that in mild persistent asthma (step 2), low dose ICS, in moderate persistent (step 3) moderate dose ICS or low dose ICS in combination with inhaled long acting β_2 agonist and in severe persistent asthma (step 4) high dose ICS or moderate dose ICS in combination with inhaled long acting β_2 agonist was started. The patients were followed for the next 6 months after initiation of inhaled corticosteroids and hospitalization and emergency department visit rates were evaluated.

Statistical analysis

All statistical analysis was performed using SPSS 19 statistical package. For qualitative parameters before and after intervention contingency coefficient and for quantitative data with normal distribution paired T test was used. In cases of none normally distributed data willcoxon statistical test was used. For all parameters $p< 0.05$ was considered as significant.

Results

After the initiation of Inhaled corticosteroids for the study population, 25(50%) patients experienced a decrease in emergency department visits in the next six months following treatment. In 24 cases no difference was noted and one of the patients even received more emergency department visits. According to wilcoxon statistical test, this reduction in emergency department visits after ICS initiation is statistically significant. ($p<0.01$)

Hospitalization rates also significantly lowered after ICS therapy initiation. ($p=0.02$)

17 patients (34%) received low dose ICs, 20 patients (40%) moderate dose and one patient (2%) was started on high dose ICS. 12 patients received a combination of low dose ICS and inhaled long acting β_2 agonist.

During the treatment period 7 (14%) patients had an emergency department visit and 43(86%) had no emergency department visits which shows a significant protective effect for ICS on emergency department visits for children with asthma.

Table 1 shows patients characteristics in the study population.

Discussion

Hospitalization and emergency department visits are good markers of asthma control[7]. Results of our study shows that inhaled corticosteroids have a protective effect against readmissions for asthma in children which is the same as the results of other studies[8-12].

Some studies have not found an association between ICS use and risk of hospitalization for asthma[13,14]. Inappropriate control of confounding factors in these studies may explain their negative results.

Previous hospitalization for asthma is recognized as a strong predictor of asthma hospitalization[15] and this study is valuable in that we have taken this into account and each patient is compared with him/her self before and after ICS initiation.

Results of this study suggests that ICS in children with asthma is underutilized , because some of our patients had been admitted to hospital or had ED visits for asthma before but were not started on ICS.

Results of this study may be rather limited by its small sample size. Further studies with larger population considering other factors might be necessary.

Conclusion

In summary, we found that use of inhaled corticosteroids reduces the risk of hospitalization and emergency department visits for asthma in children. These results reemphasize the recommendation by current guidelines for asthma treatment. Considering the little adverse effects of inhaled corticosteroids[16], this therapy should be considered for children with persistent asthma.

Table 1. Characteristics of the study population.

Mean age (years)		6.94±2.62
Sex	**Female**	N=24(48%)
	Male	N=26(52%)
Place of residence	**Urban**	N=44(88%)
	Rural	N=6(12%)
Asthma hospital admissions before ICS use		0.44±0.95
Emergency department visits before ICS use		1.52±1.94
Asthma step before ICS use	**Step II**	N=17(34%)
	Step III	N=32(64%)
	Step IV	N=1(2%)
Medication use before ICS initiation	**Systemic corticosteroids**	N=17
	β agonists (Oral)	N=5
	β agonists (Inhaled)	N=29
	Theophylin	N=10

References

1. *National Institute of Health. Fact book fiscal year 2011. Available at: http://www.nhlbi.nih.gov/about/ fact book/Fact Book 2011.pdf.*

2. *Global Initiative for asthma. Global strategy for asthma management and prevention. Available on: http:// www.ginasthma.com ; update 2011.*

3. *Global Initiative for Asthma. Global strategy for the diagnosis and management of asthma in children 5 years and younger. Available on: http://www.ginasthma.com.*

4. *National Heart, Lung and Blood Institute. Expert panel Report3: guidelines for the diagnosis and management of asthma. Bethseda, MD: National Institute of Health. Available on: http://www.nhlib.nih.gov ;2007.*

5. *Castro Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. Pediatrics 2009; 123: e519-25.*

6. *Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, et al. The inhaled steroid treatment as regular therapy in early asthma (START) study 5 year follow up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol 2008; 121: 1167-74.*

7. *Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, et al. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996; 98: 1051-1057.*

8. *Adelroth E, Thompson S. Advantages of high-dose inhaled budesonide [letter]. Lancet 1988;1:476. [CrossRef] [Medline]*

9. *Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir. Med. 1994; 88: 373–381. [CrossRef] [Medline]*

10. *Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand: what lessons have been learned? [see comments] [Review]. Thorax 1995; 50: 303–311. [CrossRef] [Medline]*

11. *Wennergren G, Kristjansson S, Strannegard IL. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in prevalence of asthma. J. Allergy Clin. Immunol. 1996; 97: 742–748. [CrossRef] [Medline]*

12. *Godfrey S, Balfour-Lynn L, Tooley M. Beclomethasone dipropionate aerosol in childhood asthma: a three- to five-year follow-up. Brit. J. Clin. Pharmacol. 1977; 4(Suppl. 3): 273S.*

13. *Mitchell EA, Bland JM, Thompson JM. Risk factors for readmission to hospital for asthma in childhood. Thorax 1994; 49: 33–36. [CrossRef] [Medline]*

14. *Godfrey S, Balfour-Lynn L, Tooley M. Beclomethasone dipropionate aerosol in childhood asthma: a three- to five-year follow-up. Brit. J. Clin. Pharmacol. 1977; 4(Suppl. 3): 273S.*

15. *Blais L, Ernest P, Biovin JF, Suiss AS. Inhaled corticosteroids and the prevention of readmission to hospital for asthma. Am J Res and critical care medicine 1998; 158(1): 126-132.*

16. *Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respiratory Medicine 2006; 100(8): 1307-1317.*

Coresponding Author
Fatemeh Behmanesh,
Department of Pediatrics,
Mashhad University of Medical Sciences,
School of Medicine,
Mashhad,
Iran,
E-mail: BehmaneshF@mums.ac.ir

Instructions for the authors

All papers need to be sent to e-mail: healthmedjournal@gmail.com

Preparing Article for HealthMED Journal

First Author[1], Second Author[2], Third Author[3]

[1] First affiliation, Address, City, Country,
[2] Second affiliation, Address, City, Country,
[3] Third affiliation, Address, City, Country.

Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
Top margin	20 mm
Bottom margin	20 mm
Left margin	20 mm
Right margin	18 mm
Column Spacing	5 mm

Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

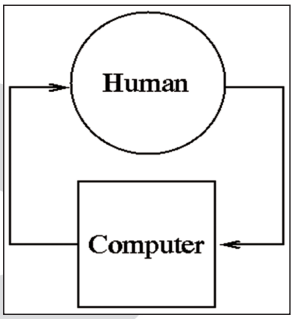


Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

Corresponding Author
Name Surname,
Institution,
City,
Country,
E-mail: