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Study on effects of cantharidin on cutaneous leishmaniasis, its mechanism and optimization of the therapeutic modes”

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Abstract

Background: Leishmaniasis is one of the major problems in many countries. Leishmania is flagellated protozoa and causative agent of leishmaniasis which is the most important health problem in many countries especially in developing country. Leishmania major causes cutaneous leishmaniasis (CL). CL is endemic in some part of Iran. Pentavalent antimony compounds are main therapy of CL, they have some side effects due to their toxicity, and also relapse is possible. Cantharidin is terpenoid and vesicant compound that can be found in Meloidae and Oedomeridae family beetles. It was used as treatment to cancer and Wart. It is also apoptosis inducer in various cancer cells.

Materials and methods: In this study, the effect of 0.5, 1, 2, 5, 10, 20 and 50 $_{\mu g/ml}$ cantharidin on the L. major promastigotes, non-infected macrophages and infected macrophages with parasite amastigotes was studied by(3-(4,5-dimethyl thiazolyl-2)-2,5-diphenyle tetrazolium bromide) MTT assay and flow cytometer in vitro. The Effect of cantharidin as 0.5, 0.05 and 0.1% ointment surveyed on the Leishmania lesions in BALB/C as well as. Parasite load as determined by Real Time PCR, and IFN-γ and IL-4 was involved by ELISA.

Results: Results showed that **the** highest cytotoxicity (56.14%) in promastigotes was in group that **treated** with 50 µg/ml cantharidin after 48h. **The** rate **in** non-infected macrophages and infected macrophages was 13.05 % and 30.17% respectively. Maximum cytotoxicity rate in promastigotes treated with 50 $_{\mu g/ml}$ cantharidin after 72$_{h}$ was determined 66.48%, 48.52% in non- infected macrophages and 62.24% in infected macrophages after 48h by flow cytometry. Group treated with 0.05% cantharidin had lowest rate of ulcer growth. Ulcer size was increased in group treated with 0.5% cantharidin. IFN-γ value in group treated with cantharidin was less than it in untreated (control) group, but IL -4 didn’t change.

Conclusion: Cantharidin through blister formation induces inflammatory reaction and neutrophils and macrophages infiltration in blister site. It can also destroy tissue by cytokines production stimulating such as myeloperoxidase. However, it can destroy parasite and infected macrophage through apoptosis inducing. Following more investigation, cantharidin can be introduced as cutaneous leishmaniasis treatment.

Key word: Leishmania major, cantharidin, macrophage, apoptosis

Introduction

Leishmaniasis is one of the most important tropical parasitic **diseases** that is caused by various species of Leishmania protozoa and depending on the species, disease and host response appear the wide range of clinical protests. Because of the importance of this disease, the World Health Organization has focused on that over time [1][3].

Leishmaniasis in many countries, particularly developing countries is a major problem of public health. Flagellated protozoan of leishmaniasis belongs to Trypanosomatidae group. Leishmaniasis divides in three forms: Cutaneous, mucocutaneous, and visceral. Most of the volume is clinical [4] [5]. Cutaneous Leishmaniasis is more than Leishmania major. Parasite is transferred through the bite of sandflies, Phlebotemus. mosquito bite, leaves a wound that remains for a few months to a year. Leishmaniasis threatens about 12 million people in 88 countries around the world [6]. The annual rate of its occurrence is 2 million that 500 thousand

relate to visceral leishmaniasis and the rest relates to cutaneous leishmaniasis. Annually, 90% of cases of cutaneous leishmaniasis is reported from Afghanistan, Brazil, Iran, Peru, Saudi Arabia, Syria, Algeria, Sudan and 90% of visceral leishmaniasis is reported in Bangladesh, India, Nepal and Sudan. According to official reports, 60,000 people died due to visceral leishmaniasis, annually [7][8]. It recalls that the true figure is more than the number of diseases, since in only one third of the countries reporting the disease is compulsory [9]. Unfortunately, the number of cases of the disease in our country is increasing [15][18]. As reported by the World Health Organization, quoted by the Center for Disease Control, the number of patients with cutaneous leishmaniasis has increased in Iran from 13,729 in 2002 to 24,092 in 2006. Factors such as the development of agricultural projects, immigration of non-immune persons to the endemic areas, migration to the cities, rapid and unplanned urban expansion, construction of houses near rodent nests, environmental changes such as dams, decrease parasite resistance to some medications and opportunities seeking visceral leishmaniasis parasite in HIV positive patients, involved in the development and increased disease [2][1].

Over time, different approaches have been used for the treatment of leishmaniasis[10] [11]. **Presently**, 5 capacity antimony compounds, Pentosodium (sodium Acetibiogloconat), Glocantim, pentamidine and amphotericin B are used for the treatment of cutaneous leishmaniasis . In addition to the side effects of these drugs, the disease may be relapsed [22][1][2].

These compounds are essential in treatment of leishmaniasis and are considered as the first drugs for treatment of it [19][20]. Using these compounds have some limitations such as toxicity, long term treatment, the expensive drugs, lack of treatment response and in some cases repeating the injection. In other word, the existence of leishmaniasis parasite with HIV virus simultaneuously causes to increase the resistance to drugs. Despite the efforts in producing the Vaccine, no vaccinate has been yet produced [26][27]. Therefore, treatment is necessary to control the disease, especially when the person is exposed to the disease [2].

The aim of this study is to analyze the effects of Cantharidin on Leishmania major by Invivo and Invitro methods that we use them after accomplishing many studies.

Materials and Methods

The study is fundamental and applicable. In this study, BALB / $_{C}$ female mice are used that were selected randomly, sampling is done non-randomly in contaminated samples, and the isolated macrophage cells are cultivated.

White laboratory mice (BALB / $_{C}$) between the ages of 8 to 9 weeks were infected with L. major promastigotes.

Grouping the mice: mice were randomly selected and were divided into 5 groups of 6.

Infected control group without treatment, the infected group treated with eucerin (as eucerin effect), the next group of contaminated under treatment with Cantharidin 0.05, 0.1, and 0.5% were considered.

In ordere to save money and time, it is used in concentration condition that leads to the best results in Invitro condition.

Infecting Mice Method

1_{ml} solution containing 2×10^{6} Leishmania major promastigotes in the stationary phase by insulin syringe in the tail of mice were injected subcutaneously. It is necessary to mention that to confirm the statistic phase of parasite the number of promastigotes in the N_3 has changed and it is counted daily. In the statistic phase the growth of parasite is decreased. After 4 to 5 weeks from injection of parasite, the small tight nodules were appeared at the injection site that it is wounded after two weeks. After the mice were contaminated with Leishmania major, macrophage cells of skin have been removed. The analysis on the mice started after the parasite is cultivated. Finally, the effect of Carthardin is studied in remarkable volume of the sample.

Preparing Cantharidin

Cantharidin as a 100 mg dried powder with a purity of 98% was purchased from Sigma Company**.** 20% concentration of Cantharidin solution (as the stock solution) by dissolving 20_{mg} Cantharidin powder in 1 ml dimethyl sulfoxide (DMSO) is provided and kept in refrigarator. The concentrations 50 µg/ml, 20, 10, 5, 2, 1, and 0.5 are provid-

ed by diluting the stock solution in the cultivation environment $RPMI_{1640}$. It is necessary to mention that all of the concentrations are provided in 2X.

Evaluating the survival rate of promastigotes, the contaminated macrophage, and non-contaminated macrophages by (3-(4,5-dimethyl thiazolyl-2) -2.5- diphenyle tetrazolium bromide) MTT:

MTT is a colorimetric method that after entering to the safe cells, it breaks the Mitochondrial dehydrogenase enzyme of tetrazolum bromide and changes to the blue insoluble Furmazan, while the dead cells are unable to do that. By taking the absorbance of the sample, the percentage of cell survival can be calculated by the formula 1.

First, we count 2×10^6 Leishmania major promastigotes in logramitmic phase of growth in each ml in the cultivation environment and we add 100 $_{\mu l}$ from the solution with FCS 20% under the hood and sterile conditions to the 96-well plates. Then, we add 100 $_{\mu l}$ Cantharidin with the specified concentration to the well. We set a plate in Incubator $21^{o\ C}$ for 24 hours, the second plate for 48 hours, and the third plate for 72 hours. In each plate, the control well in triplicate has promastigotes in without Cantharidin environment. The other well contains parasite and DMSO 2% is considered to analyze the effect of DMSO on promastigotes.

In order to analyze the mortality effect of Cantharidin on the contaminated macrophages and non-contaminated macrophages, the peritoneal macrophages of BALB / C mice were used. After cultivating the macrophage and contaminating that according to the mentioned method, 100 $_{\mu l}$ Cantharidin with the specified concentration was added to the well. Three plates incubated in incubator $37^{o\ C}$ with CO_2 5% for 24, 48, and 72 hours.

After passing the mentioned time, we add 20 $_{\mu l}$ of the provided dye MTT (with the concentration 0.5 $_{mg/ml}$). Repeatedly, the plates which contain promastigotes incubated for 3 to 5 hours in $21^{o\ C}$ as well as the plates which contain macrophage in 37^{oC}. Then, the plates were centrifuged For 10 minutes at 2000 $_{rpm}$. The cultivated plates containing contaminated macrophages do not need to be centrifuged because the cells stick to the bottom of the plate, and we are able to drain the surface liquid. The surface liquid is removed and we add 100 $_{\mu l}$ of DMSO to each well. After 15 minutes, the light absorption of the well at a wavelength of 570 nm were read by ELISA reader system.

Method of Flow Cytometry Test

American kits were used for flow cytometry Annexin V-FITC Apoptosis Detection Kit Bio Vision. Promastigotes which exposed to different concentrations of Cantharidin and the cultivated control groups were collected in 24-well plates at 24,48 and 72 hours, and in microtubes ml 1.5 $_{rpm}$ 3000 were centrifuged for 5 minutes. To collect the contaminated macrophages, Trypsin 0.25% should be used.

1. The surface solution is removed, and according to the instruction of the kit, 500 lμ of Binding butter is added to the deposit. Then, 5 $_{\mu l}$ Annexin and 5 $_{\mu l}$ propidium iodide were added to microtubes.
2. The samples were incubated for 5 minutes in the temperature of the room.
3. Color intensity of Annexin-V which is absorbed by the cells were analyzed by FACS Calibur.
4. The results were analyzed by Cell Quest software.

The non-contaminated macrophages and the contaminated macrophages were analyzed in 24 and 48 hours after the exposure of 5, 20 and 50 $_{\mu g/ml}$, but the promastigotes in 24, 48 and 72 hours after the exposure of the specified Cantharidin.

The Statistical analysis

The statistical analysis of the data is accomplished by SPSS 16 and by the method of monolateral variance analysis. The normality of the data is analyzed by Shapiro-Wilk test. The relaiblity is 95% and the value of P is considered meaningful lower than 0.05. Also, the results of data are presented in mean± S.E.

$$100\times\frac{\text{Blank absorbance - absorbance of the wells treated with Cantharidin}}{\text{Blank absorbance - absorbance of control wells}} = \text{percentage of cell survival} \quad \text{..... (1)}$$

The Results

The present study indicates that the mortality rate of Cantharidin with the concentration 0.5 $_{\mu g/ml}$ was 14.94%, 30.89, and 6.8% after 24, 48, and 72 hours in promastigotes of leishmaniasis, but the mortality rate of the concentration 50 $_{\mu g/ml}$ was 50.02%, 56.14%, and 32.48% after 24, 48, and 72 hours (diagram 1).

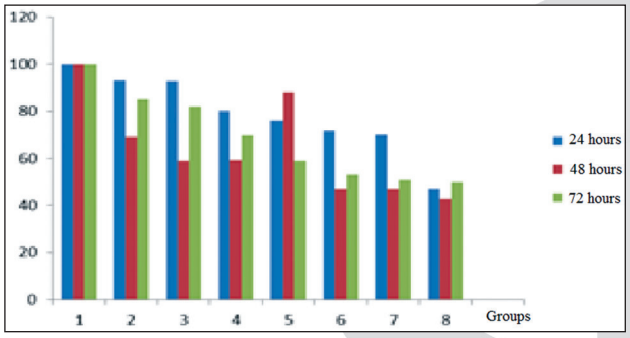


Diagram 1. The percent of survival of promastigotes of Leishmania major after exposing of 0.5 to 50 $_{\mu g/ml}$ Cantharidin for 24, 48 and 72 hours.
Group 1: Control group, 2: Leishmania major+0.5 $_{\mu g/ml}$ Cantharidin, 3: Leismania major+1 $_{\mu g/ml}$ Cantharidin, 4: Leishmania major+2 $_{\mu g/ml}$ Cantharidin, 5: Leishmania major+5 µg/ml Cantharidin, 6: Leishmania major+10 $_{\mu g/ml}$ Cantharidin, 7: Leishmania major+20 $_{\mu g/ml}$ Cantharidin, 8: Leishmania major+50 $_{\mu g/ml}$ Cantharidin

The mortality rate of Cantharidin with the concentration 0.5 $_{\mu g/ml}$ after 24, 48 and 72 hours in the non-contaminated macrophages was 15.89%, 14.03%, and 0%. The mortality rate of Cantharidin with the concentration 50 $_{\mu g/ml}$ in the non-contaminated macrophages was 23.05%, 12.98%, and 0% after 24, 48 and 72 hours (diagram 2). The mortality rate of cantharidin with the concentration 0.5 in the contaminated macrophages to Leishmania major was 2.75%, 4.94%, and 0% after 24, 48, 72 hours. The mortality rate of Cantharidin with the concentration of 50 $_{\mu g/ml}$ in the contaminated macrophages was 30.17%, 20.13%, and 11.8% after 24, 48, and 72 hours (diagram 3).

The statistical analysis of the mortality rate in promastigotes indicate that the control group is significantly different with all of the groups after 24, 48, and 72 hours ($p<0.05$). In the non-contaminated macrophage group, Cantharidin hasn't affected on macrophages after 24 hours ($p>0.05$), but it has affected on the other groups comparing to the control group after 48 and 72 hours ($p<0.05$). The control group (contaminated macrophage without Cantharidin) was different with the groups 5, 6, 7, and 8 (contaminated group+ 5 µg/ml Cantharidin, contaminated macrophage+ 10 $_{\mu g/ml}$ Cantharidin, contaminated macrophage+ 20 µg/ml Cantharidin, and contaminated macrophage+ 0.5 $_{\mu g/ml}$ Cantharidin), and the control group was different with the other groups except groups 2 and 3 (contaminated macrophage+ 0.5 $_{\mu g/ml}$ Cantharidin, and contaminated macrophage+ 1 $_{\mu g/ml}$ Cantharidin) after 72 hours ($p<0.05$).

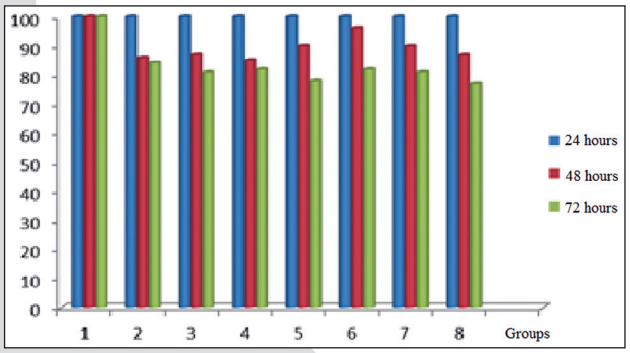


Diagram 2. The survival percent of the non-contaminated macrophage after the exposure of Cantharidin with the concentrations 0.5 to 50 $_{\mu g/ml}$ in 24, 48, and 72 hours.
1: The control group, 2: non-contaminated macrophages+ 0.5 $_{\mu g/ml}$ Cantharidin, 3: non-contaminated macrophages+ 1 $_{\mu g/ml}$ Cantharidin, 4: non-contaminated macrophages+ 2 µg/ml Cantharidin, 5: non-contaminated macrophages+ 5 $_{\mu g/ml}$ Cantharidin, 6: non-contaminated macrophages+ 10 $_{\mu g/ml}$ Cantharidin, 7: non-contaminated macrophages+ 20 $_{\mu g/ml}$ Cantharidin, 8: non-contaminated macrophages+ 50 $_{\mu g/ml}$ Cantharidin.

In the study by flow cytometry for non-contaminated macrophages after exposure to Cantharidin 50 and 5 $_{\mu g/ml}$ over 48 hours, the mortality percent was 42.48 (as 33.80% apoptosis, 6.84% necrosis and 2.2% apoptosis delay) and 89.47% of mortality (12.22% of apoptosis 14.5 % and 63.20% late apoptosis or necrosis) (Image 1).

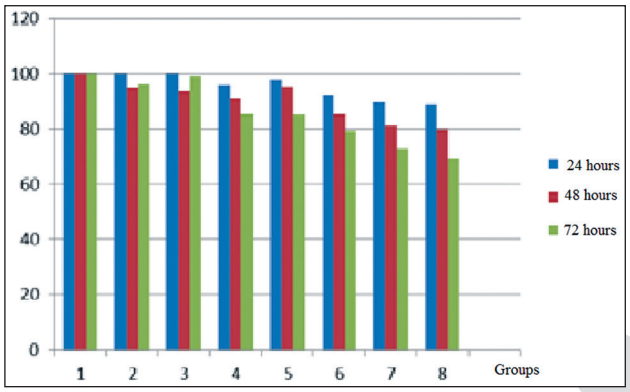
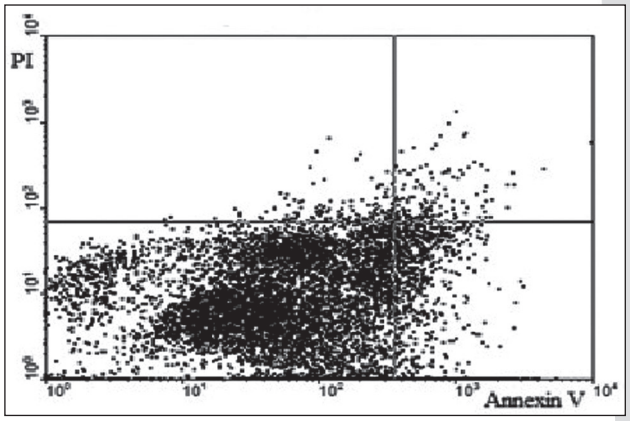
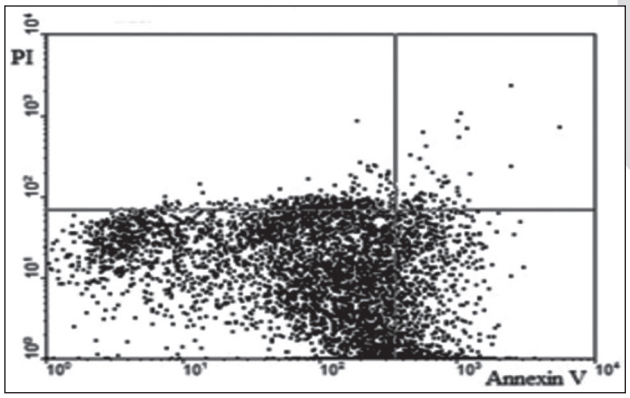


Diagram 3. The percent of survival of the macrophages which are contaminated with Leishmania major amastigotes after exposing to the concentrations of 0.5 to 50 $_{\mu g/ml}$ Cantharidin for 24, 48 and 72 hours

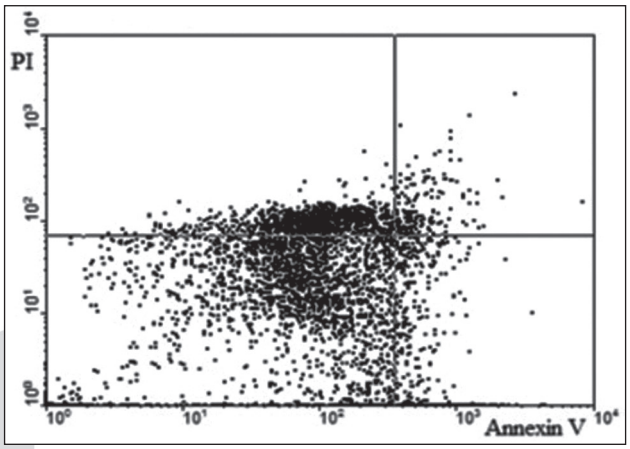
1: Control group, 2: The contaminated macrophages+ 0.5 $_{\mu g/ml}$ Cantharidin, 3: The contaminated macrophages+ 1 $_{\mu g/ml}$ Cantharidin, 4: The contaminated macrophages+ 2 $_{\mu g/ml}$ Cantharidin, 5: The contaminated macrophages+ 5 $_{\mu g/ml}$ Cantharidin, 6: The contaminated macrophages+ 10 $_{\mu g/ml}$ Cantharidin, 7: The contaminated macrophages+ 20 $_{\mu g/ml}$ Cantharidin, 8: The contaminated macrophages+ 50 $_{\mu g/ml}$ Cantharidin.



A) Macrophage (control)



B) Macrophage+ 5 $_{\mu g/ml}$ Cantharidin

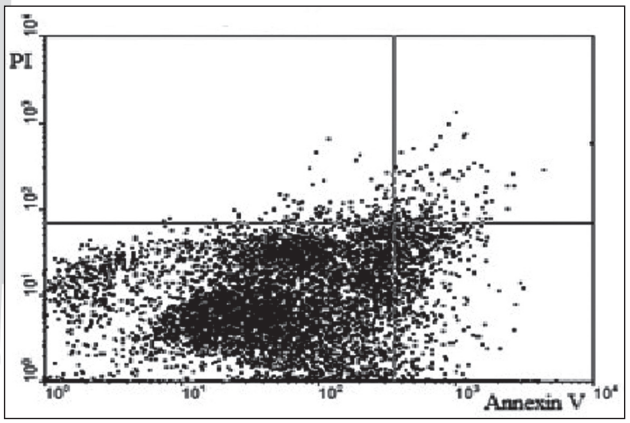


C) Macrophage+ 50 $_{\mu g/ml}$ Cantharidin

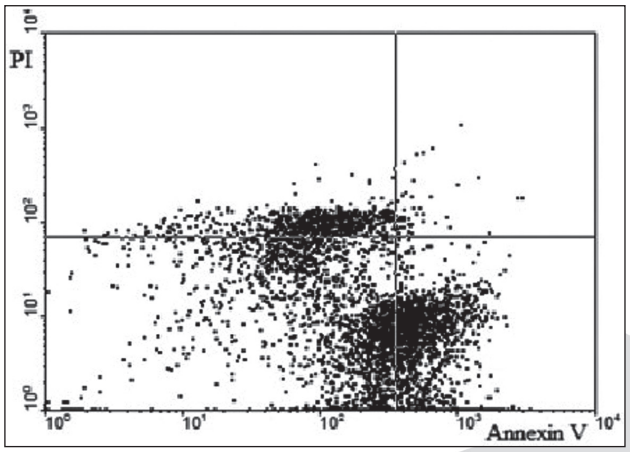
Image 1. The results of flow cytometry in non-contaminated macrophages by Cell Quest software

A) The control sample after 48 hours. B) Macrophages in the exposure of 5 µg/ml Cantharidin after 48 hours. C) The macrophages in the exposure of 50 $_{\mu g/ml}$ Cantharidin after 48 hours. X axis refers to Annexin, and V axis refers to Propidium iodide. UL (Left and upper (necrosis), UR (Upper Right) right and upper (delayed apoptosis), LL (Low Left) (left and down (living cells), LR (Low Right) (right and down (apoptosis).

The results of flow cytometry in contaminated macrophages in the exposure of 5 and 50 $_{\mu g/ml}$ Cantharidin after 48 hours indicate 62.14% (as 4.48% apoptosis, 1.5% delayed apoptosis, and 16.80% necrosis), and 45.05% (as 30.59% apoptosis, 11.85% necrosis, and 2.61% delayed apoptosis). (Image 2).



A) Control

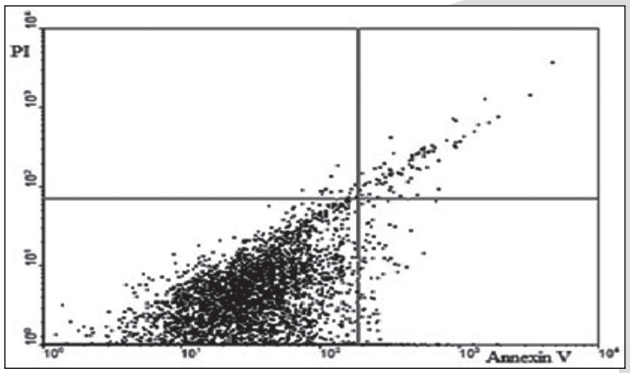


B) The contaminated macrophage+ 50 $_{\mu g/ml}$ Cantharidin

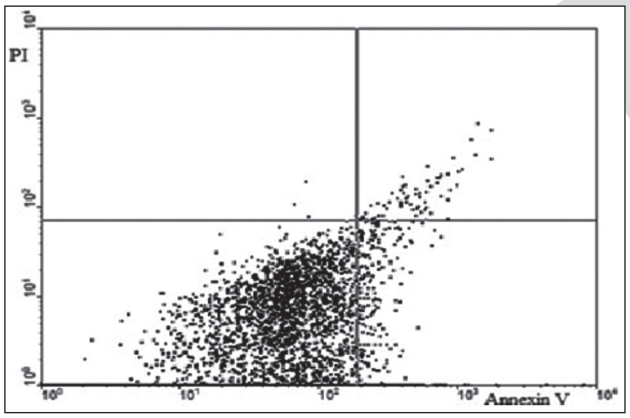
Image 2. The results of flow cytometry in contaminated macrophages by Cell Quest software

A) Sample after 48 hours. B) The contaminated macrophages in the exposure of 50 $_{\mu g/ml}$ Cantharidin after 48 hours.

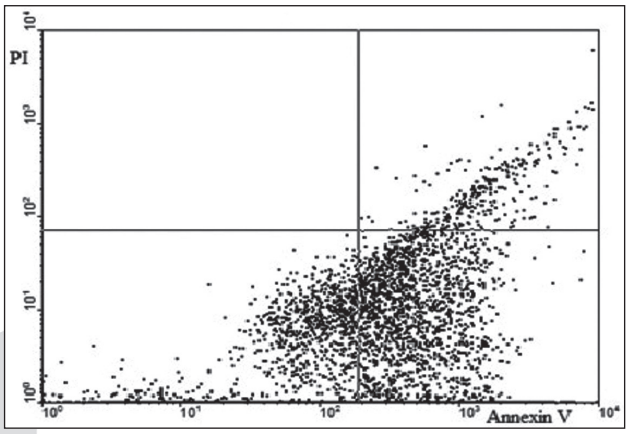
The results of flow cytometry in promastigotes of Leishmania major after exposure of 0.5 and 50 $_{\mu g/ml}$ after 72 hours indicate that the mortality rate is 66.48% (62.84% apoptosis, 3.64% delayed apoptosis, and 0% necrosis), and 13.94% the mortality rate (as 12.54% mortality rate, 1.1% delayed mortality rate, and 3% necrosis). (Image 3)



A) Leishmania major (control)



B) Leishmania major+ 0.5 $_{\mu g/ml}$ Cantharidin



C) Leishmania major+ 50 $_{\mu g/ml}$ Cantharidin

Image 3. The results of flow cytometry in promastigotes of Leishmania major by Cell Quest software

A) Sample after 72 hours. B) Promastigotes in the exposure of 0.5 µg/ml Cantharidin after 72 hours. C) The treated promastigotes with 50 $_{\mu g/ml}$ cantharidin after 72 hours.

Discussion

The results indicate that Cantharidin with the specified concentration has the most mortality effect on promastigotes over 48 hours. The highest mortality rate was observed in promastigotes which were exposed to 50$_{\mu g/ml}$ Cantharidin 48 hours. After 72 hours, the mortality rate was reduced in promastigotes. The amount of IC_{50} was measured to 3.55 µg/ml after 24 hours. In this research, Cantharidin has not affected on macrophages isolated from mice in Invitro. The highest fatality rate (23.5 %) was observed in the group that was exposed to 50 $_{\mu g/ml}$ Cantharidin after 72 hours. In a study, the highest mortalirty rate in progmatigotes referred to the concentration of 50 µg /ml after 72 hours. Also the mortality rate was more than 48 hours after 72 hours. In the mentioned study, determining the mortality rate is done by counting and directly by Neubauer slide; the amount of IC_{50} is calculated 1.9 $_{\mu g/ml}$ after 24 hours. In the present study, promastigotes of parasite is counted in logratmic level and cultivated in plate; and immediately, Cantharidin with different concentrations is added to the wells and the mortality rate is counted by MTT after 24, 48, and 72 hours, but in a study, Cantharidin is added to the wells by passing 72 hours after the cultivation of parasite in the plate [21]. Our results indicate that the mortality rate is lower than 48 hours after 72 hours, and in the mentioned study, this rate was

more than 48 hours after 72 hours. In our study, the promastigotes were set in the lograrithmic phase and grew by the existence of Cantharidin, but in the mentioned study, the growth of parasite was decreased after 3 days, and adding Cantharidin increased the rate of mortality in the promastigotes. The macrophages have an effective role in creating the immune response against the infections and secretion of cytokines. Leishmania donovani and Leishmania major by removing M -CSF (Macrophage) colony stimulating factor prevents apoptosis in macrophages. Also, Leishmania major prevents the release of cytochrome c from mitochondria and activation of caspase-3 of the contaminated macrophages. Leishmainiasis with this operation helps its survival in the host [23][24]. Cantharidin causes to increase the Caspase 3, and simultaneously, it causes to decrease the amount of protein Bcl_2 as the inhibitors of Apoptosis, and finally, it **causes** to induce apoptosis [12][13]. Leishmania doesn't have caspase and apoptosis is done through caspase-like molecules which are called Metacaspase. The **precise** mechanism of apoptosis induction in leishmaniasis and the effectiveness of Cantharidin is not clear, yet. Miltefosine in Leishmania donovani by reducing the permeability of mitochondrial membrane cause to increase the release of cytochrome c and apoptosis induction [25].

The highest concentration of Cantharidin (50 $_{\mu g/ml}$) in promastigtes of Leishmania major **was** 62.48% apoptosis. The value of the apoptosis in the non-contaminated and contaminated macrophages after the exposure of 50 µg/ml Cantharidin was 42.84% and 22.12% after 48 hours. Cantharidin with the concentration 50 $_{\mu g/ml}$ resulted 20.63% necrosis after 48 hours, while with the concentration 5 $_{\mu g/ml}$ resulted 6.84% necrosis and 33.80% the apoptosis. The value of necrosis and apoptosis in without drug macrophages (as the control group) was 1.79% and 18.69% after 48 hours. Therefore, the low concentration of Cantharidin in the non-macrophages causes apoptosis, and the high concentration causes the necrosis. In a study, IC_{50} is measured 2±0.28 $_{\mu g/ml}$ for promasitgotes, and 7.7±2.6 for macrophage [22] [28].

Cantharidin causes to decrease the survival of macrophage in Invitro codition, also, it causes to decrease ATP [24][14]. Most of the studies have been about the effect of Cantharidin on the cancer cells, and these studies resulted that Cantharidin in Hepatoma cells, Colon cells, carcinoma of the oral cavity and leukemia cells cause to apoptosis [26][25][14].

The macromaphages have an important role in creating immune response against the infections and Cytokine secretion. Leishmania donovani and Leishmania major prevents apoptosis of macrophage by removing colony stimulating factor M-CSF, but it increases the transcription of genes TNF- α (Tumor necrosis factor- alpha) ،GM-CSF(Granulocyte macrophage colony – stimulating factor), and IL- 6 (Interleukin 6). Also, Leishmania major prevents the release of Cytochrome c and induction of apoptosis of cells [29]. The precise mechanism of induction of apoptosis of cells by Cantharidin is not clear. Different studies indicate that Cantharidin in the cancer cells by increasing the Oxidative stress causes to damage DNA of cells, and it induces apoptosis through mitochondria by induction of P_{53} molecule [16][17]. There is no caspase in Leishmania, but there is Caspase-like protein which is called Metacaspase. Apoptosis happens for Leishmania in controlling its population in intestine of the mosquito and in macrophages through displacement of Phosphatidylserine. Some drugs, such as miltefosine induce apoptosis in Leishmania [30][29]. The occurrence of Phosphatidylserine (PS) in the external membrane of promastigotes is a sign of apoptosis, but In Amastigotes not only death but also it attaches the macrophage and enters it through phosphatidylinositol serine [31]. As leishmaniasis prevents apoptosis in macrophage, and Cantharidin helps to remove the parasite by induction of apoptosis in Promastigotes Leishmania major and contaminated macrophage, further studies about cutaneous leishmaniasis in Invitro should be accomplished, and it should be considered as a drug for treatment of cutaneous leishmaniasis.

Conclusion

Cantharidin affects on promastigotes of Leishmania major and the macrophages which are contaminated with parasite. It is recommended that further studies should be accomplished in Invivo conditions for the effect of this chemical compound.

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Prevalence of mouth breathers in school

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Abstract

Background: Mouth-Breathing Syndrome (MBS) induces changes in various organs and systems and is linked not only to the vital capacity of the individual, but also to his quality of life, thereby becoming a public health problem.

Objective: To identify the prevalence of mouth breathing in school.

Methods: This is a cross-sectional study with a quantitative and descriptive approach developed in two schools from the public system with children aged between five and ten years, in the city of Cajazeiras, Paraíba, Brazil. Data collection happened through the application of a questionnaire and two additional tests for the diagnosis of mouth breathing.

Results: Seventy children of both genders participated, most of them females (60%) and children aged five and seven years (30% and 22.9% of the sample, respectively, with an average age of 7.15 + 1.7 years old). The prevalence of oral breathing among the participants was 32.8%, and no significant difference was found with respect to gender and age, and, by clinical evaluation, it was pointed out that the feature that most children showed was dark circles around their eyes.

Conclusion: Mouth-breathing syndrome covers a significant number of children and more attention to their treatment is required to avoid possible complications.

Key words: mouth breathing; respiratory disorder; symptoms.

Introduction

Mouth-Breathing Syndrome (MBS) can be defined as a set of signs and symptoms present in those who breathe partially or only through the mouth[1]. The changes that occur in the medium or long term, because of this modification, may have harmful consequences for the individual[2] due to personal, physical, psychological and social relationship impacts[3]. Mouth breathing is caused by multiple factors that lead to a complete or partial and a uni- or bilateral nasal obstruction. It is a frequent complaint in otolaryngology and paediatric ambulatories and even in medical clinic.[4,5].

Given that respiratory disorders are usually problems of a multifactorial character, it is difficult to clearly define the aetiology of mouth breathing. In childhood, any disease, accident, allergy or flu can obstruct the upper airway and over time lead to a child's habit of breathing through the mouth[6]. Behavioural changes include: restless sleep, irritability, and concentration difficulties accompanied by low school performance and impaired sports skills, among others[7].

According to Menezes et al.[8], some authors believe that the term "oral breather" is wrong in such cases because exclusive oral breathing is rare and only occurs when there is a limiting factor that prevents the passage of air into the airway. Thus, a more accurate term would be "insufficient nasal breather", but not all researchers agree with this definition, preferring Mouth-Breathing Syndrome.

The lack of knowledge about it hinders the identification and subsequent referral of children to a specialized service, delaying treatment and compromising the quality of life of those individuals. Early detection would imply rapid care that would reduce the complications and poor quality of life that those individuals experience. Thus, the goal of this study is to identify the prevalence of mouth breathing in school.

Methods

This is a cross-sectional study with a quantitative and descriptive approach. The survey was conducted during March and April of 2014 in two schools from the public system: Escola Estadual de Ensino Fundamental Janduy Carneiro and Escola de Ensino Infantil e Fundamental LD Costa e Silva de Sousa, both located in the city of Cajazeiras in the central region of Paraíba, Brazil.

The selection of participants was carried out on a voluntary basis whereby 150 children, enrolled in the first to the third year of elementary school, were initially approached in both schools; however, only 70 children were included in the survey. Inclusion criteria for the study were: children aged between five and ten years old, both genders and who did not present any severe respiratory disease. Children whose parents did not accept the Informed Consent were excluded.

The selected schools were visited on different days. The researcher sent the Informed Consent and a letter to the parents explaining the study's objectives. Subsequently, a meeting with the parents was scheduled for them to sign the informed consent and complete the questionnaire related to respiratory diseases. A clinical assessment of the children was performed at another time.

A clinical examination and evaluation of the children were carried out using personal protective equipment (PPE) and the information gathered was listed on the evaluation sheet prepared by the researcher. To analyze the changes, the presence or absence of the following clinical signs was evaluated: elongated face, dropped eyes, dark circles, narrow upper lip (thin), dry lips, hypotonic lips, everted lower lip, narrow nostrils, high palate, inadequate lip sealing and anterior open bite. The presence of airway problems such as rhinitis, sinusitis, enlarged tonsils, adenoid hypertrophy, deviated septum, etc. was evaluated.

After the initial clinical assessment the participants underwent diagnostic tests through mirror testing and water in the mouth. For this procedure, the children adopted the following position: sitting with the chest upright, legs at 90 degrees. During the test the child held a mirror in front of his face that was sanitized with 70% alcohol for every test. The tests are described below:

Test 1: A reflector mirror is set underneath the child's nostrils and it is verified in which part of the mirror (upper or lower) of the mirror there was the presence of vapor arising from breath. Steam in the upper part of the mirror indicates nasal breathing and steam in the lower or upper/lower part of the mirror indicates mouth breathing.[9]

Test 2: The child is requested to put some water in their mouth and keep their lips closed without swallowing the water for three minutes. It was observed whether the child struggled to do this by the labial commissure. Children who were not able to keep their lips closed for 3 minutes were considered oral breathers. The child should have at least three facial modifications, present vapour in the lower and/or in both mirror regions or keep water in their mouth for less than three minutes[9].

For statistical analysis the children were stratified into two groups: nasal breathers and oral breathers, with the latter including both children with mixed breathing and purely oral breathers.

Initially the project was approved by the Research Ethics Committee of the Faculdade Santa Maria (number No. 563,159). All the responsibles signed a free and informed consent form and the research was conducted according to rules and guidelines that comply with resolution 466/12 of the Ministry of Health.

Data were tabulated and analyzed using SPSS (version 20). This was followed by descriptive analysis, *Pearson's* frequency percentage and *chi-square* inferential analysis (χ^2) and *Poisson regression*. The latter was used to estimate the prevalence rate through its effect exponential. A minor error or one equal to 5%, i.e. $p \leq 0.05$, was considered significant.

Results

The study population consisted of 80 children, however 10 were excluded for not having parental permission to participate in the study.

According to the data presented in Table 1, it appears that most of the sample were female (60%) and the most frequent ages were seven and five (30% and 22.9% of the sample, respectively) with an average age of 7.15 ± 1.7 years.

Table 2 shows that males had a higher frequency of airway problems than females (53.3% and

42.9%, respectively), but no statistically significant difference was presented.

Table 1. Participants' description by age and gender

Variables	F	%
Sex		
Female	42	60,0
Male	28	40,0
Age		
5 years	16	22,9
6 years	09	12,9
7 years	21	30,0
8 years	07	10,0
9 years	06	8,6
10 years	11	15,7

Q1: question 1 – airway problems presence.

Among the signs and symptoms present in MBS it was observed in the group that 30 (42.9%) out of the total number of children studied had problems in their airways, 29 (41.4%) slept with their mouth open, 32 (45.7 %) had a short upper lip, and 54 (77.1%) were positive in the mirror test and 63 (90%) in the water test (Table 3).

Table 4 shows a statistically significant association *(p <0.01)* between children with dark circles and frequent problems in the airways. Sixty per cent of those who had dark circles had problems in the airways. A statistically significant association was also observed between the presence of a short upper lip and problems in the airways (p <0.002). A proportion of 62.5% of individuals who had a short upper lip had a higher frequency of airway problems (than those who did not (26.3%). Subjects who had a flaccid lower lip had more problems with the respiratory tract (91.7%) than those who did not have this problem (32.8%). This association was statistically significant *(p <0.001).*

Table 3. Signals and symptoms of the Oral Breathing Syndrome prevalence description

Variables	F	%
Airway problems		
Yes	30	42,9
No	40	57,1
While sleeping		
Snore	24	34,3
Drool	17	24,3
Sleeps with the mouth opened	29	41,4
Presents dark circles		
Yes	35	50,0
No	35	50,0
Short upper lip		
Yes	32	45,7
No	38	54,3
Flaccid lower lip		
Yes	12	17,1
No	58	82,9
Mouth stays opened when doing nothing		
Yes	15	21,4
No	55	78,6
Eats with the mouth opened to breath		
Yes	16	22,9
No	54	77,1
Dry lip		
Yes	20	28,6
No	50	71,4
Mirror test		
Yes	54	77,1
No	16	22,9
Water test		
Yes	63	90,0
No	7	10,0

Table 2. Association between airway problems and gender

Variables			Airway problems (Q1)		Total	p
			No	Yes		
Gender	Male	F	26	16	42	0,32
		% with Gender	61,9%	38,1%	100,0%	
		% with Q1	65,0%	53,3%	60,0%	
	Female	F	14	14	28	
		% with Gender	50,0%	50,0%	100,0%	
		% with Q1	35,0%	46,7%	40,0%	
Total		F	40	30	70	
	% with Gender	57,1%	42,9%	100,0%		
	% with Q1	100,0%	100,0%	100,0%		

A total of 62.5% of children who presented oral breathing (had problems in the airways, but 37% of those who had nasal breathing had similar problems. The water-in-the-mouth test did not produce a statistically significant result (p = 0.13), but it is clear that 39.7% of the nose breathers (had problems in the airways (Table 4).

All those identified as mouth breathers had a positive result on both tests. After crossing the data, of the 70 students, 47 (67.1%) were identi-

Table 4. Association between airway problems and signals and symptoms of the Oral Breathing Syndrome

		Airway problems (Q1)			Total	P
		No	Yes			
While sleeping (Q2)	Snores	**F**	20	4	24	0,002
		% with Q 2	83,3%	16,7%	100,0%	
		% with Q 1	50,0%	13,3%	34,3%	
	Droops	**F**	10	7	17	
		% with Q 2	58,8%	41,2%	100,0%	
		% with Q 1	25,0%	23,3%	24,3%	
	Sleeps with the mouth opened	**f**	10	19	29	
		% with Q 2	34,5%	65,5%	100,0%	
		% with Q 1	25,0%	63,3%	41,4%	
Presents dark circles (Q3)	No	**F**	26	9	35	0,004
		% with Q 3	74,3%	25,7%	100,0%	
		% with Q 1	65,0%	30,0%	50,0%	
	Yes	**f**	14	21	35	
		% with Q 3	40,0%	60,0%	100,0%	
		% with Q 1	35,0%	70,0%	50,0%	
Short upper lip (Q4)	No	**F**	28	10	38	0,002
		% with Q 4	73,7%	26,3%	100,0%	
		% with Q 1	70,0%	33,3%	54,3%	
	Yes	**F**	12	20	32	
		% with Q 4	37,5%	62,5%	100,0%	
		% with Q 1	30,0%	66,7%	45,7%	
Flaccid lower lip (Q5)	No	**F**	39	19	58	0,001
		% with Q 5	67,2%	32,8%	100,0%	
		% with Q 1	97,5%	63,3%	82,9%	
	Yes	**F**	1	11	12	
		% with Q 5	8,3%	91,7%	100,0%	
		% with Q 1	2,5%	36,7%	17,1%	
Mirror Test	No	**F**	6	10	16	0,071
		% with Mirror Test	37,5%	62,5%	100,0%	
		% with Q 1	15,0%	33,3%	22,9%	
	Yes	**F**	34	20	54	
		% with Mirror Test	63,0%	37,0%	100,0%	
Water Test	No	**F**	2	5	7	0,13
		% with Water Test	28,6%	71,4%	100,0%	
		% with Q 1	5,0%	16,7%	10,0%	
	Yes	**F**	38	25	63	
		% with Water Test	60,3%	39,7%	100,0%	
		% with Q 1	95,0%	83,3%	90,0%	

Q1: Question 1 – airway problems; Q2: Question 2 – While sleeping; Q3: Question 3 – Present dark circles; Q4: Question 4 – Short upper lip; Q5: Question 5 – Flaccid lower lip

fied as nasal breathers and 23 (32.8%) as mouth breathers. There was no statistically significant difference regarding gender (Table 4).

A total of 93% of participants who ate with their mouth open had problems in the airways, while only 27.8% of those who did not eat with their mouth open also had problems in the airways ($p < 0.001$). Likewise, all people who had a dry mouth had problems in the airways and only 20% of people who did not have a dry mouth had airway problems ($p < 0.001$).

In this sample, all the individuals who kept their mouth open while doing nothing had problems in the airways, while among those who did not keep their mouth open when doing nothing only 27.3% had problems in the airways. This association was also statistically significant *($p < 0.01$)*.

Discussion

Literature is divergent regarding the prevalence of mouth breathing. In this study, we found a 32.8% prevalence of oral breathing; however, in studies by Menezes et al.[10] a prevalence of 53.3% was noted and in Paula et al.[11] there was a prevalence of 59.5%. This can be explained by methodological procedures and the different forms of diagnosis adopted in the polls. According to Santos Neto et al.[12], it is difficult for a breathing pattern to be exclusively oral, and most commonly patients breathe both orally and nasally.

In studies by Vera et al.[13] with 77 handbooks of participants diagnosed with learning disorders (LD) attending the Serviço Ambulatorial de Neurodificuldades from the de Medicina do ABC, a service in the state of São Paulo, Brazil, in the period between 2005 and 2006, a higher participation of males (63) (81.8%) was observed, with the most frequent age of 11 years, whose their main signs of SRO were excessive salivation (41) (53%), dark circles (36) (47%) and respiratory complaints (67) (87%). With regard to the prevalence of breathing in participants with LD, 41.6% had mixed breathing. In our study, the highest prevalence was female (60%); however, males had more problems in the airways (53.3%).

According to Conti et al.[14], the higher prevalence of SRO in men may be due to the narrower lower airways, which can contribute to a higher prevalence of allergic rhinitis among boys.

Among the participants of this study, 41.4% slept with their mouth open and 45.7% had a short upper lip. Sixty per cent of those who had dark circles, had airways problems ($p < 0.01$). A statistically significant difference was also observed for those who had a short upper lip ($p < 0.002$) and a higher limp lip ($p < 0.001$) with problems in the airways.

Most patients with respiratory diseases have various problems such as a deficit in the chewing process that usually is changed resulting in noisy eaters with their month partly open, as because they cannot breathe through their nose, mouth breathers have to keep their mouth open when chewing. This is one of the basic features of this type of breather[15].

According to Popoaski et al.[17], gravity and the duration of this breathing pattern can promote important systemic repercussions that will influence the correct growth in height, the emergence of hypertension, pulmonary hypertension and cor pulmonale, and lower respiratory disorders such as more incidence of cough, dyspnoea and obstructive apnoea.

One limitation of the study highlights the divergence in the literature on how to diagnose and pinpoint the symptoms related to oral breathing syndrome, which complicates comparisons among studies to establish the true prevalence of the syndrome. Moreover, the evaluated age groups are distinct with relatively small groups for stratifying and identifying the age group in which these changes can cause most damage to the life of patients.

Mouth breathing due to all the structural and functional changes that can affect the breathing process has become a public health problem and requires a multidisciplinary approach that may prevent, diagnose and treat these patients, thereby ensuring a better quality of life, and minimizing the impact on personal, professional, physical and social fields.

Early detection of this syndrome and clarification for parents, careers, teachers and any other persons involved in childcare are essential so that they can identify these changes and seek specialized care quickly. With regard to the difference in prevalence between the sexes, this may occur because men are more reactive to the signs and symptoms of the syndrome than women, and the most appropriate nomenclature for such cases needs to be further analyzed and studied.

Conclusion

Mouth-Breathing Syndrome occurs in a significant number of children and greater attention to its treatment is required to avoid possible complications.

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Balance assessment in children with cerebral palsy using the berg functional balance scale

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Abstract

Introduction: Cerebral palsy (CP) is the consequence of a disease that affects the central nervous system, taking the dysfunction of postural control and deficit of balance. The capacity to maintain balance is recognized a basic engine component.

Objective: The objective of this study was to evaluate the balance in children with cerebral palsy using the Berg Balance Scale.

Method: Thirty-eight individuals were divided into two groups for the topographical diagnosis of hemiplegia and diplegia. The criteria for inclusion were: aged 6 to 12 years, being monitored by the Rehabilitation Service of Irmandade Santa Casa de Misericórdia de São Paulo and a medical diagnosis of CP level I to III according to the Gross Motor Function Classification System (GMFCS). On the Berg Functional Balance scale, every test is rated from 0 (performance incapacity) to 4 (full capacity).

Results: The hemiparetic group consisted of 21 individuals. The results showed characteristics of a homogeneous group, with the scores ranging between 38 and 56. The diparetic group, which consisted of 17 subjects, showed great heterogeneity in the results. The maximum score of the group was 53 and the minimum 2. Similar characteristics could be seen among the individuals of the hemiplegic group, and the diplegic group presented as heterogeneous and demonstrated greater difficulty in the execution of the evaluated items. Both groups showed significant differences in balance with a value of $p < 0.001$.

Conclusion: Most children with cerebral palsy present changes in postural balance, with these changes appearing more frequently in diparetics. The Berg Functional Balance Scale is a sensitive and important tool for the assessment of balance.

Key words: cerebral palsy, postural balance, Berg Scale.

Introduction

Cerebral palsy (CP) is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain [1, 2]. According to Gagliardi et al., CP is a well-recognized neurodevelopmental condition beginning in early childhood and persisting throughout life and is considered the most common nonprogressive neurological disease of childhood [3]

Motor disorders of individuals with cerebral palsy (CP) are often accompanied by loss of functionality and dependence on others in many daily activities. Inactivity leads to a cycle of deconditioning, resulting in the impairment of multiple physiological systems. The result is physical deterioration and a subsequent further reduction in daily function [4]. However, since motor disability related to sitting, standing, walking and running appears to be the main symptom in children with CP, the assessment and treatment of CP have focused on gross motor function (capacity) [1].

In considering functionality one possibility is classifying CP by group or class. Rosembaum et al. [5] explained that the purposes of classification include: 1) description: providing a level of detail about an individual with CP that will clearly delineate the nature of the problem and its severity; 2) prediction: providing information that can

inform healthcare professionals about the current and future service needs of individuals with CP; 3) comparison: providing sufficient information to permit reasonable comparison of series of cases of CP assembled in different places; 4) evaluation of change: providing information that will allow comparison of the same individual with CP at different points in time.

Traditional cerebral palsy classification schemes have focused principally on the distributional pattern of affected limbs (e.g. hemiplegia, diplegia) with an added modifier describing the predominant type of tone or movement abnormality (e.g. spastic, dyskinetic). With regard to affected limbs, it is not difficult to differentiate hemiplegia from diplegia visually, but the severity of motor impairment of the two classifications is contested.

The study by Saxena et al. [6] compared the difference in postural stability among children with diplegia and hemiplegia and children with TD (typical development) during quiet standing, under conditions with challenges to visual and vestibular inputs. They observed that children with diplegia have increased dependence on somatosensory inputs for maintaining their balance when exposed to different environments, suggesting an altered execution of motor tasks when compared with children with TD. On the other hand, children with hemiplegia did not differ in balance control from age-matched children with TD, and possessed better coping strategies for recovering from postural instability [6].

However, it has become apparent that additional characteristics must be taken into account for a classification scheme to contribute substantively to the understanding and management of this disorder [5]. Changes in motor development are characterized by deficits in several areas, such as fine motor skills or overall balance [7].

We know that individuals with CP may have functional problems such as the delay or interruption of engine development, slowness, weakness in the march, increased energy expenditure, abnormal movement patterns, postural control dysfunction and balance deficit, this indispensable factor to their activities of daily life [8, 9]

Balance is a complex process that depends on the vision of integration, vestibular and peripheral sensation, central commands and neuromuscular responses, and, in particular, muscle strength and reaction time. For better balance, the individual seeks to maintain their body mass center within its limits of stability, this being determined by the ability to control their posture without changing the support base [10].

Postural control and stability are fundamental to motor development. Maintaining the center of gravity of the body over the support base is a complex skill. Postural control can be measured by some instruments such as the Berg Functional Balance Scale [11].

The objective of this study was to evaluate the balance in children with hemiparetic cerebral palsy and diparetics using the Berg Functional Balance Scale.

Method

A total of 38 subjects participated, including 17 subjects with CP diparetic spasticity and 21 with CP spastic hemiparesis. They were selected from the outpatient Pediatric Rehabilitation of the Irmandade Santa Casa de Misericórdia de São Paulo (ISCMSP).

The criteria for inclusion were: aged 6 to 12 years, being monitored by the Rehabilitation Service of the above institution and a medical diagnosis of CP level I to III according to the Gross Motor Function Classification System (GMFCS) [12]. This classification was created by a professional physiotherapist who was specialized in CP. Exclusion criteria were cognitive impairment, other associated pathologies and nonsigning of the Informed Consent (IC) by responsible children.

This study was approved by the Ethics Committee for review of research projects of the ISCMSP under protocol number 337/09. The participants and/or their legal guardians provided written informed consent.

This test includes fourteen (14) subtests, which correspond to the daily activities of the child, such as getting up from a seat, maintaining a standing position without support, moving from a standing to a sitting position, moving in a room, etc. Every test is rated from 0 (performance incapacity) to 4 (full capacity). Then, the scores of all subtests are added and the total performance (score) of the child in the test is calculated. The total score for all

tasks consists of 56 scores, with 0 to 20 considered poor balance and 40 to 56 good balance [13].

The best performance for each child was scored after three consecutive attempts at the same item. The materials needed for the application of the tests were: wooden benches, support with chair for the back and arms, a stopwatch, a tape and a ruler.

Data analysis

For comparison between groups (diparesis, hemiparesis), one-way ANOVA was carried out. The comparison between groups (diparesis, hemiparesis) and performances (best performance, worst performance) was carried out using two-way ANOVA. A separate analysis was made for hemiparesis group with best performance and diparesis group with better performance.

Results

The hemiparetic group was composed of 21 individuals. The results showed characteristics of a homogeneous group, with scores ranging between 38 and 56. All participants in this group had the maximum score in items 1, 2, 3, 4, 5, 6, 11 and 12.

The diparetic group was composed of 17 individuals. They performed better in tasks 4, 5, 7 and 11.

Table 1. Points of comparison on the Berg Scale among people with hemiparesis and diparesis, separated by subgroups of best and worst performers

Activity		Hemiparetic group (HG)**		Diparetic group (DG)*		*p*
		Media	EP	Media	EP	
Sitting unsupported	WP	4.0	0.2	3.5	0.2	.369
	BP	4.0	0.2	4.0	0.2	1
Standing to sitting	WP	4.0	0.3	2.8	0.3	.011*
	BP	4.0	0.2	3.7	0.2	1
Sitting to standing	WP	4.0	0.2	2.6	0.2	.001*
	BP	4.0	0.2	3.9	0.2	.982
Transfers	WP	4.0	0.2	2.5	0.2	<.001*
	BP	4.0	0.2	3.7	0.2	.658
Retrieving object from floor	WP	4.0	0.2	2.1	0.3	<.001*
	BP	4.0	0.2	3.9	0.3	.988
Turning to look behind	WP	4.0	0.2	1.9	0.2	<.001*
	BP	4.0	0.2	4.0	0.2	1
Standing with eyes closed	WP	4.0	0.3	1.6	0.3	<.001*
	BP	4.0	0.3	4.0	0.3	1
Placing alternate foot on stool	WP	4.0	0.3	1.4	0.3	<.001*
	BP	4.0	0.3	4.0	0.3	1
Turning 360 degrees	WP	3.8	0.3	0.8	0.3	<.001*
	BP	4.0	0.2	3.6	0.3	.601
Standing with feet together	WP	3.5	0.3	0.8	0.3	<.001*
	BP	4.0	0.3	4.0	0.3	1
Reaching forward with outstretched arm	WP	3.2	0.3	1.4	0.4	.005*
	BP	3.6	0.3	3.0	0.4	.545
Placing alternate foot on stool	WP	2.8	0.4	0.6	0.4	.003*
	BP	3.9	0.4	2.4	0.4	.053*
Standing with one foot in front	WP	2.6	0.3	1.3	0.3	<.001*
	BP	4.0	0.3	2.8	0.3	.039*
Standing on one foot	WP	2.2	0.3	0.3	0.3	.001*
	BP	3.9	0.3	1.8	0.3	<.001*

*EP: standard error; WP: group with the worst performance on the Berg Scale; BP: group with better performance; * statistically significant values, two-way ANOVA, post hoc Tukey HSD (p = 0.05; SPSS, version 20.0).*

The results show that there was a significant difference for most of the activities between the hemiparetic and diparetic group, which performed worse (except for item 5). The opposite occurred for those who presented better performance, as there was only a difference between them for item 13 (Table 1).

The ANOVA showed that the hemiparesis group performed better in most of the activities, except for "Sitting unsupported" (Figure 1).

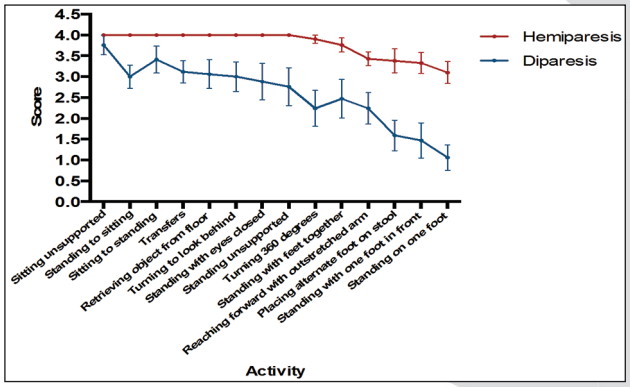

Figure 1. Representation of the values of the mean and standard error for each activity for the two groups

A separate analysis between the hemiparesis group with the worse performance and the diparesis group with the better performance showed that in all activities the scores were similar.

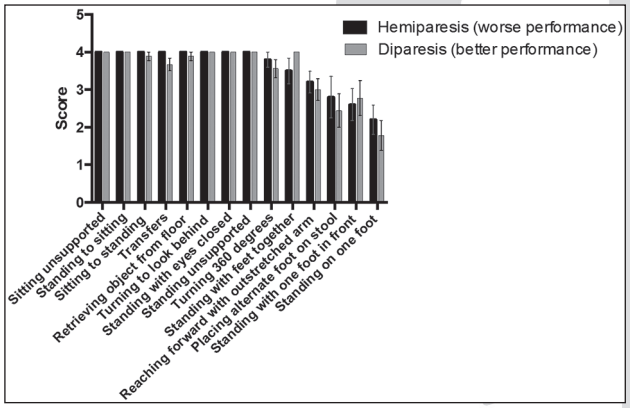

Figure 2. Representation of the mean and standard error between the group with hemiparesis and worst performing group with diparesis with better performance

Discussion

This study aimed to assess the balance in children with spastic cerebral palsy and diparetic using the Berg Balance Scale, which assesses the daily activities of children.

On analyzing the results obtained in this study, variation in the Berg Balance Test scores can be seen in the hemiparetic group, in which most participants had the maximum score (4 points), showing great performance without difficulties, decubitus changes in tasks and little difficulty in tasks with single leg support or with alternating feet. The diparetic group received no maximum score for any of the items evaluated, showing great heterogeneity in the results; the maximum score was 53 and the minimum was 2. The group had greater ease, although to demonstrate maximum score in the decubitus change jobs and greater difficulty in the following tasks: object reach, with single leg support, with alternating feet and eyes closed.

According to Alegretti et al., [14] a wide variety of problems can contribute to the lack of postural balance of diparetic patients with cerebral palsy. The impairment of motor control, including changes in anticipatory mechanisms (feedforward), feedback (feedback) and some musculoskeletal disorders, affects a child's balance reactions.

This was observed in the present study, as the group of diparetic children had greater difficulty during testing, especially in the item remain standing on one foot, where 8 children did not score and only obtained the highest score on the scale. One hypothesis is that this is due to the bilateral involvement of lower limbs.

However, we also analyzed the scores of the best and worst diparetic hemiparesis in all 14 tasks, and we found that in over 50% of the tasks, diparetic individuals performed similarly to or better than hemiparetic individuals.

On analyzing the performance in the tasks sitting unsupported, standing to sitting, turning to look behind, standing with eyes closed and standing unsupported, hemiparesis worse performance and the better diparetic performance, have not statistical difference in performing the task, leading us to believe that these two populations are functionally similar in performing these tasks.

Several studies have used the Berg Balance Scale to assess skills in people with cerebral palsy. In the study of Kembhavi et al. [15] in children with cerebral palsy classified according to the Gross Motor Function Measure (GMFM) as spastic he-

miplegia, spastic displegia, who walked without help and spastic diplegia who walked with help showed that the Berg Balance Scale can be considered a clinical measure of balance for children with cerebral palsy, but in the more homogeneous group, with a limitation with children with minor physical disabilities or mild balance impairment.

Brain lesions in children represent an important model for studying limitations in brain development. The lesional pattern is of early origin and bilateral, which constrains the compensatory potential of the brain [2].

(i) The topography and severity of periventricular lesions may have a long-term predictive value for cognitive and social capabilities in preterm birth survivors; and (ii) periventricular lesions may impact cognitive and social functions by affecting brain connectivity, and thereby the dissociable neural networks underpinning these functions. Restrictions caused by motor disability may affect active exploration of surrounding and social participation, which may in turn differentially impinge on cognitive development and social cognition [16].

Postural control and stability are fundamental to motor development. Maintaining the center of gravity of the body over the support base is a complex skill [17].

The challenges of each of the Berg Scale items are different, and each population responds in its own way to each task. However, with these results, we suggest that individuals who could have greater difficulty – because of lesional topography – can be compared in relation to functional performance with an individual who has an injury that could not involve so as to compromise the execution.

Conclusion

We conclude that most children with cerebral palsy show changes in their postural balance. This occurs more frequently in diparetic than in hemiparetic children as evaluated by the Berg Functional Balance Scale, which is a sensitive and important tool for the assessment of balance. In addition, we also conclude that the best performances of diparetic individuals do not differ functionally from the worst scores of hemiparetic individuals.

Authors' contributions

All authors participated in the study design, data acquisition and interpretation, and the drafting and revision of the manuscript. All authors read and gave their final approval to the version submitted for publication.

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Antibiotics Self-medication among university students at the western region, Saudi Arabia

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Abstract

Aims of the study: This study aimed to measure university students' knowledge and practice towards antibiotics in the western region of Saudi Arabia.

Methods: A cross sectional research design using non probability convenience sampling technique was adopted in this study. A total of 2000 pre-validated questionnaires were distributed in three main universities in the western region of Saudi Arabia. A total of 1472 respondents successfully responded to the questionnaire.

Results: A total of 66% of respondents always use antibiotics without prescription. Long waiting time and having no time were the main reasons for antibiotics self-medication 42% and 32%, respectively. Community pharmacies and friends and family were the main sources of antibiotics 52% and 42%, respectively. Students mainly take antibiotics to treat Influenza 31%, toothache 28% and common cold 27%. About 40% of students stop taking antibiotics when feel better and about only 32% end the antibiotics course.

Conclusion: students showed irrational use of antibiotics. Students have to be educated about rational use of antibiotics and dangers that result from inappropriate use of antibiotics. Therefore, educational programs and courses have to be introduced to university students to raise their knowledge and improve their practice.

Key words: antibiotics, rational use, university students, Saudi Arabia

Introduction

Antibiotics have been widely used worldwide.[1-3] Rationale use of antibiotics results in desired and favorable consequences. conversely, irrational use of antibiotics would result in two main undesired consequences; unwanted side effects and deterioration of the patient health due to acquired bacterial resistance.[4]

Hulscher and his colleagues have reviewed the use of antibiotics among general public and discussed ways to improve the antibiotic use. In their article Hulscher and colleagues concluded that patients' lack of knowledge about antibiotics, bacteria, viruses and the risks of irrational use of antibiotics were the main issues of patients behavior and practice in demanding and using antibiotics heavily.[5] Another major problem concluded in this article was irrational prescription of antibiotics by health care professionals.[5] Inexact diagnosis, fear of complications and in many cases trying to meet with patients' expectations were the major causes of irrational prescription of antibiotics.[5] A third main reason of irrational use of antibiotics is the availability of antibiotics over the counter in many countries even though in most countries antibiotics are prescribed only medicines. But these laws are not enforced in many countries.[6-11]

In addition, in many studies, it has been found that the decision of using antibiotics or even the type of antibiotic is based on patients own experience or even their relatives or friends advices.[12-14] These misleading sources of knowledge that reflect patients' poor knowledge together with easy access to antibiotics and irrational antibiotics prescribing by healthcare professionals resulted in deteriorating patients' health and the presence of antibiotics resistance.

Few studies were conducted in Saudi Arabia showed that public inappropriate believes and practice towards medicines.[15, 16] University students are considered the educated group in the family and society. It is believed that they have a significant impact on their families and society in general. If university students have wrong knowledge and inappropriate practice towards antibiotics use, it is believed that they would negati-

vely affect on the knowledge and practice of their family members as well as friends and society. On the other hand, having a good knowledge and rational use of antibiotics would positively affect on the family members and society and result in improving quality of care, reducing unwanted side effects and minimizing treatment costs.

Thus, this study aimed to measure university students' knowledge and practice towards antibiotics in the western region of Saudi Arabia.

Materials and Methods

Study design

A cross-sectional study design was adopted in three main universities in the Western region of Saudi Arabia which included Taif University, Um Al-Qura University and King Abdul Aziz University in Taif, Makkah and Jeddah, respectively.A total of 2000 questionnaires were conveniently distributed to the students from different colleges and departments in all campuses.

Data collection tool: The questionnaire

The questionnaire was developed after a comprehensive literature review. Face and content validity was done by researchers from the Clinical Pharmacy Department at Taif University. Questionnaire was divided into four sections. First section was about respondents' demographics such as gender, age, educational level, college, living area and number of family members. Section two and three were about students' practice and behavior towards using antibiotics. Fourth section was about students' knowledge and source of knowledge regarding antibiotics.

Data collection technique

Data collection was mainly in the public areas of each campus like bookshops, libraries and restaurants. First, data collectors met with students and briefed them about the study. Then, they informed them that all data will be kept confidential and their participation in the study will be voluntarily. Students were given the questionnaire upon their agreement to participate in the study and giving their verbal informed consent. Answering the questionnaire took about 10 minutes for completion.

Statistical analysis

Data obtained from this survey were coded, entered and then analyzed using the Statistical Package for Social Sciences (SPSS) Version 20. Percentages and frequencies were used to describe the results whereas Chi-square and Fisher Exact tests were used to determine the association between students' demographic profiles and their knowledge and practices towards antibiotics. All *P*-values of less than 0.05 were considered significant.

Results

A total of 1472 respondents successfully responded to the questionnaire with a response rate 73.6%. Responses distributed to 31.6% from Taif University, 34.1% Um Alqura University and 32.3% from King Abdul Aziz University. College of Health sciences represented 22% of total responses whereas science and engineering represented 39.7% of total responses. Over 96% of respondents residing in urban areas Table 1.

Table 2 refers to major practices that patients perform regarding antibiotics. A total of 66% of respondents always use antibiotics without prescription while only 6.6% never used antibiotics without prescription. More than 55% of respondents most of the time and always use their experience to treat certain diseases without physician consultation upon a successful use of the antibiotics. Sharing antibiotics was another issue practiced with around 60% of respondents. Furthermore, about 16% of respondents never completed the course of antibiotics as prescribed. Significant variations in responses were noticed. Students from Um Al-Qura University showed various responses. Where higher proportions 73.8% of them always use antibiotics without prescription. Furthermore, a higher proportion of them 48% most of the time request the physician to prescribe them antibiotics during their clinic visit. In addition, higher proportion of them 42.8% most of the time share their antibiotics with their family members without physician consultation. Students from Science and Engineering departments as well as students from Humanities department showed higher proportions of responses compared to others. Where higher proportions of students from Science and Engineering departments

Table 1. General Characteristics of the Respondents

Demographic characteristics		Frequency	Percentage
Marital Statu	Single	1355	90.3
	Married	99	6.6
	Divorced	14	1.0
University	Taif University	474	31.6
	Um Alqura University	513	34.2
	King Abdul Aziz University	485	32.3
College	Health sciences	330	22.0
	Humanities	545	36.3
	Science and engineering	596	39.7
Education level	First year	476	31.7
	Second year	349	23.3
	Third year	288	19.2
	Fourth year	185	12.3
	Fifth year	105	7.0
	Sixth year	55	3.7
Residence location	Rural	87	3.7
	Urban	1358	96.3
Number of family members	Less than 5 persons	556	37.1
	persons 5-10	682	45.5
	More than 10 persons	230	15.3

most of the time use antibiotics without prescription 51.1% and most of the time ask physicians to prescribe them antibiotics 43.1%. In addition, higher proportions of Humanity students most of the time repeat the same antibiotic of other diseases upon a successful experience of using that antibiotic 40.3%, share their antibiotics with others having the same symptoms 36.1% and sometimes complete the whole course of antibiotics 33.3%.

Table 3 represents main reasons of self-medication with antibiotics. Having no time to see the doctor and long waiting time at the medical centers where the highest causes of self-medication with antibiotics which represented 42.7% and 32.4% of the responses, respectively.

Table 4 shows main sources of antibiotics that students use without prescription. Community pharmacies represented the highest source of antibiotics 52.7% followed by friends and family 42.5%. Higher proportions of Taif residents and students from Humanities College obtain their antibiotics from community pharmacies 69% and 63.7%, respectively. Furthermore, higher proportions of students from Um Alqura University, Science and Engineering departments and living in rural areas get their antibiotics from their families and friends 57.5%, 53.7%, and 66.7%, respectively.

Table 5 represents students' use of antibiotics without prescription. Improper practice was found since only 35.5% of respondents ask for pharmacist's advice while buying antibiotics without prescription. In addition, about one-third of respondents take antibiotics more than 6 times a year. Besides, about one-quarter (24.2%) of respondents take more than one antibiotic at the same time when their symptoms remain after taking antibiotic.

Table 6 represents students' response to any side effect while taking antibiotics. Poor response was noticed from respondents since only one-quarter of them (26.4%) communicate with the pharmacist or physician when having any side effect of using antibiotics.

Perhaps it is a common sense that patients should complete the antibiotic course as prescribed. In this study, about 40.3% of respondents admitted that they do not complete the antibiotics course as they discontinue taking the antibiotics once they feel better. In addition, a bit more than quarter of respondents (27%) keep the remained antibiotics for future use. Dealing with the missed antibio-

Table 2. Students' practice towards Antibiotics

Questions	Chi-square test exact *p*-values									
	N (n) %	S (n) %	M (n) %	A (n) %	Marital status	University	College	Education Level	Residence location	Family Members
I use antibiotics without prescription	96 (6.6)	217 (14.9)	182 (12.5)	960 (66.0)	0.50	<0.001	<0.001	0.004	<0.001	<0.001
When visiting the physician, I request from him to prescribe antibiotics	45 (3.1)	276 (19.0)	670 (46.0)	465 (31.9)	0.326	0.004	<0.001	0.004	<0.001	<0.001
I give antibiotics to any of my family members without prescription	75 (5.2)	336 (23.3)	547 (37.9)	484 (33.6)	0.406	<0.001	<0.001	0.038	0.043	<0.001
If you used antibiotics to treat certain disease and your health has improved. Do you use the same antibiotic for treating any other case without consulting a physician?	142 (9.8)	361 (24.8)	526 (36.2)	424 (29.2)	0.819	<0.001	<0.001	0.236	0.104	0.021
Do you treat medical conditions if repeated with the same antibiotics without consulting physicians?	150 (10.3)	368 (25.3)	501 (34.4)	436 (30.0)	0.465	<0.001	0.012	0.238	0.001	0.001
Do you share your antibiotics with others having the same symptoms without referring to a physician?	197 (13.5)	389 (26.7)	461 (31.7)	409 (28.1)	0.465	<0.001	0.006	0.749	<0.001	0.001
Do you complete all the doses of antibiotics as prescribed?	229 (15.8)	410 (28.3)	416 (28.7)	395 (27.2)	0.638	<0.001	<0.001	0.567	0.001	<0.001
Do you check the expire date of antibiotics before using them?	403 (27.7)	312 (21.4)	321 (22.0)	421 (28.9)	0.387	<0.001	0.005	0.002	0.019	0.003

Note: N: Never; S: Sometimes; M: Most of the times; A: Always

Table 3. Reasons for using antibiotics without prescription

What are the reasons for using antibiotics without prescription?	Yes n (%)	No n (%)	Chi Square *P*-Value: Marital status	University	College	Education Level	Residence location	Family Members
Unavailability of medical Service	234 (16.3)	1221 (83.9)	0.417	0.008	0.299	0.364	0.219	0.397
Having no time to see the doctor	621 (42.7)	834 (57.3)	0.025	0.326	0.001	0.032	0.343	0.160
Cost of consultation	129 (8.9)	1326 (91.1)	0.577	0.008	<0.001	0.172	0.143	0.360
Long waiting time in medical centers	472 (32.4)	983 (67.6)	0.639	<0.001	0.097	0.001	0.035	0.014
Don't trust physicians	101 (6.9)	1354 (93.1)	0.525	0.198	<0.001	0.583	0.182	0.027
I trust pharmacists	252 (17.3)	1203 (82.7)	0.803	0.292	<0.001	0.116	0.370	0.219
Unavailability of medical insurance	134 (9.2)	1321 (90.8)	0.192	<0.001	<0.001	0.015	0.129	0.119
Medical condition is simple and doesn't require visit to the clinic	191 (13.1)	1264 (86.9)	0.065	0.327	0.006	0.454	0.875	<0.001
Have knowledge about treatment through previous experience	35 (2.4)	1420 (97.6)	0.809	0.702	0.866	0.141	0.146	0.076
Others	65 (4.5)	1455 (95.5)	0.683	<0.001	0.438	0.168	0.117	0.095

Table 4. Sources of Antibiotics without Prescription

What are the sources of antibiotics that you get without prescription?	Yes n (%)	No n (%)	Chi Square *P*-Value: Marital status	University	College	Education Level	Residence location	Family Members
Community pharmacies	767 (52.7)	688 (47.3)	0.220	<0.001	<0.001	0.793	<0.001	0.135
Friends and family	618 (42.5)	837 (57.5)	0.035	<0.001	<0.001	0.035	<0.001	0.212
Leftover antibiotics available at home	270 (18.6)	1185 (81.4)	0.747	0.004	<0.001	0.061	0.021	0.106
Other sources	145 (10.0)	1310 (90.0)	<0.001	0.061	0.010	0.023	0.021	0.430

Table 5. Respondents' use of antibiotics without prescription

Section	Yes	Marital status	University	College	Education Level	Residence location	Family members
When you buy an antibiotic without prescription, you		0.265	<0.001	<0.001	<0.001	<0.001	0.001
Ask for a specific antibiotic	295 (20.2)						
Ask for pharmacist's advice	518 (35.5)						
Ask for the cheapest antibiotic regardless of its type	286 (19.6)						
How many times do you take antibiotics through the year?		0.081	<0.001	<0.001	0.298	<0.001	<0.001
I didn't use any antibiotic	106 (7.3)						
Only once	393 (26.9)						
2-4 times	322 (22.0)						
5-6 times	182 (12.5)						
More than 6 times	458 (31.3)						
What do you do if your symptoms remain after taking the antibiotics?		0.002	<0.001	<0.001	0.048	<0.001	0.068
Increase the dose	166 (11.4)						
Stop taking the antibiotic and try other things like natural products	286 (19.7)						
I take another different antibiotic	157 (10.8)						
I take more than one antibiotic at the same time	351 (24.2)						
Ask the pharmacist	210 (14.5)						
Ask the doctor	173 (11.9)						
Others	108 (7.4)						

Table 6. Dealing with antibiotics' side effects

Section	Yes	Marital status	University	College	Education Level	Residence location	Family members
What do you do if you get any side effects while taking antibiotics?		<0.001	<0.001	<0.001	0.416	<0.001	0.033
Reduce the antibiotic dose	187 (12.8)						
Stop taking antibiotics and try other things like natural products	324 (22.2)						
Change the antibiotic with another one	161 (11.0)						
Ignore the side effects and							
Continue taking the antibiotic	456 (31.3)						
Continue taking the antibiotic with another drug to treat the side effects	53 (3.6)						
Ask the pharmacist	202 (14.2)						
Ask the physician	71 (4.9)						

Table 7. Respondents' behavior with missed dose and leftover antibiotics

Section	Yes	Marital status	University	College	Education Level	Residence location	Family members
You stop taking antibiotics when:							
You feel better	588 (40.3)						
End the whole antibiotic course	470 (32.2)	0.042	<0.001	<0.001	0.566	<0.001	0.001
All side effects disappear	183 (12.5)						
Others	218 (14.9)						
What do you do with the leftover antibiotics?							
I keep them for future use	404 (27.8)						
Throw them	472 (32.5)	0.605	0.002	<0.001	0.371	<0.001	0.001
Return them to the pharmacy	480 (33.0)						
Others	97 (6.7)						
What do you do if you forget taking antibiotic dose?							
Duplicate the next dose	177 (12.1)						
Ignore the forgotten dose and cotinue as normal	311 (21.3)	0.604	<0.001	<0.001	0.005	<0.001	<0.001
Take the forgotten dose immediately and continue with other doses as usual	172 11.8)						
Change the antibiotic with another one	83 (5.7)						
Stop taking the antibiotic	411 (28.2)						
Ask the pharmacist	114 (7.8)						
Ask the doctor	190 (13.0)						

Table 8. Major cases of using antibiotics without prescription

Section	Yes	No	Marital status	University	College	Education Level	Residence location	Family members
What are the common cases of using antibiotics without prescription?								
Tonsillitis	228 (15.6)	1233 (84.4)	0.107	<0.001	0.007	0.454	0.881	0.098
Upper respiratory tract infections	231 (15.8)	1230 (84.2)	0.310	0.003	0.002	0.001	0.906	0.145
Urinary tract infections	189 (12.9)	1272 (87.1)	0.031	0.014	0.029	0.624	0.052	0.887
Common cold	393 (26.9)	1068 (73.1)	0.130	<0.001	0.748	0.065	0.002	0.016
Influenza	454 (31.1)	1007 (68.9)	0.006	0.312	0.142	0.565	0.093	0.010
Toothache	413 (28.3)	1048 (71.7)	0.560	<0.001	<0.001	0.122	0.713	0.784
Others	118 (8.1)	1343 (91.9)	0.028	0.154	<0.001	0.297	0.671	0.001

Table 9. Sources of information regarding antibiotics uses

Section	Yes	Marital status	University	College	Education Level	Residence location	Family members
What is the main source of information regarding antibiotics uses?							
Pharmacist	496 (34.2)						
Friends and family	270 (18.6)	0.494	<0.001	0.009	0.344	<0.001	<0.001
Previous experience	99 (6.8)						
Medical publications	193 (13.3)						
Internet	315 (21.7)						
Other sources	78 (5.4)						

Table 10. Students' perceptions regarding antibiotics resistance

In your opinion, what are the main causes of antibiotics resistance?	Chi Square P-Value							
	Yes n (%)	No n (%)	Marital status	University	College	Education Level	Residence location	Family Members
Taking unnecessary antibiotics	429 (29.3)	1033 (70.7)	0.548	<0.001	<0.001	0.669	0.005	0.002
Taking antibiotics without prescription	494 (33.8)	968 (66.2)	0.804	<0.001	0.017	0.073	0.021	0.035
Taking antibiotics before eating	229 (15.7)	1233 (84.3)	0.286	<0.001	<0.001	<0.001	0.252	0.984
Taking more than one antibiotic at the same time	492 (33.7)	970 (66.3)	0.011	<0.001	0.031	0.172	0.004	0.040
Taking antibiotics with other drugs	181 (12.4)	1281 (87.6)	0.835	<0.001	<0.001	0.086	0.580	0.093
Not completing antibiotic course as prescribed	229 (15.7)	1233 (84.3)	0.572	0.013	<0.001	0.630	0.044	0.006
Repeating the same antibiotic with different trade names	174 (11.9)	1288 (88.1)	0.534	0.577	<0.001	0.714	0.134	0.028
Taking antibiotics with the conditions that cause fever	123 (8.4)	1339 (91.6)	<0.001	0.001	0.059	0.761	0.092	0.323
Other reasons	162 (11.1)	1300 (88.9)	0.304	<0.001	0.039	0.109	0.845	0.398
I don't know	235 (16.1)	1227 (83.9)	0.658	0.177	<0.001	0.077	<0.001	0.002

tics dose is another important issue, where only 11.8% of respondents take the missed antibiotic dose immediately after they remember that. Where only 20.8% of respondents prefer to call the pharmacist or physician. (Table 7)

Table 8 shows students' major cases of using antibiotics. Influenza, toothache and common cold represented the highest causes of using antibiotics without prescription 31.1%, 28.3% and 26.9%, respectively.

Pharmacists and internet were the main two sources of information regarding antibiotics 34.2% and 21.7%, respectively. Where patients' previous experience represented 6.8% only. (Table 9)

Table 10 represents students' perceptions towards resistance to antibiotics. Students perceived that taking antibiotics without prescription, taking more than one antibiotic at the same time, and taking unnecessary antibiotics as the main three causes of the development of antibiotics resistance 33.8%, 33.7% and 29.3%, respectively. Whereas only 16.1% said that they don't know the causes of the development of resistance to antibiotics.

Students showed low level of awareness regarding antibiotics safety and use. A bit more than one third of respondents know the precautions of the antibiotics that they use, know whether they are allergic to any type of antibiotics, believe that antibiotics allergy may cause death, and know which antibiotic to be used before or after food. Another serious issue is that about 36.5% of respondents believed that antibiotics are safe to use during pregnancy and breastfeeding. (Table 11)

Discussion

Irrational practice regarding antibiotics was noticed among majority of respondents. Approximately 79% of respondents use antibiotics without prescription and about same percentage usually ask physicians to prescribe them antibiotics once they visit the clinic. Same level of antibiotics self-medication was found in a study conducted in Albania[17] whereas other studies in Pakistan[18], India[12], China[19], Nigeria[20], UAE[21], Libya[22] and Jordan[14], reported lower level of antibiotics self-

Table 11. Students' awareness regarding antibiotics safety and use

Questions	Yes (n) %	No (n) %	Don't know (n) %	Marital status	University	College	Education Level	Residence location	Family Members
Were you aware about the side effects of the antibiotics that you used recently?	949 (64.9)	353 (24.1)	160 (10.9)	0.006	<0.001	<0.001	0.002	0.002	<0.001
Do you think that the frequent use of antibiotics might cause health problems?	579 (39.6)	739 (50.6)	143 (9.8)	0.668	<0.001	<0.001	0.245	0.565	0.015
Do you think that the effect of antibiotics will be decreased if used without prescription?	596 (40.9)	639 (43.9)	221 (15.2)	0.001	<0.001	<0.001	0.017	0.992	0.009
Were you aware about the precautions of the antibiotics that you used recently?	566 (38.8)	622 (42.7)	270 (18.5)	0.063	0.002	<0.001	0.069	0.035	0.619
Are you allergic to any medicine or antibiotic like penicillin?	529 (36.4)	618 (42.5)	306 (21.1)	0.476	<0.001	0.001	0.798	0.909	0.011
Do you believe that antibiotics allergy might cause death?	533 (36.6)	580 (39.9)	342 (23.5)	0.190	<0.001	0.303	0.007	<0.001	0.003
Do you think that all antibiotics have the same mechanism of action?	524 (36.2)	595 (41.1)	239 (22.7)	0.664	<0.001	0.472	0.842	0.312	0.004
Do you know which antibiotics to be taken before food and which to be taken after food?	547 (37.7)	568 (39.2)	335 (23.1)	0.039	<0.001	0.503	0.211	0.403	0.385
Do you think that frequent use of antibiotics might increaser antibiotics resistance?	536 (36.8)	545 (37.4)	376 (25.8)	0.677	<0.001	0.082	0.025	0.041	<0.001
Are antibiotics safe for pregnant women?	532 (36.5)	585 (40.2)	339 (23.3)	0.268	<0.001	0.633	0.260	0.114	0.009
Are antibiotics safe for breastfeeding women?	523 (36.0)	543 (37.4)	385 (26.5)	0.463	<0.001	0.046	0.842	<0.001	0.175
Is it acceptable to use antibiotics continuously for precautions purposes?	489 (33.8)	593 (41.0)	366 (25.3)	0.024	<0.001	0.082	0.328	0.010	0.012
Do you think that it is important to complete antibiotics courses even if you feel better?	496 (34.0)	610 (41.8)	352 (24.1)	0.025	<0.001	<0.001	0.176	0.015	0.012
Do you think that parents have to keep different types of antibiotics at home for future need?	703 (48.2)	377 (25.8)	380 (26.0)	0.056	<0.001	<0.001	0.194	0.130	0.279

medication. A study in Romania found that self-medication with antibiotics is an individual habit that is influenced by health education, source of information and beliefs about medicines[10]. Self-medication was high in this study due to the poor knowledge represented by respondents in which for example about one-third (36%) of respondents believed that antibiotics are safe to use by pregnant and breastfeeding women as well as same proportion of respondents believed that all antibiotics work through the same mechanism of action. Low level of knowledge was presented in the high frequency rate of self-medication with antibiotics that presented in this study which is more than 6 times a year. This result further confirm the correlation between the knowledge and self-medication with antibiotics.

Respondents self-medicate themselves with antibiotics mainly aimed to treat Influenza 31%, toothache 28% and common cold 27%. In Beirut, about 68.6% of patients use antibiotics to treat upper respiratory tract infections and about 33.5% to treat urinary tract infections[23]. A study in Greece found that patients use antibiotics without prescription mainly to treat fever 41%, common cold 32% and sore throat 20.6%[24]. Another study on children self-medication with antibiotics in Yemen found that patients take antibiotics to treat respiratory illnesses 80% and GIT illnesses 13%[25]. In Palestine, patients use antibiotics mainly to treat sore throat 30.3%, common cold 24.4% and teeth problems 10.4%[26].

Majority of respondents reported that having no time to see the doctor 42% and long waiting time at the medical centers 32% were the main reasons for practicing antibiotics self-medications. Whereas the simplicity of medical conditions and cost of consultation represented only 13% and 9%, respectively. A similar study conducted among Beirut residents found that antibiotics self-medication was mainly due to saving time 55.7% and saving money 33.6%[23]. Another study in Pakistan found that self-medication with antibiotics was due to the high cost of healthcare 88%, simplicity of the disease 82%, prior experience 56%, and availability of antibiotics 43%[13]. Easy access to antibiotics is another reason of antibiotics self-medication. In this study, 52% of respondents obtain their antibiotics from community pharmacies, 42% from their friends and family members while 18% from the leftover antibiotics at home. A study on Indian consumers found that main sources of antibiotics were family, friends and relatives (33.3%), community pharmacies (16.3%) and leftover antibiotics (21%)[12]. Similar study in Nigeria found that main sources of antibiotics were community pharmacies 29%, friends and relatives 18.6% and leftover antibiotics represented only 3% of antibiotics[20]. In Jordan, antibiotics were mainly obtained from community pharmacies 43.9%, leftover antibiotics 46.6% and relatives and friends 8.1%[14]. Another study examined antibiotics self-medication among school teachers in Palestine found that about 79% of teachers obtain their antibiotics from community pharmacies whereas only 14.7% of antibiotics were obtained from the leftover previous prescriptions[26].

Respondents in this study said that when they buy an antibiotic from the community pharmacy, they usually ask for specific antibiotic 20%, ask for pharmacist's advice 35% and ask for cheapest antibiotic 20%. These responses can be reflected from the sources of information that respondents rely on when dealing with antibiotics. In which pharmacists represented only 34% as a source of information whereas friends and family, experience and internet represented 47% of respondents' source of information. Similar finding was found in Albania in which pharmacists represented 36% of antibiotics information source[17]. Relying on misleading and inappropriate sources of information would definitely be reflected in patients' practices. This was found in respondents' behavior once the symptoms of the disease remain even though they completed the antibiotic course. Only 14.5% of them communicate with the pharmacist and 12% communicate with the physician. While 11% of them increase the antibiotic dose, 24% of patients take more than one antibiotic at the same time to come over disease remaining symptoms. In addition, majority of respondents 40% stop taking the antibiotics once they feel better and only 32% complete the antibiotic course. Better findings were found in a study conducted on individuals living is Kuwait where 64% of respondents complete their antibiotics courses as prescribed by the physician[27]. Findings of the current study were associated with the poor knowledge that was pre-

sented in this study. Where about 42% said that it is not important to complete the antibiotics courses and 24% didn't know whether it is important to complete the antibiotic course or not. A study in Beirut found that 38.5% of respondents complete their antibiotic courses, 68.1% of them stop taking antibiotics once the symptoms disappear, 28% stop taking antibiotics as advised by doctor[23]. Another study compared antibiotics self-medication in Yemen, Saudi Arabia and Uzbekistan found that patients stop taking antibiotics once symptoms disappear was 44% in Yemen, 39% in Saudi Arabia and 64% in Uzbekistan[28].

Dealing with missed doses and antibiotics side effects were major issues in this study. Only 12% of respondents take the forgotten dose immediately whereas 12% duplicate the next dose and about 21% ignore the forgotten dose and continue as normal. Furthermore, only 22% of respondents stop taking antibiotics once they face any side effects whereas 31% of them ignore the side effects and continue taking the antibiotic as planned. This malpractice could be a reason of the improper sources of information regarding antibiotics which was found in this study.

Education is considered an urgent need to improve public and students' knowledge and practice towards antibiotics use[29]. Proper educational programs proved to be effective and productive in many cases[30-32].

It is believed that improving university students' knowledge would be reflected in their practices and transferred to their family members and society. Thus, we would invite decision makers in Saudi Arabia to invest on educating university students on rational use of antibiotics to improve public health outcomes and quality of life as well as reducing treatment costs.

Conclusion

Antibiotics were found to be heavily and irrationally used among university students in the western region of Saudi Arabia. Students rely mainly on internet, friends, relatives and their own experience as main sources of information on antibiotics. Having no time to visit healthcare institutions and long waiting time were the main reasons for self-medication with antibiotics. Students have to be educated about rational use of antibiotics and the hazards and dangers that result from inappropriate use of antibiotics. Therefore, educational programs and courses have to be introduced to university students to raise their knowledge and improve their practice.

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Religious and spiritual coping in psychotic disorders: a systematic review of XXI century

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Abstract

Objective: To investigate the influence of religion / spirituality in the lives of patients with schizophrenia or other psychotic disorders.

Methods: A systematic review was conducted of articles on psychotic disorders, religion and spirituality, were included articles until the date of October 4, 2015, were excluded from previous studies to 2000.

Results: Of the 42 studies identified, 28 were selected articles.

Conclusion: It was noted the importance of religious and spiritual aspects in the treatment of psychotic patients, but was perceived to the need for more studies on this subject.

Key words: schizophrenia, religion, religion and medicine, spirituality, coping.

Introduction

Spirituality is a subjective term and it involves questions about the meaning of life and its relationship with the transcendental, emotions and its relationship with the transcendental, being present emotions and beliefs of non-material nature. While religion is the word used to refer to an institutional and doctrinal aspect, which will be present certain behaviors and rituals that focus on the supernatural and transcendental and can be the way to experience the spirituality. Therefore, a person can express spirituality without necessarily being religious[1,2].

Spirituality and religion are part of important aspects of human life and can influence the health aspects such as lifestyle and healthy behaviors[3]. The religious / spiritual coping is the way that the individual can use religion or spirituality to get through difficult moments of life[4].

The belief in a religion can influence both negatively in the interpretation and acceptance of illness and, in the case of schizophrenia, may be the subject of mystical and religious delusions[5], and positively, helping to overcome frustrations and negative outcomes of diseases[6].

Research suggests that religion and spirituality can improve the relationship between healthcare professional and patient, but this subject is constantly neglected and the professional have a great difficulty to talk about this theme with the patient[7,8].

Psychotic patients were stigmatized for centuries by religious institutions who understood that the psychiatric disorders had only mystical causes[9], and until the twentieth century, religiosity and spirituality were seen as negative influences on mental health because there are many opposing ideas between psychiatry and religion[10].

Among psychotic disorders, there is the schizophrenia, which may begin in young people, with prevalence of 1% over the life of the general population[11] and is an important cause of limitation to the individual, because there is a great difficulty to reinsert him in the society[12].

The prognosis of schizophrenia is unfavorable and there is a great difficulty in social adaptation after the first hospitalization, and the patient has a high suicide rate when compared to non-schizophrenic[13]. Patients with frequent relapses have no adhesion to the treatment rates between 38% and 68%, and if there's more outbreaks, greater will be the loss in

mental functions of patients and therefore poor prognosis[14]. The main reasons for non-adherence: lack of social support, impaired insight, adverse effects of psychotropic drugs and substance abuse[15,16].

In recent years, psychiatry came to understand more positively both religion and spirituality and the theme has been researched by several authors, suggesting their relevance for clinical practice[10,17]. Unfortunately, there is a scarcity of studies in the area, which explains the purpose of this study: review what the latest publications bring about the influence of religion and spirituality in the patient's life with schizophrenia and other psychotic disorders.

Methods

We conducted a qualitative systematic review of scientific literature on the theme of schizophrenia and its relationship to spirituality and religiosity. The qualitative approach was chosen because quantitative methods such as meta-analysis show that: (a) the information needed to calculate the size of the result are not always available, and can limit this analysis to a small subset of studies and (b) studies used different themes and patient groups, hindering accurate comparisons and statistical analyzes. Thus, a quantitative analysis is not suitable for this revision having a large amplitude.

The search for articles was conducted in online databases MEDLINE and LILACS in April and October 2015, limited to articles published until 10.04.2015.

Initially, the search strategy was based on the intersection of the following terms:

- "schizophrenia" [Subject descriptor]
- ("religion" or "religion and medicine" or "religion and psychology") or "spirituality" [Subject descriptor]
- coping [Words]

Proceeded to the intersection of the terms as follows: # 1 AND # 2 AND # 3. The complementation of the search for descriptors using the keyword "coping" is justified because this term, though not cataloged in MeSH, is internationally used as a synonym for confrontation. The search strategy and found articles were reviewed on two separate occasions by two independent researchers in order to ensure the adequacy of the sample.

Inclusion criteria for this study were:

a) articles presenting the title at least a combination of the established terms;
b) manuscripts written in English
c) studies of schizophrenia or other psychotic disorders and spirituality or religiosity;
d) original texts with online access;
e) prospective or retrospective observational studies (analytical or descriptive, except case reports), experimental or quasi-experimental.

Were excluded:

a) other study designs, such as case reports, case series, literature review;
b) editorials, book reviews and letters to the editor;
c) previous articles the year 2000;
d) studies in other languages.

Then each member of the sample article has been read in its entirety, and the relevant data for the research were taken from him and included a spreadsheet containing author (year), type of study, sample and main findings.

In order to increase the data analysis, the next stage involved the grouping, for heuristic reasons, the results in 7 themes: perception of the disease, substance abuse, relationship of religion to the doctor, relation of religiosity / spirituality with caregivers, relationship between religion and delusions, religious coping function and how religion and spirituality act in the prognosis of the disease.

Results

Initially, the search strategies above resulted in articles 42, being twenty-eight articles were eligible and were included in the final sample (Figure 1). According to Table 1 lists the items were organized from the information: Author (year), type of study sample.

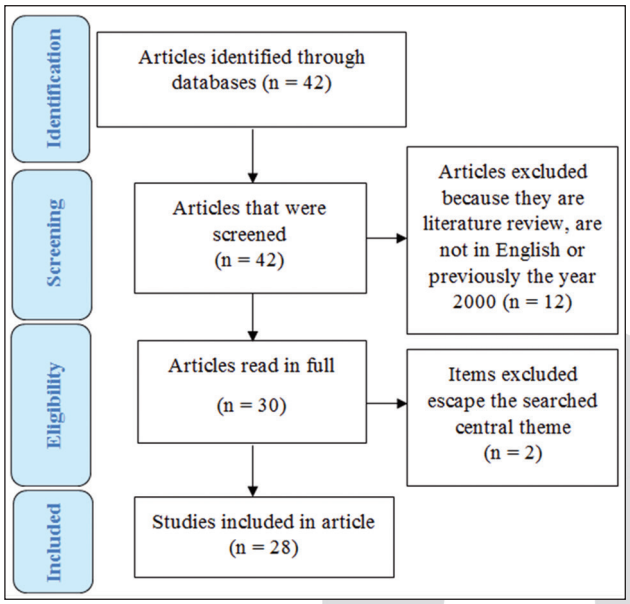

Figure 1. Flow chart showing study selection for the review

Discussion

Most of the studies included were made up of participants who had any religion, being mostly Catholics, in similar proportions in relation to sex, prevailing low socioeconomic status individuals. They involved patients with schizophrenia who were followed up in public hospitals, but were also found studies involving physicians and caregivers of these patients.

In relation of religious issues, patients with any religion was present in most studies, the predominance of Christians[18-29], one of the studies focused on the evangelical religion (Baptist)[30], others did not specify a religion[31-35], while involving some traditional oriental religions (Hindu, Buddhism, etc.)[6,36-42].

Studies have found that patients with a chronic disease and that should receive drug treatment, mostly believed that the disease had supernatural origins, like black magic[6,25].

Mohr, Gillieron, Borras, Brandt and Huguelet[26] verified that spirituality can help patients with schizophrenia, because it can offer explanations, life support and new perceptions of the disease when no other source can support.

It was seen that the more religious patients, the smaller the substance abuse indices[23-26]. However,

Table 1. Key findings that relate schizophrenia / psychotic disorders, religion and spirituality

Author (year)	Type of study	Sample	Main findings
Mohr *et al.* (2012)	Transversal and cohort	276 patients with schizophrenia or schizoaffective disorder (mostly Christian)	Religious coping performed either positively or negatively, prevailing positive way. The difficulties regarding the treatment proved to be present both in patients who had a religion with positive and negative impact.
Nolan *et al.* (2012)	Transversal	63 patients with schizophrenia (mostly Christian)	The positive religious coping prevails over the negative, found a directly proportional relationship between quality of life and religious coping.
Smith; Suto (2012)	Cohort	9 patients with schizophrenia. No explicit religion	Religious / spiritual practices can give to the patient a better way to cope and overcome the disease.
Webb *et al.* (2011)	Transversal	81 participants with severe mental illness - not explicit religion	For all diseases studied religious support and strength that religion gave them were extremely important for the recovery of the disease.
Mohr *et al.* (2011)	Cohort	115 patients diagnosed with schizophrenia or schizoaffective disorder (mostly Christian)	The religion was related to a better quality of life and clinical and functional assessment. The positive religiosity is associated with better results in negative symptoms.
Revheim; Greenberg; Citrome (2010)	Transversal	40 schizophrenic - 20 of a spiritual group (SMG) and 20 non-members of the group. The Christian majority.	Group participants were more effective in dealing with the disease. Participation in spiritual groups does not necessarily occur because of religious delusions or positive symptoms. The study does not necessarily observed spirituality ratio and quality of life.

Mohr *et al.* (2010)	Transversal	236 participants with schizophrenia or schizoaffective disorders other (mostly Christian)	Non-adherence is higher in patients who have religious delusions. The amount and duration of hospitalizations, as well as the duration of the disease are similar to those with religious delusions than those who do not have delusions (both lower than those with non-religious delusions). Religious delusions hinder participation in group religious activities. Negative religious coping was more frequent in the group with negative illusions.
Borras *et al.* (2010)	Transversal	221 patients diagnosed with schizophrenia or schizoaffective disorder and their 57 physicians	Religion is more important in the lives of patients than physicians. Physicians tend to devalue the religion, the reasons given by physicians: prioritize other clinical, little time, lack of preparation and, finally, the personal understanding that it is not helpful to address the issue.
Huang *et al.* (2009)	Transversal	10 caregivers of patients with schizophrenia - not explicit religion	Many attributed mystical connotations to the cause of disease and therefore felt obliged to take care, there is also a larger search by religion by the caregiver.
Sanseeha *et al.* (2009)	Transversal	18 participants diagnosed with schizophrenia - All Buddhists	They understood that it was a disease that had chronic and should be adequately treated with medication, but there was also the perception of supernatural powers (black magic), biological and even bad karma in the genesis of the disease.
Huguelet, P. *et al.* (2009)	Transversal	115 patients with schizophrenia or schizoaffective disorder (mostly Christian)	Inversely proportional relationship between religion and substance abuse, however for three patients religion acted negatively.
Borras *et al.* (2008)	Transversal	115 patients with schizophrenia or schizoaffective disorder (mostly Christian)	Inversely proportional relationship between tobacco use and religion. The most of smokers had not religious affiliation
Huang *et al.* (2008)	Transversal	10 caregivers of patients with schizophrenia (4 Buddhists, Taoists 4 and 2 without religion)	Most caregivers sought not psychiatric treatment for the patient before seeking medical attention. The spiritual help was sought inversely proportional to the social support so that carers receive 70% of respondents expressed that uses religion as a source of coping.
Borras *et al.* (2007)	Transversal	103 patients with schizophrenia (mostly Christian)	Most patients have personal understanding of the disease influenced by their own spiritual beliefs. The more religious were the patients, the lower the addiction rates. The adherents of treatment have more religious practices in a group than no adherent, with 31% of the no adherent and 27% of the partially adherent saw incompatibility / contradiction between religion and taking medication, compared to only 8% of adherents.

Mohr *et al.* (2007)	Transversal	115 patients with schizophrenia or schizoaffective disorder (mostly Christian)	The disease can strengthen the spirituality of the individual, however, in some cases negatively affected their development. Some interviewees had the disease as something that made it difficult to participate in religious practices group. Patients who participate in religious practices have lower smoking rates of those who do not participate.
Huguelet, P. *et al.* (2007)	Transversal	115 patients with schizophrenia or schizoaffective disorder + 30 patients with attempted suicide and without psychosis	For 64% there was no relationship between religion and suicide attempt, for 25% protection and for 11% risk. Those without suicide attempts reported more often protection factor religion.
Mohr *et al.* (2006)	Transversal	115 patients with schizophrenia or other non-affective psychosis (mostly Christian)	12% of respondents had an antagonism between religion and medication and for 10% antagonism between supportive therapy and religion. There is a high amount of religious coping in patients with psychosis. For 71% of patients religion acted positively. However, even for those patients in which there is positive coping, religion can be a risk.
Huguelet, P. *et al.* (2006)	Transversal	100 patients with schizophrenia or other non-affective psychosis + your professional caregivers (19 psychiatrists, 11 nurses and 5 social workers)	Most patients and doctors have religion, but the number of physicians with no religious affiliation is 47%. Most patients get involved with religion as a personal and solitary practice. Patients with chronic psychosis tend to be more religious than other individuals. Many physicians do not necessarily felt uncomfortable to talk about religion, but reported that they lack skills. Physicians often neglect or devalue religion / spirituality.
Sethabouppha; Kane (2005)	Transversal	15 caregivers of patients with schizophrenia (all Buddhists)	Many cited that due to Karma his family were sick and so should take care of them.
Compton; Furman, (2005)	Transversal	18 patients with schizophrenia or other non-affective psychosis + their 34 physicians	Patients with more negative symptoms also have a smaller relation with the belief and God. The greater the number of symptoms, the lower the existential well-being of the patient.
Weisman; Gomes; Lopez (2003)	Transversal	24 relatives of patients with schizophrenia	Religion was reported as something that relatives understand as a means to overcome the disease, it causes the relatives stimulate the patient to go to medical appointments, take medications at the correct time, pay more attention to the patient and the disease, encourage religiosity / spirituality.
Yip (2003)	Transversal	4 patients with schizophrenia (traditional Chinese religions)	Religion has an important impact on subjective experiences of delusions and hallucinations. Patients have built strange and bizarre behavior on religious grounds, and hallucinations / delusions can be a way to adapt their realities.

Rammohan; Rao; Subbakrishna (2002)	Transversal	60 caregivers of patients with schizophrenia (all Hindu)	At the beginning of the disease, 23% thought conditions be because black magic or evil spirits, 38% attributed to biological causes and the remainder attributed to psychological causes consequences. 33% of caregivers sought religious healing methods prior to drug therapy, and the worse the performance levels of the patient, the greater the religious coping caregiver.
Davies; Griffin; Vice (2001)	Transversal	18 participants with psychosis and not evangelicals, 29 evangelicals and with no previous treatment for mental illness, 55 not evangelicals and no previous treatment for mental illness	The psychotic group felt less positive experience hallucinations than the control group, and this felt less positive than the evangelical group. The strong religious belief can be an indicator of premorbid psychosis, and evangelicals who heard voices report that these have positive religious significance voices.
Rungreangkulkij; Chesla (2001)	Transversal	12 mothers of patients with schizophrenia (Buddhist)	Mothers understand that the disease would have several causes, including biological and supernatural. All the mothers in the study understood the disease initially as having supernatural causes, seeking healers before the physicians.
Kate *et al.* (2014)	Transversal	100 caregivers (Hindu majority) patients with schizophrenia	It is interesting the physician encourage the caregiver to develop religion and spirituality, because this can be favorable to the patient.
Kate *et al.* (2013)	Transversal	100 caregivers (Hindu majority) patients with schizophrenia	The motivation for care is the most common aspect to assume this function, and religious coping something positive for the caregiver.
Tabak; Weisman de Mamani (2014)	Transversal	112 individuals with schizophrenia or schizoaffective disorder other (without specifying religion)	Patients with higher intrinsic religion (which is equivalent to spirituality) have higher quality of life, more tools to overcome difficult times and less severe negative symptoms. The extrinsic religion (the religion of social convention) was related to a greater search for social support.

one study found that in a small percentage of the interviewed, the religion acted in a negative way, being reported by one of them that was provided him great distress after not improve even after becoming more religious, what did him abuse alcohol[23].

Studies suggest that although many doctors have religion, often do not address the topic religiosity / spirituality during the consultation. The lack of sufficient knowledge to discuss the issue and its non-recovery were the main reasons[43,44].

Huguelet, Mohr, Borras, Gillieron and Brandt[44] found that 53% of physicians surveyed had some religious affiliation, while 47% did not have any religious affiliation, however, does not justify the non-religious / spiritual approach in these cases, because only 18% of patients interviewed had no religious affiliation.

Most caregivers are family members of the patient, particularly first-degree relatives, they reported worse quality of life as a result of care provided to the patient and searched religious comfort most frequently[33,34,37,39]. It was found that religion provides a better prognosis in the disease because there is a greater incentive for going to medical appointments and better medication adherence[34].

Caregivers frequently searched not psychiatric treatments with the sick, as shamans and medicinal plants[37,39,40], and the spiritual help was sought in inverse proportion to the social support that caregivers received[37]. In some studies, caregivers

cited that as a result of actions done in previous lives their families were sick, so they felt obliged to take care of them[33,36].

Most religious caregiver search was favorable both for the health of the patient[41], but also for their own health[42].

When checking on religious coping, the positive prevails in relation to negative[18-20,28], and religious and spiritual practices being perceived as an important way to cope and overcome the disease[21,31,32].

We found a directly proportional relationship between quality of life and religious coping[19,35], also realizing a better clinical and functional evaluation[20,35]. In one study, not necessarily noticed the relationship between spirituality and quality of life[21].

It was noticed that in patients with psychotic disorders there is a high prevalence of positive religious coping. Being the judgment that spirituality is vital in their lives reported more frequently than the general population[28]. Negative religious coping was more frequent in the group with negative symptoms[22].

Psychotic disorders may also affect the perception of religion, leading to pathological religious beliefs or hindering the emergence of a healthy spirituality[26]. Compton e Furman[30] suggest that patients with more negative symptoms have a lower spiritual belief.

As regards religious delusions, contents and frequency of religious delirium are very interconnected with the patient's culture, and may even make it difficult to religious groups, and the success of the medical treatment[22]. Huguelet, Mohr, Borras, Gillieron e Brandt[44] found that 16% of patients with schizophrenia who participated in the study had positive symptoms with religious content.

Yip[38] suggested that patients may have built strange and bizarre behaviors faith-based in order to escape from a difficult reality. While Davies, Griffin and Vice[29] conducted a study involving psychotic patients, nonpsychotic evangelical and a control group (neither evangelical nor psychotic), raising the hypothesis that excessive religious belief can be a premorbid sign psychosis.

It can be seen also an antagonism between religion and remedy[18,28] or between supportive therapy and religion[28]. Regardless of coping be positive or negative non-adherence to treatment is higher in those patients with religious delusions[22].

Borras *et al.*[25] realized that adherent participated in religious practices in groups more often than non-members, which could be a reflection of the patient's clinical time. In another study[35], it was observed that religion is more related to a search for social support.

The amount and duration of hospitalizations are similar between patients with religious delusions than those who do not have any delirium, differently the religious delusions, involving a greater number and duration of hospitalizations. Therefore, religious delusions does not necessarily imply in a more serious illness or worse prognosis[22].

Huguelet *et al.*[27] realized that religion, in most cases, acts as a protective factor for suicide attempts. However, there are cases where it becomes a risk factor, such as when the disease arouses the desire to die to be close to God or when the disease becomes interpreted as a "religious condemnation".

The spirituality / religiosity may affect patient outcomes, either positive or negative, because both can improve the prognosis of the disease (either for the quality of life, medication adherence and risk of suicide) but can also worsen (with lower medication adherence and increased risk of suicide). It's important to remember that the theme also has relevance to the lives of caregivers, as they often rely on faith to be able to continue care.

Research should be implemented to give visibility to themes like this, however, although the world scientific production has been increasing significantly, could be increase more with the proper training of health professionals who work with research in project management[45].

Thus, it was found that the theme under study is relevant and requires further understood by those professionals who care for these patients. This revision realized the scarcity of studies in predominantly religious countries like the Latin American countries, and also have been seen a concentration of jobs in certain countries (more specifically certain cities), which does not provide us a full scale of results.

Conclusions

It was evident that health professionals, especially the medical profession, avoid addressing the theme and feel unprepared or do not understand how something important. It is necessary that this theme be less stigmatized and can be experienced

more and more day-day health care provider or health student, because the idea of valuing the individual is not only the disease but also the social and cultural aspects of his life.

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Use of suit therapy in Cerebral Palsy rehabilitation: a literature review

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Abstract

Introduction: Cerebral palsy is a well-recognized neurodevelopmental condition beginning in early childhood and persisting throughout life, and it is considered the most common non-progressive neurological disease of childhood. A remarkable proliferation of "alternative" therapy approaches based on ideas about the biological basis of neurodevelopmental disabilities, following this idea methods that use special garments has been highlighted and may provide greater stability, positioning, and possible function.

Objective: The purpose of this study was to analyze research findings about cerebral palsy and the use of garments in rehabilitation.

Method: A systematic literature search was done using Medline/PubMed®, Web of Science, and BVS (virtual library in health). Considering keywords, we included articles that showed the terms "cerebral palsy" and "suit" or "undergarment."

Results: The search was carried out on three platforms: Medline/PubMed®, BVS (virtual library in health), and Web of Science. We conducted a cross between keywords as follows: Initially, 122 studies were found in the three databases; 115 studies were eventually excluded because they did not fill the inclusion criteria. The data extracted from the 7 eligible studies is summarized.

Conclusion: We can conclude by means of studies that analyze the spatial parameters improved significantly in this population, although some studies suggest that this improvement occurs only after one month of treatment. Studies also conclude that individuals who used the "suit" showed improvement in Gross Motor Function Measure after treatment.

Key words: "cerebral palsy", "undergarment" and "suit".

Introduction

Cerebral palsy (CP) is a chronic neurological disorder caused by a static lesion in the immature brain and is characterized by deficits in movements and postural control.[1] Motor control during reaching, grasping, and walking is disturbed by spasticity, dyskinesia, hyperreflexia, excessive coactivation of antagonist muscles, retained developmental reactions, and secondary musculoskeletal malformations, together with paresis and defective programming.[2] Damiano et al. (1995) explained that muscle weakness has been identified as one of the primary deficits contributing to motor dysfunction in individuals with CP.[3]

Limited evidence exists regarding the efficacy of traditional rehabilitation strategies on improving ambulatory function in this population.[4] It is known that to lessen the movement problems and musculoskeletal disorders of CP, progressive functional training is used.[5]

Considering functional training, a number of exciting innovations in treatment have expanded the opportunities to help children with CP.[6, 7] At the same time, the field has experienced a remarkable proliferation of "alternative" therapy approaches based on ideas about the biological basis of neurodevelopmental disabilities and their management that differ considerably from conventional thinking.[8]

Following this trend, a method that has been highlighted is therapy that uses special garments that may provide greater stability, positioning, and possible function. Most likely, suit therapy (ST) was the initial idea to use a special garment

in rehabilitation, which consists of an intensive therapy with a holistic approach to the treatment of individuals with neurological disorders like CP, developmental delays, traumatic brain injuries, autism, and other conditions which affect a child's motor and/or cognitive functions.[9] This technique, originally named the penguin suit, was developed in Russia in 1971 to allow cosmonauts to perform resistance exercises in zero gravity conditions.[10] In 1991, Poland launched AdeliSuit™ or PolishSuit. In the early 2000s, these suits were released in other countries with different nomenclatures. In 2002 TheraSuit™ designed the suit and method in Michigan (USA), in 2005 the NeuroSuit™ in Georgia (USA), and in 2006 the PediaSuit™ in Florida (USA). Today, there are several physical therapy clinics around the world that work with this feature.[11]

In general, the protocol of intensive treatment is a method which associates the use of a suit combined with intensive physical therapy and consists of up to four hours of therapy a day, five days a week, over the course of three or four weeks. The suit consists of a vest, shorts, knee pads, and shoes, all connected with hooks and elastic cords. The suit serves as a stability vest that produces a vertically directed load of approximately 15 to 40 kg.[9, 10]

The ST protocol is customized to fit the needs of each child, with specific functional goals, and usually involves an intensive rehabilitation program. It combines the best elements of various techniques and methods, and has a sound rationale based on exercise physiology.[9]

Another type of ST is known as TheraTogs™, an orthotic undergarment fabricated from Delta-flex, a lightweight, breathable fabric that is Velcro-sensitive. It was developed to provide a gentle, passive force to correct imbalance or alignment through the combination of a trunk and shorts system along with a customized external strapping system.[12]

Those treatments are based on three principles: (1) the effect of the suit (working against resistance loads, increased proprioception, and realignment), (2) intensive daily physical therapy for one month, and (3) active motor participation by the patient.

The ST garment provides resistance to movement and emphasizes not only selective muscle activation but also transition and functional activities that require the coordination of several body segments and joints.[13]

The use of the ST in the CP patients with a decreased role of visual analyzer in achieving the standing pose as it was found under control examination enhances its significance in controlling the position of the center of gravity of the body.[14]

Children with CP are able to acquire and retain new motor skills if provided adequate feedback. Interestingly, it has been found that too much feedback in patients with CP interferes with the learning of tasks.[10] Due to this, it is necessary for future studies to examine postural changes and gait efficiency with and without suit wear in children with CP of varying functional abilities.

Therefore, the purpose of this paper is to make a systematic review to analyze the suit and garment protocols being used and to verify the most effective results in individuals with CP.

Method

This review was based on a systematic search of published articles available through July 2015. It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

The research was done using Medline/PubMed®, BVS (virtual library in health), and Web of Science searched concurrently for entries using the established keywords. Considering keywords, we included articles that showed the terms "cerebral palsy" and "suit" or "cerebral palsy" and "undergarment." The surveyed studies should contain this combination of words.

The selection of articles involved three steps. In the first step, we looked for articles in the databases and read the titles and abstracts. In the second step, was the exclusion of works by title or abstract, and the exclusion by our inclusion criteria. The third and final step was to analyze the eligible works.[16-18]

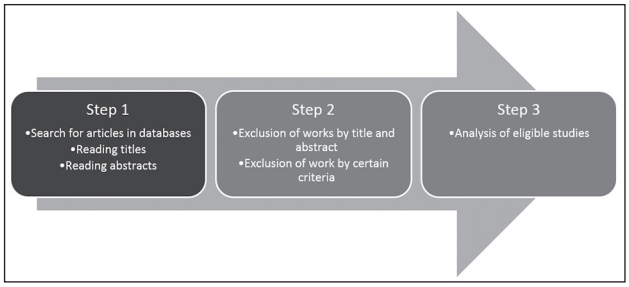

Figure 1. Searching databases

Increase confidence in the selection of articles, all potentially relevant articles were reviewed independently by two researchers, who after reading through them determined which fulfilled the inclusion criteria.[16, 17, 19]

Abstracts of identified articles were then screened for the following inclusion criteria: (1) the population included individuals with CP and (2) a suit and/or undergarment was used in this population. There were no restrictions on minimum sample size. Articles were excluded if they: (1) were not data-based (e.g. books, theoretical papers, or secondary reviews), (2) were not published in English, (3) examined populations not explicitly identified as having a diagnosis of CP, or (4) did not include a suit and/or undergarment.

All identified studies were collected in EndNote Web (Thomson Reuters) and duplicates were removed.

Results

The search was carried out on three platforms: Medline/PubMed®, BVS (virtual library in health), and Web of Science. We conducted a cross between keywords as follows:

Initially, we found 122 studies in the three databases; 115 articles were eventually excluded because they did not fill the inclusion criteria. The data extracted from the 7 eligible studies is summarized.

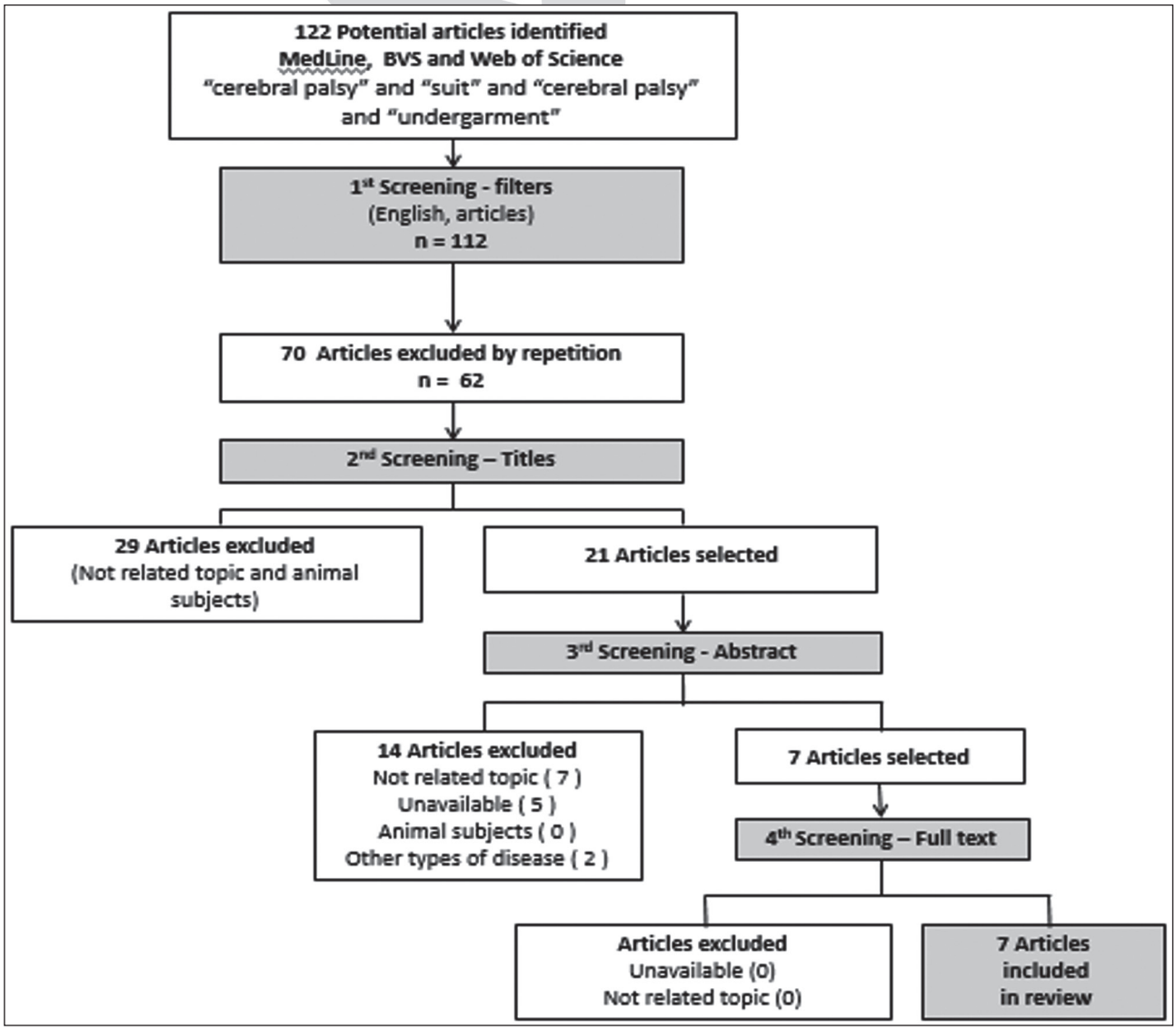

Figure 2. Literature review citation selection flow chart

Table 1. Data about sample, instruments, frequency and duration, and main outcomes of the studies included in the review

Reference	Sample	Instrument	Frequency and duration	Main outcomes
Ko *et al.*, 2015	1 girl CP level III (GMFM)	Treatment Phase - Adeli suit Baseline Phase - Spatial-temporal gait parameters 10-meter walking speed GMFM.	Baseline Phase (1x week intervals for 6 weeks) Treatment Phase (18 sessions, 50 min/ session, 1x week 18 weeks)	Spatial-temporal gait parameters significantly improved. 10-meter walking speed, GMFM, and PBS changed significantly from the baseline measurement. The AST was effective.
Bailes *et al.*, 2011	20 CP (3 to 8 years)	Treatment Phase - Thera-Suit Baseline Phase - PEDI and GMFM	Baseline Phase - before and after (4 and 9 weeks). Treatment Phase - 4 h/d, 5 d/w over a 3-week.	No significant differences were found between groups. Significant within-group differences were found for the control group on the GMFM-66 and for the experimental group on the GMFM-66, PEDI Functional Skills Self-care, PEDI Caregiver Assistance Self-care, and PEDI Functional Skills Mobility.
Bailes *et al.*, 2010	2 children CP level III (GMFM)	Treatment Phase - Therasuit Baseline Phase - PEDI and dimensions D and E of the GMFM and the gait analysis	Baseline Phase - before and after intervention Treatment Phase - 4 h/d, 5 d/w, 3 weeks	Very small improvements in function were noted in dimension D of the GMFM and PEDI with decreased function in other areas. Improved walking speed, cadence, symmetry, joint motion, and posture were found with gait analysis.
Bar-Haim *et al.*, 2006	24 children CP levels II to IV (GMFM) (n=12 AST group, n=12 NDT group)	Treatment Phase – (Adeli suit and NDT) Baseline Phase - (GMFM-66 and EIHB)	Baseline Phase - GMFM-66 and EIHB, immediately, after 1 month of treatment, and 10 months after Treatment Phase - 2h/d 5d/w, 4 weeks	The significant time effects for GMFM-66 and EIHB that were noted after 1 month of both treatments were greater than expected from natural maturation of children at this age. Improvements in motor skills and their retention 9 months after treatment were not significantly different between the two treatment modes
Rennie *et al.*, 2000	8 children (7 CP and 1 DMD)	Body lycra garments RMSE (measure of variability)	2-week introduction period followed by 6 weeks of wearing the garment for at least 6 h every day, after which they were re-assessed.	Proximal stability around the pelvis improved for 5 children and distal stability improved for 3. Five children improved in at least one aspect of the PEDI scale. Although the parents and children detected these improvements, they did not outweigh the disadvantages of wearing the suit and as a consequence only one out of 8 families considered continuing with the lycra garment.

Flanagan *et al.*, 2009	5 subjects CP level I (GMFM)	Treatment Phase - Garment -TheraTogs Baseline Phase - Vicon Motion Analysis, Bruininks–Oseretsky Test of Motor Proficiency, and Canadian Occupational Performance Measure	Baseline Phase - Analise Treatment Phase - 12 weeks of wear; 2 months and 4 months after garment wear	Kinematic data indicated increased peak hip extension and correction of anterior pelvic tilt in stance during wear time. Composite gross motor scores on the Bruininks–Oseretsky Test of Motor Proficiency and Canadian Occupational Performance Measure scores improved significantly at the end of wear time.
Mahani *et al.*, 2011	36 subjects with CP	Baseline Phase - GMFM Treatment Phase - MAST, Adeli suit, and Neurodevelopmental Treatment.	Baseline Phase - immediately before and 16 weeks after Treatment Phase - 2 hr/d, 5 d/w, 4 weeks	All groups had improvement in the GMFM after treatment, and there were significant differences among groups. In the follow-up study, no significant improvement in the GMFM was seen within groups, but again there were significant differences among groups.

GMFM = Gross Motor Function Measure; AST = Adeli suit therapy; EIHB = mechanical efficiency index; PEDI = Pediatric Evaluation of Disability Inventory; RMSE = measure of variability; DMD = Duchenne muscular dystrophy; MAST= Modified Adeli suit therapy.

Discussion

This work had the aim to identify studies related to people with CP wearing a "suit" or "garment" by using a systematic review. We observed that the number of participants in seven studies ranged from 1 to 36 subjects with CP. Four studies presented a maximum number of 7 individuals with CP, which shows that the samples were significantly smaller.[10, 12, 13, 20] However, the other three studies included more than 20 individuals with CP.[21-23]

Considering the frequency and duration of the intervention, the results showed differences among the studies, which used the shorter treatment time, carried out for three weeks[13, 23] and the longest during therapy was 18 weeks.[10] According to Bailes et al.,[13] evidence indicating greater functional benefits from participation in intensive ST is limited. The high compliance indicates that intensive treatment programs over a short period are well tolerated by children with CP and by their families.[22]

Children with diplegic CP often ambulate with a "jump gait pattern," demonstrating anterior pelvic tilt, decreased peak hip and knee extension, and persistent plantarflexion in stance phase.[24] According to Flanagan et al.,[12] during the same session, while wearing TheraTog™ garments and strapping, the subjects were noted to have pelvic and hip kinematic gait data that resembled children who are developing typically. It is believed that this may be due to the abdominal and back extensor strapping that attempts to facilitate the core trunk stabilizers.

The results from the study by Bailes et al.[23] demonstrated that children with CP who wore the TheraSuit™ with attached bungee cords during an intensive therapy program did not increase function more than children who wore a control suit (TheraSuit™ vest and shorts) during the same intensive therapy program. This was the first study to examine the different components of ST and study the effects of the suit itself. Strengths of this study include the following: the subjects were randomized to an experimental or control group, all children were of similar functional level (GMFCS III), the age range of the children was narrow, and the assessors were blinded to group assignment.[23]

The results from Bailes et al.[13] showed that both participants in this case report showed minimal gains in some areas and decline in other areas of functional performance after the Therasuit™ method of intensive ST as measured by di-

mensions D and E of the Gross Motor Function Measure (GMFM) and the Pediatric Evaluation of Disability Inventory (PEDI), respectively. Small but potentially important changes were noted in gait movement patterns after participation in this intensive program.

Bar-Haim et al.[22] reported an improved efficiency index in the Adeli suit™ treatment (AST) group, especially for children with higher levels of motor function, without the gain of additional gross motor skills. This implies that AST can serve to optimize these skills in children with a higher level of gross motor skills, as reflected by a reduced metabolic cost of external work. The authors stated that future studies on the efficacy of AST should measure changes in metabolic efficiency, fitness level, and motor skills, increase the number of participants, and homogenize the participants with CP to reduce variability.[22]

Rennie et al.[20] tried to find differences between proximal stability and distal function using a lycra garment, but they did not find any statistically significant improvement or differences. These authors speculated that the reason why improvements in proximal control did not affect motor control distally may have been because the duration of the study was too short. Additionally, the manufacturing process of the garments predisposes a bias towards proximal improvement over distal. The foot and most of the ankle are not covered by the garment, and this may reduce its efficacy for distal control.

Mahani et al.[21] tried to compare AST and neurodevelopmental treatment (NDT) protocols in treatment of children with CP. This study revealed that intensive therapeutic programs were more effective than the regular ones, as the GMFM scores improved after all the intensive programs; however, no significant improvement was noticed in any of the groups during follow-up. This finding showed the importance of intensive therapeutic programs and that improvement in GMFM scores might not be the result of natural and spontaneous recovery in children.

Ko et al.[10] demonstrated that a child's gait speed, stride time, stride length, and stride width were substantially enhanced as a function of the AST intervention. According to these authors, the AST was effective in improving gait, gross motor function, and balance in a child with diplegic CP. Clinically, neuro-rehabilitation with AST provided a complementary and alternative treatment for lower extremity rehabilitation in this child with CP. These findings provide preliminary evidence supporting the effectiveness of AST in children with spastic CP. One of the mentioned limitations is that wearing compliance is limited in some by difficulties with heat, skin discomfort, and toileting.[12]

The studies included in this review showed little evidence for using ST in CP. Future studies with a larger number of subjects and more homogeneous groups can provide data and results about the effects of using suits and the impact of these treatment programs in neurological rehabilitation.

Conclusion

We concluded that few studies were carried out using ST and that the report found some benefits to users. However, adhesion of the suit after treatment, the frequency and duration of the intervention, and improvement in the quality and quantity of movement should be investigated carefully with new research.

Authors' contributions

All authors participated in the acquisition of data and revision of the manuscript. All authors determined the design, interpreted the data, and drafted the manuscript. All authors read and gave final approval of the version submitted for publication.

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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

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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
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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)

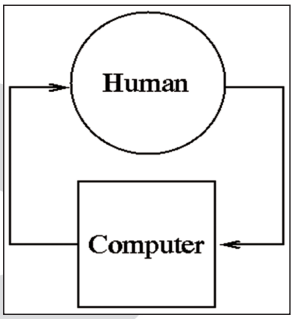

Figure 1. Text here

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.

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