Online ISSN: 2249-4618
Print ISSN: 0975-5888

Global Journal

of Medical Research: F

Diseases

Telehealth Medicine

Therapy for Kawasaki Disease

Highlights

Dynamic PET Technique

Entamoeba Histolytica in Mice

Discovering Thoughts, Inventing Future

VOLUME 15 ISSUE 4 VERSION 1.0

© 2001-2015 by Global Journal of Medical Research , USA

Global Journal of Medical Research: F
Diseases

Global Journal of Medical Research: F
Diseases

Volume 15 Issue 4 (Ver. 1.0)

Open Association of Research Society

© Global Journal of Medical Research . 2015.

All rights reserved.

This is a special issue published in version 1.0 of "Global Journal of Medical Research." By Global Journals Inc.

All articles are open access articles distributed under "Global Journal of Medical Research"

Reading License, which permits restricted use. Entire contents are copyright by of "Global Journal of Medical Research" unless otherwise noted on specific articles.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission.

The opinions and statements made in this book are those of the authors concerned. Ultraculture has not verified and neither confirms nor denies any of the foregoing and no warranty or fitness is implied.

Engage with the contents herein at your own risk.

The use of this journal, and the terms and conditions for our providing information, is governed by our Disclaimer, Terms and Conditions and Privacy Policy given on our website http://globaljournals.us/terms-and-condition/menu-id-1463/

By referring / using / reading / any type of association / referencing this journal, this signifies and you acknowledge that you have read them and that you accept and will be bound by the terms thereof.

All information, journals, this journal, activities undertaken, materials, services and our website, terms and conditions, privacy policy, and this journal is subject to change anytime without any prior notice.

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

Global Journals Inc.

*(A Delaware USA Incorporation with "Good Standing"; **Reg. Number: 0423089**)*

Sponsors: Open Association of Research Society
Open Scientific Standards

Publisher's Headquarters office

Global Journals Headquarters
301st Edgewater Place Suite, 100 Edgewater Dr.-Pl,
Wakefield MASSACHUSETTS, Pin: 01880,
United States of America
USA Toll Free: +001-888-839-7392
USA Toll Free Fax: +001-888-839-7392

Offset Typesetting

Global Journals Incorporated
2nd, Lansdowne, Lansdowne Rd., Croydon-Surrey,
Pin: CR9 2ER, United Kingdom

Packaging & Continental Dispatching

Global Journals
E-3130 Sudama Nagar, Near Gopur Square,
Indore, M.P., Pin:452009, India

Find a correspondence nodal officer near you

To find nodal officer of your country, please email us at *local@globaljournals.org*

eContacts

Press Inquiries: *press@globaljournals.org*
Investor Inquiries: *investors@globaljournals.org*
Technical Support: *technology@globaljournals.org*
Media & Releases: *media@globaljournals.org*

Pricing (Including by Air Parcel Charges):

For Authors:
22 USD (B/W) & 50 USD (Color)
Yearly Subscription (Personal & Institutional):
200 USD (B/W) & 250 USD (Color)

Integrated Editorial Board
(Computer Science, Engineering, Medical, Management, Natural Science, Social Science)

John A. Hamilton,"Drew" Jr.,
Ph.D., Professor, Management
Computer Science and Software Engineering
Director, Information Assurance Laboratory
Auburn University

Dr. Henry Hexmoor
IEEE senior member since 2004
Ph.D. Computer Science, University at Buffalo
Department of Computer Science
Southern Illinois University at Carbondale

Dr. Osman Balci, Professor
Department of Computer Science
Virginia Tech, Virginia University
Ph.D.and M.S.Syracuse University, Syracuse, New York
M.S. and B.S. Bogazici University, Istanbul, Turkey

Yogita Bajpai
M.Sc. (Computer Science), FICCT
U.S.A.Email:
yogita@computerresearch.org

Dr. T. David A. Forbes
Associate Professor and Range Nutritionist
Ph.D. Edinburgh University - Animal Nutrition
M.S. Aberdeen University - Animal Nutrition
B.A. University of Dublin- Zoology

Dr. Wenying Feng
Professor, Department of Computing & Information Systems
Department of Mathematics
Trent University, Peterborough,
ON Canada K9J 7B8

Dr. Thomas Wischgoll
Computer Science and Engineering,
Wright State University, Dayton, Ohio
B.S., M.S., Ph.D.
(University of Kaiserslautern)

Dr. Abdurrahman Arslanyilmaz
Computer Science & Information Systems Department
Youngstown State University
Ph.D., Texas A&M University
University of Missouri, Columbia
Gazi University, Turkey

Dr. Xiaohong He
Professor of International Business
University of Quinnipiac
BS, Jilin Institute of Technology; MA, MS, PhD,. (University of Texas-Dallas)

Burcin Becerik-Gerber
University of Southern California
Ph.D. in Civil Engineering
DDes from Harvard University
M.S. from University of California, Berkeley
& Istanbul University

Dr. Bart Lambrecht
Director of Research in Accounting and FinanceProfessor of Finance
Lancaster University Management School
BA (Antwerp); MPhil, MA, PhD (Cambridge)

Dr. Carlos García Pont
Associate Professor of Marketing
IESE Business School, University of Navarra
Doctor of Philosophy (Management), Massachusetts Institute of Technology (MIT)
Master in Business Administration, IESE, University of Navarra
Degree in Industrial Engineering, Universitat Politècnica de Catalunya

Dr. Fotini Labropulu
Mathematics - Luther College
University of ReginaPh.D., M.Sc. in Mathematics
B.A. (Honors) in Mathematics
University of Windso

Dr. Lynn Lim
Reader in Business and Marketing
Roehampton University, London
BCom, PGDip, MBA (Distinction), PhD, FHEA

Dr. Mihaly Mezei
ASSOCIATE PROFESSOR
Department of Structural and Chemical Biology, Mount Sinai School of Medical Center
Ph.D., Etvs Lornd University
Postdoctoral Training,
New York University

Dr. Söhnke M. Bartram
Department of Accounting and FinanceLancaster University Management SchoolPh.D. (WHU Koblenz)
MBA/BBA (University of Saarbrücken)

Dr. Miguel Angel Ariño
Professor of Decision Sciences
IESE Business School
Barcelona, Spain (Universidad de Navarra)
CEIBS (China Europe International Business School).
Beijing, Shanghai and Shenzhen
Ph.D. in Mathematics
University of Barcelona
BA in Mathematics (Licenciatura)
University of Barcelona

Philip G. Moscoso
Technology and Operations Management
IESE Business School, University of Navarra
Ph.D in Industrial Engineering and Management, ETH Zurich
M.Sc. in Chemical Engineering, ETH Zurich

Dr. Sanjay Dixit, M.D.
Director, EP Laboratories, Philadelphia VA Medical Center
Cardiovascular Medicine - Cardiac Arrhythmia
Univ of Penn School of Medicine

Dr. Han-Xiang Deng
MD., Ph.D
Associate Professor and Research
Department Division of Neuromuscular Medicine
Davee Department of Neurology and Clinical NeuroscienceNorthwestern University
Feinberg School of Medicine

Dr. Pina C. Sanelli
Associate Professor of Public Health
Weill Cornell Medical College
Associate Attending Radiologist
NewYork-Presbyterian Hospital
MRI, MRA, CT, and CTA
Neuroradiology and Diagnostic Radiology
M.D., State University of New York at Buffalo,School of Medicine and Biomedical Sciences

Dr. Roberto Sanchez
Associate Professor
Department of Structural and Chemical Biology
Mount Sinai School of Medicine
Ph.D., The Rockefeller University

Dr. Wen-Yih Sun
Professor of Earth and Atmospheric SciencesPurdue University Director
National Center for Typhoon and Flooding Research, Taiwan
University Chair Professor
Department of Atmospheric Sciences, National Central University, Chung-Li, TaiwanUniversity Chair Professor
Institute of Environmental Engineering, National Chiao Tung University, Hsin-chu, Taiwan.Ph.D., MS The University of Chicago, Geophysical Sciences
BS National Taiwan University, Atmospheric Sciences
Associate Professor of Radiology

Dr. Michael R. Rudnick
M.D., FACP
Associate Professor of Medicine
Chief, Renal Electrolyte and Hypertension Division (PMC)
Penn Medicine, University of Pennsylvania
Presbyterian Medical Center, Philadelphia
Nephrology and Internal Medicine
Certified by the American Board of Internal Medicine

Dr. Bassey Benjamin Esu
B.Sc. Marketing; MBA Marketing; Ph.D Marketing
Lecturer, Department of Marketing, University of Calabar
Tourism Consultant, Cross River State Tourism Development Department
Co-ordinator , Sustainable Tourism Initiative, Calabar, Nigeria

Dr. Aziz M. Barbar, Ph.D.
IEEE Senior Member
Chairperson, Department of Computer Science
AUST - American University of Science & Technology
Alfred Naccash Avenue – Ashrafieh

President Editor (HON.)

Dr. George Perry, (Neuroscientist)
Dean and Professor, College of Sciences
Denham Harman Research Award (American Aging Association)
ISI Highly Cited Researcher, Iberoamerican Molecular Biology Organization
AAAS Fellow, Correspondent Member of Spanish Royal Academy of Sciences
University of Texas at San Antonio
Postdoctoral Fellow (Department of Cell Biology)
Baylor College of Medicine
Houston, Texas, United States

Chief Author (HON.)

Dr. R.K. Dixit
M.Sc., Ph.D., FICCT
Chief Author, India
Email: authorind@computerresearch.org

Dean & Editor-in-Chief (HON.)

Vivek Dubey(HON.)
MS (Industrial Engineering),
MS (Mechanical Engineering)
University of Wisconsin, FICCT
Editor-in-Chief, USA
editorusa@computerresearch.org

Sangita Dixit
M.Sc., FICCT
Dean & Chancellor (Asia Pacific)
deanind@computerresearch.org

Suyash Dixit
(B.E., Computer Science Engineering), FICCTT
President, Web Administration and
Development , CEO at IOSRD
COO at GAOR & OSS

Er. Suyog Dixit
(M. Tech), BE (HONS. in CSE), FICCT
SAP Certified Consultant
CEO at IOSRD, GAOR & OSS
Technical Dean, Global Journals Inc. (US)
Website: www.suyogdixit.com
Email:suyog@suyogdixit.com

Pritesh Rajvaidya
(MS) Computer Science Department
California State University
BE (Computer Science), FICCT
Technical Dean, USA
Email: pritesh@computerresearch.org

Luis Galárraga
J!Research Project Leader
Saarbrücken, Germany

Contents of the Issue

Global Journal of Medical Research: F
Diseases
Volume 15 Issue 4 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Determination of the Compound Biological Effectiveness (CBE) Factors based on the *ISHIYAMA-IMAHORI* Deterministic Parsing Model with the Dynamic PET Technique

By Shintaro Ishiyama, Yoshio Imahori, Jun Itami & Hanna Koivunoro
University of Helsinki, Finland

Abstract- *Purpose:* In defining the biological effects ofthe ^{10}B (n,α)^{7} Li neutron capturereaction, we have proposeda deterministic parsing model (*ISHIYAMA-IMAHORI* model) to determine the Compound Biological Effectiveness (*CBE*) factor in Borono-Phenyl-Alanine (*BPA*)-mediated Boron Neutron Capture Therapy (*BNCT*). In present paper, we the case of application to actual patient data, which is founded on this model for tissuesandtumor.

Method: To determine the CBE factor, we demonstrate a specific method of howthe application of derived the following new calculation formula founded onthe deterministic parsing model with three constants, *CBE0*, *F, n* and the eigen value N_{th}/N_{max}.

Keywords: *boron neutron capture therapy,compound biological effectiveness, borono-phenyl-alanine, tumor, $^{10}B(n,\alpha)^{7}$ li,sigmoid function.*

GJMR-F Classification : *NLMC Code: QV 239, QZ 310*

Strictly as per the compliance and regulations of:

© 2015. Shintaro Ishiyama, Yoshio Imahori, Jun Itami & Hanna Koivunoro. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Determination of the Compound Biological Effectiveness (CBE) Factors based on the *ISHIYAMA-IMAHORI* Deterministic Parsing Model with the Dynamic PET Technique

Shintaro Ishiyama [α], Yoshio Imahori [σ], Jun Itami [ρ] & Hanna Koivunoro [ω]

Abstract- Purpose: In defining the biological effects of the $^{10}B(n,\alpha)^{7}Li$ neutron capture reaction, we have proposed a deterministic parsing model (*ISHIYAMA-IMAHORI* model) to determine the Compound Biological Effectiveness (*CBE*) factor in Borono-Phenyl-Alanine (*BPA*)-mediated Boron Neutron Capture Therapy (*BNCT*). In present paper, we demonstrate a specific method of how the application of the case of application to actual patient data, which is founded on this model for tissues and tumor.

Method: To determine the CBE factor, we derived the following new calculation formula founded on the deterministic parsing model with three constants, CBE_0, F, n and the eigen value N_{th}/N_{max}.

$$CBE = CBE_0 + \frac{F}{2}\left(1 - \left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right)\left\{2 - \left(\frac{N_{th}}{N_{max}}\right)^{\frac{2}{n}} + \left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right\} \qquad 0 < \frac{N_{th}}{N_{max}} < 1 \quad (1)$$

Where, N_{th} and N_{max} are the threshold value of boron concentration of N and saturation boron density and CBE_0, F and n are given as 0.5, 8 and 3, respectively. In order to determine N_{th} and N_{max} in the formula, sigmoid logistic function was employed for ^{10}B concentration data, $D_b(t)$ obtained by dynamic PET technique.

$$D_b(t) = \frac{A}{(1 + e^{-a(t-t_0)})} \quad (2)$$

Where, A, a and t_0 are constants

Results and Conclusion: From the application of sigmoid function to dynamic PET data, it is concluded that the N_{th} and N_{max} for tissue and tumor are identified with the parameter constants in the sigmoid function in eq.(2) as;

$$N_{th} = D_b \text{ at } t = 0 \text{ and } N_{max} = A \quad (3)$$

And the calculated *CBE* factor values obtained from eq. (1), with N_{th}/N_{max}.

Keywords: *boron neutron capture therapy, compound biological effectiveness, borono-phenyl-alanine, tumor, $^{10}B(n,\alpha)^{7}$ li, sigmoid function.*

Author α: Quantum Beam Science Center, Japan Atomic Energy Agency, Tokai-mura, Naka-gun, Ibaraki 319-1195 Japan.
e-mail: ishiyama.shintaro@jaea.go.jp
Author σ: Cancer Intelligence Care Systems, Inc., Koto-ku, Ariake 3-5-7 Tokyo 135-0063, Japan.
Author ρ: Department of Radiation Oncology, National Cancer Center Tukiji 5-1-1 Chuo-ku 5-1-1 Tokyo 104-0045 Japan.
Author ω: Department of Physics, University of Helsinki Department of Oncology, Helsinki University Central Hospital, Finland.

I. Introduction

Many types of pilot innovative accelerator-based neutron source for neutron capture therapy with lithium target were designed [1][2][3] and many inventions for the progressive power run-up were reported [4][5]. In Japan, implemented deployment of accelerator-driven neutron source for Boron Neutron Capture Therapy (BNCT) is accomplished in 2014 in National Cancer Center, of which system was designed with the production of neutrons via threshold ^{7}Li (p, n) ^{7}Be reaction at 25kW proton beam with energy of 2.5 MeV, which was designed to dovetail the narrow peak band resonance of lithium target and started its installation at middle of 2013. This BNCT device is expected to offer the potential for achieving the objects of which any treatment capable of sterilizing the primary tumor locally will result in a high probability of cure.

BNCT is a targeted radio-therapeutic modality used for the treatment of brain tumors and melanoma and a bimodal approach to cancer therapy. Before BNCT, Boron-10(^{10}B)-enriched compounds are used to deliver ^{10}B to tumors. Once tumor uptake of a given boron delivery agent relative to the surrounding normal tissues and blood has been maximized and then irradiation with low-energy neutron takes place. An alternative boron delivery agent, p-bononphenylalaine (BPA) instead of administration of the boron delivery agent borocaptate sodium (BSH), is being used

© 2015 Global Journals Inc. (US)

together with mode deeply penetrating epithermal neutron beam [6]. BNCT was extensively reviewed in two recent articles [7][8] and the targeting effectiveness of BNCT is dependent upon the preferential delivery of ^{10}B to the primary tumor and its metastatic spread.

In defining the biological effects of the $^{10}B(p,\alpha)^{7}Li$ neutron capture reaction relative to photons, the term compound biological effectiveness (*CBE*) factor was used as an alternative to *RBE*. Calculation of the *CBE* factor is similar to that of the *RBE* factor [9]. Equating the X-ray ED_{50} dose with a BNC dose (beam + BSH) that gives the same end point of a 50% incident of ulceration produces the following equation:

The *CBE* factor = [(X-rayED_{50}) - (thermal beam component of $ED_{50}\times RBE$]/ $^{10}B(p,\alpha)^{7}Li$ component of ED_{50}.

The *CBE* factors concerning to tumor, skin lung, liver [10][11], heart [12] and oral mucosal tissues [13] were reported and prospect of actually using BNCT for the patients has been developing under the right circumstances. However, there is no theoretical unified explanation of the *CBE* factors for normal tissues and tumor, despite significance of high precision of the *CBE* factor evaluation is requested for the patients.

Recently, the authors proposed deterministic parsing model of CBE factors (*ISHIYAMA-IMAHORI* model) and applied to human tumor brain cases and derived good results dovetailed with empirical facts[14][15].

The purpose of the present investigation was to demonstrate the unified methodology for the evaluation of the *CBE* factors for normal tissues and tumor in BNCT.

II. Materials and Methods

a) ^{10}B concentration measurement of BPA by dynamic PET technique

A brain tumor patient (grade IV) was given low dose (approximately~100μg/g) of intravenous radioactively-labeled ^{18}F-BPA before BNCT and diagnosed cancer by Positron-Emission-Tomography (PET) [16]. To obtain ^{10}B concentration in a body, ^{18}F-BPA was administrated to the patient by intravenous drip injection and PET inspection was performed in every 20 minutes to measure a change in ^{10}B concentrations in tumor, normal and blood of the patient, respectively.

b) Mathematical analysis model for the ^{10}B concentration data

After ^{10}BPA administration, boron atoms are ingested into the cell model consisted of endoplasm and cell nucleus and Imahori [17] reported the kinetic analysis for brain tumor patients by using three-compartment rate constant *(K_1, k_2 and k_3)* (Figure 1).

This model implied that the body injected ^{10}BPA begins to rapidly up-taken into cancer cell group at the injection initial and eventually suppressed increase with increasing ^{10}BPA-containing population.

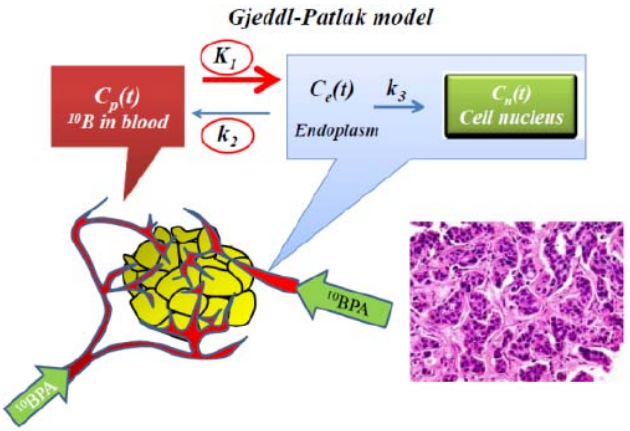


Figure 1: Gjeddle-Patlak model using three-compartment rate constanta *(k_1, k_2 and k_3)*

As a function that can better represent this phenomenon, the sigmoid function are frequently applied as natural population increasing model. Accordingly, logistic function based on the sigmoid function was employed to analyze dynamic PET data. The logistic function in present study was defined as:

$$D_b(t) = \frac{A}{(1 + e^{-a(t-t_0)})} \quad (1)$$

Where $D_{bnormal}$ and D_{btumor} are ^{10}B concentrations in tumor, normal tissues and time-dependent function. A, a and t_0 in eq. (1) are constants, respectively.

III. Results and Discussions

a) Dynamic PET measurement for normal tissues and tumor

Typical changes in ^{10}B concentration in normal tissue, tumor and blood are illustrated in the figure by ^{10}BPA administration by intravenous and drip injection methods (Figure 2).

© 2015 Global Journals Inc. (US)

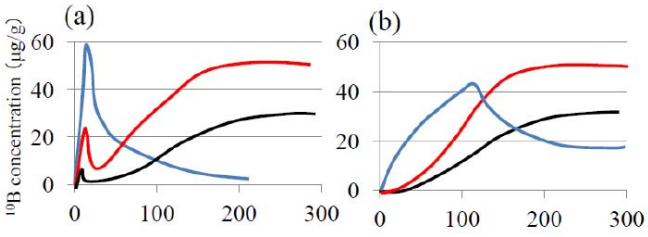


Figure 2 : Typical change in ^{10}B concentration in tumor, normal tissues and blood measured by Dynamic PET technique with ^{10}BPA administration by (a) Intraveous injection and (b) Drip injection methods

Sudden increase and peak in ^{10}B concentration in blood, normal tissue and tissue were found just before intravenous injection of BPA administration. Whereas, the changes in ^{10}BPA concentration after drip injection show modest slow changes in ^{10}B concentration in normal tissues, tumor and blood, respectively **(Figure 3)**.

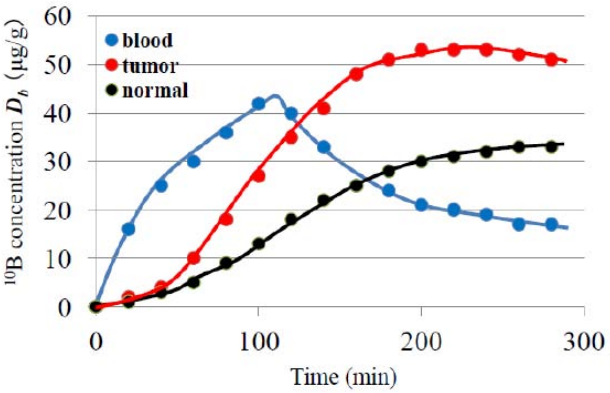


Figure 3 : Change in ^{10}B concentration in blood, tumor and normal tissue measured by Dynamic PET technique

These typical changes after ^{10}BPA administration indicate compatibility to define saturation boron concentration, N_{max} and threshold of boron density, N_{th} for the determination of CBE factors by *ISHIYAMA-IMAHORI* model [14][15] as below:

$$CBE = CBE_0 + \frac{F}{2}\left(1 - \left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right)\left\{2 - \left(\frac{N_{th}}{N_{max}}\right)^{\frac{2}{n}} + \left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right\} \qquad 0 < \frac{N_{th}}{N_{max}} < 1 \quad (2)$$

and this is because that we chose drip injection in present study.

As for a typical change in ^{10}B concentration in blood, tumor and normal tissue of a brain tumor patient (Grade IV), logistic function in eq. (1) was applied to these data. Compatibility of the function to normal tissue and tumor are provided in the figures **(Figure 4 and 5)**.

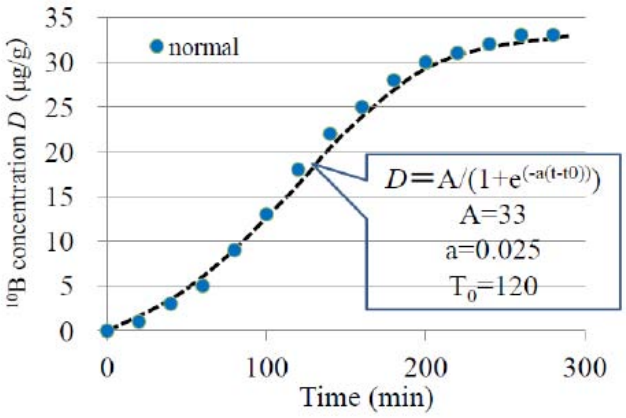


Figure 4 : A change in ^{10}B concentration in normal tissue measured by dynamic PET technique and logistic function

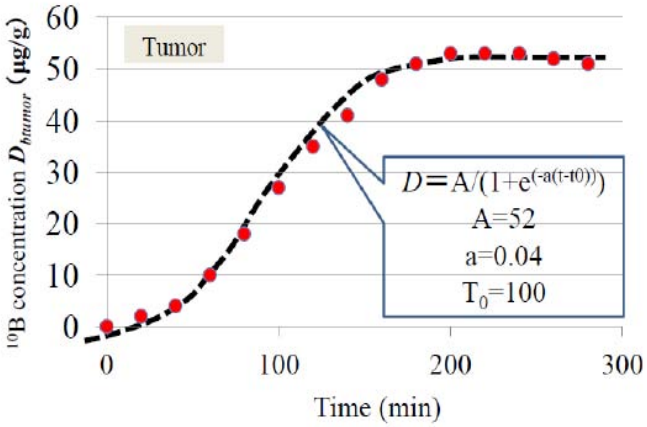


Figure 5 : A change in ^{10}B concentration in tumor measured by dynamic PET technique andlogistic function

From these results, it is clear that very good data fitting curves of the logistic function to dynamic PET data were observed and each constant in eq. (1) are obtained in the tumor and normal tissue. These results are listed in the table **(Table 1)**.

© 2015 Global Journals Inc. (US)

Table 1 : Constants in eq. (1) logistic function obtained for tumor and normal tissue

	A	a	t_0
Tumor	52	0.04	100
Normal	33	0.025	120

$$D = A/(1+e^{(-a(t-t0))})$$

Table 2 : The Values of N_{th} and N_{max} defined by eq. (3) for tumor and normal tissue

	N_{th}	N_{max}	N_{th}/N_{max}
Tumor	0.935	52	55.62
Normal	1.565	33	21.09

N_{th}=D at t=0
N_{max}= A

b) *Determination of the CBE factor depend on boron dose level*

To obtained threshold and saturation density of boron, N_{th} and N_{max} in tumor and normal tissue from eq.(1), we defined N_{th} and N_{max} as follows:

$$N_{th} = D_b \text{ at } t = 0 \text{ and } N_{max} = A \quad (3)$$

These values of N_{th}, N_{max} and N_{th}/N_{max} for normal tissue and tumor are listed in the table (Table 2).

From these results, The *CBE* factors for normal tissue and tumor in a brain tumor patient were calculated by eq. (2) and these results are given in the table 3 (Table 3).

Table 3 : The Values of N_{th}/N_{max} and CBE factor defined by eq. (2) for tumor and normal tissue

	N_{th}/N_{max}	*CBE*
Tumor	0.018	5.43
Normal	0.047	4.35

c) *Application of the calculation method and its clinical significance*

The charm of the BNCT treatment is that again and again for the same patients and their affected area is capable of irradiation treatment. Therefore, the cure of intractable cancer in a short time by BNCT treatment is not a dream. However, BNCT treatment at this stage is time-consuming due to the following reasons. Normally, cancer patients are given low doses of intravenous radioactively-labelled 18F-BPA before BNCT and diagnosed cancer by Positron-Emission-Tomography (PET). Physicians developed a treatment plan by BNCT based on PET diagnosis and then after administrates high dose of BPA to the patients.

So practical value of present research is that the diagnosis and treatment cycle can be achieved at the same time shorten with high accuracy.

Present research results, ie by 18F-BPA drip injection administration and dynamic PET measurement method, *ISHIYAMA–IMAHORI* model immediately provides a high-precision CBE factor and BNCT treatment for a kind of cancer and its severity in patients individual.

IV. Conclusions

ISHIYAMA –IMAHORI model below immediately provides a high-precision CBE factor and BNCT treatment for a kind of cancer and its severity in patients individual by 18F-BPA drip injection administration and dynamic PET measurement method

$$CBE = CBE_0 + \frac{F}{2}\left(1-\left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right)\left\{2-\left(\frac{N_{th}}{N_{max}}\right)^{\frac{2}{n}}+\left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right\} \qquad 0<\frac{N_{th}}{N_{max}}<1$$

And N_{th}/N_{max} is obtained by the flowing logistic function

$$D_b(t) = \frac{A}{(1+e^{-a(t-t_0)})}$$

Where B_b is ^{10}B concentration in tumor and normal tissue, and A, a and t_0 are constants.

References Références Referencias

1. Bayanov B, V. Belov, V. Kindyuk, E. Oparin, S. Taskaev; "Lithium neutron producting target for BINP accelerator-based neutron source", Appl. Radiat. Isot. 61,817-821 (2004).
2. Willis C, J. Lenz, D. Swenson; "High-power lithium target for accelerator-based BNCT", Proc. of LINAC08, Victoria, BC, Canada, MOP063, 223-225(2008).
3. Halfon S., M.Paul, A.Arenshtam, D. Berkovits, M. Bisyakoev, I.Eliyahu, G. Feinberg, N. Hazenshprung, D.Kijel, A.Nagler, I. Silverman ; "High power accelerator-based boron neutron capture with a liquid lithium target and new

© 2015 Global Journals Inc. (US)

capture with a liquid lithium target and new applications to treatment of infections diseases", Appl. Radiat. Isot. **69**, 1654-1656 (2011).
4. Ishiyama S, Y. Baba, R. Fujii, M. Nakamura, Y. Imahori; "In-situ vacuum deposition technique of lithium on neutron production target for BNCT", Nucl. Instrum. Meth. Phys. Res., **B288**, 18-22 (2012a).
5. Ishiyama S, Y. Baba, R. Fujii, M. Nakamura, Y. Imahori; "Synthesis of lithium nitride for neutron producton target of BNCT by in-situ lithium deposition and ion implantation", Nucl. Instrum. Meth. Phys. Res. **B 293**, 42-47 (2012b).
6. Coderre J.A., G.M. Morris, P.L. Micca, C.D.Fishe and G.A.Ross; "Comparative assessment of single-dose and fractional boron neutron capture therapy", *Radiat Res* **166**, 310-317(1995).
7. Bath, R.F., A.H. Soloway, JH. Goodman, R.A., Gahbauer, N. Gupta, T.E. Blue, W. Yang and W. Tjarks; "Boron neutron capture therapy of brain tumors: an merging therapeutic modality2, *Neyrosurgery,* **44**:433-451(2004).
8. Coderre J.A. and G.M. Morris; "The irradiation biology of boron neutron capture therapy", *Rariat Res* 151:1-18 (1999)
9. Morrsi GM, J.A.Coderre, J.W.Hopewell, P.L.Micca and M. Rezvani; "Response of the skin to boron neutron capture therapy with p-boronopenylalanine or borocaptate sodium", *Radiother Oncol* 39:253-259(1994a).
10. Fukuda H., T.Kobayashi, J.Hiratsuka and et.al; "Estimation of Absorbed Dose in the Covering Skin of Human Melaoma Treated by Boron Capture Therapy", Pigment cell Research Vol.2, Issue 4,pp.365-369(1989)
11. Kiger, JL, W.S. 3rd Kiger, K.J. Riley, P.J. Binns, H. Patel, J.W. Hopewell and O.K. Harling, P.M. Busse and J.A. Coderre; "Functional and histological changes in rat lung after boron neutron capture therapy", *Radiat Res* **171**(1) 60-69(2008).
12. Suzuki M, S.Masunaga, Y.Kinachi, M.Takagai, Y.Sakurai, T.Kobayashi and K. Ono; "The effects of boron neutron capture therapy on liver tumors and normal hepatocytes in mice", *Jpn. J. Cancer Res*. **91**(10) 1058-1064(2000).
13. Morris GM, Dr.Smith, H.Patel and et. Al., "Boron microlocalization in oral mucosal tissue", *British J. of Cancer* **82**(11),1764-1771(2000b)
14. ISHIYAMA, S and IMAHORI, Y; "Deterministic Parsing Model of the Compound Biological Effectiveness (CBE) Factor for Intracellular ^{10}Boron Distribution in Boron Neutron Capture Therapy", International Congress on Neutron Capture Therapy (ICNCT2014) 14-19 June, Finland PaP501, pp.162-163(2014)
15. ISHIYAMA, S "Deterministic Parsing Model of the Compound Biological Effectiveness (CBE) Factor for Intracellular ^{10}Boron Distribution in Boron Neutron Capture Therapy", *J. of Cancer Therapy*, 2014, Published Online December 2014 in SciRes. http://www.scirp.org/jounal/ict doi
16. Imahori Y, S.Ueda, Y.Ohmori and et. al., "Fluorine-18-labeled fluoroboronophenylalanine PET in Patients with Glioma, J Nucl Med, Vol. 39, No. 2, 325-333 (1998).
17. Imahori Y *et. al*., Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part II., Clin Cancer Res 4 (8): 1833-1841. (1998).

© 2015 Global Journals Inc. (US)

This page is intentionally left blank

© 2015 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 15 Issue 4 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Participation of T, B and NKT Lymphocytes and CD1 Molecule in the Infection by *Entamoeba histolytica* in Mice

By Fabrício MS Oliveira, Bernardo C Horta, Luana O Prata, Andrezza F Santiago, Andréa C Alves, Ana MC Faria, Maria A Gomes & Marcelo V Caliari

Federal University of Minas Gerais, Brazil

Abstract- Studies have shown that CD1 double negative mice ($CD1d^{-/-}$) develop larger liver abscesses due to their inability to present amebic antigens to NK T lymphocytes. Therefore, we conducted flow cytometry studies to determine the frequency of NK T, $CD4^+$ T, $CD8^+$ T and B lymphocytes in mice with amebic colitis. The frequency of NK T, $CD8^+$ T and B lymphocytes was reduced in the MLN of mice in the CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups compared to the CTRL-WT and Eh-WT groups. There was also a significant decrease in the frequency of B lymphocytes in the spleens of the animals in the Eh-WT group when compared with the CTRL-$CD1^{-/-}$, Eh- $CD1^{-/-}$ and CTRL-WT groups. The results of the flow cytometry analysis highlight the importance of NK T lymphocytes in the immune response of mice to amebic intestinal infection and the importance of CD1 molecules in the activation of T and B lymphocytes.

Keywords: amebic colitis, Entamoeba histolytica, natural killer T lymphocytes.

GJMR-F Classification : NLMC Code: WC 524

Strictly as per the compliance and regulations of:

© 2015. Fabrício MS Oliveira, Bernardo C Horta, Luana O Prata, Andrezza F Santiago, Andréa C Alves, Ana MC Faria, Maria A Gomes & Marcelo V Caliari. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Participation of T, B and NKT Lymphocytes and CD1 Molecule in the Infection by *Entamoeba histolytica* in Mice

Fabrício MS Oliveira [α], Bernardo C Horta [σ], Luana O Prata [ρ], Andrezza F Santiago [ω], Andréa C Alves [¥], Ana MC Faria [§], Maria A Gomes [χ] & Marcelo V Caliari [ν]

Abstract- Studies have shown that CD1 double negative mice (CD1d$^{-/-}$) develop larger liver abscesses due to their inability to present amebic antigens to NK T lymphocytes. Therefore, we conducted flow cytometry studies to determine the frequency of NK T, CD4^{+} T, CD8^{+} T and B lymphocytes in mice with amebic colitis. The frequency of NK T, CD8^{+} T and B lymphocytes was reduced in the MLN of mice in the CTRL-CD1$^{-/-}$ and Eh-CD1$^{-/-}$ groups compared to the CTRL-WT and Eh-WT groups. There was also a significant decrease in the frequency of B lymphocytes in the spleens of the animals in the Eh-WT group when compared with the CTRL-CD1$^{-/-}$, Eh-CD1$^{-/-}$ and CTRL-WT groups. The results of the flow cytometry analysis highlight the importance of NK T lymphocytes in the immune response of mice to amebic intestinal infection and the importance of CD1 molecules in the activation of T and B lymphocytes.

Keywords: amebic colitis, Entamoeba histolytica, natural killer T lymphocytes.

I. Introduction

Entamoeba histolytica is a protozoan of the genus Entamoeba and the causative agent of amoebiasis, a disease that produces approximately 50 million cases of two major clinical syndromes worldwide per year, amoebic colitis and amoebic liver abscess [1,2]. Amoebiasis is the most serious protozoiasis that affects the human intestine and comes only after malaria in deaths resulting from parasitic diseases [3]. The estimated mortality rate of this disease is approximately 100,000 deaths per year, and the majority of deaths occurs as a result of severe complications associated with invasive intestinal or extra-intestinal disease [1].

Author α: Postgraduate Program in Pathology, Institute of Biological Sciences, Federal University of Minas Gerais. Av. Antônio Carlos 6627, Belo Horizonte, Minas Gerais, Brazil.
e-mail: fabriciom19@yahoo.com.br
Author ν ρ: Department of General Pathology, Institute of Biological Sciences, Federal University of Minas Gerais. Av. Antônio Carlos 6627, Belo Horizonte, Minas Gerais, Brazil. e-mails: caliari@icb.ufmg.br, luerdesprata@hotmail.com
Author σ ω ¥ §: Department of Biochemistry and Immunology, Institute of Biological Sciences, Federal University of Minas Gerais. Av. Antônio Carlos 6627, Belo Horizonte, Minas Gerais, Brazil.
e-mails: andrezzasantiago@hotmail.com, berbardoch_bio@yahoo.com.br, afaria@icb.ufmg.br
Author χ: Department of Parasitology, Institute of Biological Sciences, Federal University of Minas Gerais. Av. Antônio Carlos 6627, Belo Horizonte, Minas Gerais, Brazil. e-mail: magomes@icb.ufmg.br

Entamoeba histolytica exhibits a complex glycoconjugate anchored by glycosylphosphatidylinositol (GPI), a lipopeptidophosphoglycan (LPPG) of *E. histolytica* (EhLPPG) on its surface; this has also been observed in other protozoa. Differences in the quantity and antigenicity of EhLPPGs in pathogenic and non-pathogenic amoebae have indicated that this glycoconjugate is associated with the pathogenicity of *E. histolytica* [4,5]. EhLPPG is involved in the immune response against *E. histolytica* infection by the activation of natural killer T lymphocytes (NK T) [6].

Some authors have demonstrated that NK T cells constitute an important barrier to the development of amoebic liver abscesses in their initial stages [6]. They found that CD1 deficient mice (CD1d$^{-/-}$) develop larger liver abscesses due to their inability to present antigens derived from amebic lipopeptidophosphoglycan to NK T lymphocytes. The results obtained by our group reinforce the idea that CD1 molecules are involved in the resistance of mice with experimentally induced amoebic colitis to *Entamoeba histolytica* trophozoites, possibly due to the presentation of antigens to invariant natural killer *T* (*i*NK T) lymphocytes and the stimulation of MUC-2 production [7]. Likewise, the reduction in activated NK T lymphocyte populations in CD1d-deficient mice results in an increased susceptibility of the mice to *Toxoplasma gondii* infection [8].

NK T lymphocytes appear to be related to both types of secondary immune responses, Th1 and Th2, due to their ability to initiate the production of large quantities of IFN-γ and IL-4 [6,9,10]. Due to the rapid-onset of the effector functions of *i*NK T lymphocytes after their activation, it have been described their participation in a wide variety of immune reactions, from the response against pathogens and neoplastic cells to autoimmune mechanisms [11,12].

The production of IFN-γ by *i*NK T lymphocytes activated with EhLPPG can initiate a Th1-type adaptive response, which is able to increase the secretion of IFN-γ and contribute to an increase in the efficiency of the immune response against *E. histolytica*; this reduces the number of trophozoites and the expansion of amebic abscesses [6]. Recent studies have suggested that

© 2015 Global Journals Inc. (US)

CD1d and *i*NK T lymphocytes are involved in controlling bacterial colonization in the gastrointestinal tract of mice. Intestinal colonization by both Gram-negative and Gram-positive bacteria has been shown to be higher in CD1d-deficient mice. In the same study, the authors observed that NK T lymphocytes were able to stimulate Paneth cells, which also express CD1d, to secrete antimicrobial peptides [13]. Thus, mice deficient in NK T lymphocytes, especially *i*NK T lymphocytes, have an increased susceptibility to infections [14,15].

Amoebiasis is one of the most important parasitic diseases affecting the world's population, making the understanding of the mechanisms and events related to its pathogenicity increasingly necessary. The present study demonstrated the importance of NK T lymphocytes via the identification and proliferation of these lymphocytes using flow cytometry in the spleen and mesenteric lymph nodes in an experimental model of *E. histolytica*-induced colitis.

II. Methods

a) Animals

In total, 32 female mice approximately 70 days old were used in this experiment, including 16 C57BL/6 *wild-type* (WT) (8 Eh-WT infected and 8 CTRL-WT controls) and 16 C57BL/6CD1$^{-/-}$ mice (8 Eh-CD1$^{-/-}$ infected and 8 CTRL-CD1$^{-/-}$ controls). The animals were obtained from the vivarium at the Institute of Biological Sciences (Instituto de Ciências Biológicas -ICB) of the UFMG and the vivarium at FIOCRUZ/Belo Horizonte. The C57BL/6CD1$^{-/-}$ mice were kindly provided by Professor Ricardo Tostes Gazzinelli. All procedures involving animals were conducted according to the guidelines of the Ethics Committee in Animal Experimentation (CETEA/UFMG) (266/2008).

b) Culture and inoculation of trophozoites

The EGG axenic strain of *E. histolytica,* which was isolated in 1988 in the Amoebiasis Laboratory of the Department of Parasitology of the ICB-UFMG from a patient with dysenteric colitis and amebic liver abscesses, was used for this study. A serological analysis via ELISA and zymodeme and PCR analyses were all positive for *E. histolytica* [16,17]. Trophozoites were thawed in a water bath and maintained in Pavlova medium at 37°C; they were subcultured every three days. Sixteen mice (8 Eh-CD1$^{-/-}$ and 8 Eh-WT) divided into subgroups of 4 animals each were anaesthetized with a 2% xylazine (10 mg/kg) and 5% ketamine (150 mg/kg) solution. Subsequently, an approximately 2-cm horizontal incision in the abdomen was performed, and 10^6 trophozoites in 0.1 mL of YI-S-32 culture medium were inoculated intracecally. The sixteen control mice (8 CTRL-CD1$^{-/-}$ and 8 CTRL-WT) were also divided into groups of 4 animals each and intracecally inoculated with sterile YI-S-32 culture medium.

c) Preparation of cellular suspensions of the spleen and mesenteric lymph nodes (MLN)

The animals were sacrificed 48 hours post-infection via cervical dislocation under general anesthesia with a 2% xylazine (10 mg/kg) and 5% ketamine (150 mg/kg) solution prior to removing the spleen and MLN. The spleen cell suspensions were washed with water and 10x PBS to remove red blood cells via hemolysis. After the washes, the spleen and MLN cell suspensions were maintained in a RPMI complete medium to count the viable cells using a Neubauer chamber and erythrocin as a marker of cell viability. The concentrations of each suspension were then standardized to 5 x 10^6 cells/mL.

d) Flow cytometry analysis

Following isolation of cells from the spleen and MLN, the cells were resuspended in PBS (pH 7.2) containing 0.2% fetal bovine serum and 0.1% sodium azide at a concentration of 2 x 10^7 cells/mL. Then, 25 μL of the cell suspension was added to a 96-well U bottom plate and incubated for 30 minutes at 4°C with 10 μL of a solution of phenotypic anti-marker monoclonal antibodies, including CD3, NK1.1, CD4, CD8, CD19 and CD69 (PharMingem, *San Diego, CA, USA)*, diluted in PBS and conjugated with the fluorochromes phycoerythrin (PE), fluorescein (FITC) and CyChrome (Cy). The plates were subsequently centrifuged for 10 minutes at 1200 rpm and 4°C, and the supernatant was discarded by rapid inversion. The pellet was then washed twice with PBS-azide. The pellet was resuspended in 200 μL of the fixative Mac Facs Fix. The suspensions were stored at 4°C and protected from light until data were acquired using a three color FACScan (*Becton Dickinson, Mountain View, California, USA*). IgG2a-FITC and IgG2b-PE antibodies were used as negative controls for cells incubated with immune-globulins of the same isotype used in the labeled antibody. The samples were analyzed using the program Cell Quest. During acquisition, 30,000 events were collected for analysis. The identification of the cell populations of interest and the determination of the percentage of cellular populations and subpopulations were performed using a computer system coupled to the flow cytometer.

e) Statistical analyses

The program Prism 5.0 was used to perform the statistical analyses. One-way ANOVA followed by the Tukey test, as a post-test, were used when analyzing more than two groups, and the unpaired t-test was used when comparing two groups. A Gaussian distribution was assumed for all groups when they were subjected to the Shapiro-Wilk test for normality. The results were expressed as means ± SEM, and differences were considered significant at $p \leq 0.05$.

© 2015 Global Journals Inc. (US)

III. Results

The experimental model used in this study allowed for a phenotypic analysis by flow cytometry of NK T, $CD4^+$ T, $CD8^+$ T and B lymphocytes in the spleen and MLN. They were also used to define the cell frequency profiles of wild-type and CD1-deficient mice in response to *E. histolytica* infection.

At 48 hours post-infection, spleens and mesenteric lymph nodes were collected to determine the frequency of NK T, $CD4^+$ T, $CD8^+$ T and B lymphocytes by flow cytometry in the CTRL-WT, Eh-WT, CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ mice.

The frequency of $CD3^+$ $NK1.1^+$ NK T lymphocytes was significantly reduced in the MLN of mice in the CTRL-$CD1^{-/-}$ (4.76 ± 1.59%) and Eh-$CD1^{-/-}$ (3.19 ± 1 57%) groups compared to the Eh-WT (20.24 ± 6.09%) and CTRL-WT (13.00 ± 1.45%) groups ($p < 0.05$) (Figure 1A). This reduction was expected, as CD1 molecules are required for the activation and proliferation of NK T lymphocytes.

In the spleen, there was no significant difference in the frequency of NK T lymphocytes for the CTRL-WT (8.18 ± 1.12%), Eh-WT (8.16 ± 1.16%) CTRL-$CD1^{-/-}$ (7.60± 0.8563%) and Eh-$CD1^{-/-}$ (8.46 ± 1.39%) groups (Figure 1B).

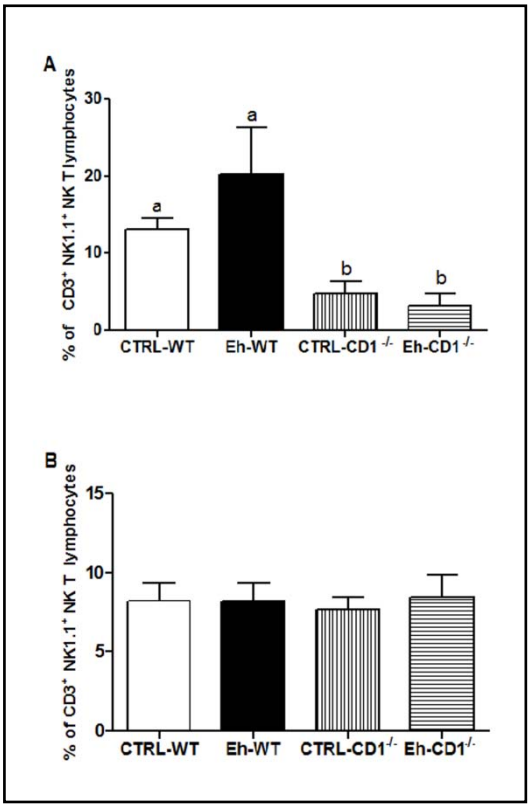


Figure 1 : Frequency of $CD3^+$ $NK1.1^+$ NK T lymphocytes in the mesenteric lymph nodes (A) and in the spleen (B) of C57BL/6 WT and C57BL/6 $CD1^{-/-}$ controls and infected mice with *Entamoeba histolytica.* Data are shown as means ± SEM, n =8, $p<0.05$.

There was also no significant difference in the frequency of $CD4^+$ $CD69^+$ T lymphocytes in the MLN among the CTRL-WT (13.68 ± 3.57%), Eh-WT (14.84 ± 2.0%), CTRL-$CD1^{-/-}$ (11.08 ± 0.27%) and Eh-$CD1^{-/-}$ (11.05 ± 0.39%) groups (Figure 2A). The frequency of $CD4^+$ $CD69^+$ T lymphocytes in the spleen also did not vary significantly among the CTRL-WT (6.97 ± 0.54%), Eh-WT (7.78 ± 0.45%), CTRL-$CD1^{-/-}$ (7.66 ± 0.57%) and Eh-$CD1^{-/-}$ (7.08 ± 0.39%) groups (Figure 2B).

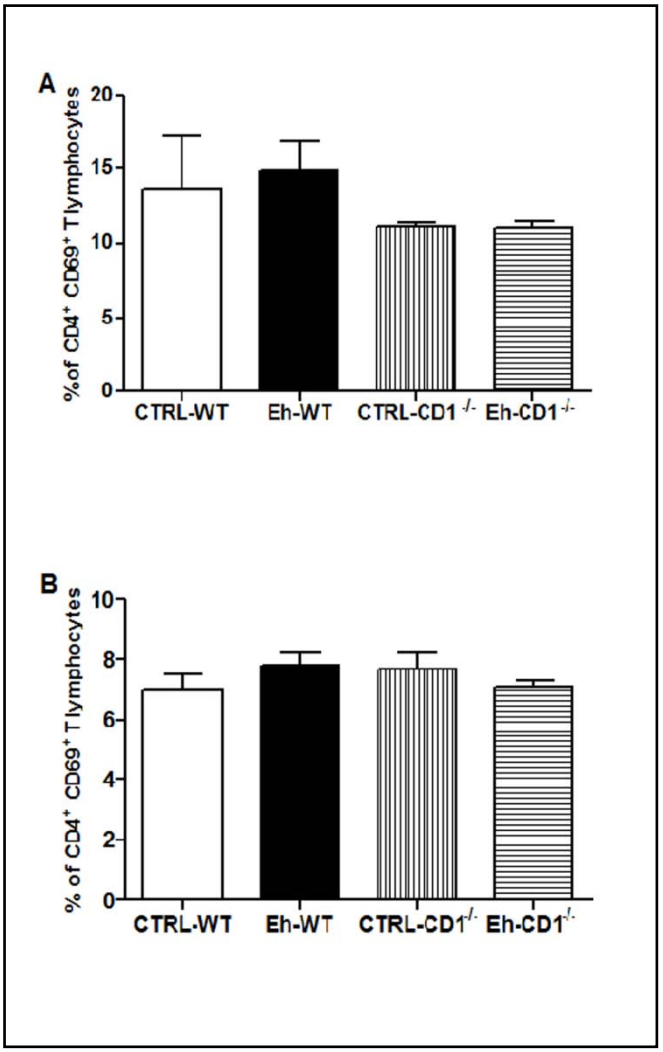


Figure 2 : Frequency of $CD4^+$ $CD69^+$ T lymphocytes in the mesenteric lymph nodes (A) and in the spleen (B) of C57BL/6 WT e C57BL/6 $CD1^{-/-}$ controls and infected mice with *Entamoeba histolytica.* Data are shown as means ± SEM, n =8, $p<0.05$.

A significant reduction was observed in the frequency of $CD8^+$ $CD69^+$ T lymphocytes in the MLN of the CTRL-$CD1^{-/-}$ (7.99 ± 0.43%) and Eh-$CD1^{-/-}$ (6.74 ± 0.84%) groups compared to the CTRL-WT (31.64 ± 9.29%) and Eh-WT (35.68 ± 3.71%) groups ($p < 0.05$) (Figure 3A).

In the spleen, there was no significant difference in the frequency of $CD8^+$ $CD69^+$ T lymphocytes for the CTRL-WT (17.50 ± 2.54%), Eh-WT (13.57 ± 2.71%),

© 2015 Global Journals Inc. (US)

CTRL-CD1$^{-/-}$ (12.68 ± 1.48%) and Eh-CD1$^{-/-}$ (8.78 ± 0.47%) groups (Figure 3B).

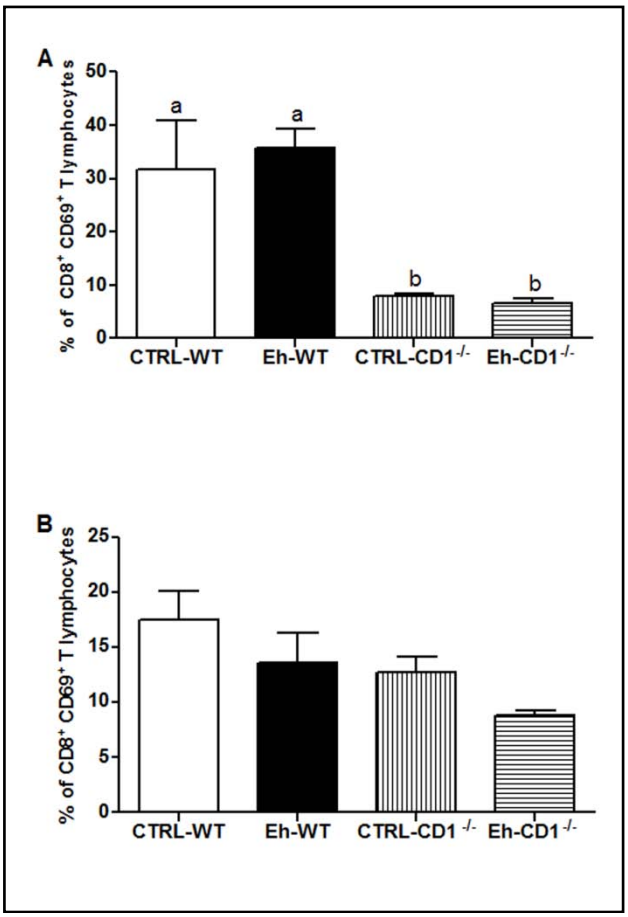


Figure 3 : Frequency of CD8$^+$ CD69$^+$ T lymphocytes in the mesenteric lymph nodes (A) and in the spleen (B) of C57BL/6 WT e C57BL/6 CD1$^{-/-}$ controls and infected mice with *Entamoeba histolytica.* Data are shown as means ± SEM, n =8, p<0.05.

The MLN of the animals in the CTRL-CD1$^{-/-}$ (1.55 ± 0.25%) and Eh-CD1$^{-/-}$ (0.87 ± 0.11%) groups showed a significant reduction in the frequency of CD19$^+$ CD69$^+$ B lymphocytes compared to the CTRL-WT (38.70 ± 6.97%) and Eh-WT (64.88 ± 10.46%) groups (p <0.05). There was also a significant increase in the frequency of CD19$^+$ CD69$^+$ B lymphocytes in the MLN of the Eh-WT group (64.88 ± 10.46%) compared to the CTRL-WT group (38.70 ± 6.97%) (p < 0.05) (Figure 4A).

The frequency of CD19$^+$ CD69$^+$ B lymphocytes in the spleen of animals in the Eh-WT group (3.52 ± 0.23%) was lower than in the CTRL-CD1$^{-/-}$ (7.60 ± 0.85%), Eh-CD1$^{-/-}$ (8.46 ± 1.39%) and CTRL-WT (4.74 ± 0.44%) groups (p < 0.05) (Figure 4B).

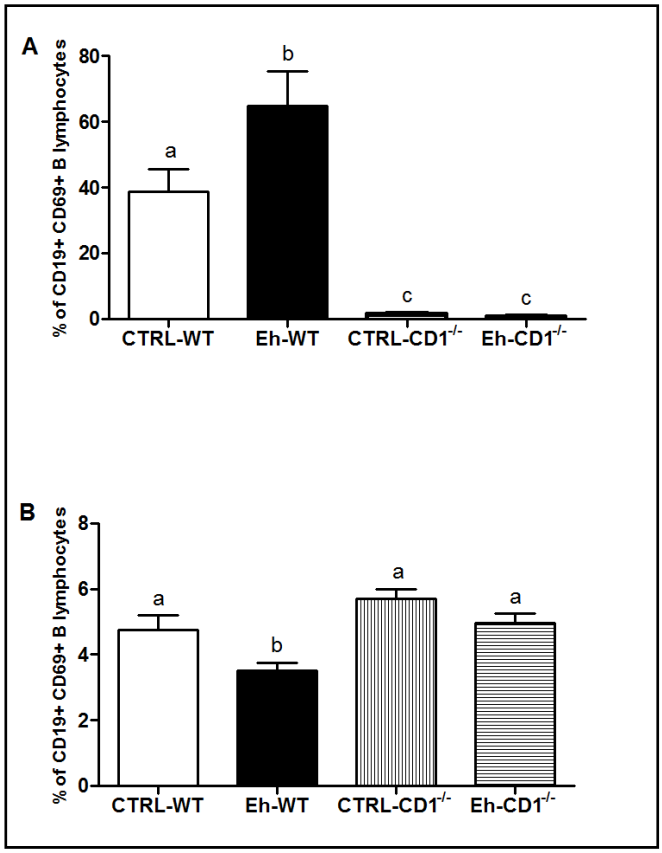


Figure 4 : Frequency of CD19$^+$ CD69$^+$ B lymphocytes in the mesenteric lymph nodes (A) and in the spleen (B) of C57BL/6 WT e C57BL/6 CD1$^{-/-}$ controls and infected mice with *Entamoeba histolytica.* Data are shown as means ± SEM, n =8, p<0.05.

IV. Discussion

The aim of this study was to analyze, using flow cytometry, the frequency of NK T, CD4$^+$ T, CD8$^+$ T and B lymphocytes in the spleens and MLN of wild-type mice (C57BL/6 WT) and mice genetically deficient for CD1d molecules (C57BL/6CD1$^{-/-}$) in response to *E. histolytica* infection. It is important to note that, to date, this is the only study that has used flow cytometry to analyze NK T lymphocytes and their involvement in amebic colitis.

In previous study, we demonstrated that CD1-deficient mice (CD1$^{-/-}$), which consequently have a lower number of NK T lymphocytes, are more susceptible to amebic infection and to the development of cecal lesions. Furthermore, we found that a decrease in the production of the mucin MUC-2 in C57BL/6CD1$^{-/-}$ mice is associated with a reduction in the number of NK T lymphocytes and to the appearance of more severe cecal lesions [7].

The frequency of CD3$^+$ NK1.1$^+$ NK T lymphocytes in MLN was significantly lower in mice from the CTRL-CD1$^{-/-}$ and Eh-CD1$^{-/-}$ groups compared to the Eh-WT and CTRL-WT groups. NK T lymphocytes are activated directly through the recognition of glycolipidic

© 2015 Global Journals Inc. (US)

antigens by CD1 molecules [12]. Thus, this reduction in the $CD3^+$ $NK1.1^+$ NK T lymphocytes in the MLN of the C57BL/6$CD1^{-/-}$ mice was expected because CD1 molecules are required for the activation and proliferation of *i*NK T lymphocytes. This analysis confirmed that C57BL/6$CD1^{-/-}$ mice actually have a reduced frequency of NK T lymphocytes relative to wild-type mice, making them appropriate for our study.

The significant increase in $CD3^+$ $NK1.1^+$ NK T lymphocytes in the MLN of the animals of the Eh-WT group indicated that these lymphocytes play a major role in the immune response to amebic trophozoites. In a previous study, we found that the mice in the Eh-WT group had fewer trophozoites and less intense cecal lesions than the Eh-$CD1^{-/-}$ group [7].

The higher frequency of $NK1.1^+$ lymphocytes in the submucosa and lamina propria of the mice in the Eh-WT group, combined with the smaller numbers of trophozoites observed in these mice compared to the control mice, suggest that these lymphocytes may act in the immune response to amebic intestinal infection. This hypothesis is strengthened by the observation that the mice in the Eh-$CD1^{-/-}$ group had reduced numbers of $NK1.1^+$ lymphocytes, elevated tissue parasitism and more severe lesions [7].

The results of other studies are consistent with our findings and have shown that $NK1.1^+$ lymphocytes are an important barrier against the development of amebic liver abscesses in their early stages [6]. These authors reported that CD1-deficient mice developed larger liver abscesses due to their inability to present antigens derived from amebic lipopeptidophosphoglycan to NK T lymphocytes. Likewise, the reduction in the activated NK T lymphocyte population in CD1d-deficient mice resulted in an increased susceptibility to *Toxoplasma gondii* infection [8]. To verify whether NK T lymphocytes secrete IFN-γ following EhLPPG stimulation, lymphocytes were removed from $CD1d^{-/-}$ and $J\alpha18^{-/-}$ mice deficient in *i*NK T lymphocytes or in all NK T lymphocyte subpopulations and cultured with antigen presenting cells (APCs) stimulated by EhLPPG. The authors observed a great reduction in IFN-γ secretion in $CD1d^{-/-}$ and $J\alpha18^{-/-}$mice, indicating that *i*NK T lymphocytes are an important source of IFN-γ when exposed to EhLPPG. IFN-γ production by EhLPPG-activated *i*NK T lymphocytes may initiate a Th1-type adaptive response that is able to amplify the secretion of IFN-γ and increase the efficiency of the immune response to *E. histolytica*, thus reducing the number of trophozoites and the expansion of amebic abscesses [6]. Previous research has also shown that NK T lymphocytes are important in controlling bacterial colonization of the gastrointestinal tract of C57BL/6 mice [13]. In that study, the authors showed that intestinal colonization by both Gram-negative and Gram-positive bacteria was higher in C57BL/6$CD1^{-/-}$ mice.

In our study, no significant difference in the frequency of $CD4^+$ $CD69^+$ T lymphocytes in the MLN was observed among the CTRL-WT, Eh-WT, CTRL- $CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups. The frequency of $CD4^+$ $CD69^+$ T lymphocytes in the spleen also did not vary significantly among the CTRL-WT, Eh-WT, CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups. However, in the MLN of the animals in the CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups, there was a lower frequency of $CD8^+$ $CD69^+$ T lymphocytes compared to the CTRL-WT and Eh-WT groups. This reduction may have occurred because of the deficiency in activated NK T cells. CD1d-deficient NK T cells produce a variety of cytokines when activated, and the absence of these cells can lead to a decrease in the proliferation of $CD8^+$ $CD69^+$ T cells. Some authors have observed that in the mesenteric, inguinal, axillary and cervical lymph nodes and spleens of $J\alpha18^{-/-}$ and $CD1d^{-/-}$ mice, the activation of NK T cells mediated by α-galactosylceramide increases the homeostatic proliferation of $CD8^+$ T cells but not $CD4^+$ T cells [18]. In our study, no significant difference in the frequency of $CD4^+$ $CD69^+$ lymphocytes in the MLN or spleen was observed among the CTRL-WT, Eh-WT, CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups. The increase in the homeostatic proliferation of $CD8^+$ T cells has been shown to be related to the production of IL-4 by activated NK T cells. Thus, IL-4 acts directly on $CD8^+$ T cells to induce their proliferation [18]. However, with respect to the cytotoxic T lymphocytes, studies by other authors have shown that there is a lack of these cells in mice with amebic colitis or liver abscesses. The immunohistochemical characterization of $CD8^+$ and $CD4^+$ T lymphocytes in humans with amebic colitis did not find significant numbers of these cells or contact between these cells and trophozoites in either lesioned regions or intact areas of the intestinal tract [19].

Some authors propose that the main immune mechanisms used in intestinal *E. histolytica* infections occur during the first days following infection and are mediated by innate immunity, which is independent of T lymphocytes [20]. We did not find significant differences in the frequencies of $CD8^+$ $CD69^+$ T cells in the spleens of mice in the CTRL-WT, Eh-WT, CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups. However, the results showed a trend toward a reduction in the frequency of $CD69^+$ $CD8^+$ T lymphocytes in the spleens of the CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups compared to the CTRL-WT and Eh-WT groups.

CD1d molecules are constitutively expressed in dendritic cells, B lymphocytes and macrophages in both humans and mice, although the levels of expression may vary among cell types [21]. The quantitative analysis of lymphocytes showed a significant reduction in the frequency of B lymphocytes ($CD19^+$ $CD69^+$) in the MLN of animals in the CTRL-$CD1^{-/-}$ and Eh-$CD1^{-/-}$ groups compared to the CTRL-WT and Eh-WT groups. It is possible that this reduction in recently activated B lymphocytes in the MLN is related to the scarcity of

© 2015 Global Journals Inc. (US)

activated *i*NK T lymphocytes in CD1-deficient mice. The MLN drain directly into the lymph of the cecal mucosa, where there are many *i*NK T lymphocytes. Some authors have shown that the *in vivo* activation of murine *i*NK T lymphocytes with α-galactosylceramide induces the production of IL-4 by these lymphocytes and leads to the expression of activation markers, such as CD69, B7-2 and I-A^b in B lymphocytes [22]. In humans, the *in vitro* activation of NK T lymphocytes with α-galactosylceramide induces the production of IL-4 and IL-13, which stimulate B lymphocyte proliferation and the total production of IgG1 and IgM antibodies [23].

When we compared the number of recently activated B lymphocytes in the MLN of mice in the Eh-WT group to that of mice in the CTRL-WT group, we observed a significant increase in these lymphocytes in the *E. histolytica* infected mice. In addition to participating in antigen presentation via MHC and CD1d, B lymphocytes also act in the immunity to *E. histolytica* through the production of IgA and IgG. The humoral response to *E. histolytica* in mice with amebic colitis may act both locally and systemically depending on the level of intestinal and extra-intestinal invasion caused by the protozoan [24]. The significant increase in the number of recently activated B lymphocytes in the MLN of the Eh-WT group suggests the activation of humoral immunity and its likely participation in the resistance against trophozoites, although the time of infection in this study did not allow for a more detailed analysis. The ability of MLN to drain directly into the lymph from the intestine, where the inflammatory focus is located, could also aid in the delivery of antigens and the activation of B lymphocytes.

In contrast to our observations in the MLN, there was a reduction in the frequency of recently activated B lymphocytes in the spleens of the animals in the Eh-WT group compared to those in the CTRL $CD1^{-/-}$, Eh-$CD1^{-/-}$ and CTRL-WT groups. B lymphocytes appear to participate in immunity to *E. histolytica*. Thus, the recruitment of recently activated B lymphocytes from the spleen to the MLN or other organs, where these cells would have increased exposure to antigens from the site of inflammation and would be activated to produce IgA and IgG, may be occurring. This migration would explain the reduction in the frequency of these cells in the spleen.

V. Conclusions

Combined with the pathological study that we performed previously, the results of this flow cytometry analysis reinforce the importance of NK T lymphocytes in immunity against intestinal amebic infection and of CD1 molecules in the activation of T and B lymphocytes. The direct involvement of these cells in experimental amebic colitis still requires further study.

Competing interests

The authors declare that they have no competing interests.

VI. Acknowledgments

This work was supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPEMIG (Fundação de Amparo à Pesquisa de Minas Gerais) and PRPq/UFMG (Pró-Reitoria de pesquisa da UFMG). The authors are grateful to João da Costa Viana, Mirna Maciel D'Auriol Souza and Gislene Arlindo da Silva for technical assistance.

References Références Referencias

1. World Health Organization (WHO). Report of a consulation of experts on Amoebiasis (México), Weekly Epidemiological Record, Geneva. 1997 ; 72
2. Stanley JR, SL, and Reed SL. Microbes and microbial toxins, Paradigms for microbial-mucosal infections. VI. Entamoeba histolytica, parasite-host interactions. Am J Physiol Gastrointest Liver Physiol. 2001; 280: 1049-1054.
3. Stanley JR SL. Amoebiasis. The Lancet. 2003; 361: 1025-1034.
4. Brigl M, Bry L, Kent SC, et al. Mechanism of CD1d-restricted natural killer T cell activation during microbial infection. Nat Immun. 2003; 4: 1230-1237.
5. Moody S, Becker S, Nuchamowitz Y, Mirelman D. Identification of significant variation in the composition of lipophosphoglycan-like molecules of *E. histolytica* and *E. dispar*. J Eukaryot Microbio. 1998; 45: 9-12.
6. Lotter H, González-Roldán N, Lindner B, et al. Natural Killer T cells activated by a lipopeptidophos-phoglycan from Entamoeba histolytica are critically important to control amebic liver abscess. PLoS Pathog. 2009; 5: 1-11.
7. Oliveira FMS, Coelho BH, Prata LO, et al. Susceptibility to intestinal infection is related to reduction in natural killer T-lymphocytes in C57BL/6 mice. Current Infectious Disease Reports. 2012; 4 : 22-29.
8. Smiley ST, Lanthier PA, Couper KN et al. Exacerbated Susceptibility to Infection-Stimulated Immunopathology in CD1d-Deficient Mice. The Journal of Immunology. 2005; 174: 7904-7911.
9. Macdonald HR. NK1.1 $^+$ T cell receptor-alpha/beta$^+$ cells: new clues to their origin, specificity, and function. J Exp Med. 1995; 182: 633-638.
10. Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1 specific NK1 T cells: development, specificity, an function. Annu Rev Immunol. 1997; 15: 535-562.
11. Kronenberg M. Toward an understanding of NKT cell biology: progress and paradoxes. Annu Rev Immunol. 2007; 23: 877-900.

© 2015 Global Journals Inc. (US)

12. Tupin E, Kinjo Y, Kronenberg M. The unique role of natural killer T cells in the response to microorganisms. *Nat Rev* Microbiol. 2007; 5: 405-417.
13. Nieuwenhuis EE, Matsumoto T, Lindenbergh D, et al. Cd1d-dependent regulation of bacterial colonization in the intestine of mice. J Clin Invest. 2009; 119: 1241-1250.
14. Arase H, Arase N, Ogasawara k, et al. An $NK1.1^+$ $CD4^+$ single-positive thymocyte subpopulation that expresses a highly skewed T cell antigen receptor family. Proc Natl Acad Sc. 1992; 89: 6506-6510.
15. Bendelac A, Schwartz RH. CD4C and CD8C T cells acquire specific lymphokine secretion potentials during thymic maturation. Nature. 199; 353: 68-71.
16. Gomes MA, Pesquero JB, Furst C, et al. An improved method to distinguish *Entamoeba histolytica* and *Entamoeba dispar*. Parasitology. 1999; 119: 359-362.
17. Martinez AM, Gomes MA, Viana JC, et al. Isoenzyme profile as parameter to differentiate pathogenic strains of *Entamoeba histolytica* in Brazil. Rev Inst Med Trop. 1996; 38: 407-412.
18. Ueda N, Kuki H, Kamimura D, et al. CD1d- resticted NKT cell activation enhanced homeostatic proliferation of $CD8^+$ T cells in manner dependent on IL-4. International Immunology. 2006; 18: 1397-1404.
19. Ventura-Juárez J, Barba-Gallardo LF, Muñoz-Fernández L, et al. Immunohistochemical characterization of human fulminant amoebic colitis. Parasite Immunology. 2007; 29: 201-209.
20. Asgharpour A, Gilchirist C, Baba D, et al. Resistance to Intestinal *Entamoeba histolytica* Infection is conferred by Innate Immunity and $Gr\text{-}1^+$ Cells. Infection and Immunity 2005; 73: 4522-4529.
21. Brossay LD, Jullien S, Cardell BC, et al. Mouse CD1 is mainly expressed on hemopoietic-derived cells. J. Immunol. 1997; 159: 1216-1224.
22. Kitamura H, Otha A, Sekimoto M, Sato M, et al. α-galactosylceramide induces early B-cell activation through IL-4 production by NKT cells. Cell. Immunol. 2000; 199: 37-42.
23. Galli G, Nuti S, Tavarini S, et al. CD1d-restricted help to B cells by human invariant natural Killer T lymphocytes. J Exp Med. 2003; 1997: 1051-57.
24. Carrero JC, Cervantes-Rebolledo C, Aguilar-Díaz H, et al. The role of the secretory immune response in the infection by *Entamoeba histolytica*. Parasite Immunology. 2007 ; 29 : 331-338.

© 2015 Global Journals Inc. (US)

This page is intentionally left blank

© 2015 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 15 Issue 4 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Usefulness of an Initial Single Intravenous Immunoglobulin Therapy for Kawasaki Disease

By Toshimasa Nakada
Aomori Prefectural Central Hospital, Japan

Abstract- Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children. Coronary artery lesions (CAL) are one of the most important complications of this disease. An appropriate therapy during acute phase of Kawasaki disease to prevent large CAL has not been established. Recent studies disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial intravenous immunoglobulin (IVIG) therapy on CAL development in the acute phase of Kawasaki disease and that an initial single IVIG therapy with delayed administration of anti-inflammatory drugs might be useful for prevention of large CAL. Furthermore, recent study disclosed that variable factors including IVIG resistance, responsiveness, and relapse of disease were associated with CAL complications and that an initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors of Kawasaki disease.

Keywords: kawasaki disease, intravenous immuno-globulin therapy, coronary artery lesions, aspirin, flurbiprofen.

GJMR-F Classification : NLMC Code: WO 285

Strictly as per the compliance and regulations of:

© 2015. Toshimasa Nakada. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Usefulness of an Initial Single Intravenous Immunoglobulin Therapy for Kawasaki Disease

Toshimasa Nakada

Abstract- Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children. Coronary artery lesions (CAL) are one of the most important complications of this disease. An appropriate therapy during acute phase of Kawasaki disease to prevent large CAL has not been established. Recent studies disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial intravenous immunoglobulin (IVIG) therapy on CAL development in the acute phase of Kawasaki disease and that an initial single IVIG therapy with delayed administration of anti-inflammatory drugs might be useful for prevention of large CAL. Furthermore, recent study disclosed that variable factors including IVIG resistance, responsiveness, and relapse of disease were associated with CAL complications and that an initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors of Kawasaki disease.

Keywords: kawasaki disease, intravenous immunoglobulin therapy, coronary artery lesions, aspirin, flurbiprofen.

I. Introduction

Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children [1] . Coronary artery lesions (CAL) are one of the most important complications of this disease. During the acute phase (before day 30 from disease onset), coronary artery aneurysms develop. During the convalescent phase (after day 30), large aneurysms develop into subsequent stenosis and these stenotic lesions cause myocardial ischemia and even death. On the other hand, small aneurysms regress without leaving stenotic lesions. Long-term follow-up studies have shown that a maximum CAL size >5 mm was a statistically significant predictive risk factor for myocardial ischemia, and that all CAL≤5 mm in size regressed to normal size [2]. Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm [3]. Therefore, the prevention of CAL of >5 mm may be an important goal in the acute treatment of Kawasaki disease to prevent coronary artery stenosis in later stages of the disease [4].

Treatment with intravenous immunoglobulin (IVIG) therapy reduces the occurrence of CAL caused by Kawasaki disease [5,6]. The current standard therapy during the acute phase of Kawasaki disease is 2g/kg/day IVIG therapy [7]. Combination regimens of IVIG and other drugs including steroids and infliximab have been tried as the initial therapy for patients with Kawasaki disease [8,9]. However, the treatment for the prevention of large CAL has not been established, and not enough studies have been performed with regard to initial IVIG monotherapy in spite of the safety and effectiveness of this therapy [4,10].

II. Aspirin's Role in the Treatment of the Acute Phase of Kawasaki Disease

Currently, the standard therapy for pediatric patients with Kawasaki disease is the combination of IVIG and aspirin. Platelets are activated during the acute phase of Kawasaki disease, which provides biological plausibility for antiplatelet therapy in these patients [11]. However, the role and impact of anti-inflammatory drugs (ADs), including high or medium-dose aspirin on IVIG therapy during the acute phase of Kawasaki disease remain unclear. Previous study highlighted insufficient evidence for the addition of aspirin to IVIG therapy regarding suppression of CAL caused by Kawasaki disease [12].

Two studies have shown that ADs may be unnecessary in the acute phase of Kawasaki disease [13,14]. Another two studies disclosed that the prevalence of CAL differed between patients who received initial IVIG therapy without ADs and those who received concomitant ADs with initial IVIG [15,16]. In one of these studies [15], the regimen of IVIG was 400 mg/kg day over 5 days, which is not standard at present. Current initial IVIG protocol for Kawasaki disease is 2g/kg/day. Recent two studies using 2g/kg/day initial IVIG therapy showed that the prevalence of CAL was lower in the patients received initial IVIG therapy without concomitant ADs compared to those with concomitant ADs (Table 1). These studies showed that an initial IVIG therapy without concomitant ADs may be useful for suppression of CAL caused by Kawasaki disease.

Author: Department of Pediatrics, Aomori Prefectural Central Hospital, Aomori City, Japan. e-mail: toshimasanakada@yahoo.co.jp

© 2015 Global Journals Inc. (US)

Table 1 : Comparison of the prevalence of coronary artery lesions between the patients who received 2g/kg/day initial IVIG therapy with and without concomitant ADs administration

Studies	patients without concomitant ADs	patients with concomitant ADs	P
Study A	1.5 % (2/134) (n = 134)	12.1 % (8/66) (n = 66)	0.003
Study B	3.9% (2/51) (n = 51)	7.8% (10/129) (n = 129)	0.514

IVIG: intravenous immunoglobulin, ADs: anti-inflammatory drugs (Aspirin or Flurbiprofen)
Study A: Clinical Medicine Research 2015;4:127-131
Study B: Korean Circulation Journal 2013;43:182-186

III. Effects of ADs on Intravenous Immunoglobulin Therapy in the Acute Phase of Kawasaki Disease

Recent study disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease [17].

It was previously reported that ADs, including aspirin, affected the immunological function of T-cells [18,19,20]. A recent study suggested that the pathway comprising T-cells may play a role in the mechanism of action of IVIG [21,22]. Furthermore, a recent immunological study highlighted that T cell activation in the early and middle stages was involved in the mechanism underlying cardiovascular injury in Kawasaki disease [23]. These findings suggest that ADs can alter the effects of IVIG on Kawasaki disease.

IV. An Initial Single ivig Therapy with Delayed Administration of ADs for Prevention of Large cal Caused by Kawasaki Disease

Recent study showed a usefulness of an initial single IVIG therapy with delayed administration of ADs (aspirin or flurbiprofen) for prevention of large CAL caused by Kawasaki disease [4]. In this study, all 132 patients received 2g/kg/day initial IVIG therapy. 74 patients received aspirin and 58 patients received flurbiprofen after completion of initial IVIG infusion. Initial IVIG therapy resistance occurred in 31 of 132 patients (23%), and 10 patients (8%) received additional IVIG. One patient received urinastatin and one patient received plasma exchange as third-line therapy. Before the 30th day, the prevalence of CAL was 2% (2/132); after 30 days, it was 1% (1/132). The maximal internal CAL diameters were 4.8mm (Z score = 6.3) among all patients.

Patients who received initial IVIG monotherapy with delayed administration of ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration. However, patients who received initial IVIG therapy with concomitant use of ADs may receive a negative impact of ADs during IVIG therapy. This difference may be a mechanism that the combination order of initial IVIG therapy with administration of ADs may lead to the prevention of large CAL.

V. Background Factors Associated with the Complications of cal Caused by Kawasaki Disease

Recent study disclosed that variable factors including IVIG resistance, responsiveness, and relapse of disease were associated with CAL complications and that an initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors of Kawasaki disease [10].

Another study showed that a patient who had received initial IVIG and prednisolone combination therapy developed large CAL after relapse [24]. This demonstrated the difficulties associated with administration of appropriate additional therapy after initial therapy with steroids. A single IVIG therapy does not modify the clinical course of Kawasaki disease. This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at appropriate times during the clinical course. With these advantages and reported outcomes of CAL, initial single IVIG therapy may be superior to combination treatment with initial IVIG therapy and steroids.

VI. Conclusions

Aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease. Patients who received initial IVIG monotherapy with delayed administration of these ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration. Furthermore, a single IVIG therapy does not modify the clinical course of Kawasaki disease. This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at appropriate times during the clinical course. An initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors including IVIG-

© 2015 Global Journals Inc. (US)

resistance, -responsiveness, and relapse of Kawasaki disease.

References Références Referencias

1. Burns JC, Glod é MP. Kawasaki syndrome. Lancet 2004; 364: 533–544.
2. Muller F, Knirsch W, Harpes P, Pretre R, Valsangiacomo BE,Kretschmar O. Long-term follow-up of acute changes in coronary artery diameter caused by Kawasaki disease: risk factors for development of stenotic lesions. Clin Res Cardiol 2009; 98: 501–507.
3. Tsuda E, Kamiya T, Ono Y, Kimura K, Kurosaki K, Echigo S. Incidence of stenotic lesions predicted by acute phase changes in coronary arterial diameter during Kawasaki disease. Pediatr Cardiol 2005; 26: 73–79.
4. Nakada T. Prevention of large coronary artery lesions caused by Kawasaki disease. Medical Research Archives 2015 DOI:http://dx.doi.org/10.18103/mra.v0i3.138
5. Furusho K, Kamiya T, Nakano H et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984; 2: 1055–1058.
6. Newburger JW, Takahashi M, Beiser AS et al. Single intravenous infusion of gamma globulin as compared with four infusion in the treatment of acute Kawasaki syndrome. N Engl J Med 1991; 324: 1633–1639.
7. Research committee of the Japanese Scociety of Pediatric Cardiology; Cardiac Surgery committee for development of guidelines for medical treatment of acute Kawasaki disease. Guidelines for medical treatment of acute Kawasaki disease: report of the Research committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int 2014; 56: 135-158.
8. Kobayashi T, Saji T, Otani T et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomized, open-label, blinded-endpoints trial. Lancet 2012; 379: 1613–1620.
9. Tremoulet AH, Jain S, Jaggi P et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet 2014; 383: 1731–1738.
10. Nakada T. Background factors associated with the complications of coronary artery lesions caused by Kawasaki disease. Clinical Medicine Research 2015; 4: 127-131
11. Yahata T, Suzuki C, Yoshikawa A et al. Platelet activation dynamics evaluated using platelet-derived microparticles in Kawasaki disease. Circ J 2014; 78: 188–193
12. Baumer JH, Love SJ, Gupta A et al. Salicylate for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2006 Oct 18; (4): CD004175
13. Hsieh KS, Weng KP, Lin CC et al. Treatment of acute Kawasaki disease: aspirin's role in the febril stage revisited. Pediatrics 2004; 114: e689–e693
14. Lee G, Lee SE, Hong YM et al. Is high-dose aspirin necessary in the acute phase of Kawasaki disease? Korean Circ J 2013; 43: 182–186
15. Ito H, Kiyosawa N. Effectiveness of aspirin therapy in acute phase of Kawasaki disease. Prog Med 2002; 22: 1640–1643
16. Nakada T. Difference in the prevalence of coronary arterial lesions in Kawasaki disease according to the time of initiation of additional aspirin or flurbiprofen therapy. Med J Aomori 2012; 57: 15–19
17. Nakada T. Effects of anti-inflammatory drugs on intravenous immunoglobulin therapy in the acute phase of Kawasaki disease. Pediatr Cardiol 2015; 36: 335-339
18. Benammar C, Hichami A, Yessouufou A et al. Zizyphus lotus L. (Desf.) modulates antioxidant activity and human T-cell proliferation. BMC Complement Altern Med 2010; 10: 54
19. Buckland M, Lombardi G. Aspirin and the induction of tolerance by dendritic cells. Handb Exp Pharmacol 2009; 188: 197–213
20. Huang L, Mackenzie G, Ouyang N et al. The novel phospho-non-steroidal anti-inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvant-induced arthritis in rats. Br J Pharmacol 2011; 162: 1521–1533
21. Inoue Y, Kaifu T, Sugahata-Tobinai A et al. Activating Fc gamma receptors participate in the development of autoimmune diabetes in NOD mice. J Immunol 2007; 179: 764–774
22. Yamamoto M, Kobayashi K, Ishikawa Y et al. The inhibitory effects of intravenous administration of rabbit immunoglobulin G on airway inflammation are dependent upon Fcc receptor II b on CD11c(?) dendritic cells in a murine model. Clin Exp Immunol 2010; 162: 315–324
23. Zhang YY, Huang XM, Kang ML et al. Changes in CD69, CD25 and HLA-DR expressions in peripheral blood T cells in Kawasaki disease. Zhonghua Er Ke Za Zhi 2006; 44: 329–332
24. Ashida A, Ozaki N, Kishi K, Katayama H, Okasora K, Tamai H. A case report of refractory Kawasaki disease with bilateral giant coronary aneurysms treated with intravenous immunoglobulin and prednisolone combination therapy. Progress in Medicine 2013; 33: 1471-1474

© 2015 Global Journals Inc. (US)

This page is intentionally left blank

© 2015 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 15 Issue 4 Version 1.0 Year 2015
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Advantages and Challenges to using Telehealth Medicine

By Patrick O'Connell, RN
Adelphi University, United States

Abstract- *Objective:* Research was conducted to evaluate advantages and challenges to using telehealth medicine. Technology is discussed in relation to ease of healthcare provider use and client use. Ethical issues were evaluated for issues concerning safety and surveillance.

Method: Reviews of literature using nursing data base (ProQuest-Health and Medical Complete) with the term telehealth in nursing was used. Limits used to narrow the search were full text, peer reviewed, English language, human only and dates between 2011 and 2014.

Results: The literature search located 34 articles from ProQuest. A total of 7 articles that support advantages or disadvantages to using telehealth were used.

Conclusion: The articles had mixed result for advantages and challenges at the healthcare provider level and the patient level. Issues with weak signals, misinterpreted data, and patient reading errors were evaluated for safety issues. Several clients and caretakers failed to report results during studies hindering outcomes. Client satisfaction and quality of life were addressed to evaluate the client and family views of telehealth medicine.

Keywords: *telehealth, nursing, healthcare, informatics, communication.*

GJMR-F Classification : *NLMC Code: WP 100*

Strictly as per the compliance and regulations of:

© 2015. Patrick O'Connell, RN. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Advantages and Challenges to using Telehealth Medicine

Patrick O'Connell, RN

Abstract- *Objective:* Research was conducted to evaluate advantages and challenges to using telehealth medicine. Technology is discussed in relation to ease of healthcare provider use and client use. Ethical issues were evaluated for issues concerning safety and surveillance.

Method: Reviews of literature using nursing data base (ProQuest-Health and Medical Complete) with the term telehealth in nursing was used. Limits used to narrow the search were full text, peer reviewed, English language, human only and dates between 2011 and 2014.

Results: The literature search located 34 articles from ProQuest. A total of 7 articles that support advantages or disadvantages to using telehealth were used.

Conclusion: The articles had mixed result for advantages and challenges at the healthcare provider level and the patient level. Issues with weak signals, misinterpreted data, and patient reading errors were evaluated for safety issues. Several clients and caretakers failed to report results during studies hindering outcomes. Client satisfaction and quality of life were addressed to evaluate the client and family views of telehealth medicine.

Keywords: telehealth, nursing, healthcare, informatics, communication.

I. Introduction

With populations aging world-wide and age-related chronic diseases increasing; there is an increased need for healthcare access (Wade, Shaw, and Cartwright, 2012).Health informatics has been growing in the healthcare industry since the 1950 and 1960's (Stenlund and Mines, 2012). Information can be gathered, stored, retrieved and shared by multiple disciplines as a way to improve quality and safety in patient care delivery. This article discusses factors that enhance or inhibit safe patient care delivery using telehealth technology. Healthcare providers will be evaluated to identify benefits and limitations to using information technology as a way to collaborate with other disciplines or clients. Ways to improve information delivery and clear up misunderstandings will be addressed to offer information clarity for both healthcare provider and client recipients.

As healthcare service needs are increasing, information technology is also increasing to meet the demand of global populations. Welfare technology (WT) was launched to improve healthcare access, reduce financial burden, and conduct research (Hoffman, 2012). Ethical challenges concerning tracking, disease monitoring, surveillance and privacy will be discussed to identify risk/benefit outcomes using telehealth technology.

The purpose of this research is to evaluate data that supports advantages and challenges to using telehealth medicine. This information can be used by healthcare organizations to implement programs or change current practices in an effort to offer better healthcare delivery for global populations. Views of using technology information by healthcare providers and clients can be used to improve education needs or improve system design.

II. Advantages to using Information Technology

Telehealth medicine is growing constantly to offer healthcare world-wide.It is an avenue to assess, diagnose, plan, implement and evaluate data over time or distances. Education and communication can be valuable to clients without access to healthcare. Research can be obtained or shared to improve evidence based knowledge.

Hoffman (2012) conducted a study with 281 out of 1976 articles to evaluate advantages and ethical challenges to using information technology. His research revealed several positive results. Many identified that mobility technology can increase flexibility, agility, and movability. Internet based psychotherapy and telemedicine for home services resulted in reduced mortality, better medication compliance, and improved safety from falls or security issues. His research also identified that elderly clients welcome new technology and surveillance as it reduces fear and insecurities.

Having the remote capability to offer specialty care and access to rapid assessment and treatments can be an answer to a shortage of experts in underserved locations. Technology may benefit clients with sensory impairment, social isolation, and depression. The speed of healing processes using hospital services at home may be more effective and will promote dignity (Bonanno, Bramanti, Pirrotta, Spadero Bramanti and Lanzafame, 2013).

Stenlund and Mines (2012) suggested that videoconferencing along with telephone, facsimile, and e-mail is a great way to communicate. Video-

Author: Adelphi University, Project Management and Information Technology NUR. e-mail: patrickoconnell@mail.adelphi.edu

© 2015 Global Journals Inc. (US)

conferencing allows communication over long distances while viewing and hearing each other. Using this technique addresses issues such as geographic barriers, weather concerns, access to healthcare providers, reduced stress, access to education, monitoring and travel time.

Watanabe, Fairchild, Pituskin, Borgersen, Hanson and Fassbender (2012) conducted a study using forty-four initial consultation clients and 28 follow-up visit clients using video conferencing. The result showed that most of the clients or caretakers expressed a high degree of satisfaction with various aspects of the virtual clinic. Only 6.8 percent indicated discomfort with telehealth equipment or format. Nineteen of 44 percent of physicians returned surveys and all of them agreed that their patients received an easy to use and valuable service that would be difficult to access by other means. Videoconferencing can be beneficial for oncology consultations, home hospice nursing visits, team meetings, and education for clients or healthcare providers.

Vinson, McCallum, Thornlow and Champagne (2011) were responsible for designing a pilot program for reorganizing their ambulatory clinic under hospital guidelines to enhance reimbursements. Strategies that were implemented to improve outcomes and reduce costs were telehealth nursing, telephone triage, and telephone nursing. A total of 136 of 344 patients consented to participate in this pilot study. The results revealed that 81.2 percent of the clients rated telehealth medicine as being high or very high in value and 88.1 percent of the clients stated that their needs were met. Only 1.1percent of the calls were urgent. Hospital and clinic visits drastically decreased for situations such as prescription refills, test results, advice about medication, self-care questions, and after hour visits. Feedback from 75 percent of the providers revealed that only 55.6 percent of the providers refer their patients to telehealth however; those providers rate the service as high level of satisfaction. The cost of this service was made up by adjusting the clinic staffing cost. They used existing phone jacks, cable wires, and office space to reduce overall expenses for setting up the service. Multiple disciplines were set up with individual programs that were linked to one network so that information could be shared simultaneously.

III. Disadvantages to using Information Technology

Although there are many advantages to using information technology, there are disadvantages and ethical issues as well. Watanabe, Fairchild, Pituskin, Borgersen, Hanson and Fassbender (2012) found that rural family physicians were not aware of the virtual clinic despite advertising over the fax, telephone, internet and media. Recommendations were delayed due to lack of physician contact or unavailability. Appointments took more time to enter into the telehealth system than hand written. Several clients had to travel long distances to visit the telehealth site for pain management. This study lacked a control group and had a small number of participants. There was no follow-up data to compare. There was not a cost analysis for set-up, staff training, or impact on the healthcare system.

Wade, Shaw, and Cartwright (2012) conducted a study to identify reasons for failed readings of telehealth monitoring equipment on elderly people with chronic diseases. They identified that of 255 people, 112 people did not meet the criteria for participation and 50 were already using some form of telehealth system. Thirty-two clients lacked capacity and did not have care assistance to help them with their readings on a regular basis. The clients were given questions to answer daily. All caretakers were trained and observed in the use of the telehealth equipment. Of 43 participants, (56%) had caretakers, (39%) had orthopedic issues, (16%) had mobility impairment or falls, (10%) had cardiovascular issues, (10%) had neurology issues, (5%) had respiratory issues, (5%) had malignancy issues, (4%) had renal issues, (3%) had infection, and (8%) were other issues.

Of the 43 clients in this study, (100%) were required to take daily heart rate readings, (98%) were required to take daily blood pressures, (46%) required daily weight readings, and (42) required daily pulse oximetry readings. Results found that there was an overall (13%) failure rate. Weight failed (17%), blood pressure failed (15%), heart rate failed (14%), pulse oximetry failed (15%), and daily questions failed (6%). The finding suggested that inaccurate reading were about even with or without caretakers. The study did not elaborate whether the caretakers were family, friends, hired nurses, or companions. It also did not mention the age of the caretakers. Readings were recorded as both reported, but wrong and unreported. Caretakers did not document the reason for reading failure. Caretakers were left to their clinical judgement whether a client needed a follow-up appointment.

This study suggests that reading errors can have harsh negative consequences. It is dangerous because it provides false information to medical staff. Non-reporting withholds vital information necessary for practitioners to form a plan of care.

Ethical question that needs to be answered before implementing a telehealth program: Who will benefit? Is it more useful for the client, healthcare providers or the stakeholders? What is the end point? Will it reduce mortality or increase quality of life? Will it be cost effective? Who will be installing and monitoring the devices? How will consent be obtained? If these questions can be answered through studies, client/family satisfaction scores, physician surveys, etc.;

© 2015 Global Journals Inc. (US)

then a pilot program is ready to be implemented (Hoffman, 2012).

Hoffman (2012) suggests that implementing technology may be age discriminating by enhancing differences and inequalities. It is not fair to expect family members to learn new technology. This added burden may alter family ties. Monitoring and tracking devices may infringe on a person's right to privacy, autonomy, surveillances, and confidentiality.

IV. Making Technology more user Friendly

Hoffman (2012) suggests that subjective barriers can be overcome by installingdevices such as labeling, mirror doors without knobs, coded door openers, etc. to enhance a person's right to dignity and privacy. Risk vs. benefit in relation to surveillance and privacy may be complicated. Surveillance of an elderly person with cognitive decline, a pacemaker/defibrillator, or diabetes mellitus may need surveillance for safety reasons.

Karim, Zulkifley, Mustafa, Sagap and Latar (2013) suggested that the natural presence of gesture, interaction, instructions, face expression, and voice helps explain meaning of a speech however; long distance communication loses clarity and signal strength which leads to misunderstandings and misinterpretations. Telepointer communication can be used to convey human gesture by pointer motion. Telepointers can be classified by low level such as a laser pointer or high level such as hand gestures, sketching, drawing or overlaying hands.

Telepointer technology allows the sender to point at exact areas being represented while simultaneously letting the observers see the same views. Telepointer provides coordinate information, creates a presence of self, and gains audience attention. This technology can be used for education, consultation, surgery, and many other needs.

Wade, Shaw, and Cartwright (2012) suggests that monitoring equipment for home use should be as easy as following a few simple prompts or pressing a button. Instructions to the care givers explaining the importance of reporting monitor results is necessary. Elderly clients can decompensate quickly without prompt attention by medically trained staff.

V. Discussion

All of the articles showed evidence of advantages and disadvantages to using telehealth technology. The advantages clearly outweigh the challenges and ethical dilemmas. A majority of client's, caretakers, and physicians expressed satisfaction with telehealth technology. More needs to be studied about the ease of monitoring device use to improve reading errors. Caretakers need more instruction about the importance of reporting monitor results.

Ethical issues need to be studied further to identify if elderly people with cognitive decline have the right to refuse telehealth monitoring equipment. Assessment of safety and security needs to be evaluated for people refusing care. Are there ways to keep an elderly person safe and secure while maintaining their right of dignity and privacy? Is surveillance and tracking intruding on a person's privacy if used as a safety measure?

Telehealth technology should be easy to use for the client and the provider. Before implementing new telehealth technology, questions need to be answered such as: Who will benefit? Is it more useful for the client, healthcare providers or the stakeholders? What is the end point? Will it reduce mortality or increase quality of life? Will it be cost effective? Who will be installing and monitoring the devices? How will consent be obtained?

Telepointer technology can help give clarity to a presentation, instructions, explanation, etc. Using low to high level telepointer technology can offer human gesture from pointer motion. Using the telepointer can resolve misunderstandings or misinterpretations.

This analysis is intended to support advantages and disadvantages to using telehealth medicine. This information can be used as guidance to make evidence based decisions before implementing a telehealth program.

References Références Referencias

1. Hoffman, B. (2013). Ethical challenges with welfare technology: A review of the literature, *Science and Engineering Ethics, 19*:2, 389-406. doi: http://dx.doi.org/10.1007/s11948-011-9348-1
2. Karim, R., Zakaria, N., Zulkifley, M., Mustafa, M., Sagnap, I, Later, N. (2013). Telepointer technology in telemedicine: A review, *Biomedical Engineer Online 12*:21. doi:http://dx.doi.org/10.1186/1475-925X-12-21
3. Stenlund, D., Mines, B. (2012). Videoconferencing and dietician services: In rural Ontario communities, Canadian Journal of Dietetic Practice and Research, 73:4, 176-80. Retrieved September 26, 2015 from http://search.proquest.com/docview/1268815249?accountid=8204
4. Timpano, F., Bonanno, L., Bramanti, A., Spadaro, L., Bramanti, P. Lanzafame, P. (2013). Tele-health and neurology: What is possible? *Neurological Science*, 34:12, 2263-70. doi: http://dx.doi.org/10.1007/s10072-012-1285-5
5. Vinson, M., McCallum, R., Thornlow, D., Champagne, M. (2011.Design, implementation, and evaluation of population-specific telehealth nursing services, *Nursing Economics, 29*:5, 265-72.

© 2015 Global Journals Inc. (US)

Retrieved September 26, 2015 from http://search.proquest.com/docview/898419520?accountid=8204

6. Wade, R., Shaw, K., Cartwright, C. (2012). Factors affecting provision of successful monitoring in home telehealth, *Gerontology, 58*:4, 371-7.doi: http://dx.doi.org/10.1159/000335033
7. Watanabe, S., Fairchild, A., Pituskin, E., Borgersen, P., Hanson, J., Fassbender, K. (2013). Improving access to specialist multidisciplinary palliative care consultation for rural cancer patients by videoconferencing: Report of a pilot project, *Supportive Care in Cancer, 21*:4, 1201-7. doi: http://dx.doi.org/10.1007/s00520-012-1649-7

© 2015 Global Journals Inc. (US)

Global Journals Inc. (US) Guidelines Handbook 2015

www.GlobalJournals.org

FELLOWS

FELLOW OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (FARSM)

Global Journals Incorporate (USA) is accredited by Open Association of Research Society (OARS), U.S.A and in turn, awards "FARSM" title to individuals.The 'FARSM' title is accorded to a selected professional after the approval of the Editor-in-Chief/Editorial Board Members/Dean.

- The "FARSM" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall,Ph.D., FARSS or William Walldroff, M.S., FARSM.

FARSM accrediting is an honor. It authenticates your research activities. After recognition as FARSM, you can add 'FARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, and Visiting Card etc.

The following benefits can be availed by you only for next three years from the date of certification:

FARSM designated members are entitled to avail a 40% discount while publishing their research papers (of a single author) with Global Journals Incorporation (USA), if the same is accepted by Editorial Board/Peer Reviewers. If you are a main author or co-author in case of multiple authors, you will be entitled to avail discount of 10%.

Once FARSM title is accorded, the Fellow is authorized to organize a symposium/seminar/conference on behalf of Global Journal Incorporation (USA). The Fellow can also participate in conference/seminar/symposium organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent.

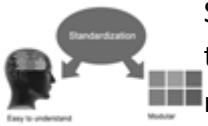
You may join as member of the Editorial Board of Global Journals Incorporation (USA) after successful completion of three years as Fellow and as Peer Reviewer. In addition, it is also desirable that you should organize seminar/symposium/conference at least once.

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

The FARSM can go through standards of OARS. You can also play vital role if you have any suggestions so that proper amendment can take place to improve the same for the benefit of entire research community.

As FARSM, you will be given a renowned, secure and free professional email addres with 100 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.



The FARSM will be eligible for a free application of standardization of their researches. Standardization of research will be subject to acceptability within stipulated norms as the next step after publishing in a journal. We shall depute a team of specialized research professionals who will render their services for elevating your researches to next higher level, which is worldwide open standardization.

The FARSM member can apply for grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A. Once you are designated as FARSM, you may send us a scanned copy of all of you credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria. After certification of all your credentials by OARS, they will be published on your Fellow Profile link on website https://associationofresearch.org which will be helpful to upgrade the dignity.

The FARSM members can avail the benefits of free research podcasting in Global Research Radio with their research documents. After publishing the work, (including published elsewhere worldwide with proper authorization) you can upload your research paper with your recorded voice or you can utilize chargeable services of our professional RJs to record your paper in their voice on request.

The FARSM member also entitled to get the benefits of free research podcasting of their research documents through video clips. We can also streamline your conference videos and display your slides/ online slides and online research video clips at reasonable charges, on request.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

The FARSM is eligible to earn from sales proceeds of his/her researches/reference/review Books or literature, while publishing with Global Journals. The FARSS can decide whether he/she would like to publish his/her research in a closed manner. In this case, whenever readers purchase that individual research paper for reading, maximum 60% of its profit earned as royalty by Global Journals, will be credited to his/her bank account. The entire entitled amount will be credited to his/her bank account exceeding limit of minimum fixed balance. There is no minimum time limit for collection. The FARSM member can decide its price and we can help in making the right decision.

The FARSM member is eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get remuneration of 15% of author fees, taken from the author of a respective paper. After reviewing 5 or more papers you can request to transfer the amount to your bank account.

MEMBER OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (MARSM)

The ' MARSM ' title is accorded to a selected professional after the approval of the Editor-in-Chief / Editorial Board Members/Dean.

The "MARSM" is a dignified ornament which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., MARSM or William Walldroff, M.S., MARSM.

MARSM accrediting is an honor. It authenticates your research activities. Afterbecoming MARSM,you can add 'MARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, Visiting Card and Name Plate etc.

The following benefitscan be availed by you only for next three years from the date of certification.

MARSM designated members are entitled to avail a 25% discount while publishing their research papers (of a single author) in Global Journals Inc., if the same is accepted by our Editorial Board and Peer Reviewers. If you are a main author or co-author of a group of authors, you will get discount of 10%.

As MARSM, you willbe given a renowned, secure and free professional email address with 30 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

The MARSM member can apply for approval, grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A.

Once you are designated as MARSM, you may send us a scanned copy of all of your credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria.

It is mandatory to read all terms and conditions carefully.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

AUXILIARY MEMBERSHIPS

Institutional Fellow of Open Association of Research Society (USA) - OARS (USA)

Global Journals Incorporation (USA) is accredited by Open Association of Research Society, U.S.A (OARS) and in turn, affiliates research institutions as "Institutional Fellow of Open Association of Research Society" (IFOARS).

The "FARSC" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., FARSC or William Walldroff, M.S., FARSC.

The IFOARS institution is entitled to form a Board comprised of one Chairperson and three to five board members preferably from different streams. The Board will be recognized as "Institutional Board of Open Association of Research Society"-(IBOARS).

The Institute will be entitled to following benefits:

The IBOARS can initially review research papers of their institute and recommend them to publish with respective journal of Global Journals. It can also review the papers of other institutions after obtaining our consent. The second review will be done by peer reviewer of Global Journals Incorporation (USA) The Board is at liberty to appoint a peer reviewer with the approval of chairperson after consulting us.

The author fees of such paper may be waived off up to 40%.

The Global Journals Incorporation (USA) at its discretion can also refer double blind peer reviewed paper at their end to the board for the verification and to get recommendation for final stage of acceptance of publication.

The IBOARS can organize symposium/seminar/conference in their country on behalf of Global Journals Incorporation (USA)-OARS (USA). The terms and conditions can be discussed separately.

The Board can also play vital role by exploring and giving valuable suggestions regarding the Standards of "Open Association of Research Society, U.S.A (OARS)" so that proper amendment can take place for the benefit of entire research community. We shall provide details of particular standard only on receipt of request from the Board.

The board members can also join us as Individual Fellow with 40% discount on total fees applicable to Individual Fellow. They will be entitled to avail all the benefits as declared. Please visit Individual Fellow-sub menu of GlobalJournals.org to have more relevant details.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

We shall provide you intimation regarding launching of e-version of journal of your stream time to time. This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

After nomination of your institution as "Institutional Fellow" and constantly functioning successfully for one year, we can consider giving recognition to your institute to function as Regional/Zonal office on our behalf.
The board can also take up the additional allied activities for betterment after our consultation.

The following entitlements are applicable to individual Fellows:

Open Association of Research Society, U.S.A (OARS) By-laws states that an individual Fellow may use the designations as applicable, or the corresponding initials. The Credentials of individual Fellow and Associate designations signify that the individual has gained knowledge of the fundamental concepts. One is magnanimous and proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice.

Open Association of Research Society (US)/ Global Journals Incorporation (USA), as described in Corporate Statements, are educational, research publishing and professional membership organizations. Achieving our individual Fellow or Associate status is based mainly on meeting stated educational research requirements.

Disbursement of 40% Royalty earned through Global Journals : Researcher = 50%, Peer Reviewer = 37.50%, Institution = 12.50% E.g. Out of 40%, the 20% benefit should be passed on to researcher, 15 % benefit towards remuneration should be given to a reviewer and remaining 5% is to be retained by the institution.

We shall provide print version of 12 issues of any three journals [as per your requirement] out of our 38 journals worth $ 2376 USD.

Other:

The individual Fellow and Associate designations accredited by Open Association of Research Society (US) credentials signify guarantees following achievements:

- The professional accredited with Fellow honor, is entitled to various benefits viz. name, fame, honor, regular flow of income, secured bright future, social status etc.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

- In addition to above, if one is single author, then entitled to 40% discount on publishing research paper and can get 10%discount if one is co-author or main author among group of authors.
- The Fellow can organize symposium/seminar/conference on behalf of Global Journals Incorporation (USA) and he/she can also attend the same organized by other institutes on behalf of Global Journals.
- The Fellow can become member of Editorial Board Member after completing 3yrs.
- The Fellow can earn 60% of sales proceeds from the sale of reference/review books/literature/publishing of research paper.
- Fellow can also join as paid peer reviewer and earn 15% remuneration of author charges and can also get an opportunity to join as member of the Editorial Board of Global Journals Incorporation (USA)
- • This individual has learned the basic methods of applying those concepts and techniques to common challenging situations. This individual has further demonstrated an in–depth understanding of the application of suitable techniques to a particular area of research practice.

Note :

"

- In future, if the board feels the necessity to change any board member, the same can be done with the consent of the chairperson along with anyone board member without our approval.
- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

Process of submission of Research Paper

The Area or field of specialization may or may not be of any category as mentioned in 'Scope of Journal' menu of the GlobalJournals.org website. There are 37 Research Journal categorized with Six parental Journals GJCST, GJMR, GJRE, GJMBR, GJSFR, GJHSS. For Authors should prefer the mentioned categories. There are three widely used systems UDC, DDC and LCC. The details are available as 'Knowledge Abstract' at Home page. The major advantage of this coding is that, the research work will be exposed to and shared with all over the world as we are being abstracted and indexed worldwide.

The paper should be in proper format. The format can be downloaded from first page of 'Author Guideline' Menu. The Author is expected to follow the general rules as mentioned in this menu. The paper should be written in MS-Word Format (*.DOC,*.DOCX).

The Author can submit the paper either online or offline. The authors should prefer online submission.Online Submission: There are three ways to submit your paper:

(A) (I) First, register yourself using top right corner of Home page then Login. If you are already registered, then login using your username and password.

(II) Choose corresponding Journal.

(III) Click 'Submit Manuscript'. Fill required information and Upload the paper.

(B) If you are using Internet Explorer, then Direct Submission through Homepage is also available.

(C) If these two are not conveninet , and then email the paper directly to dean@globaljournals.org.

Offline Submission: Author can send the typed form of paper by Post. However, online submission should be preferred.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Preferred Author Guidelines

MANUSCRIPT STYLE INSTRUCTION (Must be strictly followed)

Page Size: 8.27" X 11'"

- Left Margin: 0.65
- Right Margin: 0.65
- Top Margin: 0.75
- Bottom Margin: 0.75
- Font type of all text should be Swis 721 Lt BT.
- Paper Title should be of Font Size 24 with one Column section.
- Author Name in Font Size of 11 with one column as of Title.
- Abstract Font size of 9 Bold, "Abstract" word in Italic Bold.
- Main Text: Font size 10 with justified two columns section
- Two Column with Equal Column with of 3.38 and Gaping of .2
- First Character must be three lines Drop capped.
- Paragraph before Spacing of 1 pt and After of 0 pt.
- Line Spacing of 1 pt
- Large Images must be in One Column
- Numbering of First Main Headings (Heading 1) must be in Roman Letters, Capital Letter, and Font Size of 10.
- Numbering of Second Main Headings (Heading 2) must be in Alphabets, Italic, and Font Size of 10.

You can use your own standard format also.
Author Guidelines:

1. General,

2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

1. GENERAL

Before submitting your research paper, one is advised to go through the details as mentioned in following heads. It will be beneficial, while peer reviewer justify your paper for publication.

Scope

The Global Journals Inc. (US) welcome the submission of original paper, review paper, survey article relevant to the all the streams of Philosophy and knowledge. The Global Journals Inc. (US) is parental platform for Global Journal of Computer Science and Technology, Researches in Engineering, Medical Research, Science Frontier Research, Human Social Science, Management, and Business organization. The choice of specific field can be done otherwise as following in Abstracting and Indexing Page on this Website. As the all Global

Journals Inc. (US) are being abstracted and indexed (in process) by most of the reputed organizations. Topics of only narrow interest will not be accepted unless they have wider potential or consequences.

2. ETHICAL GUIDELINES

Authors should follow the ethical guidelines as mentioned below for publication of research paper and research activities.

Papers are accepted on strict understanding that the material in whole or in part has not been, nor is being, considered for publication elsewhere. If the paper once accepted by Global Journals Inc. (US) and Editorial Board, will become the copyright of the Global Journals Inc. (US).

Authorship: The authors and coauthors should have active contribution to conception design, analysis and interpretation of findings. They should critically review the contents and drafting of the paper. All should approve the final version of the paper before submission

The Global Journals Inc. (US) follows the definition of authorship set up by the Global Academy of Research and Development. According to the Global Academy of R&D authorship, criteria must be based on:

1) Substantial contributions to conception and acquisition of data, analysis and interpretation of the findings.

2) Drafting the paper and revising it critically regarding important academic content.

3) Final approval of the version of the paper to be published.

All authors should have been credited according to their appropriate contribution in research activity and preparing paper. Contributors who do not match the criteria as authors may be mentioned under Acknowledgement.

Acknowledgements: Contributors to the research other than authors credited should be mentioned under acknowledgement. The specifications of the source of funding for the research if appropriate can be included. Suppliers of resources may be mentioned along with address.

Appeal of Decision: The Editorial Board's decision on publication of the paper is final and cannot be appealed elsewhere.

Permissions: It is the author's responsibility to have prior permission if all or parts of earlier published illustrations are used in this paper.

Please mention proper reference and appropriate acknowledgements wherever expected.

If all or parts of previously published illustrations are used, permission must be taken from the copyright holder concerned. It is the author's responsibility to take these in writing.

Approval for reproduction/modification of any information (including figures and tables) published elsewhere must be obtained by the authors/copyright holders before submission of the manuscript. Contributors (Authors) are responsible for any copyright fee involved.

3. SUBMISSION OF MANUSCRIPTS

Manuscripts should be uploaded via this online submission page. The online submission is most efficient method for submission of papers, as it enables rapid distribution of manuscripts and consequently speeds up the review procedure. It also enables authors to know the status of their own manuscripts by emailing us. Complete instructions for submitting a paper is available below.

Manuscript submission is a systematic procedure and little preparation is required beyond having all parts of your manuscript in a given format and a computer with an Internet connection and a Web browser. Full help and instructions are provided on-screen. As an author, you will be prompted for login and manuscript details as Field of Paper and then to upload your manuscript file(s) according to the instructions.

To avoid postal delays, all transaction is preferred by e-mail. A finished manuscript submission is confirmed by e-mail immediately and your paper enters the editorial process with no postal delays. When a conclusion is made about the publication of your paper by our Editorial Board, revisions can be submitted online with the same procedure, with an occasion to view and respond to all comments.

Complete support for both authors and co-author is provided.

4. MANUSCRIPT'S CATEGORY

Based on potential and nature, the manuscript can be categorized under the following heads:

Original research paper: Such papers are reports of high-level significant original research work.

Review papers: These are concise, significant but helpful and decisive topics for young researchers.

Research articles: These are handled with small investigation and applications

Research letters: The letters are small and concise comments on previously published matters.

5.STRUCTURE AND FORMAT OF MANUSCRIPT

The recommended size of original research paper is less than seven thousand words, review papers fewer than seven thousands words also.Preparation of research paper or how to write research paper, are major hurdle, while writing manuscript. The research articles and research letters should be fewer than three thousand words, the structure original research paper; sometime review paper should be as follows:

Papers: These are reports of significant research (typically less than 7000 words equivalent, including tables, figures, references), and comprise:

(a)Title should be relevant and commensurate with the theme of the paper.

(b) A brief Summary, "Abstract" (less than 150 words) containing the major results and conclusions.

(c) Up to ten keywords, that precisely identifies the paper's subject, purpose, and focus.

(d) An Introduction, giving necessary background excluding subheadings; objectives must be clearly declared.

(e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition; sources of information must be given and numerical methods must be specified by reference, unless non-standard.

(f) Results should be presented concisely, by well-designed tables and/or figures; the same data may not be used in both; suitable statistical data should be given. All data must be obtained with attention to numerical detail in the planning stage. As reproduced design has been recognized to be important to experiments for a considerable time, the Editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un-refereed;

(g) Discussion should cover the implications and consequences, not just recapitulating the results; conclusions should be summarizing.

(h) Brief Acknowledgements.

(i) References in the proper form.

Authors should very cautiously consider the preparation of papers to ensure that they communicate efficiently. Papers are much more likely to be accepted, if they are cautiously designed and laid out, contain few or no errors, are summarizing, and be conventional to the approach and instructions. They will in addition, be published with much less delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and to make suggestions to improve briefness.

It is vital, that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

Format

Language: The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than 1.4 × 10-3 m3, or 4 mm somewhat than 4 × 10-3 m. Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

Structure

All manuscripts submitted to Global Journals Inc. (US), ought to include:

Title: The title page must carry an instructive title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) wherever the work was carried out. The full postal address in addition with the e-mail address of related author must be given. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining and indexing.

Abstract, used in Original Papers and Reviews:

Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Key Words

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy and planning a list of possible keywords and phrases to try.

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art.A few tips for deciding as strategically as possible about keyword search:

- One should start brainstorming lists of possible keywords before even begin searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

Acknowledgements: Please make these as concise as possible.

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

The Editorial Board and Global Journals Inc. (US) recommend that, citation of online-published papers and other material should be done via a DOI (digital object identifier). If an author cites anything, which does not have a DOI, they run the risk of the cited material not being noticeable.

The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

Tables, Figures and Figure Legends

Tables: Tables should be few in number, cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g. Table 4, a self-explanatory caption and be on a separate sheet. Vertical lines should not be used.

Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.

Preparation of Electronic Figures for Publication

Even though low quality images are sufficient for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit (or e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings) in relation to the imitation size. Please give the data for figures in black and white or submit a Color Work Agreement Form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution (at final image size) ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs) : >350 dpi; figures containing both halftone and line images: >650 dpi.

Color Charges: It is the rule of the Global Journals Inc. (US) for authors to pay the full cost for the reproduction of their color artwork. Hence, please note that, if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a color work agreement form before your paper can be published.

Figure Legends: Self-explanatory legends of all figures should be incorporated separately under the heading 'Legends to Figures'. In the full-text online edition of the journal, figure legends may possibly be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should notify the reader, about the key aspects of the figure.

6. AFTER ACCEPTANCE

Upon approval of a paper for publication, the manuscript will be forwarded to the dean, who is responsible for the publication of the Global Journals Inc. (US).

6.1 Proof Corrections

The corresponding author will receive an e-mail alert containing a link to a website or will be attached. A working e-mail address must therefore be provided for the related author.

Acrobat Reader will be required in order to read this file. This software can be downloaded

(Free of charge) from the following website:

www.adobe.com/products/acrobat/readstep2.html. This will facilitate the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof.

Proofs must be returned to the dean at dean@globaljournals.org within three days of receipt.

As changes to proofs are costly, we inquire that you only correct typesetting errors. All illustrations are retained by the publisher. Please note that the authors are responsible for all statements made in their work, including changes made by the copy editor.

6.2 Early View of Global Journals Inc. (US) (Publication Prior to Print)

The Global Journals Inc. (US) are enclosed by our publishing's Early View service. Early View articles are complete full-text articles sent in advance of their publication. Early View articles are absolute and final. They have been completely reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made after sending them. The nature of Early View articles means that they do not yet have volume, issue or page numbers, so Early View articles cannot be cited in the conventional way.

6.3 Author Services

Online production tracking is available for your article through Author Services. Author Services enables authors to track their article - once it has been accepted - through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The authors will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript.

6.4 Author Material Archive Policy

Please note that if not specifically requested, publisher will dispose off hardcopy & electronic information submitted, after the two months of publication. If you require the return of any information submitted, please inform the Editorial Board or dean as soon as possible.

6.5 Offprint and Extra Copies

A PDF offprint of the online-published article will be provided free of charge to the related author, and may be distributed according to the Publisher's terms and conditions. Additional paper offprint may be ordered by emailing us at: editor@globaljournals.org .

Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

1. Choosing the topic: In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

2. Evaluators are human: First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

3. Think Like Evaluators: If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

4. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

5. Ask your Guides: If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

6. Use of computer is recommended: As you are doing research in the field of Computer Science, then this point is quite obvious.

7. Use right software: Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

8. Use the Internet for help: An excellent start for your paper can be by using the Google. It is an excellent search engine, where you can have your doubts resolved. You may also read some answers for the frequent question how to write my research paper or find model research paper. From the internet library you can download books. If you have all required books make important reading selecting and analyzing the specified information. Then put together research paper sketch out.

9. Use and get big pictures: Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

10. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

11. Revise what you wrote: When you write anything, always read it, summarize it and then finalize it.

12. Make all efforts: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. Have backups: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

14. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

17. Never use online paper: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

Please carefully note down following rules and regulation before submitting your Research Paper to Global Journals Inc. (US):

Segment Draft and Final Research Paper: You have to strictly follow the template of research paper. If it is not done your paper may get rejected.

- The **major constraint** is that you must independently make all content, tables, graphs, and facts that are offered in the paper. You must write each part of the paper wholly on your own. The Peer-reviewers need to identify your own perceptive of the concepts in your own terms. NEVER extract straight from any foundation, and never rephrase someone else's analysis.

- Do not give permission to anyone else to "PROOFREAD" your manuscript.

- Methods to avoid Plagiarism is applied by us on every paper, if found guilty, you will be blacklisted by all of our collaborated research groups, your institution will be informed for this and strict legal actions will be taken immediately.)
- To guard yourself and others from possible illegal use please do not permit anyone right to use to your paper and files.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Criterion for Grading a Research Paper (Compilation) by Global Journals Inc. (US)

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals Inc. (US).

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

save our planet

Global Journal of Medical Research

Visit us on the Web at www.GlobalJournals.org | www.MedicalResearchJournal.org
or email us at helpdesk@globaljournals.org

ISSN 9755896

© Global Journals