Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: F

Diseases

Cancer, Ophthalmology & Pediatric

Treatment in Merkel Cell Progression and Management

Highlights

Brief Update on Approach

Reconstructive Plastic Surgery

Discovering Thoughts, Inventing Future

VOLUME 20 ISSUE 3 VERSION1.0

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Volume 20 Issue 11 was originally issued as F3

Global Journal of Medical Research: F
Diseases
Cancer, Ophthalmology & Pediatric

Volume 20 Issue 11
Originally issued as F3

Global Journal of Medical Research: F
Diseases
Cancer, Ophthalmology & Pediatric

Volume 20 Issue 3 (Ver. 1.0)

Open Association of Research Society

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

The Importance of Diagnosis and Specialized Treatment in Merkel Cell Carcinoma: Case Report in a Young Healthy Woman, Literature Review and Brief Update on Approach

By Cristina da Silva, Liliane & Regazzini, Rosana Cardoso de Oliveira
University of State of São Paulo

Abstract- Merkel Cell Carcinoma (MCC) is extremely rare and aggressive, with an overall survival of 40% in 5 years. The non-oncological physician has large difficulty about the correct approach of this pathology. We report the sixth case of MCC in a young healthy patient (woman, 19 years old) described in the medical literature, who was treated twice for sebaceous cyst, evolved with local disease progression, needed a larger resection and, after adjuvant therapy, remains no tumor recurrence. Despite being an extremely rare neoplasm, therapeutics should not be underestimated by non-oncological physician because this cancer is too aggressive, and the correct oncological approach could result in increased progression-free survival for these patients.

Keywords: *merkel cell carcinoma, young, healthy.*

GJMR-F Classification: *NLMC Code: WP 460*

THE IMPORTANCE OF DIAGNOSIS AND SPECIALIZED TREATMENT IN MERKEL CELL CARCINOMA CASE REPORT IN A YOUNG HEALTHY WOMAN LITERATURE REVIEW AND BRIEF UPDATE ON APPROACH

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The Importance of Diagnosis and Specialized Treatment in Merkel Cell Carcinoma: Case Report in a Young Healthy Woman, Literature Review and Brief Update on Approach

A Importância do Diagnóstico e Tratamento Especializado no Carcinoma de Células de Merkel: Relato de Caso de Mulher Jovem Saudável, Revisão de Literatura e Breve Atualização sobre Abordagem.

Cristina da Silva, Liliane α & Regazzini, Rosana Cardoso de Oliveira σ

Resumo- O carcinoma de Células de Merkel (CCM) é extremamente raro e agressivo, com sobrevida global de 40% em 5 anos. Observa-se, no meio médico não oncológico, grande dificuldade na abordagem correta desta patologia. Relatamos o sexto caso de CCM em paciente jovem (19 anos), saudável descrito na literatura médica e que foi por 2 vezes abordada para cisto sebáceo, evoluiu com progressão local da doença, necessidade de maior área de ressecção oncológica e, após terapia adjuvante, segue livre de doença. Apesar de ser uma neoplasia extremamente rara, a terapêutica não deveser subestimada pelo meio médico, uma vez que, devido a agressividade e mortalidade, a abordagem oncológica correta resultará em aumento da sobrevida livre de doença para estes pacientes.

Palavraschave: *carcinoma de células de merkel, jovem, saudável.*

Abstract- Merkel Cell Carcinoma (MCC) is extremely rare and aggressive, with an overall survival of 40% in 5 years. The non-oncological physician has large difficulty about the correct approach of this pathology. We report the sixth case of MCC in a young healthy patient (woman, 19 years old) described in the medical literature, who was treated twice for sebaceous cyst, evolved with local disease progression, needed a larger resection and, after adjuvant therapy, remains no tumor recurrence. Despite being an extremely rare neoplasm, therapeutics should not be underestimated by non-oncological physician because this cancer is too aggressive, and the correct oncological approach could result in increased progression-free survival for these patients.

Keywords: *merkel cell carcinoma, young, healthy.*

I. Introdução

O carcinoma de Células de Merkel (CCM)é extremamente raro e agressivo, correspondendo a segunda causa de morte por câncer de pele, após melanoma.[1-5]Nas últimas décadas, avanços médico-científicos objetivaram compreender a fisiopatologia desta neoplasia[3]. Nos Estados Unidos, opoliomavírus está associado a cerca de 80% dos casos de CCM. Já na Austrália, esta associação corresponde a aproximadamente 25% dos casos. Para todos os casos de CCM, incluindo os casos não associados ao poliomavírus, idade avançada, exposição aos raios ultravioleta (UV) e imunossupressão são importantes fatores de risco para o desenvolvimento desta neoplasia[3].

Por ser uma neoplasia rara e agressiva, cuja sobrevida global é de 40% em 5 anos[4], observa-se, no meio médico não oncológico,grande dificuldade na abordagem correta desta patologia[5].

Ao retratar esta dificuldade de abordagem, este estudo pretente auxiliar o meio médico, com uma breve atualização do manejo do Carcinoma de Células de Merkel.

Relato de Caso: LBD, 19 anos, feminina, saudável e sem patologias prévias, com nodulação, de crescimento acelerado, em região escapular direita (Figura 1), desde 2017, associado a desconforto local ao decúbito dorsal. Procurou unidade básica de saúde, em 2017, quando foi diagnosticada com cisto sebáceo dorsal esubmetida a drenagem local, sem sucesso. Devido a progressão e incômodo local, a paciente retornou à unidade básica de saúde, sendo então direcionada à Cirurgia Geral somente em outubro de 2018 e, em novembro de 2018, submetida à ressecção da lesão dorsal, cujo laudo histopatológico foi compatível de Carcinoma de Células de Merkel, com margem anterior e posterior comprometidas pela neoplasia(Figura 2). Em dezembro de 2018, foi encaminhadaaoHospital Oncológico do Interior de Minas Gerais/Brasil,eobservada,em região escapular direita, cicatriz de cirurgia em formato de cruz medindo cerca de 5,0 X7,0 cm, com deiscência de área central e presença de lesão nodular subcutânea, medindo cerca de 2 cm de diâmetro, sob cicatriz cirúrgica prévia

Author α: Surgeon Oncologic, master student at University of State of São Paulo, Campus of Ribeirão Preto, Brazil.
Author σ: Clinic Oncologist, Passos'sCancer Regional Hospital, Brazil.
e-mail: dralilianesilva@gmail.com

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(Figura 3) e sem linfonodomegalias ao exame físico. Os exames de estadiamento solicitados não evidenciaram lesões à distância e imunohistoquímica confirmou diagnóstico prévio, sendo, por isso, indicada ressecção ampla da lesão residual em dorso à direita e biópsia de linfonodo sentinela. Na admissão do bloco cirúrgico, em janeiro de 2019, observou-se doença locorregional avançada (Figura 4), medindo cerca de 15,0 X15,0 cm. Diante desta apresentação, a equipe indicou ressecção higiênica seguida de quimio e radioterapia adjuvante.(Figura 5 e 6).O histopatológico final foi compatível com carcinoma de pequenas Células de Merkel, infiltrando o subcutâneo e músculo estriado, com margens cirúrgicas livres. A terapia adjuvante foi composta por quimioterapia, com 6 ciclos de cisplatina eetoposídeo, e por radioterapia a 50Gy, 33 sessões.Até o momento, exames de segmentonão revelaram doença à distância.

II. Discussão

Em 1875, o patologista alemão Merkel descreveu, pela primeira vez, um tipo celular complexo, composto de axônios sensoriais, grânulos neuroendócrinos, junções desmossomais e queratoinócitos, presente na camada basal da pele, folículos capilares e mucosa oral. Posteriormente este tipo celular passou a ser denominado como Células de Merkel[6].

O Carcinoma de Células de Merkel (CCM), descrito pela primeira vez em 1972 por Toker[6],é atualmente definido como um tumor neuroendócrino, extremamente raro, de rápida progressão, alta mortalidade emaior prevalência a partir da sexta década de vida[3-8], com escassos relatos de ocorrerencia em pacientes jovens[6,8-11].

A associação com o poliomavírus se deve ao fato do vírus integrar seu DNA viral ao DNA das células do hospedeiro, o que, em alguns pacientes, pode resultar em expressão oncogênica aberrante nas Células de Merkel[1-3]. No entanto, hoje já se sabe que a inativação do p53 também pode estar associado a patogênese do CCM[1-3].Além disso, já está cientificamente comprovado que a radiação ultravioleta é capaz de danificar o DNA humano, e este dano, em pacientes poliomavírus negativo,está associado ao desenvolvimento desta neoplasia[1-3].

Clinicamente o tumor se apresenta como nódulo indolor vermelho ou rosado, de crescimento acelerado, geralmente em áreas expostas ao sol, mas pode ocorrer em mucosa ou folículo piloso[1-11]. Mundialmente disseminada, a regra do AEIOU – nódulo assintomático, de expansão rápida, em paciente Imunossuprimido, idade maior que 50 anos (old)e local de exposição aos raios UV e pele clara – tem auxiliado no diagnóstico clínico de aproximadamente 89% dos Carcinomas de Células de Merkel, uma vez que os pacientes portadores desta neoplasia apresentam ao menos 3 destas 5 características[3].Diversos autores[1,2,7,12,13] afirmamque o estado imunodeprimido do paciente o predispõe à infecção pelo poliomavírus. Assim sendo, as potologias associadas à idade avançada são entendidas como imunodepressivas e por isso, os pacientes idosos apresentam maior registro de incidência desta rara neoplasia, quando poliomavírus positivo[1,2,7,12,13]. No entanto, apesar de rara, a ocorrência em pacientes com menos de 50 anos existe e é igual a 5% dos casos. Destes, a grande maioria apresentam-se polimavírus positivo devido a imunodepressão[6,8-11]. Em revisão de literatura, apenas 5 casos de Carcinoma de Células de Merkel, em paciente jovem saudável, foram descritos na literatura (Tabela 1).

Todos estes 5 casos demonstram que a identificação e a abordagem oncológica é imprescindível para a evolução do caso. De modo geral, o manejo oncológico desta neoplasia preconiza a realização, quando possível, de ressecção alargada, com cerca de 2cm de margens microscopicamente livres da neoplasia, e biópsia do linfonodo sentinela[3,6,8-11]. A radioterapia e quimioterapia adjuvantes contribuem para evitar a recidiva tumoral, mas não estão indicadas como monoterapia isolada sem cirurgia[3,12-13].Neste relato de caso, o atraso para o encaminhamento oncológico resultou em progressão local da doença e, consequentemente, maior área de ressecção e sofrimento tecidual.

Como a recorrência, em 90% dos casos, ocorre nos primeiros 3 anos, o NCCN recomenda que o segmento oncológico, após o tratamento término do esquema adjuvante, seja a cada 3-6 meses nos 2 primeiros anos após diagnóstico e, posteriormente, a cada 6-12 meses[12]. A cada consulta de segmento oncológico o paciente deve ser submetido a exame físico com palpação linfonodal, e um exame radiológico deve ser solicitado conforme avaliação caso-a-caso,se clinicamente indicado. Para pacientes de alto risco de recidiva, avaliações de rotina com tomografia computadorizada e/ou PET-CT podem ser consideradas anualmente até 5 anos. Se a recorrência locorregional for diagnosticada, um reestadiamento completo é obrigatório[2,7,12].

III. Conclusão

Apesar de ser uma neoplasia extremamente rara, cuja ocorrência em paciente jovem saudável é ainda mais rara, seu diagnóstico e abordagem não devem ser subestimados pelo meio médico, uma vez que, devido a agressividade e mortalidade, a abordagem oncológica correta em resultará aumento da sobrevida livre de doença para estes pacientes. Este relato estimulou o desenvolvimento de um estudoprospectivo, atualmente em andamento, destinado a capacitar profissionais de saúde no reconhecimento oncológico precoce.

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Conflito de Interesse

Não existe conflito de interesse.

Tabela 1: Jovem saudável diagnosticado com Carcinoma de Células de Merkel - Revisão de literatura

Autor/ Referência/ Ano	Idade	Gênero	Topografia da lesão	Estadia-mento Inicial	Primeira abordagem	Estadiamento após abordagem oncológica	Segunda abordagem	Tratamento adjuvante	Prognóstico
SudeendraPrabhu, R.S. Smitha, V.A. Punnya, [9], 2009.	28	Masculino	Mucosa oral (alveolar)	IIA	Ressecção alargada (mandibulecto-mia) com esvaziamento cervical			Radioterapia	Sem evidência de doença após 18 meses de segmento
Christian R. Halvorson et al, [10], 2011.	33	Feminino	Face	I	Biopsia incisional por dermatologista	I	Ressecçãoalargada	Radioterapia por 6 semanas	Sem evidência de doença
SaeedMarzban,[11] 2011	17	Masculino	Regiãooccipital	I	Biopsia excional com cirurgião geral	IV	Ressecçãoalargada	Óbito três dias após a ressecção alargada	
Roy S, Das I, Nandi A, Roy R., [6], 2015.	15	Masculino	Mucosa oral	IIIB	Biopsia por tru-cut	Ressecção alargada com esvaziamento cervical	QT Neoadjuvante cyclophosphamide, doxorubicin and vincristine	QT adj cyclophosphamide, doxorubicin and vincristine + RxT 60Gy 30 frações por 6 semanas	Sem evidência de doença 9 meses após início do segmento
Ha NH et al, [8], 2018.	35	Masculino	Lóbulo da orelha	I	Excisão pela Cirurgia Plástica	IIIB	Ressecção alargada com esvaziamento cervical unilateral		Sem evidência de doença 33 meses após início do segmento

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Figura 1: Aspecto inicial da lesão dorsal - Foto cedida pela paciente

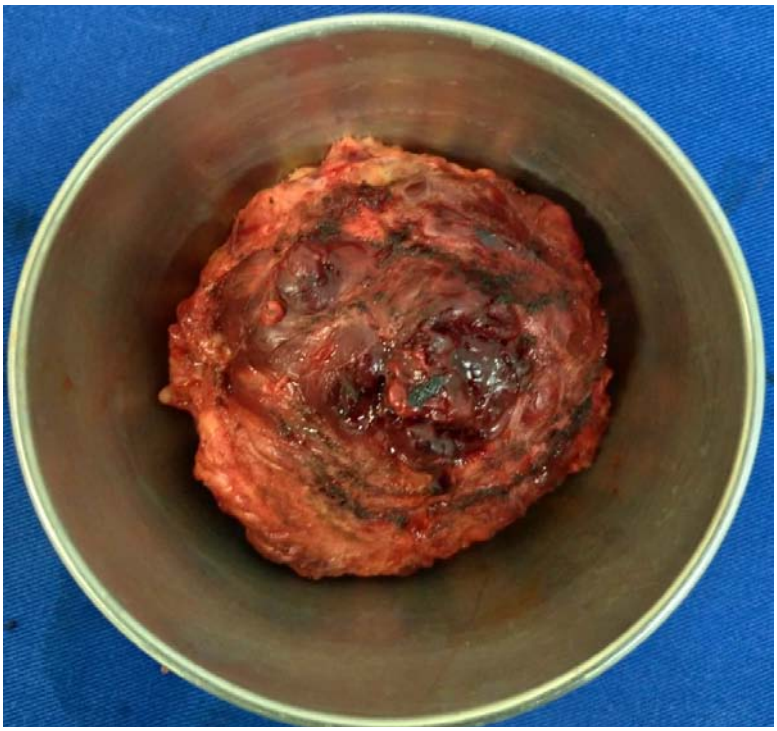


Figura 2: Produto de ressecção realizada pelo cirurgião geral – Foto cedida pela paciente

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Figura 3: Aspecto quando a paciente chegou à cirurgia oncológica



Figura 4: Aspecto da lesão em bloco cirúrgico

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Figura 5: Superior Marcação cirúrgica. Inferior Esquerda Produto de Ressecção Oncológica. Inferior Direita Defeito final Pós Ressecção Oncológica



Figura 6: Da esquerda para direita: Pós Operatório Imediato, 20 dias de pós operatório, 70 dias de pós operatório

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

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GJMR-F Classification: NLMC Code: WO 600

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Dr. María de Lourdes Vallejo Villalobos [α], Dr . Ángeles Quintero Ina [σ], Dr. Andrea Blanco Silva [ρ] & Dr. Dennice Janete Felix Sifuentes [ω]

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I. Introduction

Christian Bernard performed the first human heart transplant in 1967. Currently, the average frequency of this procedure is approximately 1% of the population with heart failure. Heart transplantation is the definitive treatment of advanced heart failure and has been shown to improve results and long-term survival (1, 4)

Currently, between 5000 and 1000 heart transplants are performed worldwide and this is increasing, on July 21, 1988, Dr. Rubén Argüero et al. They perform the first heart transplant in Mexico at the Specialty Hospital of the Medical Center "La Raza" of the Mexican Social Security Institute (1, 5, 11). The 1-year survival rate for heart transplant recipients is close to 80-90% and is increasing every year and 5-year survival is 65% (1, 2, 11). Heart transplanted patients are also exposed to trauma and accidents. The most common causes of trauma were car accidents and falls, which is why as anesthesiologists we must know the physiological and pharmacological problems of immunosuppression, the risks of infection, the potential for rejection and the behavior of these patients to anesthetic drugs (1.8). Transplanted patients are immunosuppressed and are more susceptible to the effects of soft tissue damage and poor bone healing. These patients should receive the same initial resuscitation as any trauma victim. And choosing the most appropriate anesthetic technique is a challenge, so it must be planned and analyzed before the surgical procedure minimizing hemodynamic changes. (2, 3, 4, 5)

II. Clinical Case

This is a 24-year-old male with a preoperative diagnosis of a bloody area in the left tibial region secondary to a bicycle fall in October 2018, which is programmed electively for taking and applying cutaneous auto grafting and allograft placement in the donor area. Which has the following important background; Post-operative cardiac transplant at 23 years due to heart failure and dilated cardiomyopathy secondary to vincristine, presenting after 15 days post-transplant acute pulmonary edema and pleural effusion so they put water seals on both sides, renal failure managed with hemodialysis from 23 years , at 6 months of extrauterine life, he presented leiomyosarcoma in his left shoulder without complications, which on the day of his pre-anesthetic evaluation used the following drugs: Sirolimus 1 mg per day. Mycophenolic acid 1 tablet every 12 hrs, spironolactone 25 mg every 12 hrs, furosemide 40 mg every 24 hrs, propanolol 20 mg every 12 hrs, pravastatin 10 mg every 24 hrs, omeprazole 40 mg every 24 hrs and prednisone 5 mg orally every 24 hrs. With Cushing syndrome fascie, weight 62 Kg Height: 158 cm with the following laboratory report hemoglobin 12.6 mg / dl, hematocrit 41% platelets 233000, leukocytes 6100, Glucose 80 mg / dl, creatinine 0.8 mg / dl, Prothrombin time 14 sec Thromboplastin time 31.9 sec, fibrinogen 511mg / dl Na 140 meq K 3.6 meq. Electrocardiogram: Sinus rhythm Heart rate 100 per minute with mild hypertrophy of the right ventricle, no arrhythmias, no ST elevation, absence of q waves, no ventricular extrasystoles. Echocardiogram: Preserved

Author α: Chief Service Anesthesiologist. High Specialty Medical Unit Traumatology Hospital "Dr. Victorio de la Fuente Narváez" IMSS (Mexican Social Security Institute. e-mail: lourdes2vv@hotmail.com

Author σ: Anesthesiologist and Algologa. High Specialty Medical Unit Traumatology Hospital "Dr. Victorio de la Fuente Narváez" IMSS Mexican Social Security Institute.

Author ρ: Resident Physician of Anesthesiology Third year National Medical Center. IMSS (Mexican Social Security Institute).

Author ω: Resident Physician of Anesthesiology Third year La Raza National Medical Center. IMSS Mexican Social Security Institute.

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systolic function, 70% ejection fraction, no data on right ventricular dysfunction or pericardial effusion. Sirolimus levels of 12.4 ng / ml. Cardiac catheterization without pulmonary hypertension and with coronary arteries without obstructive lesions.

Patient is admitted to the operating room after authorization of informed consent is monitored, Blood Pressure 130-80 mmHg, Heart Rate 103 per minute, Respiratory Rate 18-22 breaths per minute, O2 Saturation 96-97%. Ondasetron 4 mg is administered intravenously, sedation with midazolam 2 mg intravenously, fentanyl 65 mcg intravenously, Oxygen is placed through nasal tips 3 liters per min, aseptic and antisepsis of the inguinal region is performed, subsequently scanned with Sonosite Edge II ultrasound with transducer linear 13-6 Hz with stimuplex for neurostimulation with 0.3-0.5 mA 0.3 ms 2 Hz, same region is located femoral artery and vein with pulsed doppler and doppler, femoral nerve is identified, skin is infiltrated with 2 cc of 1% lidocaine, 50 mm echogenic needle is inserted in the plane reaching the femoral nerve sheath and 20 ml of 2% ropivacaine is administered for surgical anesthesia, without presenting transanesthesia complications, latency 7 minutes satisfactory analgesia, cleaning and debridement of bloody area and taking of skin graft of left thigh approximately 5 cm and placed graft in bloody area of left tibia, as well as placement of aloinjerto of cultured skin (EPIFAST) in donor area.

No changes in hemodynamic parameters were observed after the administration of sedation, or after the administration of local anesthetic, buprenorphine was administered 130 mcg intravenously for postoperative analgesia, see Fig 1 . During his recovery stay he did not present significant changes in hemodynamic parameters, neither nausea nor vomit. Analgesia in the manipulated region was maintained for 6 hrs.

PARAMETERS	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Heart Frecuency	103 for min	103 for min	101 for min	101 for min	102 for min	101 for min
Breath Frecuency	19 for min	20 for min	22 for min	21 for min	21 for min	22 for min
Aretial Presion	130-80 mmHg	130-85 mmHg	130-85 mmHg	130-85 mmHg	130-80 mmHg	130-80 mmHg
O2 Saturatión	97%	97%	96%	96%	96%	96%
EVA	0	0	0	2	3	3

Figure1: Hemodinamics parameters



Figure 2: Technique for performing ultrasound-guided femoral nerve block in the left inguinal region

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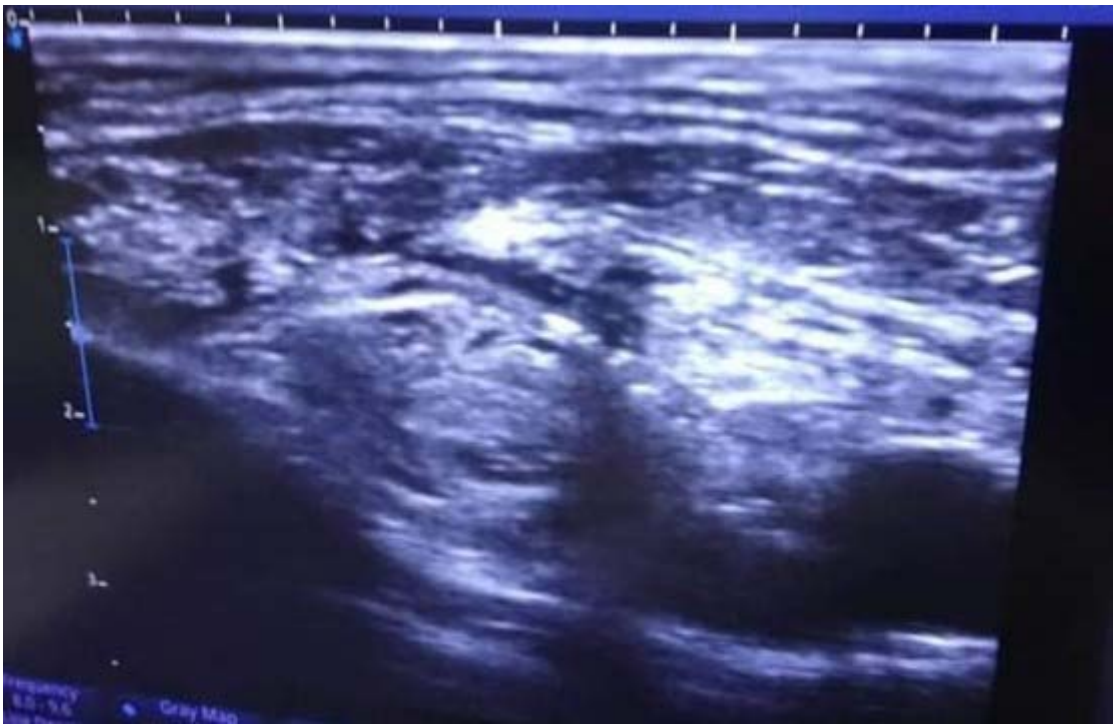


Figure 3: Econoanatomic image of the femoral nerve of the left inguinal region, observing femoral artery and femoral nerve resting on the iliopsoas muscle

III. Discussion

Patients with advanced HF before transplantation show different degrees of systolic or diastolic dysfunction (or both). The first leads to a decrease in ejection fraction and cardiac output, the second results in higher filling pressures. The reduction in cardiac output results in a reduction in the supply of blood, oxygen and nutrients to the terminal organs, which is only aggravated by partial venous congestion. After the cardiac output improves, and perfusion of the final organ is largely restored. But the transplant does not completely restore the patient to a non-pathological state. (1, 3.4)

The heart in normal conditions is innervated by sympathetic and parasympathetic fibers of the autonomic nervous system. And the sympathetic innervations towards the heart comes from the cervical ganglia and the upper thoracic sympathetic chain (T1-T4), the branches of the vagus nerves contribute to parasympathetic entry. The cardiac plexus, containing the sympathetic parasympathetic and postganglionic preganglionic fibers, is found at the base of the heart. The autonomic nervous system is the conduit through which it provides a supply of visceral sensory fibers to the pericardium (1, 3, 9).

During the transplant, the postganglionic neural axons that innervate the heart are transected, which is why it is considered a denervated heart. The cardiac reserves of nor epinephrine are depleted and the autonomous influence on the heart ceases. This includes the response to baroreceptors. Afferent denervation prevents vasoregulatory responses by means of the renin-angiotensin axis, and the perception of pain secondary to ischemia (angina) is lost. (4, 5) That is why we chose a nerve block for our patient to avoid as much as possible hemodynamic changes that could cause decreased cardiac output.

Coronary allograft vasculopathy (CAV) has been an important impediment to the long-term survival of heart transplant recipients, and one third of the patients developed atrio-ventricular communication after 5 years. Atrioventricular arrhythmias are rare but ectopic. Extrasystoles are common. The presence of arrhythmias generally indicates a severe acute rejection of coronary heart disease allograft (4, 5) In the case of our patient, he entered with a sinus rhythm which he maintained throughout the perioperative period.

Regional anesthesia in this group of patients represents risks (epidural or spinal technique), since coagulation studies and platelet count should be normal. Patients taking azathioprine or antithymocyte globulin (ATG) may have thrombocytopenia, which increases the risks associated with central neural block. In neuroaxial blockade, the appropriate level of blockage should be taken into account, since a level of blockage that is too high can inhibit sympathetic nerves and cause vasodilation that is unfavorable for a transplanted heart; a very low level is not suitable for surgery since the resulting pain may cause an increase in myocardial oxygen consumption. (1,5) Azathioprine withdrawal in the perioperative period in patients taking warfarin may precipitate bleeding, since bleeding 6-

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mercaptopurine, the immediate metabolite of azthioprine, induces liver micro enzymes that metabolize warfarin. Local anesthetics such as bupivacaine can have cardio toxic effects at a conventional dose in these patients if they also have impaired renal function. (1) By choosing a nerve block for our patient, we minimize the risk of complications due to coagulation disorders, although were not present in the same should be avoided, using ropivacaine further reduces the risk of cardiac arrhythmias.

Peripheral nerve block has taken great importance in recent years and with the advances in technology such as the use of ultrasound to guide them have increased the safety and complications of both neuroaxial anesthesia and general anesthesia, nerve block Ultrasound guided femoral, taking the femoral artery and vein as a reference, the transducer is placed transversely on the anterior aspect of the anterior thigh below the inguinal ligament see Fig 2, on the femoral artery identifying the femoral artery, femoral vein, the iliac muscle, fascia lata, iliac fascia, and Sartorius muscle. The femoral nerve is below the iliac fascia at the angle between the iliac muscle and the femoral artery, see Fig 3, flat techniques are preferred to visualize the path of the needle and it has been used successfully in hip and surgery. Knee for post-surgical analgesia since it grants post-surgical analgesia on the anterior thigh and knee (12, 13). That is why we decided to implement it in the management of skin loss lesions in reconstructive plastic surgery.

When a general anesthesia is chosen, it should be taken into account that the transplanted heart does not have sympathetic, parasympathetic or sensory innervation since it was lost in the transplant surgery, and the loss of vagal influence causes a resting heart rate higher than normal (91-101 bpm). Two P waves can be observed so there is a P: 1 that represents the SA of the recipient node and the other one that represents the donor SA node. Although the innate pacemaker remains intact from the original heart, its electrical activity cannot be conducted through the suture line. (1,3)

Intrinsic mechanisms and coronary self-regulation remain intact, carotid sinus massage and Valsalva maneuver have no effect on heart rate, there is loss of cardiac bar reflexes and loss of sympathetic response to laryngoscopy and tracheal intubation. The denervated heart may have a more dull heart rate response at an anesthetic depth or inadequate analgesia. In the denervated heart, the response of catecholamines is different from that of the normal heart because intact sympathetic nerves are required for the normal uptake and metabolism of catecholamines. The transplanted heart may respond to direct-acting drugs (eg, sympathomimetics) (5, 10, 11).

Epinephrine and norepinephrine have an increased inotropic effect on heart transplant recipients. Both have a greater proportion of β to α or inotropic to vasoconstrictor. Dopamine acts by the release of norepinephrine and is a less effective inotropic in the denervated heart (1, 4, 5). Isoproterenol and dobutamine have similar effects on denervated and normal hearts. Therefore, both are effective inotropics in the denervated heart and are frequently used Ephedrine, has reduced responses on blood pressure and heart rate. There is still a response of venous contrition reflects hypotension. Therefore, intravascular volume is even more important. Circulating catecholamines cause a delayed increase in rate and contractility (5). The Frank-Starling mechanism remains operative in the transplanted heart (4, 10, 11) Patients with a transplanted heart are "dependent on preload." (3) These patients are at high risk of presenting atrial flutter or fibrillation in a few years, this is due to the onset of reinnervation, complete neuronal control is achieved after 15 years of transplantation (5) First degree atrioventricular block is frequent, and up to 30% have a right branch block (4)

Vagolytics, such as atropine, are ineffective in increasing heart rate, other positive chronotropic medications, such as ephedrine and is oproterenol. Inhaled anesthetics have myocardial depressing properties, they are well tolerated unless there is significant heart failure, dopamine is an ineffective inotropic. Epinephrine / nor epinephrine may have exaggerated beta-mimetic effects on heart rate because the increase in blood pressure will not lead to a decrease in heart rate through the baroreceptor reflex (i.e., the efferent vagus nerve). Implanted mechanical pacemakers normally work in heart transplant recipients since the heart cables are placed directly in the myocardium (2, 3, 4,5). In the case presented, there was no need to use any vasoactive drug since the patient had hemodynamic stability.

Trans esophageal echocardiography has a very important role prior to surgery, invasive hemodynamic monitoring in heart transplant recipients is performed according to the type of surgery and the hemodynamic state of the patient (3, 4,5) Some authors prefer general anesthesia , since there is the possibility of an altered response to hypotension after spinal or epidural anesthesia. In our patient we chose a safer technique that was ultrasound-guided neurostimulation-guided femoral nerve block to maintain surgical anesthesia and optimal postoperative analgesia.

Preoperative evaluation is of great importance to determine the safest anesthetic application to the post-transplant patient. Professionals should focus the evaluation on the current function of the heart taking into account the level of exercise tolerance, evaluation of the transesophageal echocardiogram and stress test results, and / or should request a cardiology assessment. An echocardiography should be performed to detect Vasculopathy that is common in patients more than 1 year after transplantation and is the most frequent

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cause of repeated transplantation or death after 1 year (4, 5,6). Close communication must be made between the surgeon and the anesthesiologist, to detect preoperative arrhythmias that occur in 5% of patients, complete blood count, renal function tests, liver function tests, serum electrolytes as well as coagulation tests. Cyclosporine should be administered 4-7 days prior to surgery to maintain therapeutic levels. As well as the administration of prednisone or methylprednisolone (1. 4, 5)

Patients with heart transplants often receive corticosteroid therapy, it is important to provide more glucocorticoids to those patients who present with chronic corticosteroid use (5 mg / day of prednisone or equivalent). (one)

IV. Mmunosuppressors to Avoid Rejection

The immunosuppressive drugs available today can be classified into:

Inductors:

OKT3, thymoglobulins and antagonists of IL-2 receptors (daclizumab and basiliximab). Anticalcineurinics:
Cyclosporine and tactrolimus.
Antimetabolites or purine synthesis inhibitors:
Mycophenolate mofetil and azathioprine.
Corticosteroids
Antiproliferatives
Sirolimus and everolimus.

These drugs can be combined in various ways, constituting immunosuppression guidelines, which can be classified according to their indication: induction, maintenance and rejection. r purpose to block the immune response in the initial period of transplantation (when it is more intense), but with the cost of a higher incidence of infections and neoplasms. (14) In the case of our patient he was being treated with sirolimus and steroids.

V. Transanesthetic

The objective of surgical intra-management of patients with heart transplants who undergo non-cardiac surgery is to avoid hypotension, vasodilation and acute decrease in preload due to the importance of diastolic volume to maintain cardiac output (8). Standard monitoring is indicated and varies according to the type of surgery, anesthesia technique and the patient's condition. Invasive CVP and arterial monitoring were not used in this case due to the patient's preoperative period as it was thermodynamically stable, the surgical risk was minimal in this case given the anesthetic management that was performed (3,4,8).

Side effects of immunosuppressive medications, which could have an impact on the management of anesthesia. The use of medications that produce active metabolites such as morphine, meperidine and non-depolarizing muscle relaxants should be prevented. Any anesthetic that inhibits or induces CYP-450 can affect the plasma concentration of tacrolimus. Barbiturates induce CYP-450, therefore lowering the blood level of tacrolimus. Propofol inhibits CYP-450, respiratory failure has been observed in approximately one third of patients with the administration of tacrolimus and propofol (4, 5, 6,7) Cyclosporine has shown a similar behavior with barbiturates, fentanyl and is oflurane. Infectious complications are an important cause of morbidity and mortality; the causative agents associated were bacteria (43.6%), viruses (41.7%), fungi (10.2%), P pneumocyst is carinii (4%) and protozoa (0.6%). (3) Oral to nasal intubation is preferred since there is a risk of infection with the latter caused by nasal flora. Airway obstruction may occur in patients with lympho proliferative processes and diabetes (5), such as In the case of our patient who presented leiomyosarcoma in the left shoulder, cyclosporine can lead to gingival hyperplasia and cause bleeding (4), non-steroidal anti-inflammatory drugs should be avoided to control pain due to the risk of bleeding, so in our patient we use opioids for its management. (5)

The dose of benzodiazepines should be reduced when the patient consumes immunosuppressants as they increase their potency. Atracurium and cisatracurium are preferred since these are safer in patients with liver and kidney disorders. Neostigmine generally has no effect on heart transplantation. But precautions should be taken when reinnervation begins (> 1 year post-transplant) because there is evidence of bradycardia and cardiac arrest with neostigmine despite the concurrent use of an antimuscarinic agent. Cyclosporic increases the analgesic effect of fentanyl (4.5.6).

In the case of our patient, the presence of clinical signs of Sepsis such as elevated temperature, elevated white blood cells, cell count and the presence of chills was monitored.

VI. Postoperative Care

Preload status, renal function and infection prevention should be monitored. Immunosuppressants should be continued after the operation and the blood level should be monitored. In the case of our patient, the healing was followed by accelerating it in the donor area with the application of cutaneous allograft which was removed after 5 days presenting complete re-capitalization and without presenting infection data. And the integration of the skin graft in the traumatized area was observed at 7 days (5, 7.9).

VII. Conclusions

The anesthesiologist should have a solid knowledge about the newly established functions of a transplanted heart, its specific perioperative care considerations and the pharmacological effects of

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immunosuppressive medications, the importance of preload dependence; administering direct vasoactive drugs if necessary; and awareness of the infectious risk, potential for rejection, and the possible side effects of an immunosuppressive regimen are very important to prevent perioperative complications (5,14). So the success of the anesthetic surgical procedure is due to the maintenance of the preload, the sinus rhythm and after load. (4,8) In the clinical case, we present a safer and more effective alternative for the management of traumatic injuries in reconstructive plastic surgery without significant changes in hemodynamic parameters and with adequate postoperative analgesia and without peri anesthetic complications (12,13)

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Transmission and Prevention of Wuhan Coronavirus Disease 2019 (COVID-19) During Minimum Sunspot Number

By Tai-Jin Kim

Abstract- Porpoises, infected by Cetacean Morbillivirus from the feces of humpback whales in the East Sea, swam along the Yangtze River to reach Dongting Lake. Infected porpoises could be stranded and moved to Huanan Seafood Wholesale Market. Wuhan is low-lying and susceptible to flooding from the Yangtze River. Agricultural water in Hubei should prevent the harmful algal blooms for clean water. Sterilization by ultraviolet is recommended in air, water and confirmed patient with dialyzer to recover the Wuhan coronavirus disaster. The vaccine can be developed by culturing blood from CeMV infected porpoises in the Yangtze River or Dongting Lake, along with Wuhan coronavirus confirmed patient blood. Existing MMR Vaccine can be applied to cure the confirmed patient. CO_2 emissions increased continuously with years (R_2 = 0.9497) causing high levels of UVB radiation on the Earth. Due to 11 years cycle of the sunspot number, there can be another dangerous outbreak at Dongting Lake with millions of migratory birds in China in coming years between 2030 and 2032.

Keywords: transmission, prevention, wuhan coronavirus, cetacean morbillivirus, minimum sunspot number.

GJMR-F Classification: NLMC Code: QW 168.5.C8



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Keywords: transmission, prevention, wuhan coronavirus, cetacean morbillivirus, minimum sunspot number.

I. Introduction

Wuhan is located where the Yangtze and Han rivers converge. This low-lying city, the capital of Hubei province, has always been prone to floods. The average elevation of the urban area varies slightly from 20 to 26 m and is lower than the average river water level of the Yangtze River Valley. Wuhan's low-lying geography made it hard for storm water to be discharged into the Yangtze when water levels in the river were high. Wuhan is known as "Sponge City", absorbing excessive rainfall through soil infiltration and retaining it in underground tunnels and storage tanks, only discharging it into the river once water levels there are low enough (WU et al., 2019).

Wuhan is located inland of central China. The city is undergoing a major construction and development stage. Moreover, the industrial structure of Wuhan, as a heavily industrialized city, means that great energy consumption is necessary for economic development (LI, 2019).

Author: e-mail: tjkim@suwon.ac.kr

Wuhan is surrounded by hundreds of lakes, with the Yangtze River passing through the city with the Three Gorges Dam further upriver. Therefore, Wuhan is a good place for migratory birds to stay during the winter season.

Wuhan produces the highest CO_2 emissions due to heavy industries. Therefore, the ozone hole area in Wuhan is high enough not to absorb the ultraviolet radiation, leading to the strong mutation of infectious viruses. The Wuhan coronaviruses is a zoonotic disease, meaning it spread to people from animals. It originated in Huanan Seafood Wholesale Market, where 7 working people died of pneumonia while thousands of people died as a result of human to human transmission. The outbreak was linked primarily to stallholders who worked at the Market (WOODWARD, 2020).

The Wuhan coronavirus outbreak started in November of 2019 and has continued till March of 2020, which was close to the period of the epidemic curve of highly pathogenic avian influenza (HPAI) from November to April as confirmed in data from the World Organization for Animal Health (2017) (KIM, 2018). Symptoms include sore throats, headaches, and fevers, as well as pneumonia-like breathing difficulties.

The purpose of the present study is to show the transmission and the prevention of Wuhan Coronavirus Disease 2019 (COVID-19) during the minimum sunspot number period.

Parameters of carbon dioxide emissions, ozone hole area, sunspot number, harmful algal blooms, Asian dust, porpoise, cetacean morbillivirus, agricultural water purification, Yangtze River, the Three Gorges Dam and migratory bird, were studied to see their effects on the outbreak of COVID-19.

II. Experiment

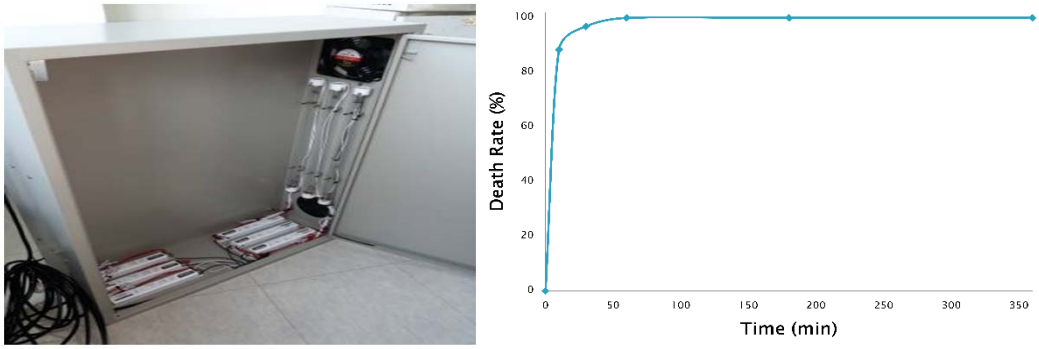
a) *UV Radiation of Indoor Air, Drinking Water and Confirmed Patient*

i. *Indoor Air*

Ultraviolet (UV) radiation was effective in the prevention of the avian influenza virus (KIM, 2018). At the moment, there is no Wuhan coronavirus in New Zealand, Norway, Iceland and Chile, where UV radiation

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is so strong that it causes skin cancer (KIM, 2018). In the present experiment, UV radiation in air indoors was created by six lamps of 50W artificial UV. Fig. 1 showed the UV chamber layout in Fig 1-A while Fig. 1-B showed the time curve of viral death efficiency (%). Within 50 minutes the viral death rate reached almost 100% for the avian virus



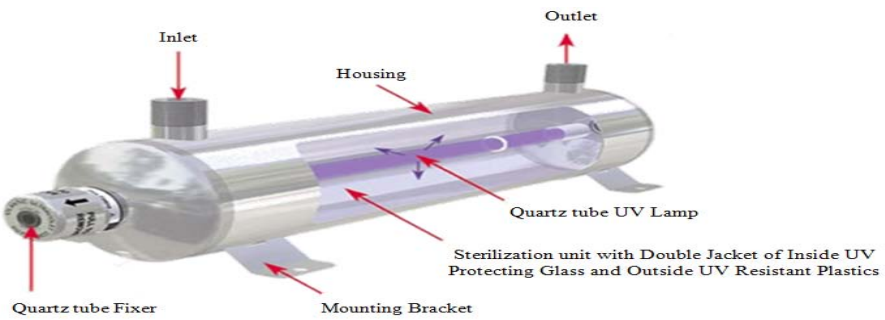
(A) (B)

Figure 1: Experiments for UV radiation with artificial UV lamp at 254nm

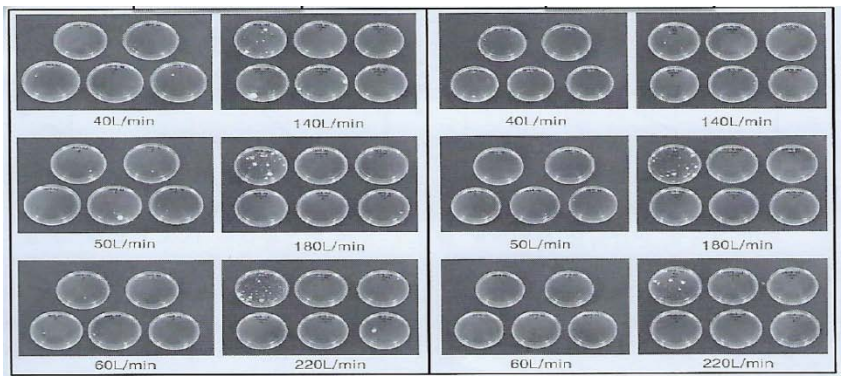
A) UV chamber with six lamps of 50W for indoor air application,
B) Time curve of viral death efficiency (%)

b) Drinking Water

Sterilization of drinking water was undertaken by UV sterilization apparatus (Fig. 2). Serial experiments showed that no microorganism colonies were observed below 60 L/min while the recycle loop showed better efficiency of sterilization than that of common one. Recycle loop allowed the longer duration of UV radiation for enhancement of inactivation efficiency of microorganisms in linear water flow. It was therefore recommended that a recycle loop below 60 L/min was used for efficient sterilization of drinking water.



(A)



(B)

Figure 2: UV sterilization apparatus for drinking water application (KIM, 2018)

A): Layout of tube for drinking water by UV sterilization apparatus.
B): Microorganisms in culture dishes for samples with various flow rates in the UV sterilization apparatus. The results showed that a flow rate below 60 L/min was required to kill microorganisms in drinking water with UV sterilization apparatus.

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c) Confirmed Patient

Blood of the confirmed people was also circulated in the UV sterilization apparatus to see that a flow rate below 60 L/min was good enough to sterilize the infected blood. Therefore, the blood recirculation with UV sterilization apparatus may not only enhance the recovery of the confirmed people from the Wuhan coronavirus but also allow not to be infected again to the coronavirus due to the sterilization of the residual Wuhan coronavirus in the blood stream of the confirmed patient with dialyzer.

d) Asian Dust

Wuhan is the capital of Hubei province with a land area of 8,494 km^2 and a population of more than 10 million. It is a major transport hub with dozens of railways, roads, and expressways passing through the city and connecting to major cities in China and currently is in a boom of construction. It has been estimated that the emissions from industrial activities accounted for 34% of secondary particulate matter, 57% of primary dust, and 45% of total SO_2 emissions in Wuhan (QUEROL et al., 2006). The seasonal patterns of air pollution in Wuhan exhibited strong seasonal distributions with the highest value in winter.

As one of the highest industrial developmental areas in China, Wuhan, has inevitably experienced severe haze induced by the air pollutants (PM2.5, PM10, NO_2, SO_2, O_3, and CO) in recent years (WANG et al., 2017).

The harmful algal blooms (HABs) in Yangtze River, Han River, Dongting Lake, Poyang Lake, Honghu Lake and the Three Gorges Dam (Fig. 6) could have deteriorated the water quality in Wuhan for the recent outbreak of Wuhan coronavirus.

In order to examine the effect of Asian dust on the freshwater, samples of the Asian dust were collected at Anmyon Island (36˚34'3"N, 126˚19'45.6"E) near Seoul in South Korea by air pollution monitoring equipment (Tisch Environmental Inc.). Fig. 3 shows the weekly distribution of iron (Fe) concentration in the Asian dust (red color) and chlorophyll-a in Daechung Lake (blue color) in South Korea from January 2006 to December 2012. Iron concentration was measured by ICP at Korean Basic Science Support Center while chlorophyll-a was determined by the standard process test for water contamination. It was observed that the concentration of chlorophyll-a reached the peak value after Fe supply via Asian dust with a lag time of 11 days. It turned out that Asian dusts enhanced the outbreak of HAB.

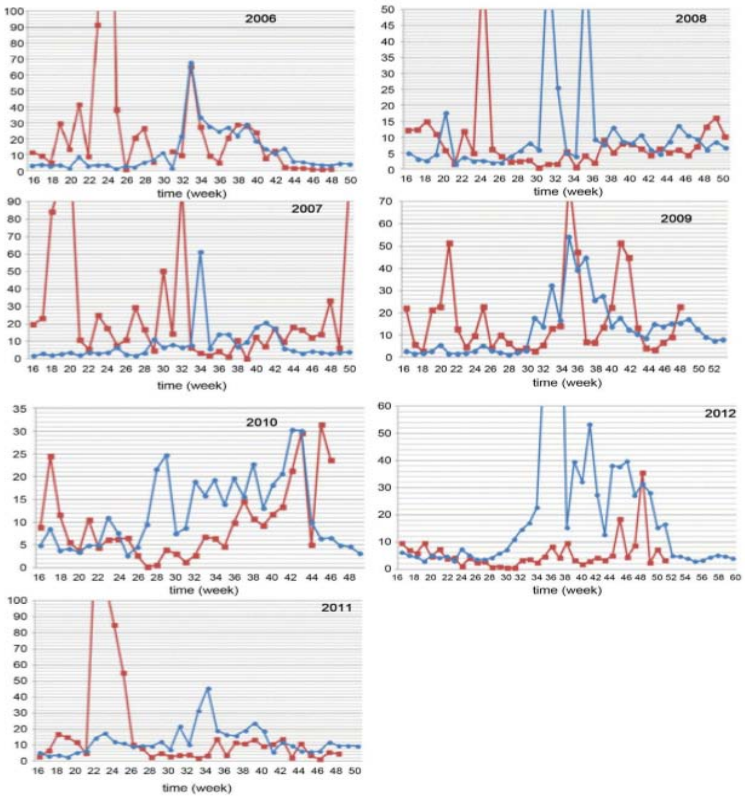


Figure 3: The weekly distribution of Fe concentration of Asian dust (μg/m^3) (-■-) on Anmyon Island and chlorophyll-a (10μg/l) (-■-) in Daechung Lake in South Korea from 2006 to 2012.

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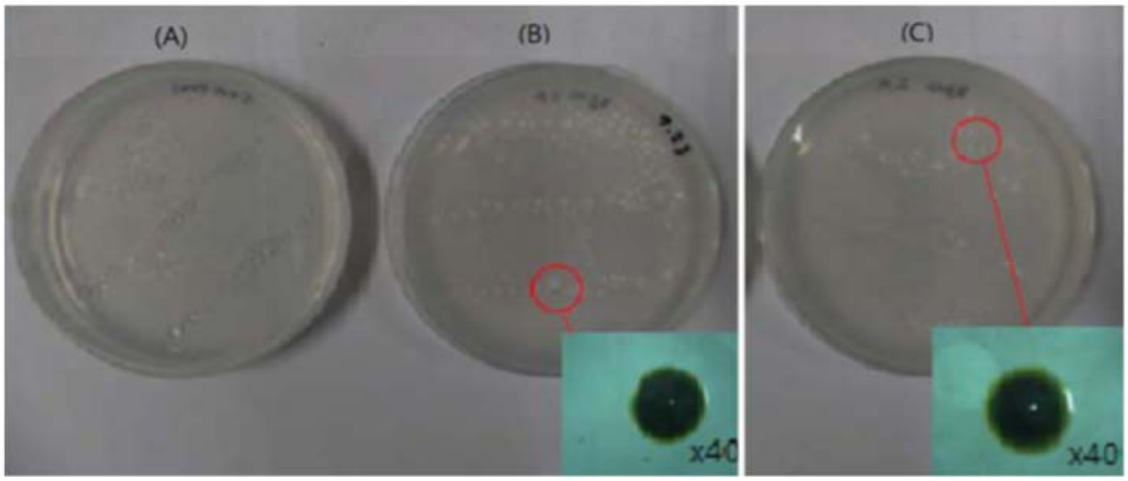


Figure 4: Petri dish cultures at 26℃ left for 14 days for the control without the dissolved Asian dust (A) and with one fold (B) and two folds (C) of the dissolved Asian dust, magnified 40 times (KIM, 2014)

40 times magnification colonies showed the sample with Asian dust, which were in accordance with the result showing the presence of *Antinobacteria, Bacilli, Sphingobacteria* in Asian dust (YAMAGUCHI et al., 2012). It was therefore important to prevent the Asian dust from being deposited on the surface of freshwater in the purification plant for the drinking water for Wuhan citizens.

e) Prevention of Harmful Algal Blooms

Harmful Algal Blooms (HAB) were analyzed to prevent the outbreak of HAB in freshwater. Parameters inducing HAB were sunlight, Aeolian dust, environmental factors (current, pH, dissolved oxygen, food web, turbulence, growth phase), enzyme, iron, nutrients (carbon, nitrogen, phosphorus, sulfur, silicon, minerals) while the critical growth parameter for the outbreak of HAB was iron (Fe). HAB development was halted in freshwater due to the sulfur compounds (H_2S, sulfates) inducing the deficiency of the dissolved Fe in the water. The atomic ratio of N/P is commonly known to be 16/1 in fresh water for HAB. Therefore, phosphorus can be a relatively limiting factor in freshwater. HAB could be prevented by control of growth parameters such as pH, temperature, sunlight, turbulence, nitrogen, phosphorus, iron, and sulfur compounds prior to reaching the early exponential phase of algal growth (KIM, 2018)

Most casualties of the Wuhan coronavirus were observed around Wuhan city, Hubei province, China. There can be a few reasons as follows:

1) The Initial outbreak occurred at the Huanan Seafood Wholesale Market located in downtown Wuhan. 2) Wuhan is surrounded by 164 lakes which are located between the Yangtze River (9m depth) and Han River. Wuhan has an elevation of 30m during floods. Wuhan is known as ''Sponge City'', storing water underground during floods. 3) The Three Gorges Dam (175 m) on the Yangtze River reserves most of the water in Hubei province, as shown in Fig. 5 (LIAN et al., 2014). 4) Many migratory birds, dolphins and porpoises live in Dongting Lake, Poyang Lake and Honghu Lake. 5) Water around the Han River and Yangtze River are used for rice irrigation, which releases the nutrients of nitrogen and phosphate (MAO, 2001). 6) Asian dusts from Taklamakan and Gobi Deserts carry the iron enriched nutrients to the water.

7) Therefore, the water in Wuhan was contaminated by HAB. In fact, an excess level of ammonia- nitrogen has been found in drinking water supplies of more than 300,000 people in Wuhan (CHINA.ORG.CN, 2014).



Figure 5: Location of the Three Gorges Dam (TGD) and sketch map of the study area (LIAN et al., 2014)

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It was evident that the shortage of iron (Fe) in the algal culture reduced the growth of algae, as shown in Fig. 6. It was important to remove the iron from the agricultural water by aeration so that Fe^{2+} is oxidized to Fe^{3+} to be sedimented and filtered to prevent Harmful Algal Blooms (HAB) in the Wuhan and Yangtze Rivers (Fig. 7).

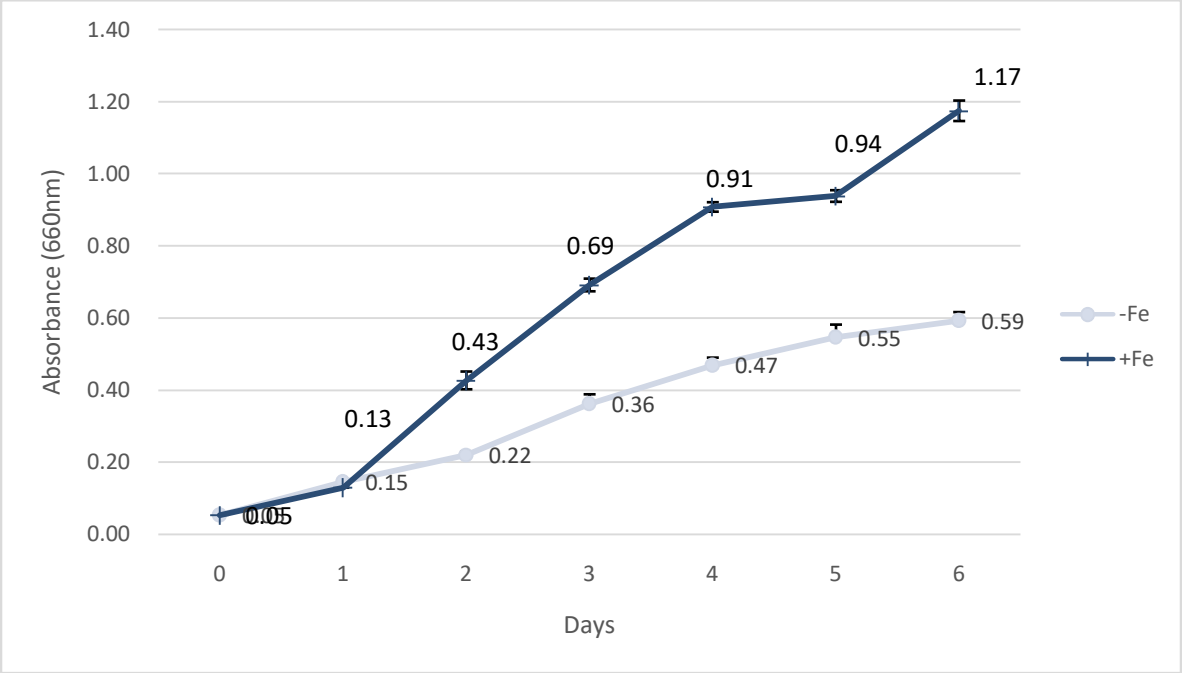


Figure 6: Growth curve of *Chlorella vulgaris* with various JM media; with its own Fe (+Fe, -+-), without its own Fe (Fe, -●-) (Modified from KIM, 2019)

HAB removes oxygen from the water, killing fish and other aquatic life, which then decay and release toxins. Smelling foul, the water cannot be consumed by human and animals (CHINA DAILY, 2018).

The location of the Three Gorges Dam (TGD) is in the center of Hubei province and the Yangtze River and Han River converge in Wuhan, as shown in Fig. 7. Since the first impoundment of the TGD in 2003, HAB has occurred frequently in the near-dam tributaries (LIAN et al., 2014).

It was proposed that the Wuhan coronavirus was caused by the polluted Yangtze, Han Rivers and the TGD with frequent outbreaks of HAB.

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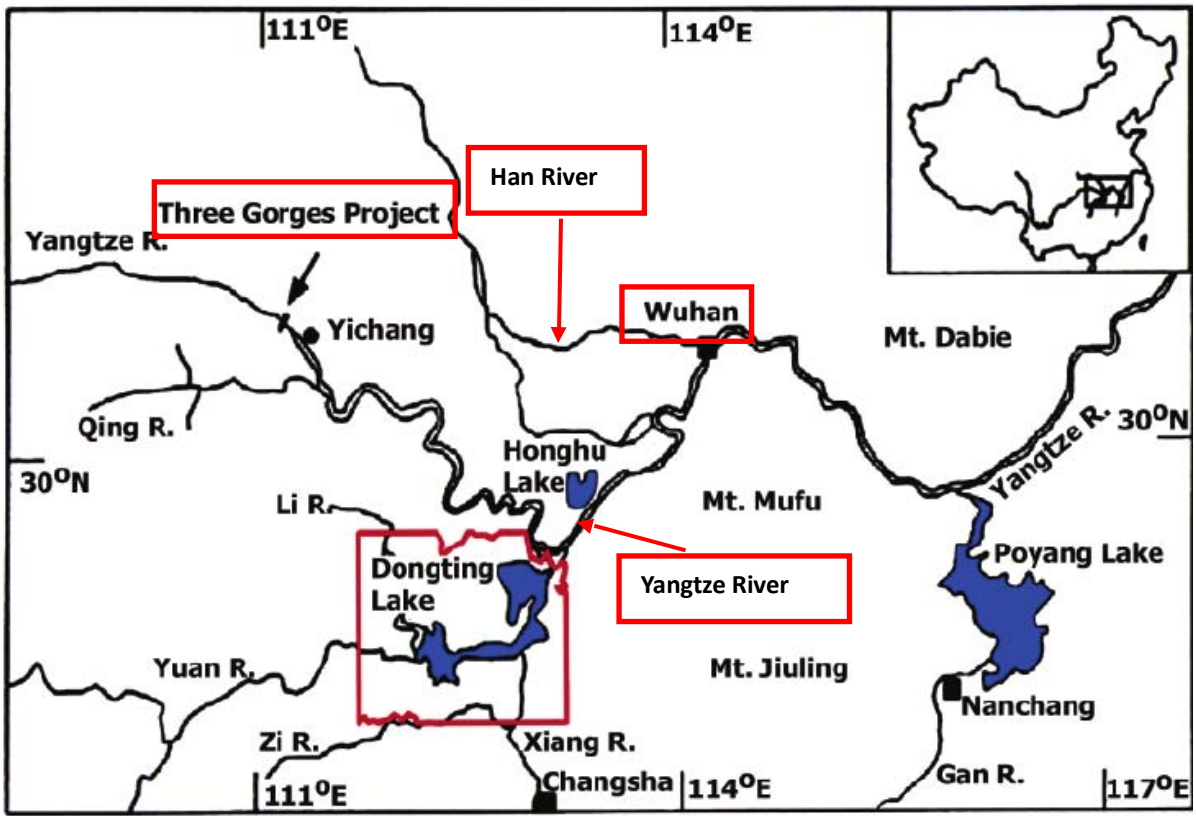


Figure 7: Location of the Dongting Lake region (ZHAO et al., 2005)

In order to protect the water quality from HAB, the Three Gorges Dam flushes the bottom of the Yangtze River. Several water mills are working on the surfaces of Dongting Lake and others to improve the water supply and drainage in Wuhan. It is necessary to infill the low land to be dried and quarantine the wetland to prevent the spread of the coronavirus. In addition, the bottom of the Yangtze River should be desilted for easy drainage from Wuhan to the Yangtze River.

Since Dongting Lake is connected with the Yangtze River and located in the upstream of Wuhan, the water quality of Dongting Lake is important to Wuhan. HAB could be prevented in freshwater by sulfur compounds (H_2S, sulfates) inducing the deficiency of the dissolved Fe in the water. It was clear that H_2S bubbling inhibited the growth of HAB (Fig. 8).

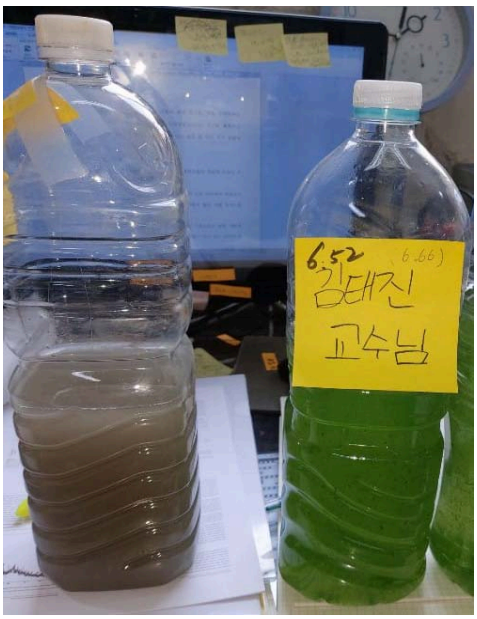


Figure 8: After treatment without growth of HAB (Left) and before treatment with growth of HAB (Right) of H_2S bubbling

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Since the Wuhan coronavirus was mainly caused by HAB in the Yangtze and Han Rivers, the bubbling of H_2S from Biogas is a simple and cheap method to prevent water pollution in Wuhan. Hubei province has the highest irrigated rice production in China (9,123kg ha^{-1} as of 1998) (MAO, 2001). Water pollution in rice irrigation was mainly caused by nitrogenous and phosphorus fertilizers. Furthermore, the Asian dust provides the iron (4 ~ 6 wt%). Therefore, the water pollution should be prevented by reducing nitrate, phosphate and iron in the rice irrigation water before its release to the Yangtze River. Nitrogen can be removed by denitrification biotechnologies (BEDNAREK et al., 2014). Phosphorus can be also removed by integrated buffer zones (ZAK et al., 2018). Iron can be chiefly oxidized through bubbling air by water mills. After oxidation, insoluble iron hydroxide particles sediment to the bottom of the reservoir to be filtered. H_2S bubbling can be also used to sediment the iron in the agricultural irrigation water. The HAB in Wuhan and Hubei can be thus prevented by filtration of key nutrients such as nitrogen, phosphorus and iron.

III. Results

a) Porpoise

The Indo-Pacific finless porpoise (*Neophocaena Phocaenoides*), or finless porpoise has been found around the Korean peninsula in the Yellow and East Seas, although a freshwater population is found around Jiuduansha near Shanghai at the mouth of China's Yangtze River (Fig. 9).



Figure 9: Location of the Jiuduansha wetland comprised of the Shanghai (LI et al., 2011).

The finless porpoise lives in the coastal waters of Asia, especially around Japan, Korea, China, Indonesia, Malaysia, India, and Bangladesh. The porpoises stay in shallow waters, up to 50 m deep, close to the shore, in waters with soft or sandy sea-beds, or in estuaries and mangrove swamps. In exceptional cases, they have been encountered as far as 135 km offshore in the East China and Yellow Seas, albeit still in shallow water. Finless porpoises can grow to as much as 2.27 m in length and can weigh up to 72 kg.

The existence of three distinct populations is widely accepted for the finless porpoise (*Neophocaena Phocaenoides*) in Chinese waters: The Yellow Sea, Yangtze River and South China Sea populations (LI et al., 2011).

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Figure 10: A photograph of finless porpoise (*Neophocaena Phocaenoides)* photographed by P. Baillehache (LI et al., 2011)

Dongting Lake as the largest freshwater lake in China (ZHAO et al., 2005) is a very important habitat and wintering site on the migration route of East Asia's migrating birds. Each year nearly two million waterfowls come here for winter and share the waters with local birds, likely resulting in cross-infection between wild birds and domestic fowl.

Porpoises swim along the Yangtze River to Dongting Lake. It is therefore possible that porpoises may carry both cetacean morbillivirus (CeMV) and avian influenza virus (AIV) at the Dongting Lake to induce an evolutionary virus such as Wuhan coronavirus disease 2019 (COVID-19) during the minimum sunspot number, as illustrated stepwise in Fig. 21.

b) Respiratory System

The respiratory and circulatory systems combine to provide an efficient delivery system that carries oxygen to and removes carbon dioxide from human body tissues. This transportation involves four separate processes; 1) breathing, which is the movement of air into and out of the lungs, 2) gas exchange by pulmonary diffusion, which is the exchange of oxygen and carbon dioxide between the lungs and the blood, 3) transport of oxygen and carbon dioxide through the blood, and 4) capillary gas exchange, which is the exchange of oxygen and carbon dioxide between the capillary blood and the metabolically active tissues. Gas exchange in the lungs serves to replenish the blood's oxygen supply, which is depleted at the tissue level, where it is used for oxidative energy production, and the removal of carbon dioxide which is the result of ATP production (WILMORE, 2004).

A typical pair of human lungs contain about 300 million alveoli, producing 70m^2 of surface area. The diameter of an alveolus is between 200 and 500μm.

Alveoli are an important part of the respiratory system (Fig. 11) whose function it is to exchange oxygen and carbon dioxide molecules to and from the bloodstream. There tiny, balloon-shaped air sacs sit at the very end of the respiratory tree and are arranged in cluster throughout the lungs. Pneumonia is an inflammatory condition of the lung parenchyma, which and be caused by both viruses and bacteria. Pneumonia is an infection that inflames the alveoli in one or both lungs and can result in the air sacs filling with pus (ELDRIDGE, 2019).

Alveoli with 70m^2 surface area for the human have the air sac filled with pus during pneumonia. The buoyancy force of the CeMV infected whale is lacking air in the sac. The infected whale is thus afloat to be moved to the beach by the current until stranding death of pneumonia, inducing shortage of oxygen in the blood stream for heart attack.

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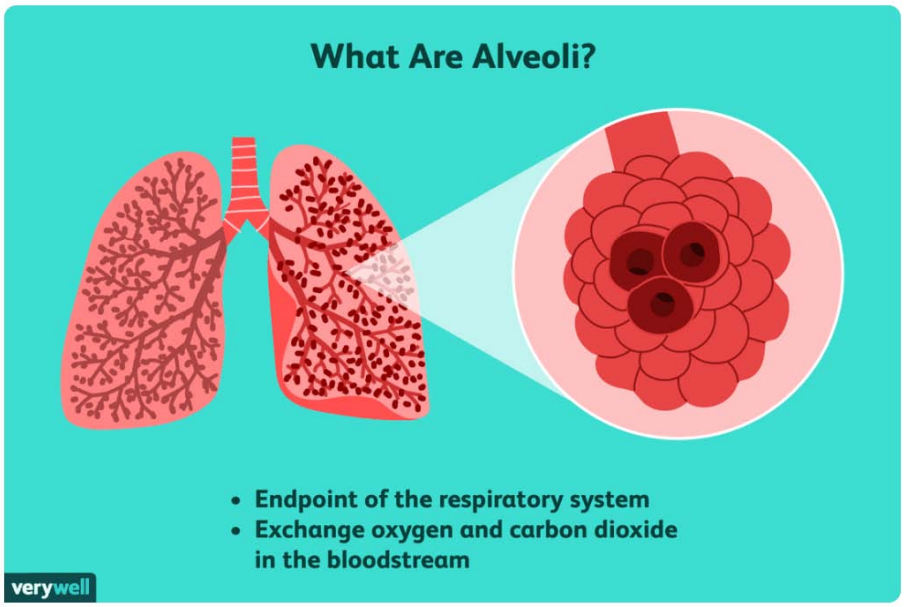


Figure 11: What are alveoli? (ELDRIDGE, 2019)

Measurements of the real time blood saturation of oxygen, exhaled O_2 and CO_2 concentrations before and after 3 minutes of exercise. The running machine ST-3000 from Gee Hoo Industrial, Taiwan was used for the experiment. Fig. 12 showed the overall set up from the oxygen supply system to the measurement system through the test subject on the running machine.

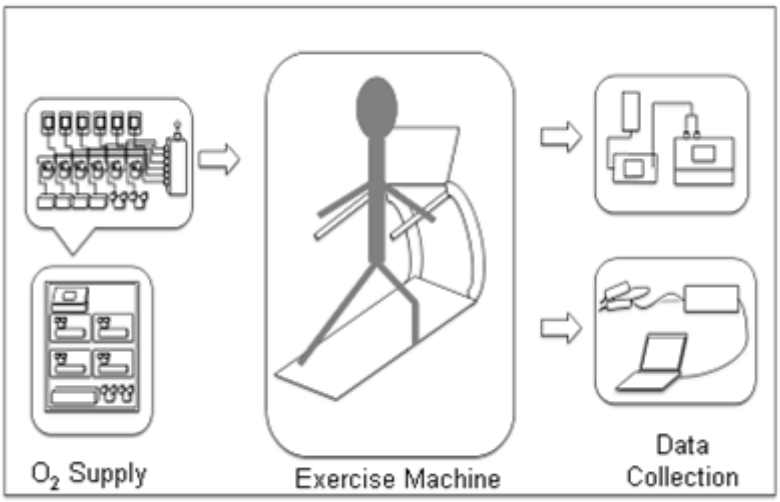


Figure 12: Overall set-up of experimental system with O_2 supply, exhaled O_2/CO_2 measurement

Fig. 13 implied that the oxygen saturation (%) decreased sharply, whose case could be equivalent to the degree of the confirmed patient infected by the coronavirus. At high altitude of 4,000 m there was less amount of oxygen. Since oxygen saturation (%) was rapidly decreased with increase of altitude, it was expected that there would be the stepwise decrease of oxygen saturation (%) for the confirmed patient infected by the coronavirus until death of pneumonia, if not cured.

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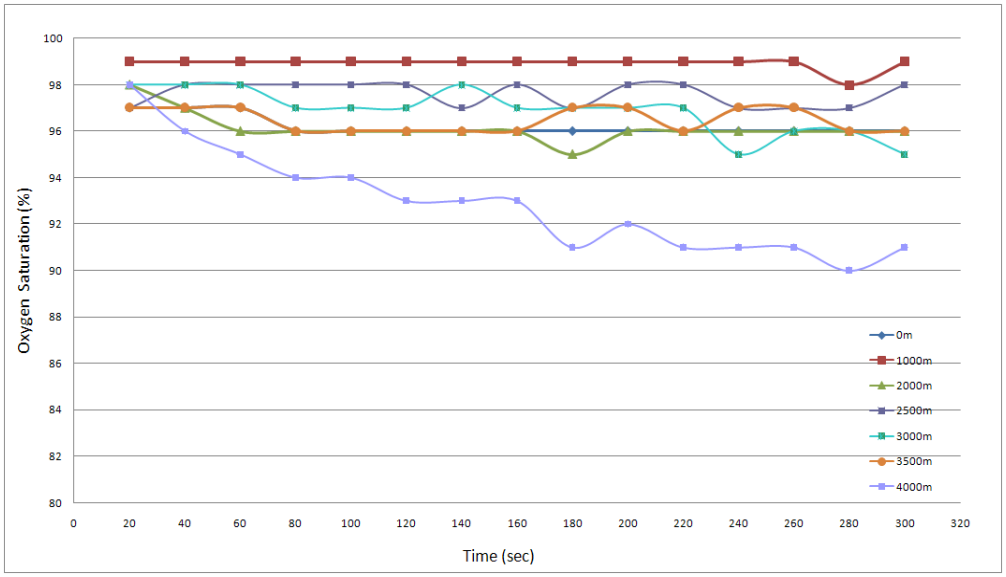


Figure 13: Time distribution curve of oxygen saturation at 0km/h walk load with various altitudes for a male of age 26

Fig. 14 showed that concentration of exhaled oxygen (%) was sharply decreased with time when walking load was increased from 0 to 6 km/h. It was necessary to relax and have a rest for proper recovery from the Wuhan coronavirus.

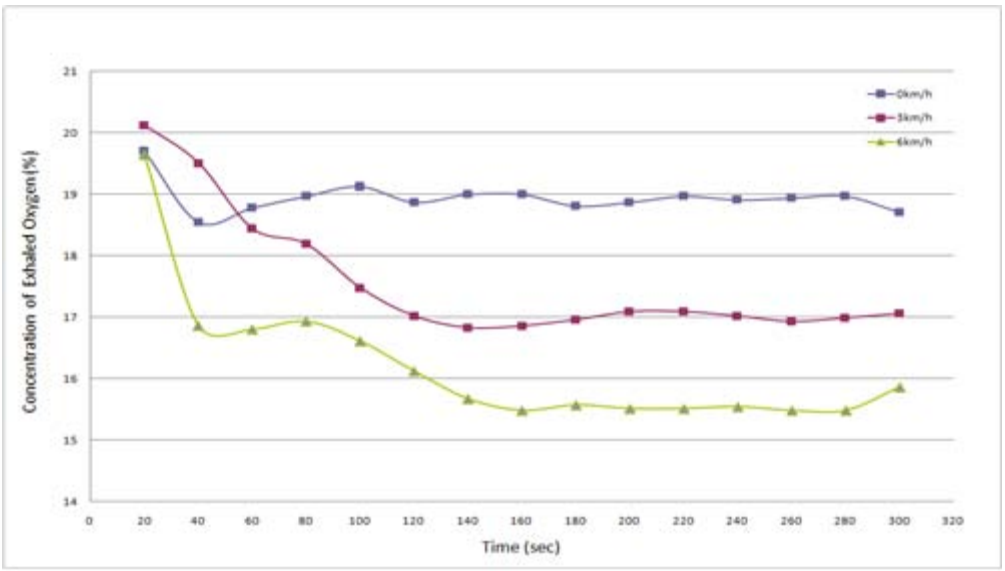


Figure 14: Time distribution curve of concentration of exhaled oxygen 1,000m with various walk loads for a male of age 26

c) Cetacean Morbillivirus

Remdesivir and chloroquine effectively inhibited the novel coronavirus (2019-nCoV) in vitro, (WANG et al., 2020) in The Wuhan Institute of Virology.

Cetacean morbillivirus (CeMV) is a virus that infects dolphins, porpoises and whales (BARRETT, 1999). Humans, dogs, cats, cattle, seals and cetacean serve as natural hosts of morbillivirus (RIMA et al., 2019). Symptoms of infection are often a severe combination of pneumonia, encephalitis and damage to the immune system, which greatly impair the cetacean's ability to swim and stay afloat unassisted (STONE et al., 2011). Large groups of gregarious species were found to be the likely reservoirs and sources of CeMV infections in susceptible species in the Atlantic and Pacific Oceans (VAN BRESSEM et all., 2014).

Human blood test for the presence of a non-segmented, single-stranded RNA genome of negative polarity (BARRETT, 1999) for Wuhan coronavirus, may allow the initial screening of the confirmed case by means of blood kit, although the final confirmation can be decided by CT film for pulmonary calcification. Such a simple screening may facilitate to separate the infected patient from the healthy ones for less numbers

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of death and confirmed people along with fast recovery due to the short duration of the infection by Wuhan coronavirus. The recovered patient can be stayed in the chamber of UV radiation lamp at 254 nm while wearing sunglass, not to be re-infected by the Wuhan coronavirus. RNA Viruses showed the coronavirus in cetaceans for species of bottlenose dolphin and beluga whale (LEGER et al., 2018).

Unusual mortality event linked to CeMV has caused the death in stranded dolphins (GROCH et al, 2018), porpoises and whales (WVEC, 2017 and GROCH et al., 2018). Since the humpback whale is 666 times heavier (40,000kg) than the human (60kg), the impact of CeMV in the evolutionary mutated form of the Wuhan coronavirus to people can be very critical.

As the event of an unusual Mortality Event (UME), there have been humpback whales stranded in the Atlantic Coast (NARK, 2019) and gray whales (OFFICE OF PROTECTED RESOURCES, 2020) strandings in the West Coast (as of February 8, 2020).

Since Cetacean Morbillivirus (CeMV) induced the Wuhan coronavirus in China, the West Coast and the Atlantic Coast of the USA can be open to the danger of the Wuhan coronavirus, as occurred recently in the states of Oregon and Washington with 6 deaths by the Wuhan coronavirus.

There are a few common features between Cetacean Morbillivirus (CeMV) and Wuhan coronavirus as follows;

1) Same symptoms of pneumonia.
2) Wuhan coronavirus started in the Wuhan Seafood Wholesale Market while CeMV from dolphins, porpoises and whales.
3) Wuhan city produces the highest level of CO_2 emissions in the world. The resulting thin ozone layer and excessive UV radiation provide ideal conditions for the worst viral mutation.
4) Water pollution in Wuhan and Hubei caused by agricultural irrigation and industrial pollutants in the Yangtze and Han rivers and the Three Gorges Dam.
5) The Wuhan coronavirus has been named by the Coronavirus Disease 2019 (COVID-19). The event of whale deaths has been declared an "Unusual Mortality Event" while World Health Organization declared the outbreak of COVID-19 as a "public health emergency of international concern".

d) Vaccine Development

A Wuhan coronavirus vaccine can be developed by culturing blood from CeMV infected porpoises in the Yangtze River or Dongting Lake, along with bloods from the Wuhan coronavirus confirmed patient. CeMV were inoculated and incubated at 37℃ (WENDY et al., 2018). The virus inactivated at a temperature between 60 and 95℃ (WHO, 2011) could be used as vaccines for the Wuhan coronavirus.

Porpoises and humpback whales infected by CeMV can be initially tested for its efficacy of curing the CeMV. At the same time migratory birds infected by LPAI/HPAI can be examained together. Finally, the developed vaccines can be injected to the confirmed patient to examine the efficacy of curing the Wuhan coronavirus. This work of vaccine development can be followed by the teams in NIH and CDC in the United States.

Measles is spread person-to-person through the air. Measles can cause pneumonia, seizures, brain damage and even death (vaccine information. o rg/measles).

Since human is the host of morbillivirus, MMR Vaccine (Measles, Mumps and Rubella Vaccine) can be applicable to the confirmed patient for curing the Wuhan coronavirus.

Cetacean morbillivirus (CeMV) and Measles morbillivirus (MeV) are belong to morbillivirus. Porpoises, dolphins and whales are infected by CeMV. Stranded porpoises might cause the Wuhan coronavirus in Huanan Seafood Wholesale Market for wet meat with infected blood into the sinkhole after bloodshed. Such a blood might spread around the whole city of Wuhan through the underground sinkholes with infected CeMV. The strongest UV radiation under the conditions of the highest CO_2 emissions, the worst polluted waters from 4,000 industries and highest productivity agricultural farming and the period of the minimum sunspot number in 2019 to 2020, could create an evolutionary virus from the animal of porpoises to humans. Since measles morbillivirus (MeV) are hosted by humans, it can be possible that MMR Vaccine can be a good candidate to cure the Wuhan coronavirus presumably initiated from CeMV.

Existing MMR Vaccine can be applicable to curing the Wuhan coronavirus, since the morbillivirus is common genus of CeMV for porpoises and measles morbillivirus for human.

e) CO_2 Emissions

It is evident that global CO_2 emissions increase continuously over the years ($R^2 = 0.9497$), as shown in Fig. 15. CO_2 emissions induced the increase of the ozone hole area ($R^2 = 0.4116$) (Fig. 16) with a linear relationship ($R^2 = 0.3947$) (Fig. 17). The ozone is known to absorb the solar UV radiation to decrease the UVB (NIH, 1989). CO_2 emissions were proportional to the ozone hole area and thus CO_2 emissions leads to powerful UVB radiation on the Earth.

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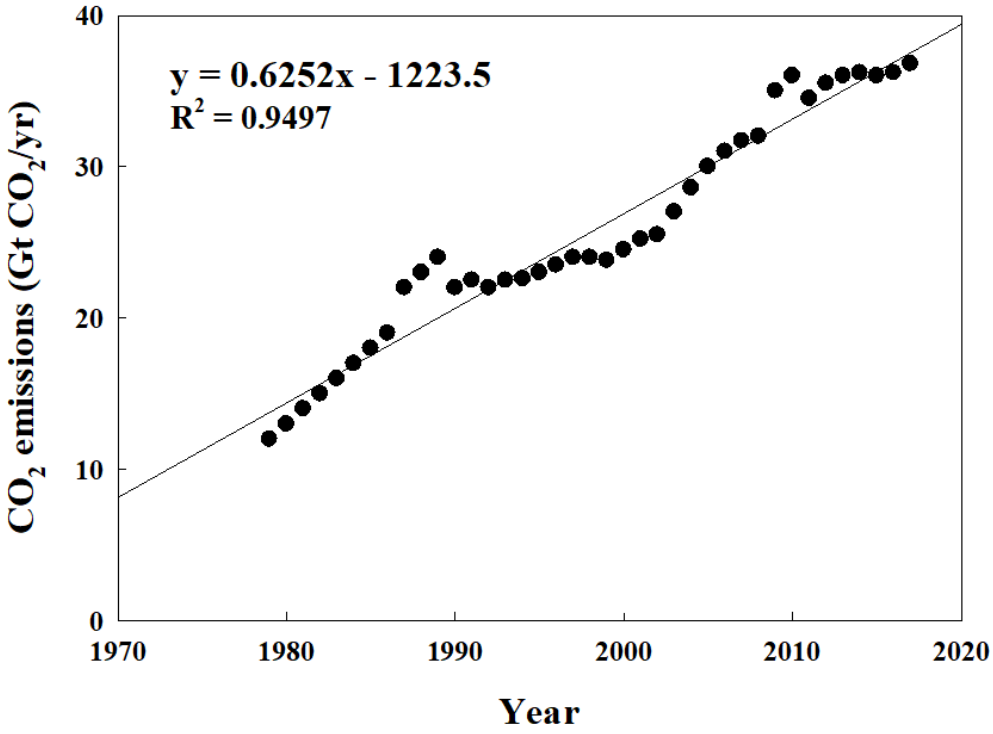


Figure 15: Yearly distribution of global CO_2 emissions from 1979 to 2015

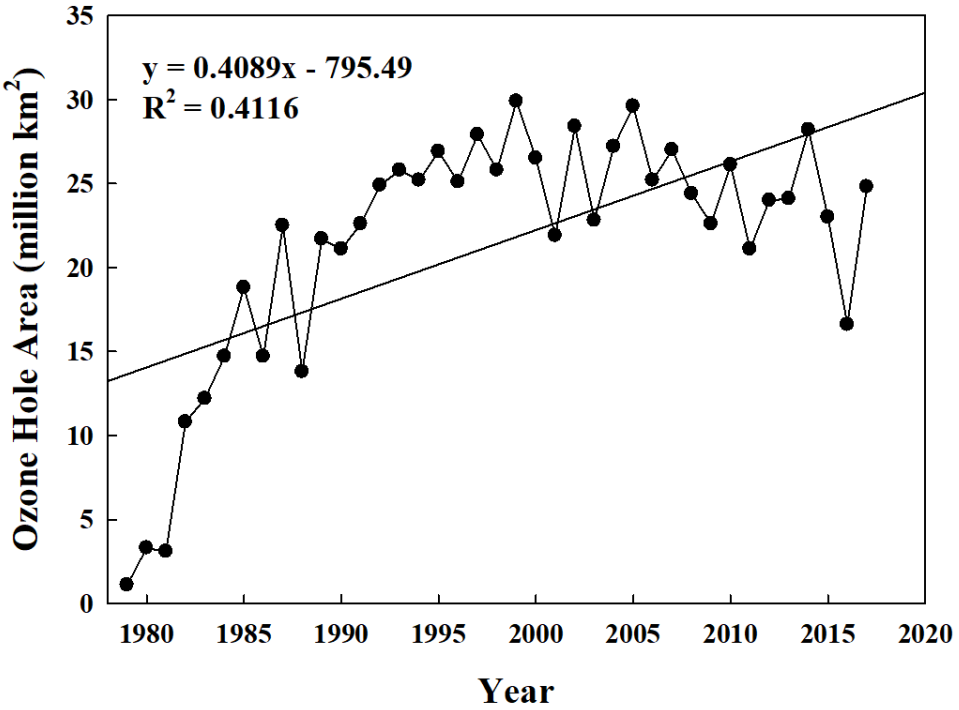


Figure 16: Yearly distribution of ozone hole area in the Antarctic from 1979 to 2015

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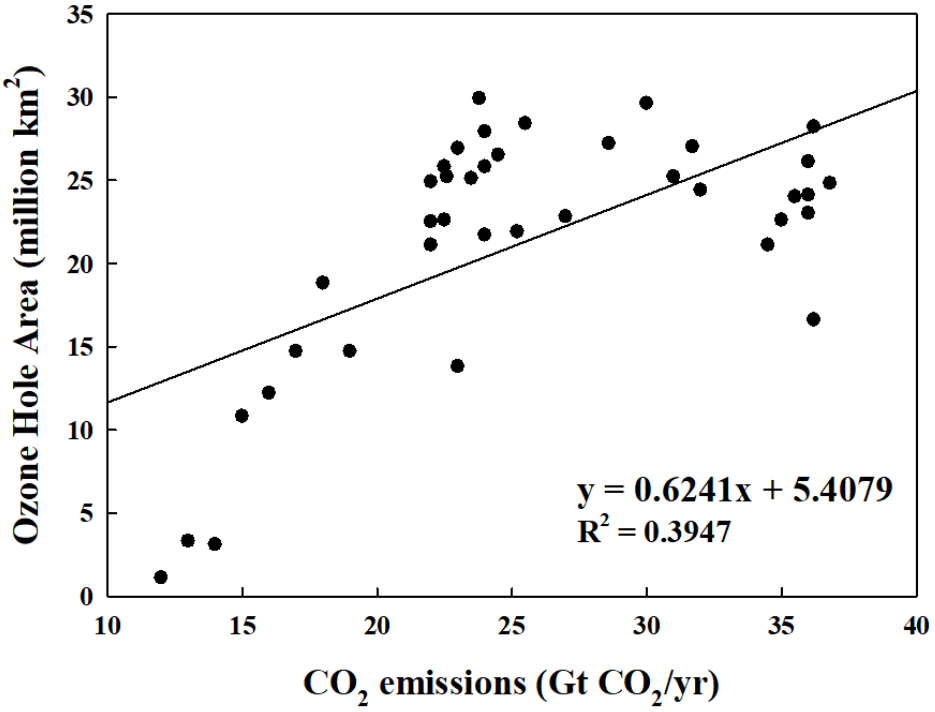


Figure 17: Linear relationship (R^2 = 0.3947) between global CO_2 emissions and ozone hole area in the Antarctic from 1979 to 2015

China is the greatest producer of CO_2 emissions in the world. Fig. 18 shows the carbon emission characteristics of 12 major Chinese cities from 2004 to 2008 (WANG et al., 2012).

Wuhan has the highest CO_2 emissions in the world resulting in a large ozone hole area.

Wuhan showed CO_2 emission leading to the highest level in heating and industrial fuel use among 12 Chinese cities in the study.

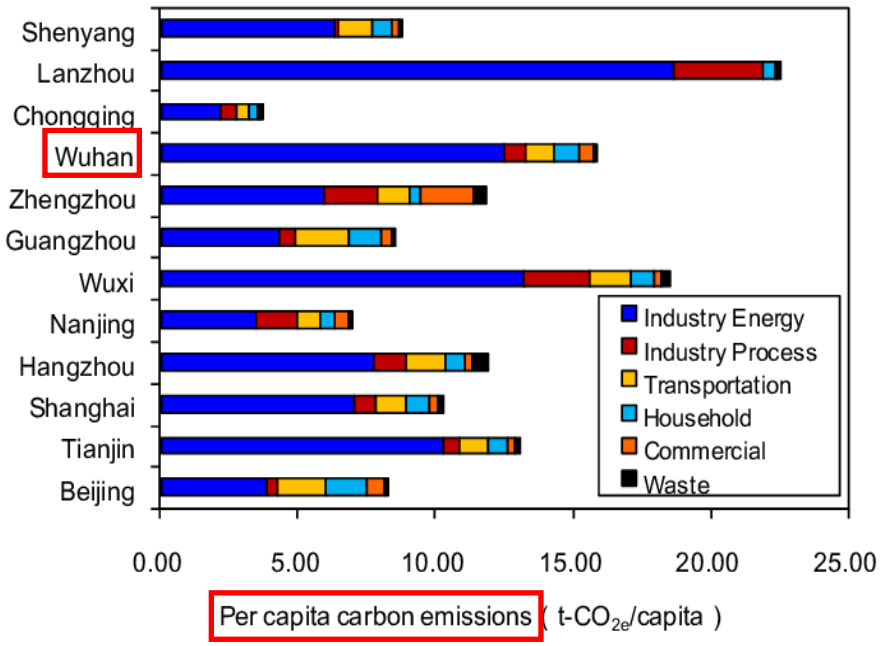


Figure 18: Carbon emission characteristics of 12 major Chinese cities from 2004 to 2008 (WANG et al., 2012)

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The spread of the Wuhan coronavirus around China is shown in Fig. 19; data available from John's Hopkins University (Feb. 2020). All the 12 Chinese cities with excessive CO_2 emissions in Fig. 18 were superimposed in the recent map of the Wuhan coronavirus distribution in Fig. 19. Therefore, it could be proposed that the Wuhan coronavirus was induced by the highest CO_2 emissions in China, during the minimum sunspot number period, causing the strongest UV radiation leading to the worst mutation of the virus. Since Wuhan seemed to be the initiator of the Wuhan coronavirus due to the contaminated water and infected air by Asian dust and air pollutions in Wuhan (WANG et al., 2017), there were many casualties specifically in Wuhan and Hubei; an area with large bodies of polluted water in the Yangtze River, Han River and the Three Gorges Dam. The outbreak spread from Wuhan to most industrialized cities with high CO_2 emissions and polluted water during the minimum sunspot number from 2019 to 2020.

It is imperative to reduce CO_2 emissions by replacement of fossil fuel combustion plants with nuclear power plants. Polluted waters from 4,000 factories of the highest in China along the Three Gorges Dam, Yangtze River and Han River should be purified not only for the present Wuhan coronavirus but also for the coming diseases in 2030 to 2032 considering 11 years cycle of the sunspot number.



Figure 19: Wuhan coronavirus distribution map in China, John Hopkins University's Center for System, Science and Engineering (CSSE) (Feb. 2020)

f) Sunspot Number

Solar flare (sunspots) with an 11-year cycle alter the amount of UVR (ultraviolet radiation) reaching the Earth. Solar flares increase ozone concentration in the stratosphere (above 50km) thereby reducing the amount of surface UVB. When solar flares are inactive and minimal, there is a decrease in the ozone concentration, allowing increased UVB to penetrate to the Earth's surface (NIH, 1989).

A significant viral mutation is therefore expected in the periods of the minimum sunspot number in a location with the highest CO_2 emissions, which is the case with the Wuhan coronavirus from 2019 to the present day in China.

2019- 2020 falls within the period of the minimum sunspot number showing significant linearities with the La Nina Index (R^2=0.9922) (KIM, 2020), HPAI outbreak (R^2=0.9967) (KIM, 2018), record low temperatures in Chicago (R^2=0.9995) (KIM, 2019), and humpback whale strandings (R^2=0.6128) (KIM, 2018). Since the standard deviation of the sunspot number is 14 months or 1.1 years (KIM, 2018), there can be excessive UV radiation in the Poles during coming years between 2030 to 2032. These factors may have led to the mutation and spread of the new dangerous disease near at the Dongting Lake with millions of migratory birds in China during coming years between 2030 to 2032.

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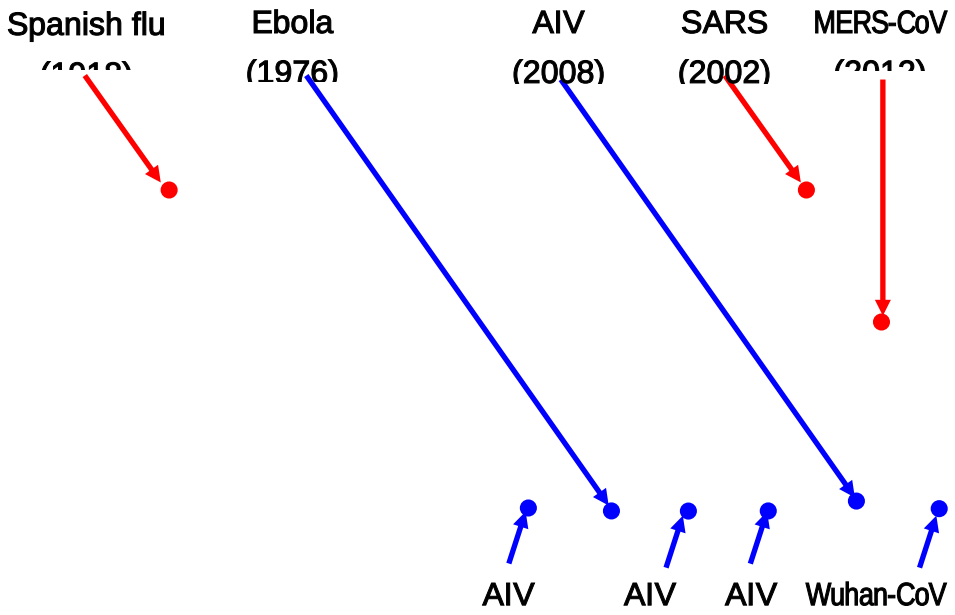


Figure 20: Summarized the outbreaks of serial diseases associated with the sunspot number from Spanish flu 1918 to Wuhan coronavirus 2020

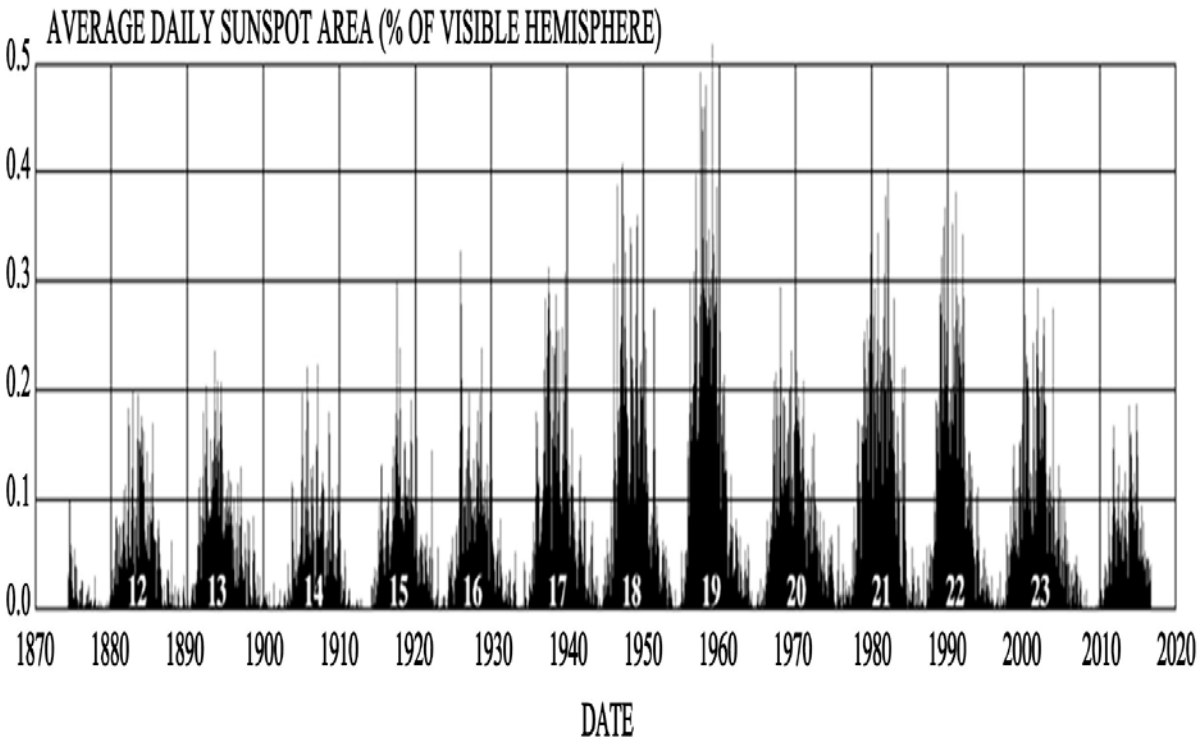


Figure 20: Sunspot number (Maximum period expressed in red color, Minimum period expressed in blue color) from 1870 to 2020

The 1918 Spanish flu, 2002 SARS and 2012 MERS-CoV occurred in the period of the maximum sunspot number in areas with high CO_2 emissions, causing excessive UV radiation, resulting in extensive casualties. In addition, AIV, Ebola, Wuhan-COVID-19, all originated and spread from locations with high CO_2 emissions during the minimum sunspot number period.

The extent of UVB radiation is stronger in the period of the minimum sunspot number than that of the maximum sunspot number due to a decrease in the ozone concentration (NIH, 1989) for the excessive viral mutation along with extensive casualties.

There have been 2,978 deaths and 86,914 confirmed cases of the Wuhan coronavirus in 64

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countries as of March 1, 2020. In contrast, SARS caused 775 deaths and MERS caused 858 deaths with 2,494 confirmed cases. The present Wuhan coronavirus is more dangerous than the others.

The highest CO_2 emissions in Wuhan during the minimum sunspot number could induce the strongest UV radiation for easy production of the mutant virus. Deteriorated air quality by the highest CO_2 emissions as well as poor water quality by polluted Yangtze and Han Rivers from the Three Gorges Dam with HAB and pollutants from 4,000 factories could be major causes of Wuhan coronavirus.

Another dangerous outbreak is expected at Dongting Lake with millions of migratory birds in China, during years between 2030 and 2032 due to 11 years cycle of the sunspot number.

g) Transmission

Fig. 21 postulates that the Wuhan Coronavirus Disease 2019 (COVID-19) came the evolutionary virus originated from the Antarctic through migratory birds (KIM, 2018) and humpback whales from Alaska (KIM, 2018). Humpback whales infected by cetacean morbillivirus (CeMV) migrated to the East Sea. In addition, migratory birds infected by low pathogenic avian influenza (LPAI) flew to Dongting Lake (Fig. 7).

Porpoises could be infected by CeMV from the feces of humpback whales in the East Sea. Porpoises swam along the Yangtze River to reach Dongting Lake, where evolutionary mutation could have occurred between migratory birds, humpback whales and then porpoises. Porpoises could have been stranded and then died of pneumonia due to infection by CeMV and evolutionary avian virus. Such dead porpoises could have been moved to the Huanan Seafood Wholesale Market in Wuhan, the starting point of the outbreak, for wet meat by several stallholders. Since catching porpoises is prohibited by law, they might wash out the infected blood leading to the spread of the coronavirus, resulting in deaths caused by pneumonia.

Blood washed out from infected porpoises with evolutionary CeMV could have spread via underground streams which connect the sinkholes located in and around the Huanan Seafood Wholesale Market in Wuhan. This could explain why there was a sudden outbreak in Wuhan with such a high mortality rate.

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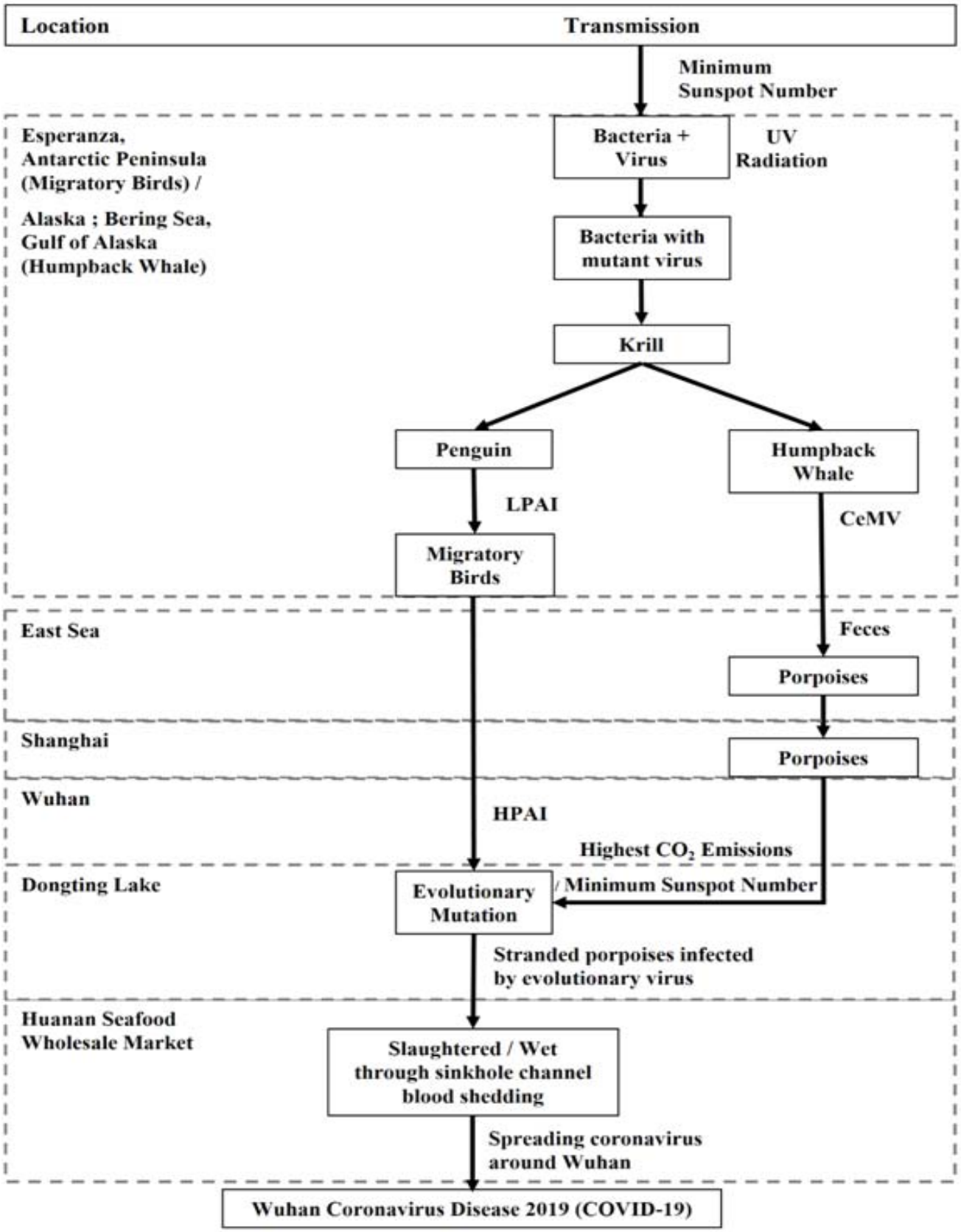


Figure 21: Transmission route of evolutionary virus between avian influenza virus and cetacean morbillivirus under the highest CO_2 emissions and the minimum sunspot number with strong UV radiation for mutant of Wuhan Coronavirus Disease 2019 (COVID-19).

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A heavily industrialized city such as Wuhan must be careful of excessive CO_2 emissions and polluted water quality in the period of the minimum sunspot number causing the outbreak of a serious disease like the Wuhan coronavirus. SARS in 2002-2003 in Guangdong in China and MERS in 2012-2014 in Saudi Arabia could have been caused by excessive CO_2 emissions even in the maximum sunspot number. Since CO_2 emissions enhance UV radiation at a specific location, any serious disease can originate and spread.

In the case of Wuhan, water polluted by agricultural irrigation and industrial chemicals flows downstream from the Three Gorges Dam, Han River and Yangtze River (LIAN, 2014). In addition, Wuhan is prone to flooding with a lower elevation than the Yangtze River making conditions even more conducive to the spread of a deadly virus.

h) Prevention

Several treatments are recommended to stop the propagation of the Wuhan coronavirus as follows:

— Physical method; Aerosol filtration by face mask, Relative humidity (>40%) by humidifier, Temperature (>55℃) by heater.

Since Asian dusts carry bacteria, aerosol filtration is necessary to prevent the outbreak of viral diseases. Effective sanitization is important in viral epizootic outbreaks to avoid further spread of the pathogen. The surface temperature should be kept above 35℃ for at least 7.6h or greater than 55℃ to ensure sufficient inactivation of HPAIV (ELVING et el., 2012). It is recommended to use the air cleaner, humidifier and heater for indoor air quality without the viral infection. High relative humidity (>40%) leaded to loss of infections influenza virus from simulated coughs (NOTI et al., 2013).

— *Biological method;* Lactobacillus, Leuconostoc, Weissella from Korean Kimchi is the new superfood due to its high probiotics, vitamin A and B for enhancement of poultry immunity. Yogurt may boost the immune system.

— *Chemical method;* O_3, pH, Water should be spread to disinfect the floor, with caustic lime being added later to induce a chemical reaction for heat (200℃) and pH (11∼12).

— *Photochemical method;* UV radiation in indoor air, drinking water and blood circulation of the confirmed patient.

The contaminated waters can be sterilized by physical methods (UV radiation, boiling) and chemical methods (ozone treatment, CaO treatment for high pH (11-12) and high temperature (200℃) during the chemical reaction with water) (KIM, 2018)

If drinking water frequently, the coronavirus in the inhaled air is dissolved in the stomach for steriliza -tion by stomach acid, instead of pathway to the lung alveoil leading to calcification and ultimely pneumonia.

Since UVR (ultraviolet radiation) exposure is strong in Wuhan City due to excessive CO_2 emissions, polluted water and the minimum sunspot, minimizing UVR using proper clothing, appropriate application of physical and/or chemical sunscreens, behavior modification, and awareness of photosensitizing medications are recommended.

IV. Conclusion

Transmission of the Wuhan coronavirus could have been initiated in the Antarctic. Avian Influenza Virus (AIV) and Cetacean Morbillivirus (CeMV) mutated under excessive UV radiation while being carried by migratory birds and humpback whales, respectively, in the period of the minimum sunspot number from 2019 to 2020.

Porpoises infected by Cetacean Morbillivirus (CeMV) from the feces of humpback whales in the East Sea swam along the Yangtze River to Dongting Lake. There are many migratory birds and waterfowl that could have transmitted the evolutionary new virus to porpoises. Cetacean mammals such as dolphins, porpoises and whales died of pneumonia due to CeMV and were stranded on the beach. Infected and stranded porpoises could then have been moved to Huanan Seafood Wholesale Market in Wuhan. The stallholders could have been infected by inhaling the blood from infected porpoise treatment for wet meat. Direct infection of Wuhan coronavirus (COVID-19) could have been transmitted to the stallholders resulting in 7 deaths caused by pneumonia. Indirect infection from infected blood could have spread around the Wuhan area through the sinkholes and underground waterways originating at the wet Market. As a result, all the sinkholes in the city of Wuhan must be disinfected immediately.

Wuhan is known as ''sponge city'' and thus a water purification scheme has to be developed. Wuhan is below the Yangtze River during flooding. The case of the Netherlands can be referenced to handle the water irrigation. As for the Three Gorges Dam, its water level can be lowered to have enough water in the downstream area including Wuhan while the bottom of the Yangtze River should be desilted from the present 9m to 15m for clean water and uninfected Wuhan. Agricultural water in Hubei province, which has the highest rice productivity in China, should have nitrogen, phosphorus and iron removed to prevent the harmful algal blooms (HAB) resulting in clean water quality in Wuhan.

The high concentration of carbon dioxide should be decreased by closing fossil fuel power plants and increasing nuclear power plants. The simple sterilization by ultraviolet 254nm is recommended in air, water and confirmed patient to make a quick recovery from the Wuhan coronavirus disaster. Several treatments

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are recommended to stop the propagation of the Wuhan coronavirus as follows: physical method (face mask, humidifier, heater), biological method (Korean kimchi and yogurt), chemical method (O_3, pH by acetic acid, caustic lime, frequent water drinking for dissolution of the coronavirus and its disinfection at the stomach instead of its infection to the respiratory system) and photochemical method (UV radiation in indoor air, drinking water and blood circulation from the confirmed patient with dialyzer).

A Wuhan coronavirus vaccine can be developed by culturing blood from CeMV infected porpoises in the Yangtze River or the Dongting Lake, along with Wuhan coronavirus confirmed human blood. Existing MMR Vaccine can be applied to cure the confirmed patient.

It is evident that global CO_2 emissions increase continuously over the years (R^2 = 0.9497). CO_2 emissions induced the increase of the ozone hole area (R^2 = 0.4116) with a linear relationship (R^2 = 0.3947). The ozone is known to absorb the solar UV radiation to decrease the UVB. CO_2 emissions were proportional to the ozone hole area and thus CO_2 emissions induce strong UVB radiation on the Earth.

It can be concluded that the Wuhan coronavirus was caused by the highest CO_2 emissions and polluted water during the period of the minimum sunspot number, providing the strongest UV radiation causing the worst mutation of the Wuhan coronavirus. The virus was caused by contaminated water and infected air, meaning there were many casualties specifically in the industrial and agricultural areas of Wuhan and Hubei.

UVB radiation is stronger during the minimum sunspot number period than that of the maximum sunspot number due to a decrease in the ozone concentration.

The Wuhan coronavirus has caused 2,978 deaths and there have been 86,914 confirmed cases in 64 countries as of March 1, 2020. In contrast, SARS resulted in 775 deaths while MERS caused 858 deaths with, 2,494 confirmed cases. The present Wuhan coronavirus is more dangerous than the others. Another dangerous outbreak is expected at Dongting Lake with millions of migratory birds in China, during years between 2030 and 2032 due to 11 years cycle of the sunspot number.

The highest CO_2 emissions in Wuhan, as well as the spread of polluted floodwater from the Yangtze River, Han River and the Three Gorges Dam during the minimum sunspot number could have resulted in strong UV radiation creating perfect conditions for viral mutation in Wuhan and Hubei province. Overall, deteriorating air quality and high CO_2 emissions as well as the polluted water could be the major reasons for the outbreak of the Wuhan coronavirus.

Acknowledgment

The author expresses sincere gratitude to the University of Suwon and G-Land of South Korea for their financial supports. Editing work undertaken by Professor Jonathan Wright is also greatly appreciated. Typing work undertaken by Kyunghoon Min is also greatly appreciated.

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Prospective for the Potential Effect of Local Anesthetics on Stem-Like Cells in Colon Cancer

By Hengrui Liu
University of Cambridge

Abstract- Colorectal cancer is the third most prevalent cancer and the second most frequent cause of cancer-related death in the world. Surgical resection of the primary tumor is the central aspect of the current multiple modes of treatment and has been associated with better prognosis. The process of surgery, including anesthetic regimens, has increasingly been recognized to affect colon cancer recurrence and metastasis. Both retrospective clinical studies and laboratory studies have reported that colon cancer cells are inhibited by some local anesthetics. However, the application of local anesthetics in colon cancer treatment is limited by our understanding of the mechanisms underlying their effects on cancer biology. Local anesthetics have been proved to preferentially inhibit cancer stem cells which imply that local anesthetics target colon cancer stem cell to suppress cancer progressing. Here this paper will review and propose several potential studies, including using colon cancer cell lines and animal models to test the effect of local anesthetics on population, viability, and migration of colon cancer stem-like cell, and screen and search for potential molecular targets underlying these effects.

GJMR-F Classification: *NLMC Code: WO 200*



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A Prospective for the Potential Effect of Local Anesthetics on Stem-Like Cells in Colon Cancer

Hengrui Liu

Abstract- Colorectal cancer is the third most prevalent cancer and the second most frequent cause of cancer-related death in the world. Surgical resection of the primary tumor is the central aspect of the current multiple modes of treatment and has been associated with better prognosis. The process of surgery, including anesthetic regimens, has increasingly been recognized to affect colon cancer recurrence and metastasis. Both retrospective clinical studies and laboratory studies have reported that colon cancer cells are inhibited by some local anesthetics. However, the application of local anesthetics in colon cancer treatment is limited by our understanding of the mechanisms underlying their effects on cancer biology. Local anesthetics have been proved to preferentially inhibit cancer stem cells which imply that local anesthetics target colon cancer stem cell to suppress cancer progressing. Here this paper will review and propose several potential studies, including using colon cancer cell lines and animal models to test the effect of local anesthetics on population, viability, and migration of colon cancer stem-like cell, and screen and search for potential molecular targets underlying these effects.

I. Background

Colorectal cancer is the third most prevalent cancer and the second most frequent cause of cancer-related death in the world[12].Surgical resection of the primary tumor is the central aspect of the current multiple modes of treatment and has been associated with better prognosis. However, metastasis is the dominant cause of death in patients with colon cancer.[3] On top of cell migration, chemokines have been implicated in additional aspects of malignant transformation, such as proliferation, survival, and angiogenesis.[4]

The process of surgery, including anesthetic regimens, has increasingly been recognized to affect colon cancer recurrence and metastasis.[5]Retrospective clinical studies have suggested that the use of regional anesthesia leads to improved patient outcomes.[6,7] Laboratory studies have reported that colon cancer cells are inhibited by some local anesthetics.[8]However, the application of local anesthetics in colon cancer treatment is limited by our understanding of the mechanisms underlying their effects on cancer biology.

Emerging evidence has indicated a subpopulation of stem-like cells within tumors, known as CSCs, which contribute to cancer treatment failure and cancer relapse.[9,10]The cancer stem cell hypothesis is rising to be an attractive cellular mechanism that proposes a hierarchical organization within the colon tumor bulk and justifies the functional heterogeneity of solid tumors responsible for the aggressive nature of the malignancy and therapeutic refractoriness.[11,12]

Amide-linked local anesthetics, lidocaine, ropivacaine, and bupivacaine, have been proved to preferentially inhibit colony formation and self-renewal of cancer stem cells.[13]A recent study also showed that local anesthetics inhibit colon cancer not through inducing apoptosis or damaging the cell (cytotoxicity) but through arresting cell proliferation cycle.[14]These conclusions imply that local anesthetics target colon cancer stem-like cell to suppress cancer progressing. We aim to determine the effect of local anesthetics on population, viability, and migration of colon cancer stem-like cell, and screen and search for potential molecular targets underlying these effects. The information about their potency and efficacy against colon cancer stem-like cells and the potential targets would help explain the mechanism of effect of regional anesthesia on colon cancer.

II. Hypothesis and Potential Research in this Field

Here, based on previous knowledge and studies, this review proposed a hypothesis that local anesthetics target colon cancer stem cell to suppress cancer progressing. There are several aspects that can be explored: a) to explore the effects of local anesthetics on colon cancer stem-like cells. b) to explore the effects of local anesthetics on colon cancer stem-like cell in a murine cancer model. c) to explore the effects of local anesthetics on the stem-like cell population in clinical colon cancer tissue. d) to explore the potential stemness-correlate molecular mechanism underlying the effect.

III. Potential Available Methods and Strategies

This review proposed several potential available Methods and strategies.

a) The sorting of stem-like cell subpopulation

Immuno-magnetic cell sorting of stem cell subpopulation can be used.[15]Human colorectal

Author: Department of Biochemistry, University of Cambridge, Cambridge CB2 1QW, UK.
e-mail: hengrui.liu1@stonybrookmedicine.edu
Department of Anesthesiology, Health Science Center, Stony Brook University, Stony Brook, NY 11794, USA.

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carcinoma cell lines HCT116, SW480 and HT29 can be exposed to FITC-conjugated anti-CD44, anti-ALDH, and anti-LGR5 antibody, and further labeled with dextran-coated magnetic nan oparticles using bispecific Tetrameric Antibody Complexes (TAC). These cells will be subjected to immuno-magnetic cell separation and $CD44^+$, $ALDH^+$, and $LGR5^+$ cells can be identified as cancer stem cells.

Sphere culture[16,17]can also be used as another method to extract cancer stem-like cells. Cells can be cultured in ultralow attachment plates and the sphere passage cells can be identified as cancer stem cells.

b) The effects of local anesthetics on colon cancer stem-like cell

The colon cancer cell lines and cancer stem-like cell line (sorted cancer cell line derived cells) can be used to test the effects of local amide-linked local anesthetics (lidocaine, ropivacaine, and bupivacaine). Local anesthetics have a wide range of uses in clinical practice and their plasma concentrations can vary widely and the peak plasma concentrations ranging between 1 and 3 μM. [18,19] Clinically relevant concentrations can be used to treat the cell. 1, 2, 4, 12, 24, 48, and 72 hcan be set as treatment time.

Cell viability, migration, invasion, and adhesion of cell lines can be determined using MTT, Cell Cytotoxicity Assay Kit, apoptosis ELISA Kit, Flow Cytometry, wound healing, trans well, matrices assay, colony-for mingas say, tryps in detaching assay, etc. Self-renewal ability of cell linescan be determined using serial replating assays[20]. The population of cancer stem-like cells in HCT116 and HT29can be determined by cancer stem cell markers stain using the Immunohis to chemistry and Flow Cytometry method.

c) The effects of local anesthetics on colon cancer stem-like cell in a murine colon cancer model.

Immuno deficient NSG mouse model[21] with implantation of green fluorescent protein-labeled colon cancer cells (HT29) and cancer stem-like cells (HT29sorted by the method described previously) can be used. In the long-term treatment group, the primary tumor can be treated with clinically relevant concentration local perfusion of local anesthetics per day, while in the short-term treatment group, the animals can only be treated during the surgery.

Tumor development can be monitored through longitudinal magnetic resonance imaging-based morpho metric analysis and survival. Established serum markers of tumor spread can be measured serially and circulating tumor cells can be detected via fluorescence measurements. The primary tumor can be excised and collected after four weeks and the primary recurrent tumor and metastatic tissue (lung, brain, bone, etc.) can be collected. The population of cancer stem-like cell and in tumor and metastatic tissue can be determined by markers stain using Immuno his to chemistry method.

d) The effects of local anesthetics on the stem-like cell population in clinical colon cancer tissue

To determine whether local anesthetics can decrease colon cancer stem-like cell population in cancer tissue from patients, the colon cancer tissues with complete clinical pathological data can be collected from patients with and without lidocaine treatment. The Paraffin-embedded tissue microarray was constructed and the cancer stem-like cell population in cancer tissue can be determined by cancer stem cell markers[22,23,24] ($CD44^+$, $CD24^{-/low}$, $ALDH^+$ and $LGR5^+$) stain using the Immunohis to chemistry method.

e) The effect of local anesthetics on stemness-correlate molecular features

The colon cancer cell lines and cancer stem-like cell line can be treated with local anesthetics. Total protein and total RNA of cells can be extracted, and proteomic analysis and gene array method can be used to screen altered protein and gene expression. QPCR, Immun of luorescence stain, Western blot, and Immunohis to chemistry methods can be used to confirm the results. Gene-knock-out method can be used to test the potential targets of local anesthetics involved in stemness-correlate signal.

IV. Conclusion

This study hopes to emerge with a detailed clarification of the effect of local anesthetics on population, viability, and migration of colon cancer stem-like cell and specific molecular targets underlying these effects, and in turn, deepen our understanding of local anesthetics in colon cancer treatments. Here, this review proposed that a) Colon cancer stem-like cells will be identified and sorted out of colon cancer cell lines. b) Local anesthetics can suppress viability, migration, invasion, and adhesion more in colon cancer stem-like cellline than in colon cancer cell lines. The population of colon cancer stem-like cell in colon cancer cell lines will decrease after treating with local anesthetics. c) The population of colon cancer stem-like cell in tumor and metastatic tissue will decrease and cancer progression will be suppressed in local anesthetics treatment groups. d) The tumor tissue from patients with local anesthetics treatment has less cancer stem-like cells. e) Several targets of Local anesthetics will be identified. Advantageous molecular targets of stemness will be suppressed and disadvantageous targets of stemness will be promoted in colon cancer cells. Knocking out/down these targets can block the effects of the local anesthetics.

Acknowledgment

The author thanks the support of Zongxiong Liu, Weifen Chen, and Yaqi Yang.

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

An Overview of Cognitive Disturbances in Multiple Sclerosis, Progression and Management

By Raed Almalki

Abstract- This review will concentrate on discovery of cognitive disability in MS and available treatment options to decrease symptoms. We performed a search using electronic databases; MEDLINE, and EMBASE, through October, 2019. Search strategies used following MeSH terms in searching: “Multiple Sclerosis”, “Cognitive”, “screening”, “management”. Cognitive dysfunctions are constant signs and symptoms of multiple sclerosis (MS) and occur in up to 65% of individuals. Especially memory, attention, executive and visual constructive functions suffer. These problems strongly impact individuals' capacity to work, social relationships, and quality of life. Signs and symptoms of physical disabilities can occur separately. Cognitive disorders are clear indicators of MS progression, since they stand for highly complicated features that depend on the integrity of the neuronal networks. Yet, severe dementia is relatively uncommon.

GJMR-F Classification: NLMC Code: WL 360



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An Overview of Cognitive Disturbances in Multiple Sclerosis, Progression and Management

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I. Introduction

It is well acknowledged that neurodegenerative diseases, such as Alzheimer's illness and Parkinson's illness, result in cognitive decrease, but only over the last twenty decades cognitive impairment was found as a crucial attribute of numerous sclerosis (MS) that impacts up to 65% of individuals [1]. Multiple sclerosis (MS) is a chronic and incapacitating disorder influencing generally grownups early in their life. This disorder is characterized by the forming of lesions in the brain and spine. Syndromes of the ailment prevail and greatly based on the location of the lesions and the level of inflammatory and degenerative pathology within the main nerve system. Cognitive disability can occur from the onset of MS and in clinically isolated syndrome (CIS) [2], [3]. Remission of cognitive symptoms is unusual, and cognitive decrease might suggest modern illness despite secure physical symptoms [1], [4].

Impaired cognitive function might demonstrate damage to brain areas that do not impact physical working and, for that reason, may not be discovered during regular neurological assessment. Generally, cognitive function has not been consisted of in basic clinical evaluations, and cognitive examinations are extensively viewed to be complicated, time-consuming, and costly to execute. On top of that, couple of cognitive tests have been validated in MS populaces. Consequently, cognitive impairment is possibly under-diagnosed in MS. There is increasing acknowledgment that impaired cognitive function adds to the profound impact that MS has on individuals' daily functioning, including the capability to work, drive, and keep and delight in social relationships, causing a decreased quality of life [4]. It is crucial, as a result, that cognitive function is considered when assessing the effect of MS on individuals' life. Moreover, early detection of cognitive disability is important to make it possible for therapeutic treatment to relieve symptoms or protect against more cognitive decline, although just how finest to handle MS-related cognitive impairment is currently unclear. There have been few researches examining the impacts of medicinal treatments on cognitive outcomes in MS and robust data showing cognitive gain from authorized MS treatments are currently lacking. Cognitive impairment may additionally minimize individuals' capacity to comprehend and comply with therapy programs [1].

There is a clear need for ongoing investigation into cognitive impairment in MS to establish prevention, management, and treatment approaches. This review will concentrate on discovery of cognitive disability in MS and available treatment options to decrease symptoms.

II. Methodology

We performed a search using electronic databases; MEDLINE, and EMBASE, through October, 2019. Search strategies used following MeSH terms in searching: "Multiple Sclerosis", "Cognitive", "screening", "managment ". Then we also searched the bibliographies of included studies for further relevant references to our review. Studies had to be relevant to our criteria which should be review, systematic reviews, or clinical studies restriction to only English language published articles with human subject were applied in our search strategies.

III. Discussion

- Etiology and prevalence, progression of cognitive dysfunction

MS is defined by inflammatory demyelination and neurode generation resulting in damages to white and parts in the central nervous system (CNS). This CNS obtained damages results in a wide variety of signs, including adjustments in cognitive working [5].

Author: *e-mail: raiedalmalke@gmail.com*

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Cognitive change prevails in grownups and children with MS. Depending on the example researched (community vs clinic) and the criteria used, the frequency in grownups varies from 34% to 65% and is about 33% in individuals under 18 years of age [6], [5].

Cognitive disability happens in all MS phenotypes, including clinically isolated syndrome (CIS), and has likewise been shown in radio logically isolated syndrome (RIS) [7]. As a matter of fact, cognitive problems appear to precede the appearance of structural irregularities on magnetic resonance imaging (MRI) and may serve as a very early marker of illnesses activity [8]. In a potential research of cognitive efficiency before the first medical signs of MS, Cortese et al. located that males in the Norwegian Conscript Service data source that later on created MS showed dramatically lower intelligent quotient ratings than male controls, and those that established primary progressive MS (PPMS) scored substantially less than controls two decades before their first MS signs and symptoms [9].

Significant decrease in cognitive performance has been documented in some, nevertheless not all, longitudinal scientific reports over short periods (1- 3 years), there is solid consensus that cognition declines in individuals over longer (10- 20 years) amount of times [10], [4].Overall, the frequency and seriousness of cognitive problems shows up greatest in secondary progressive MS (SPMS) and PPMS individuals[11]. In a 10-year follow-up of cognitive working in individuals with MS, level of physical disability, progressing disease course, and enhancing age forecasted the level of cognitive decline, and constraints in a person's work and social activities were associated with degree of cognitive decrease independent of the person's degree of physical disability [10]. Nevertheless, not all people with MS experience cognitive disability and not every one of those with disability progression significantly. Grownups with early cognitive impairment tend to reveal better decrease [12]. MRI forecasters of cognitive results over 7 years included diffuse brain damage and dynamic main brain atrophy during the very first 2 years after medical diagnosis [13]. Some, however not all, longitudinal studies of cognition in pediatric MS show getting worse with time [6]. Younger age at start might be a risk variable for pediatric MS-associated cognitive problems.

- *Cognitive Impairment in Multiple Sclerosis*

All cognitive domains might be affected in MS; however, the most affected ones are episodic memory and data processing rate [5]. Working memory, executive function, verbal fluency, and interest have additionally been widely explained, with a current passion in social cognition disability [9].Although medical phenotypes might vary in the frequency or seriousness of cognitive impairment, primary factors are physical disability as measured by EDSS, and individuals' age [14]. Other individual attributes such as sex, hereditary variables, and cognitive reserve may additionally play a pertinent function [14]. For a recap of the most constant cognitive domains affected in MS see Table 1.

Table 1: Frequency of cognitive impairment in individuals with multiple sclerosis (MS) by cognitive domain [15]

Cognitive Domain	Frequency
Learning Memory	40–65%
Visual Episodic Memory	20–75%
Verbal Episodic Memory	15–80%
Complex Attention	5–25%
Information processing Speed	15–50%
Executive Function	15–25%
Working Memory	15–60%
Inhibitory control	15–30%
Language	20–58%
Verbal Fluency	15–25%
Social Cognition	20–40%

The cognitive domains harmed in MS appear to have an interpatient variability, nevertheless a characteristic pattern might be defined: memory, data processing effectiveness, executive functioning, interest, processing rate, are one of the most typically compromised features [16].

Impaired memory is one of one of the most constantly damaged cognitive features in MS and is seen in 40- 65% of individuals; besides, MS-related memory disorders most commonly influence long-lasting and working memory [17]. The nature of the MS associated memory disabilities is a subject of debate in the literature, some scientific reports suggest that memory dysfunctions in MS result mostly from damaged retrieval from long-term memory, whereas encoding and storage ability appears to stay intact [16]. Recent

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research study on the nature of memory disorder in MS shows that MS individuals have problem with acquisition of new knowledge instead of retrieval from lasting storage [18]. At first, based upon the job of Rao and colleagues it was thought that memory difficulty was because of damaged retrieval, nevertheless more current descriptions are based in poor acquisition additional to data processing insufficiency.

Damaged speed of data processing has been identified as a vital deficit in MS and is seen in 20- 30% of individuals[17].Data processing efficiency describes the capacity to keep and adjust all the obtained data in the brain for short time duration and to the speed with which one can process that data. Processing speed shortages are observed on also one of the most basic jobs in MS individuals and relate to reduced neuronal conduction speed additional to demyelinating. This reduced data processing might affect an individual's capability to finish tasks and to cope in demanding work [16].

Executive functions worry to the cognitive capabilities necessary to actions routed to goals and to the adjustment to atmosphere demands and modifications; examples are planning, organization, reasoning, and abstract conceptualization. Shortages in executive functions in MS individuals (discovered in 19% of the individuals) happen much less regularly than memory or processing speed impairment. However, MS individuals have certain disability deficits in some executive features, specifically in producing approaches, divergent reasoning, issue fixing and estimate [16]. So, abstract reasoning, verbal fluency, planning, or problem-solving abilities, have been shown to be often reduced in MS individuals.

Interest is likewise a complicated cognitive function and understands different facets like alertness, vigilance, selective or focused and divided focus. Up to 25% of MS individuals have deficiencies in attention, specifically in complicated functions like discerning and divided attention [21].

- *Treatment of cognitive deficits in MS*

Heretofore, healing strategies to avoid or reduce cognitive disorder in MS are unusual. Therapeutic techniques include training of preserved cognitive abilities and mediation of methods in order to compensate obtained deficiencies. Second participation difficulties and subjective psychological strains ought to be reduced by therapy. Causal and symptomatic medicinal treatment alternatives are reviewed as well as the impacts of cognitive retraining and psychological treatments (see following section).

IV. Causal Treatment

Early causal therapy is considered to reduce cognitive disability or to slow down development of cognitive deficits. Some authors report a favorable influence of treatment with Interferon-beta 1a and 1b on cognitive disability, specifically on memory and attention (tertiary research endpoints) [22], [23]. Examining the scientific reports and tests concerning Interferon-beta therapy in MS individuals on cognition, Montalban and Rio reminded us recently of reticent data analysis: due to technical distinctions, heterogeneity of neuropsychological impairment, variation in the performance of the neuropsychological examinations, psychometric difficulties of the used examinations in addition to the effect of discovering and the interpretation of problem, the understanding of the available results stays difficult and somewhat complex [24]. Investigations confirming efficiency of therapy with glatiramer acetate and intravenous immunoglobulin have not discovered distinctions in between the therapy and control group concerning cognitive criteria [22]. The evaluation of the influence of steroid treatment is conflicting. There are positive and adverse effects on cognitive function reported in a time-dependent way.

Examining MS individuals throughout and after a relapse under treatment with methylprednisolone, Patzold et al. reported improved cognitive performance operationali zed by PASAT (Paced Auditory Serial Addition Test) [25]. On top of that, the Multiple Sclerosis Functional Composite (MSFC) consisting of PASAT was found to be extra sensitive to identify motor and cognitive useful modifications compared to the EDSS, which is insensitive to cognitive shortages. In contrast, Brunner et al. reported a relatively easy to fix impairment of lasting memory exploring the effect of acute high dosage steroid treatment in MS individuals[18]. Temporary memory, attentional functions and alertness remained unaffected. Another research study reported a careful deterioration of declarative memory retrieval in individuals obtaining 500 or 2000 mg of methylprednisolone over 5 days at day 6, which was totally relatively easy to fix at day 60 [26]. A single trial has actually examined the impacts of immunosuppressive treatments on cognitive function in 30 progressive MS individuals. Zéphir et al. found a significant improvement in global cognitive effectiveness, encoding capabilities, planning capabilities and inhibition after 6 and 12 months of monthly treatment with cyclophosphamide combined with methylprednisolone [27].

V. Management of Symptoms

Active management, fixating the person with numerous scleros is, is advocated whatsoever phases of the problem to minimize disorder impact, increase lifestyle, and espouse a viewpoint of health [22]. Resolving the array of numerous sclerosis signs and symptoms is a crucial part of management (table 2). While medication therapies are readily available for some symptoms, the proof base is poor and well-designed trials with ample numbers are the exception, though scientific reports of fampridine offer a useful design going forward [28]. Several signs and symptoms,

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such as spasticity, call for a multidisciplinary strategy and cautious treatment option. Range health care might allow the analysis of spasticity from remote settings to improve patient management. The value of recovery in cognitive dysfunction is now much better valued [29]. This appreciation is coupled to a much better understanding of underlying devices relating to connection and even more innovative approaches to treatment, such as telerehabilitation [30]. Portable technology, such as wearable motion displays, could provide unbiased information outside healthcare facility visits, however proper screening and recognition are needed prior to unification into professional technique.

Furthermore, workout has a central role in the management of numerous sclerosis following several positive scientific reports in mobility throughout relapsing remitting several sclerosis and progressive numerous sclerosis [28]. The effects of workout on cognition have also been checked out however the evidence base continues to be limited, mechanisms are not well comprehended, and translation right into medical practice is poor [29]. Avoidance of falls, related to continence problems, previous drops, and medicine, is another crucial element of good management. Multidisciplinary, goal-orientated recovery incorporates all these aspects, but methodologically sound researches are few and the proof base is poor [31].

VI. Cognitive Rehabilitation

Cognitive recovery has deserved certain interest over the past years. 3 This technique, likewise called 'cognitive exercise', focuses on various tasks to educate and discover cognitive competencies. While some incorporated cognitive rehabilitation programs exist for people with MS in medical setups, only a few have been methodically examined [31].

One research contrasted a 6-week cognitive treatment making use of Reha Com software with placebo and no-treatment groups and found advantages in verbal understanding and executive functioning [32].

Table 2: Symptomatic management in multiple sclerosis[22-32]

	Pharmacological treatment	Non-pharmacological treatment
Spasticity	For generalised spasticity: first-line: baclofen, tizanidine, gabapentin (especially for associated spasms); second-line: dantrolene, diazepam, and clonazepam (at night); third-line: add cannabidiol or tetrahydrocannabinol; and fourth-line: baclofen pump, phenol injections. For focal spasticity: botulin toxin injections, phenol injections	Exercise, physiotherapy, hydrotherapy
Fatigue	Amantadine, modafinil, and fampridine (not approved for multiple sclerosis fatigue)	Exercise, cognitive behavioural therapy, occupational therapy, energy conservation management, and aerobic training
Ataxia and tremor	Propanolol, clonazepam, levetiracetam, isoniazid (limited by side-effects), botulin toxin injections if focal, limb tremor128	Physiotherapy, surgical interventions in selected cases
Bladder dysfunction	For overactive bladder: oxybutynin, tolterodine, solifenacin, desmopressin spray (if nocturia), botulin toxin A intravesical and sphincter injection, cannabinoids,130 mirabegron, intravesicular capsaicin	Tibial nerve stimulation and sacral neuromo dulation, intermittent self-catheterisation, indwelling and suprapubic catheter ,surgical interventions
Sexual dysfunction	First-line: sildenafil; second-line: intraurethral alprostadil	Cognitive and behavioural therapy, pelvic floor physiotherapy.
Bowel dysfunction	For constipation: laxatives, rectal stimulants (suppositories, enemas), transanal irrigation	Physiotherapy, increase level of exercise, abdominal massage, biofeedback retraining, surgery.
Depression and emotional lability	Antidepressants (SSRIs or SNRIs), amitriptyline for emotional lability, dextromethorphan and quinidine for pseudobulbar symptoms	Cognitive and behavioural therapy (for depression)
Cognitive impairment	Donepezil, memantine (although not confirmed by a randomised trial)	Cognitive rehabilitation, behavioural interventions, occupational therapy
Pain	For neuropathic pain: first-line: amitriptyline, duloxetine, gabapentin, pregabalin; second-line: tramadol, capsaicin cream (if localised). For trigeminal neuralgia: first-line: carbamazepine, oxcarbazepine; second-line: lamotrigine, gabapentin, pregabalin, baclofen. For musculoskeletal pain: common analgesia, baclofen (if spasticity)	Physiotherapy, surgical procedures for trigeminal neuralgia

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VII. Conclusion

Cognitive dysfunctions are constant signs and symptoms of multiple sclerosis (MS) and occur in up to 65% of individuals. Especially memory, attention, executive and visual constructive functions suffer. These problems strongly impact individuals' capacity to work, social relationships, and quality of life. Signs and symptoms of physical disabilities can occur separately. Cognitive disorders are clear indicators of MS progression, since they stand for highly complicated features that depend on the integrity of the neuronal networks. Yet, severe dementia is relatively uncommon.

Cognitive impairment in MS is essential and relates to purposeful functional disability and adverse effects on quality of life. The truth that cognitive disability and associated disability can predate the beginning of physical ailment amplifies the value of managing this element of the ailment and maximizing clinical end results. Management of cognitive disability might include slowing of further deterioration of problems or enhancement in currently impaired cognition. Cognitive recovery needs to be one part of a detailed treatment technique that begins immediately when MS is identified. It needs to focus largely on the patient, nevertheless it ought to also include family members and caretakers, and welcome cognitive strategies, pharmacologic therapy, psychopathology and assistance for psychosocial troubles.

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Global Journal of Medical Research: F
Diseases
Volume 20 Issue 3 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Low Cost ND: YAG Medical Laser as a Lithotripter and Laser Cautery Machine

By Dr. Sagar A. Jawale

Introduction- Lasers have extensive application in medical sciences today but unfortunately the cost of medical Lasers is exorbitant and it is beyond the capacity of an average doctor to afford it. To solve this problem, I did my own research and developed low cost medical Laser which most of the doctors can afford.

GJMR-F Classification: NLMC Code: WO 511



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Low Cost ND: YAG Medical Laser as a Lithotripter and Laser Cautery Machine

Dr. Sagar A. Jawale

I. Introduction

Lasers have extensive application in medical sciences today but unfortunately the cost of medical Lasers is exorbitant and it is beyond the capacity of an average doctor to afford it. To solve this problem, I did my own research and developed low cost medical Laser which most of the doctors can afford.

II. Aims and Objectives

To develop a cost-effective medical laser for vast majority of medical applications such as lithotripsy, photocoagulation, cauterization, Laser tissue welding etc.

III. Technology

20-watt 950 nm ND: YA Gdiode laser machine: (Photo 2,4) It was made by coupling a 0.1 mm optical fiber (Photo 1) to a 20- watt 950 nm ND YAG diode laser(Photo 3). Photo 4 shows the interior of the machine showing Laser diode with cooling fan and power supply and exhaust fan. The machine has a foot switch to precisely control the on and off function. It has a power control nob which controls power from 0-20 Watts. The fiber is detachable from the main machine. It can be detached and sterilized by putting in Formalin chamber or by Ethylene Oxide gas. Patent is applied at Mumbai office for this invention.

A Laser Diode (Photo 3) is a semiconductor device similar to a light-emitting diode (LED). It uses p-n junction to emit coherent light in which all the waves are at the same frequency and phase. This coherent light is produced by the laser diode using a process termed as "Light Amplification by Stimulated Emission of Radiation", which is abbreviated as LASER. And since a p-n junction is used to produce laser light, this device is named as a laser diode.

Neodymium-doped yttrium aluminum garnet (Nd: YAG) is a crystal that is commonly used as a lasing medium for solid-state lasers. J. E. Geusic et al first explained the laser operation of Nd: YAG at Bell Laboratories in 1964. Nd: YAG is formed by replacing a small quantity of yttrium ions in the YAG crystal structure with triply ionized neodymium that serves as a dopant. The ions are replaced due to the fact that they are of same size. The neodymium ion acts as the lasing medium in the Nd: YAG crystal.

Nd: YAG laser consists of a four-level gain medium that offers extraordinary laser gain at moderate pump intensities and excitation levels. The gain bandwidth of the laser is relatively small, which in turn improves laser's gain efficiency thereby minimizing threshold pump power. It emits infrared light in the range of 1064 nm. It can be lamp pumped or diode pumped. Lamp pumping can be achieved because of the four-level characteristics and broadband pump absorption of the laser in the 800 nm band region.

Specifications of laser diode used in this machine are: Output power:20 Watts, continuous type, Waverlength 950 nm,spectral width 6 nm,threshold current 600 mA,Operating current 11 Amp,Operating voltage 5.7 Volt,Operating temperature 25 degree centigrade, life 50,000 hour.

Specifications of the fiber used are:Type-single mode, Core diameter 100 micrometer,numeric aperture 0.15, cladding diameter 125 micrometer,buffer diameter 250 micrometer, total outer diameter of jacket 1 mm.

Author: Institute of Pediatric Surgery, Jalgaon-425001, Maharashtra, India. e-mail: drsagarjawale@gmail.com

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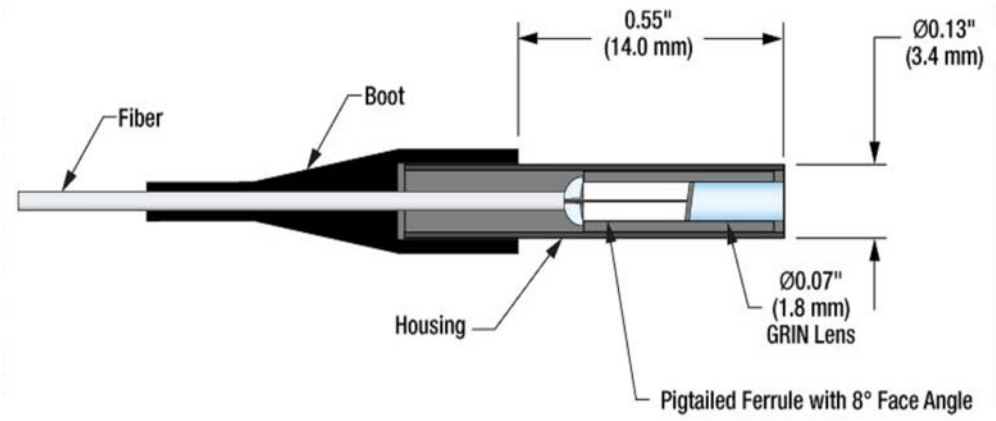


Photo 1: Fiber coupled with GRIN lens in pigtailed ferrule

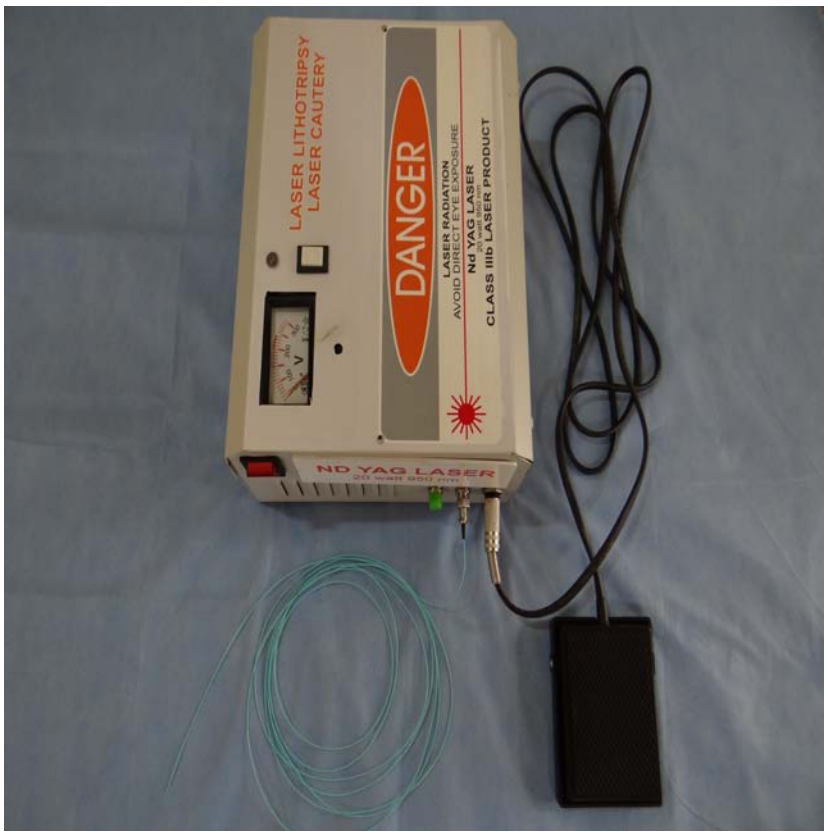


Photo 2: 20 Watt Nd: YAG Laser machine

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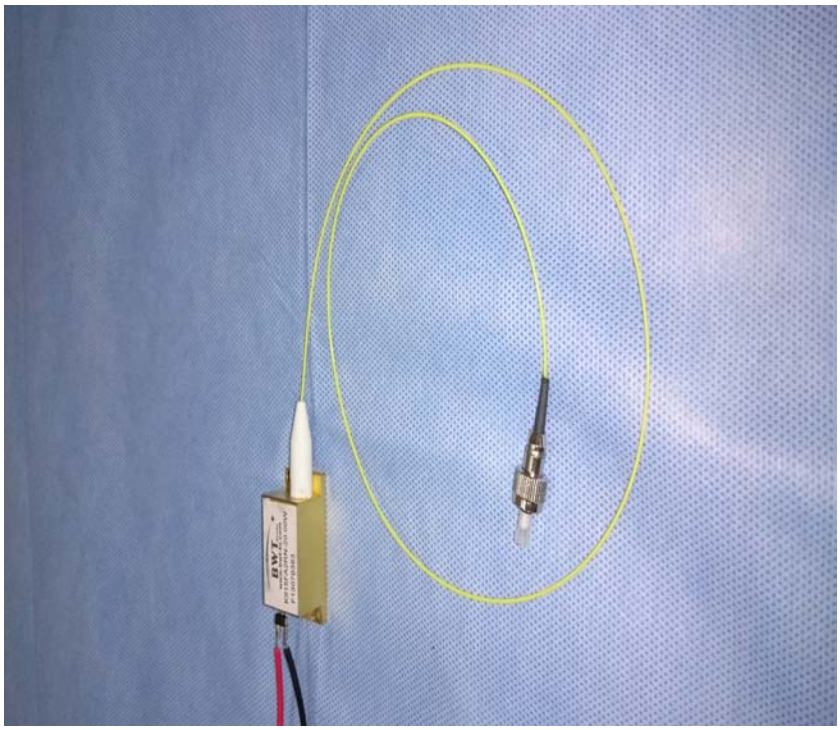


Photo 3: Laser diode coupled with 0.1 mm optical fiber



Photo 4: Showing inner view of the machine-Laser diode with cooling fan and power supply

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Photo 5: Kidney stone broken partially by Nd: YAG Laser

IV. Discussion

Medical lasers cost in the range of USD 50,000-75,000. It is beyond the capacity to afford particularly in third world countries like India. The machine [Photo1,3] is made in just USD 500 vs market cost of USD 50,000. It is commercialized at a reasonable cost of USD 1000. That makes it the cheapest medical laser in the market in that category. Such an invention is unique and reported for the first time in medical literature. A patent is registered for this innovation at Mumbai office.

ND: YAG Laser has vast applications in medical sciences for the treatment of tumors [4] Nd: YAG lasers emitting light at 1064 nm have been the most widely used laser for laser-induced thermotherapy, in which benign or malignant lesions in various organs are ablated by the beam. Other applications are hereditary hemorrhagic telangiectasi a [5], head and neck hemangiomas [6], in surgical gastroenterology [7], for tracheobronchial lesions [8,9] etc. Nd: YAG lasers are used in ophthalmology to correct posterior capsular opacification, a condition that may occur after cataract surgery, and for peripheral iridotomy in patients with acute angle-closure glaucoma, where it has superseded surgical iridectomy. Frequency-doubled Nd: YAG lasers (wavelength 532 nm) are used for pan-retinal photocoagulation in patients with diabetic retinopathy. In certain cases these lasers are also used to treat eye floaters. [10].

In oncology, Nd: YAG lasers can be used to remove skin cancers.[11] They are also used to reduce benign thyroid nodules,[12] and to destroy primary and secondary malignant liver lesions.[13] [14]To treat benign prostatic hyperplasia (BPH), Nd: YAG lasers can be used for laser prostate surgery—a form of transurethral resection of the prostate. These lasers are also used extensively in the field of cosmetic medicine for laser hair removal and the treatment of minor vascular defects such as spider veins on the face and legs. Nd: YAG lasers are also used to treat Venous Lake lip lesions.[15] Recently used for Dissecting cellulitis of the scalp, a rare skin disease.[16] Using hysteroscopy the Nd: YAG laser has been used for removal of uterine septa within the inside of the uterus.

In Dentistry, Nd: YAG dental lasers are used for soft tissue surgeries in the oral cavity, such as gingivectomy, periodontal sulcular debridement, LANAP, pulpotomy, frenectomy, biopsy, and coagulation of graft donor sites.

The same 20- watt 950 nm ND: YAG diode laser machine can be used as a cautery machine by adding a laser guide (Photo 5) to the optical fiber. It can be used as an end ocautery in laparoscopy [Photo 6] by adding a long laser guide. The Laser cautery is far more versatile and superior to the conventional electro cautery. Carbon does not form at the tip of the fiber which needs to be cleaned periodically as in electro cautery. Laser cautery is far more precise and damage to surrounding tissues is negligible as compared to electro cautery. The lasers have great photo coagulating properties. Bleeding that does not stop with electro cautery stops with laser cautery. The use of lasers in laparoscopy is quite new.

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Photo 6: Laser guide for open surgery

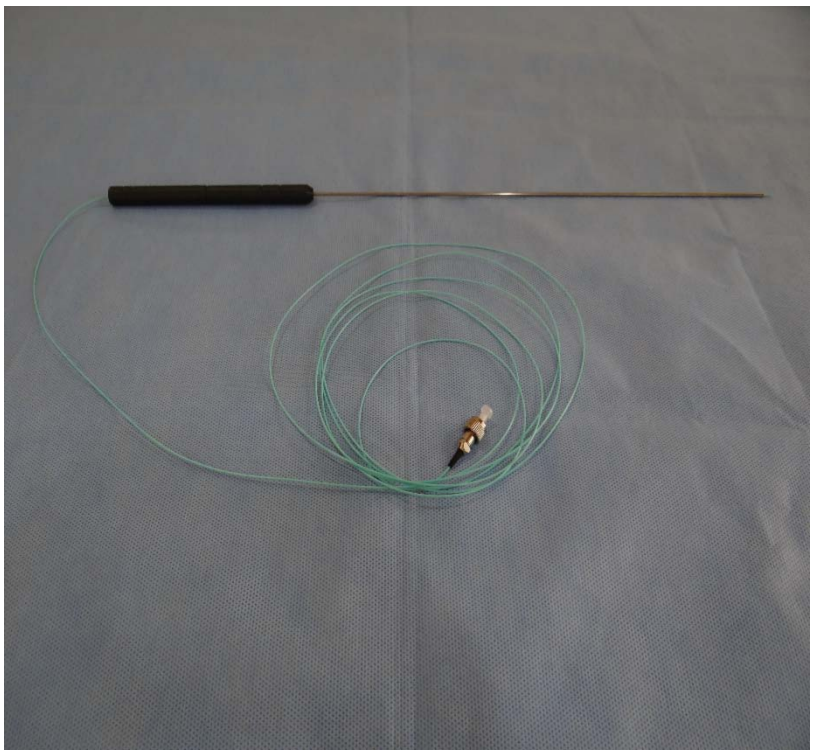


Photo 7: Laser guide for laparoscopic surgery

The 1 mm optical fiber jacket can pass through working channel of rigid as well as flexible endoscopes. The author has used the machine for breaking bladder, ureteric and kidney stones (Photo 5) and for photocoagulation of facial hemangiomas. The laser was found to be more effective as lithotripter particularly for gall stone which are softer that renal stones.

The author has also used the machine for following applications. Laser tissue welding (Photo 8) is a novel technique where 40 % human albumin is put into

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a wound and 5 -Watt Infrared laser of 950 nm is applied over it. At 60-degree centigrade temperature it leads to a formation of a watertight bond of proteins over the tissues by the photo polymerization effect of laser and gives about two weeks of healing in just two minutes. A costly USD 10,000 machine is used for the purpose which is also not commercially available. My laser machine kept at 5-watt power achieved the same result. Tissues such as spleen, liver, pancreas, brain and kidneys where sutures do not hold well are indications for this technique.



Photo 8: Circumcision done with Gluteraldehyde albumin dye induced laser tissue welding

Gluteraldehyde Albumin glue Induced Laser Tissue Welding (2), (Photo 8): 0.9 ml 40 % human albumin is taken in 1 ml syringe and mixed with 0.1 ml of 10 % glutaraldehyde solution. The syringe is shaken vigorously to mix both the components. My Laser machine is set at 5 watts power and illuminated over this bond for 60 seconds to polymerize it. It forms a watertight strong bond over the tissues. The technique has vast applications in surgery such as for sealing post-operative wounds, CLW closure, reinforcement of suture line of bowel an astomos is, Bowel perforation, sealing dura repair, hypospadias surgery, urological operations etc.

Frenotomy Operation by Methylene blue Dye enhanced Laser Tissue Cutting (3), (Photo 8) This new technique is reported for the first time in the medical literature. Cheap infra-red Lasers do not act on tissues which are of the same color and in fact reflected. To solve this problem, I infiltrated tissues with opposite color Methylene blue which is already FDA approved for use in human body. My Infrared laser now acted only on blue infiltrated areas and saving surrounding tissues of any co lateral damage. Because of the Methylene blue dye, my cheap infrared laser can be used for this purpose. Otherwise, a high frequency 2000 nm and high wattage (40 Watt) laser has to be used which is extremely costly (USD 50,000) and is not affordable to most surgeons. The only disadvantage of laser against electrocautery was cost which is eliminated in this technique. The technique also becomes a foundation as a learning experience for its wider application in other areas of surgery such as Photocoagulation in liver surgery, renal surgery, brain surgery, on pancreas etc.

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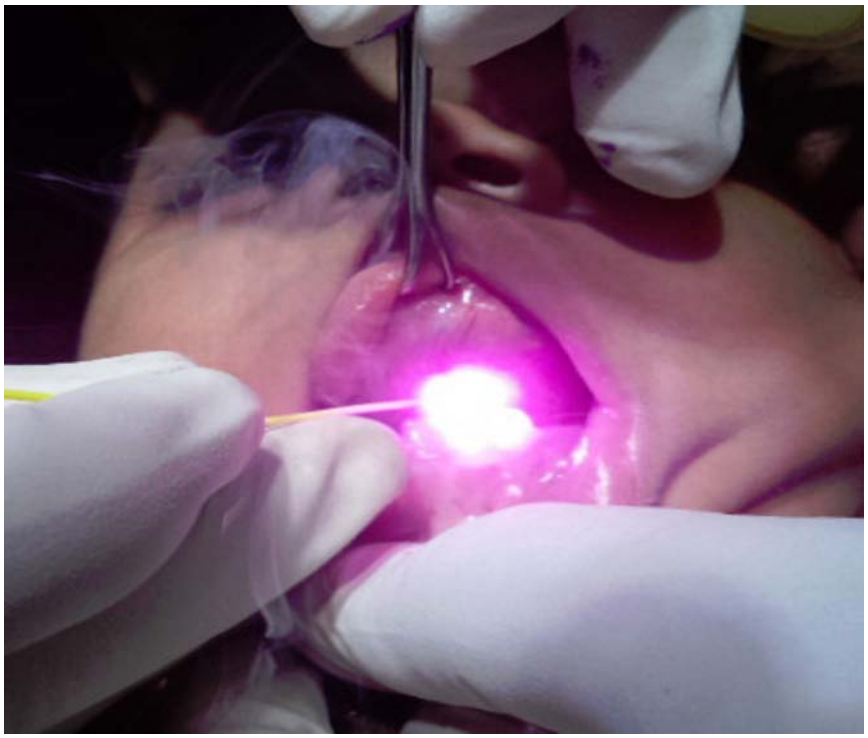


Photo 8: Frenotomy operation done by methylene blue dye enhanced laser tissue cutting

V. Conclusion

I successfully developed the cheapest ND: YAG medical laser in the world which can act as a lithotripter for gall stones and kidney stones. It can also act as a laser cautery in open and laparoscopic surgery. The machine has a potential to make a variety of laser surgeries affordable to a vast number of patients worldwide.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
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.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

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



Format Structure

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

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative 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) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

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

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning 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 a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be 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. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). 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: Authors are advised 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. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. 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.

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

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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

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

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. 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 for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

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

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon 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 for 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 of 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 criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to 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 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.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

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

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite 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 approaches 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. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a 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 limit the initial two items to no more than one line each.

Reason for writing the article—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 for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity 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 of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets 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 for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory 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 soundly written procedures segment allows a capable scientist to replicate 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 to give the least amount of information that would permit another capable scientist to replicate 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 section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show 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:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the 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—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and 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.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as 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. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give 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 manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit 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 section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an 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 implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully 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 the prospect, and let it drop at that. Make a decision as to whether each premise is supported or 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 an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of 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 other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

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

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.

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

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ISSN 9755896



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