IMAGE: A MAP OF THE STARS OF THE ORION CONSTELLATION

JournalPreview

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

London Journals Press

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London Journal of Medical and Health Research

Journal Content
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London Journals Press

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University do Cariri

ABSTRACT

The heating up in the civil construction sector, the red ceramic industries in the Cariri-CE region had an increase in the production of products, resulting in an increase in the consumption of raw materials and becoming one of the sectors that generate more waste in the region. The increase in the amount of waste is mainly due to the lack of qualified labor, little technology and lack of quality control, which have contributed to obtaining products with properties below expectations and which, in many cases, do not meet the technical standards, making it unfeasible for consumption and thus resulting in high product losses, generating a very large amount of waste.

Keywords: sustainable development, residue; red pottery, cariri of region – CE.

Classification: DDC Code: 658 LCC Code: HD31

Language: English

London Journals Press

LJP Copyright ID: 392861

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Sustainable Development for Residues Generated in the Red Ceramics Industries in the Region of Cariri – CE-Brazil

Maria Isabel Brasileiro Rodrigues[α], Jonathan Vinicius Moreira Torquato[σ], Davi Alves de Moura[ρ], Priscila Pereira Mota[ↀ], André Wesley Barbosa Rodrigues[¥] & Laédna Souto Neiva[§]

RESUMO

Com o aquecimento no setor da construção civil, as indústrias de cerâmica vermelha da região do Cariri-CE teve uma alta na produção dos produtos, resultando em um aumento no consumo de matérias-primas e tornando-se um dos setores que mais geram resíduos na região. O aumento na quantidade de resíduo se dá principalmente pela falta de mão de obra qualificada, pouca tecnologia e falta de controle de qualidade, os quais vêm contribuindo para a obtenção de produtos com propriedades aquém do esperado e que, em muitos casos, não atendem às normas técnicas, ficando inviáveis para o consumo e acarretando, desta maneira, em elevadas perdas de produtos, gerando uma quantidade de resíduo muito grande. A geração de resíduos torna-se um agravante ainda mais intenso quando: grande parte do resíduo não recebe destinação correta, sendo lançados na natureza, aos redores da própria fábrica onde, possivelmente, deveria ser uma área de preservação ambiental permanente. Esse estudo teve como objetivo avaliar a inserção do resíduo na própria massa argilosa para produção dos produtos cerâmicos em substituição a argila menos plástica (magra), como forma de diminuir o impacto ambiental irreversível causado pelo descarte indiscriminado do resíduo. A partir da análise das propriedades físicas, química e mecânica estudada, a adição do resíduo na massa cerâmica em substituição a argila menos plástica (magra) mostrou-se favorável para produção de tijolos.

Palavras-chave: desenvolvimento sustentável. resíduo. cerâmica vermelha. região do cariri - CE.

Author α ¥ §: Doctor Teacher of Federal University do Cariri - UFCA – Brazil
σ: Graduate of Federal University of Cariri – UFCA
ρ ↀ: Graduating of Federal University of Cariri-UFCA

ABSTRACT

The heating up in the civil construction sector, the red ceramic industries in the Cariri-CE region had an increase in the production of products, resulting in an increase in the consumption of raw materials and becoming one of the sectors that generate more waste in the region. The increase in the amount of waste is mainly due to the lack of qualified labor, little technology and lack of quality control, which have contributed to obtaining products with properties below expectations and which, in many cases, do not meet the technical standards, making it unfeasible for consumption and thus resulting in high product losses, generating a very large amount of waste. The generation of waste becomes an even more intense aggravating factor when: a large part of the waste does not receive the correct destination, being thrown into nature, around the factory itself, which possibly should be an area of permanent environmental preservation. This study aimed to evaluate the inclusion of the residue in the clayey mass for the production of

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ceramic products, replacing less plastic (lean) clay, as a way to reduce the irreversible environmental impact caused by the indiscriminate disposal of the residue. From the analysis of the physical, chemical and mechanical properties studies, the addition of the residue to the ceramic mass in replacement of the less plastic (lean) clay proved to be favorable for the production of bricks.

Keywords: sustainable development, residue; red pottery, cariri of region – CE.

I. INTRODUÇÃO

A indústria de cerâmica vermelha no Brasil corresponde a 4,8% da Indústria da Construção Civil, segundo a Associação Nacional da Indústria Cerâmica[1]. A mesma associação relata que há aproximadamente 6.903 cerâmicas e olarias no Brasil responsáveis por 300 mil empregos diretos e 900 mil de indiretos, gerando um faturamento anual de R$ 18 bilhões [(1)]. No Estado do Ceará, como um todo, existem aproximadamente, 260 fábricas de produtos de cerâmica vermelha em atividade, distribuídas na sua maioria em pelo menos 10 municípios[2]. Atualmente, existe cerca de dois Arranjos Produtivos locais no Ceará, um centrado no município de Russas e outro no sul do Estado, na região conhecida como Região do Cariri. Na região do Cariri, esse número chega a aproximadamente 30 empresas [3], sendo estas indústrias de minerais não metálicos, caracterizada como indústria nativa da região, tendo uma estrutura de gestão marcadamente familiar, onde a presença das micro e pequenas olarias ainda são importantes. O processo de fabricação, na maioria das fábricas, é simples, envolvendo a mistura de dois tipos de argilas (argila mais plástica (gorda) com adição de uma argila menos plástica (magra)) com água e passando por uma extrusora. Segundo Carvalho[4], o processo em sua totalidade, na maioria das cerâmicas, não tem controle eficaz, e há imensas perdas em todas as suas fases. Os materiais cerâmicos estão entre aqueles mais tradicionalmente utilizados na construção civil. A indústria da cerâmica estrutural ou vermelha é uma atividade de base ao possibilitar a construção civil, em geral, desde produtos mais simples aos mais sofisticados.

Atualmente, há uma grande quantidade de indústrias de cerâmica vermelha na região do Cariri, devido ao baixo custo do investimento inicial e a facilidade de matéria-prima encontrada para esse fim. Entretanto, boa parte do produto final dessas empresas não atende às normas especificadas de qualidade e ainda possuem os índices de produtividade baixos. Os principais motivos para essa problemática são: a falta de mão-de-obra qualificada, desconhecimento da matéria-prima e a falta do controle de qualidade dos produtos. Consequentemente, há imensas perdas de produtos que resultam em uma grande quantidade de resíduos gerados. Em indústria de cerâmica vermelha, situada na cidade de Crato – CE, na qual esse estudo vem sendo realizado, pôde-se constatar que a mesma possui uma perda de mais ou menos 10% de sua produção de tijolos, acarretando em uma grande produção de resíduo e que no final, todo esse resíduo encontra-se descartado aos arredores da fábrica.

Independentemente da reutilização do resíduo gerado, a sua inserção na própria massa para fabricação de novos tijolos acarreta benefícios de ordem econômica, social e ambiental, vislumbrando umas das melhores alternativas para reduzir as perdas econômicas e ambientais.

Pesquisas anteriores mostram que a incorporação desses resíduos em massas cerâmicas é possível e que ainda pode resultar em benefícios para as etapas de processamento[5]. A reciclagem e a reutilização de resíduos como novos materiais ultrapassam o contexto da análise da resistência mecânica e estabilidade dimensional de um novo produto e deve ser inserida em um contexto mais geral de avaliação ambiental. Esta avaliação envolve um melhor conhecimento do produto e consequentemente, sua caracterização e análise comportamental[6]. Segundo Silva[7], todo processo de industrialização constitui-se num dos componentes principais da poluição ambiental, podendo originar grandes conflitos, evitáveis quando tomadas providências que promovam o desenvolvimento harmônico e sustentável.

Resíduos descartados nas indústrias da cerâmica vermelha, referentes ao descarte de produtos anteriormente processados e após queima, são

materiais não plásticos, que provavelmente pode vir a ser incorporado em massas para a produção de produtos cerâmicos, substituindo a incorporação de argilas não plásticas ou pouco plásticas[8].

Diante disso, esse estudo coletou argilas usadas nas massas de uma indústria local, assim como quantidades de resíduos gerados de produtos já queimados, com a finalidade de estudar a incorporação dos mesmos nas massas cerâmicas da própria empresa geradora do resíduo, avaliando propriedades química e físico-mecânicas dos corpos de prova para produtos a serem produzidos. A finalidade é de que os próprios resíduos gerados pela indústria voltem para a produção como matéria-prima cerâmica, contribuindo provavelmente para a preservação ambiental, para o aperfeiçoamento de política social e incentivar os gestores das indústrias a dar um destino apropriado para seu resíduo.

II. MATERIAIS E MÉTODOS

Os materiais utilizados foram coletados de empresas do setor da cerâmica vermelha da região do cariri-CE, sendo eles os resíduos queimados e as argilas (mais plástica (gorda) e a menos plástica (magra). Os resíduos queimados, provenientes do processo de fabricação de telhas, tijolos e lajotas, os quais já haviam sido processados e queimados nas temperaturas de sinterização, foram coletados de locais impróprios para o descarte. Após a coleta dos resíduos, eles foram submetidos à trituração e posteriormente peneiramento em peneira 40 mesh, para homogeneizar o tamanho das partículas. A argila mais plástica (gorda) foi seca em estufa a 110 ºC por 24 h, moída em um moinho martelo e passada em peneira 40 mesh. A análise química da argila mais plástica (gorda) e do resíduo foi determinada por análise semi-quantitativa sem padrões com análise de elementos químicos de flúor a urânio, em espectrômetro por fluorescência de raios X (Axios Advanced Panalytical). Foram preparadas posteriormente três massas cerâmicas contendo adições de 5%, 10% e 15% em peso de resíduo juntamente com a argila mais plástica (gorda) e também foi usada a massa pronta utilizada na indústria para fabricação dos produtos. Para cada massa com adição do resíduo e argilas puras (mais plástica (gorda) e a menos plástica (magra)) foram determinados os índices de plasticidade pelo método de Atterberg. Para cada massa com adição do resíduo e a massa pronta da indústria confeccionou-se 10 corpos de prova. Os corpos de prova foram conformados por prensagem uniaxial em formas retangulares com peso médio de 25 gramas cada, secos a temperatura ambiente por 24 h e, após, em estufa a 110°C até massa constante. Após, foram pesados e medidos (largura, comprimento e espessura) e seguiram para o processo de queima em forno, no laboratório, a temperaturas que variaram de 850 a 1050°C com patamar de queima de 2 horas. As características físicas determinadas foram retração linear de secagem e queima, absorção de água, porosidade e perda de massa. As determinações das características físicas seguiram os ensaios da NBR 15.310 [8]. Os corpos de prova também passaram por ensaio do módulo de ruptura à flexão.

III. RESULTADOS E DISCUSSÃO

Na tabela I esta apresentada às composições químicas do resíduo e das argilas coletadas, obtidas por fluorescência de raios X. A análise mostrou que a sílica (SiO_2) é o principal constituinte das amostras com percentuais que variam de 65,36% a 57,34%, seguido da alumina (Al_2O_3) que varia de 31,13% a 18,5% e do óxido de ferro (Fe_2O_3) que variou de 8,07% a 5,75%. Os compostos SiO_2 e Al_2O_3 indicam a provável presença do argilomineral do grupo caulinita. O óxido de ferro proporcionou a cor avermelhada dos blocos cerâmicos. Além disso, observou-se baixos teores de óxidos alcalinos (K2O e Na2O) e alcalinos terrosos (MgO e CaO), sendo os óxidos alcalinos importantes para as formulações cerâmicas, pois atuam como agentes fundentes contribuindo para a sinterização das peças. Os óxidos minoritários são atribuídos a prováveis fases acessórias e foram incluídas na análise. De maneira geral, observa-se uma similaridade entre as três amostras quanto aos resultados da análise química. Há também a presença do titânio, em forma de óxido ou como impureza em outros

minerais. Esse óxido tende a intensificar a cor desenvolvida por outros elementos, como no caso o Ferro [5]. Comparando-se o resíduo utilizado no estudo com outro resíduo estudado na região do Rio de Janeiro[10], notou-se uma similaridade entre os percentuais dos principais constituintes (SiO_2, Al_2O_3 e Fe_2O_3) mesmo sendo em regiões diferentes.

Tabela I: Composição química das amostras coletadas

Amostra	SiO_2	Al_2O_3	Fe_2O_3	K_2O	MgO	TiO_2	CaO	MnO	Cr_2O_3	V_2O_5	Rb_2O
Resíduo	65,36%	18,50%	8,07%	4,04%	2,64%	0,96%	0,22%	0,067%	0,062%	0,052%	0,02%
Argila Gorda	61.95%	22.68%	6.4%	3.28%	3.74%	0.96%	0.78%	0,16%	0,16%	0,16%	0,16%
Argila Magra	57.34%	31.13%	5.75%	2.17%	1.32%	0.85%	--	1,39%	1,39%	1,39%	1,39%

Fonte: O autor

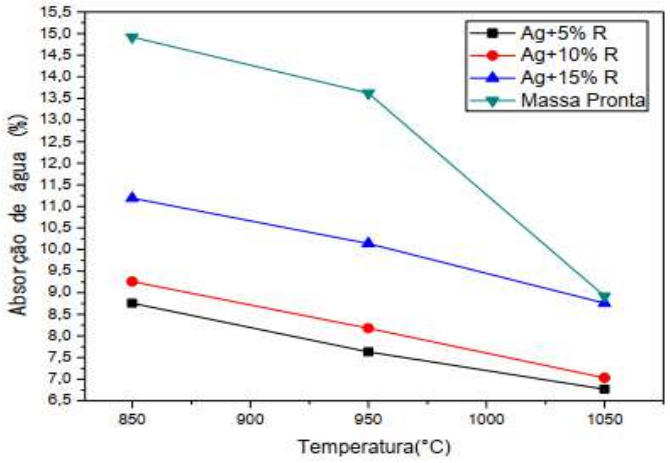
Na Tabela II esta apresentada os resultados do ensaio de plasticidade pelo método de Atterberg, realizado para as amostras de argila mais plástica (gorda), esta utilizada na composição das massas juntamente com o resíduo, do resíduo e das massas formuladas com argila mais plástica (gorda) com adição de 5, 10 e 15% de resíduo. De acordo com os valores apresentados na tabela II, os limites de liquidez das amostras variaram entre 43 a 54%, os limites de plasticidade variaram entre 21 a 27% e os índices de plasticidade variaram entre 17 a 32%. De acordo com o limite de liquidez, o limite de plasticidade e o índice de plasticidade as amostras encontram-se dentro do intervalo para cerâmica vermelha. A partir do Índice de Plasticidade e do Limite de Plasticidade pode-se construir um gráfico para classificação destas argilas em zona de extrusão ótima e zona de extrusão aceitável [11]. Para uma extrusão aceitável a argila deve apresentar Índice de Plasticidade entre 10 e 34% e Limite de Plasticidade entre 18 e 31%. No entanto, para uma extrusão ótima, a argila deve apresentar Índice de Plasticidade entre 15 e 25% enquanto o Limite de Plasticidade deve estar entre 18 e 25%. Para índices de plasticidade abaixo de 10, a extrusão pode ser problemática, causando grande mudança na consistência da argila com a variação de pequena quantidade de água. Para as adições na argila mais plástica (gorda) de 5, 10 e 15% do resíduo, os valores observados do Limite de Plasticidade foram iguais a 25,61%, 26,5% e 26,11%, respectivamente. Quanto menor Limite de Plasticidade menor quantidade de água para conformação [11]. Não foi possível determinar os índices para amostra do resíduo, tendo em vista que o mesmo já sofreu todas as transformações inerentes ao processo de queima.

Tabela II: Valores do Limite de liquidez, limite de plasticidade e índice de plasticidade pelo Método Atterberg das amostras

Amostra	Limite de liquidez	Limite de plasticidade	Índice de plasticidade
Argila Gorda	53,12%	21,62%	31,5%
Resíduo	--	Não plástico	--
5%	48,35%	25,61%	22,74%
10%	47,99%	26,52%	21,47%
15%	43,75%	26,11%	17,63%

Fonte: O autor

Na Figura 1, está ilustrado o gráfico com os resultados de absorção de água para as massas cerâmicas sinterizadas em diferentes condições de temperatura.

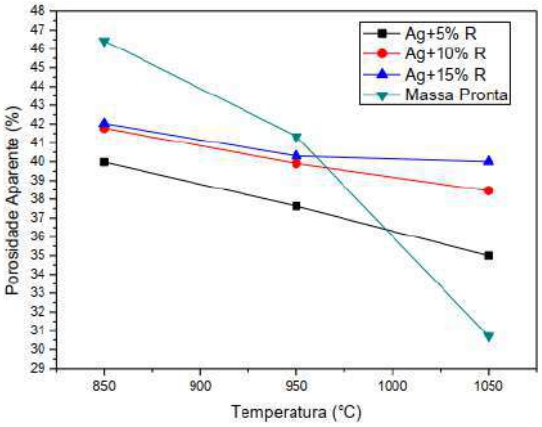


Fonte: O autor

Figura 1: Absorção de Água das massas cerâmicas sinterizadas em diferentes condições de temperatura

Verificou-se que com o aumento da temperatura houve uma diminuição na absorção de água de todas as amostras analisadas. Isto, provavelmente, está relacionado com o grau de vitrificação, que aumenta com a temperatura de sinterização e diminui a absorção de água devido a redução da porosidade. Esse processo de vitrificação ocorre devido à formação de uma fase líquida dentro da peça, proporcionado pelo aumento da temperatura, a qual preenche os poros existentes, aumentando o coalescimento das partículas não fundidas [12]. Segundo a norma ABNT NBR 15270-2[13], o índice máximo de absorção de água indicado para bloco cerâmico é de 22%, e para telhas do tipo romana segundo a ABNT NBR 13582[14] é de 18%. Observou-se que todas as amostras analisadas apresentaram valores dentro do exigido pela norma em todas as temperaturas usadas e, portanto, tem potencial para ser aplicado em produtos de cerâmica vermelha.

Na Figura 2, está ilustrado o gráfico com os resultados de porosidade aparente para as massas cerâmicas sinterizadas em diferentes condições de temperatura.



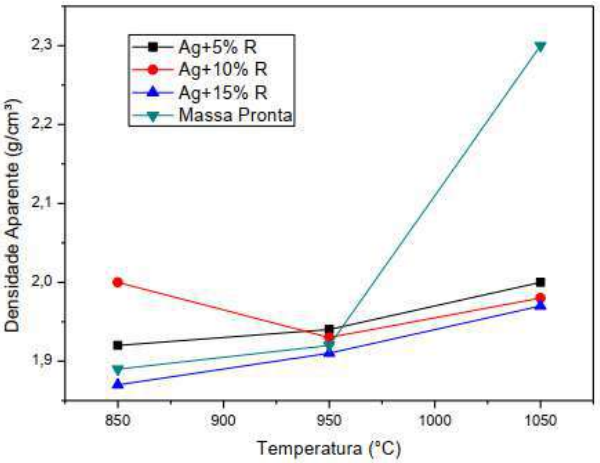
Fonte: O autor

Figura 2: Porosidade Aparente das massas cerâmicas sinterizadas em diferentes condições de temperatura

Baseado no gráfico da Figura 2 verificou-se que com o aumento da temperatura houve diminuição na porosidade para todas as composições. Este resultado corroborou com os resultados obtidos para absorção de água (Fig. 1). Pôde-se observar também que o acréscimo do teor de resíduo na argila mais plástica (gorda) propiciou um aumento da porosidade aparente e da absorção de

água das massas cerâmicas. Isto, possivelmente, foi decorrente de um empacotamento descontínuo, com a presença de vazios, ocasionado pela incorporação do resíduo [5]. De acordo com Souza Santos [15], os valores da porosidade aparente para a produção de blocos cerâmicos devem está entre 5% e 35%. Foi verificado que somente a massa pronta e a argila mais plástica (gorda) com a incorporação de 5% de resíduo, queimadas a 1050°C, encontram-se dentro do intervalo indicado citado anteriormente. Dessa forma, a adição de 5% de resíduo não afetou negativamente a porosidade aparente.

Na Figura 3, está ilustrado o gráfico com os resultados de densidade aparente para as massas cerâmicas sinterizadas em diferentes condições de temperatura.

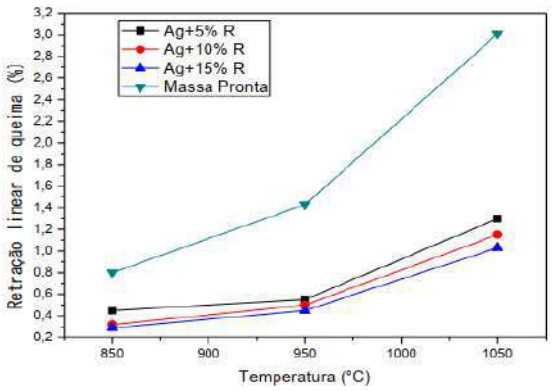


Fonte: O autor

Figura 3: Densidade Aparente das massas cerâmicas

A partir do gráfico da Figura 3, pôde-se observar que com o aumento da temperatura houve um aumento na densidade aparente de todas as amostras analisadas, e que a adição do teor de resíduo na argila mais plástica (gorda) prejudicou a densificação. Desta maneira, esses resultados corroboram com os resultados da absorção de água e porosidade analisados anteriormente.

Comparando esses resultados ao estudo de Gouveia [16], verificou-se que os valores estão próximos. Segundo Souza Santos [15], os valores de densidade aparente das argilas devem estar entre 1,7 e 2,1 g/cm³. Logo, a incorporação de resíduo na argila mais plástica (gorda) não interferiu negativamente nos valores de densidade aparente. Os resultados da retração linear de queima dos corpos de prova estão representados no gráfico da Figura 4.



Fonte: O autor

Figura 4: Retração linear das amostras em função da temperatura de queima

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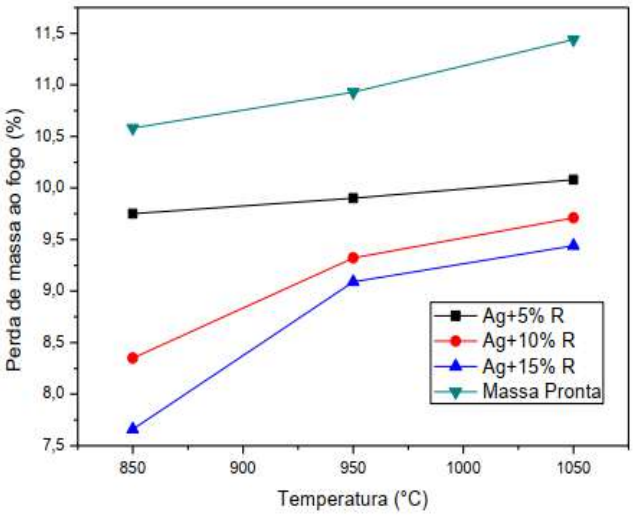
A partir do gráfico da Figura 4, verificou-se que com a elevação da temperatura de queima houve um aumento da retração linear das composições. Este comportamento foi mais pronunciado na temperatura de queima 1050°C. Notou-se também que o acréscimo de teor de resíduo na argila mais plástica (gorda) reduziu a retração linear de queima, semelhante ao evidenciado no estudo de Vieira, Teixeira e Monteiro [17]. Esse resultado encontra-se de acordo com os dados anteriormente apresentados nas Figuras 3 e 4.

Este comportamento, já esperado, foi decorrente ao maior grau de sinterização, ocorrido com o aumento da temperatura, que faz com que haja a formação de uma maior quantidade de fase líquida e esta por sua vez, age unindo as partículas e retraindo o corpo cerâmico. Segundo a literatura[15], no processamento industrial a retração linear de queima considera-se ótima com valores menores que 1,5% e com a situação aceitável entre 1,5 a 3%. Foi observado que a argila mais plástica (gorda) com adição do resíduo e a massa pronta ficaram dentro dos valores citados anteriormente.

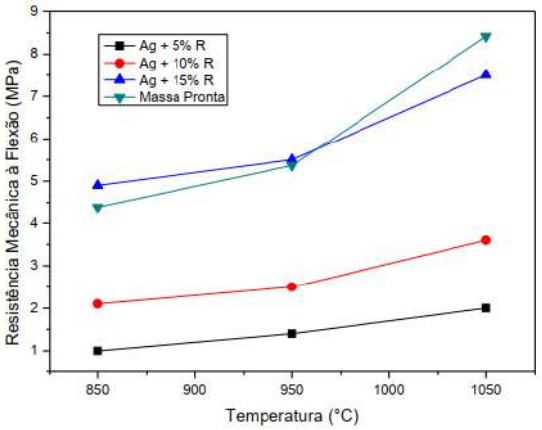
Na Figura 5, está ilustrado o gráfico de perda de massa ao fogo para cada amostra com a temperatura de queima. De acordo com os resultados de perda de massa ao fogo para as massas cerâmicas analisadas, houve um aumento na perda de massa conforme a elevação de temperatura. Isto acontece devido à perda de águas (água livre, adsorvida e de constituição) e matéria orgânica durante o processo de queima [18]. Foi observado que a perda de massa ao fogo para as massas com a incorporação de resíduo foi menor em relação à massa pronta utilizada na indústria e esse valor subiu quanto maior foi o teor do resíduo. Segundo estudo realizado por Gouveia[16] este comportamento é decorrente do resíduo durante o primeiro processo de sinterização, o qual já passou pelo processo de perda de matéria orgânica e outras reações inerentes ao processo de sinterização. Já a massa pronta apresentou valores mais expressivos de perda de massa ao fogo, devido à decomposição dos materiais argilosos. Assim, nesse estudo, a adição de resíduo na massa cerâmica minimizou os efeitos da perda de massa e não acarretaram danos às massas cerâmicas, assim como aconteceu nos estudos realizado por Gouveia [16].



Fonte: O autor

Figura 5: Perda de Massa ao Fogo das massas cerâmicas

A ruptura a flexão indica a capacidade do material em suportar esforços exercidos por uma carga podendo resultar em ruptura do mesmo. Os resultados de ruptura a flexão estão representados na Figura 6.



Fonte: O autor

Figura 6: Resistência Mecânica à Flexão das massas cerâmicas sinterizadas em diferentes temperaturas

A partir do gráfico da Figura 6, foi possível verificar que com o aumento da temperatura de queima, houve aumento da resistência mecânica.

Observou-se que os valores de módulo de ruptura aumentaram com o aumento da temperatura e que são diretamente proporcionais à densidade aparente das peças e inversamente à absorção de água. Observa-se também que a adição do resíduo contribui para o aumento da resistência mecânica, sendo esse aumento evidenciado em temperaturas superiores. Desta forma, ficou evidenciado que a geração de um corpo cerâmico com uma maior resistência, indica a ocorrência da eliminação dos vazios provocados pela queima a esta temperatura. De acordo com a ABNT NBR 15270[13], os limites de tensão à flexão indicados para uso em cerâmica devem ser: Trf ≥ 1,5 MPa para tijolos. Foi observado que a massa pronta e a argila gorda com a incorporação de resíduo de 5% na temperatura de 1050°C e com a adição de 10 e 15% nas três temperaturas estudadas, ficaram dentro dos valores da Norma. Observou-se também que as amostras com 15% de resíduo apresentaram valores muito próximos da massa utilizada pela indústria mostrando que tem potencial para ser aplicado em produtos de cerâmica vermelha.

IV. CONCLUSÕES

Após analisar dados dos ensaios realizados com as massas formuladas com o resíduo de tijolos já queimados adicionados a argila plástica (gorda) da indústria cerâmica local, foi possível concluir que:

- A temperatura se mostrou um fator decisivo para produção de peças cerâmicas e influencia diretamente nas propriedades tecnológicas do produto cerâmico. O aumento da temperatura propiciou uma melhora nas propriedades analisadas como um todo. Das condições avaliadas até 1050°C as massas cerâmicas com adição do resíduo apresentaram propriedades necessárias para aplicação como cerâmica vermelha;
- A sílica (SiO2) é o constituinte majoritário das matérias-primas utilizadas, seguido do Al2O3 (óxido de alumina);
- As quantidades de resíduos adicionados à argila plástica (gorda) estão dentro dos estabelecidos como fontes de matéria-prima para a produção de um novo produto cerâmico alternativo;
- A partir da análise das propriedades física, química e mecânica estudada, a adição do resíduo na massa cerâmica em substituição a argila menos plástica (magra) mostrou-se favorável para produção de tijolos, podendo retornar ao processo de produção e desta maneira, diminuir impactos causados pela destinação incorreta dos mesmos além de diminuir o uso de matérias primas não renováveis pela natureza.

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Effects of Inhaled Anesthetics on Global Warming and Solutions-A Review

Qingya Zeng & Gang Chen

Fujian Medical University

ABSTRACT

Accelerated changes in climate are already affecting human health, multiplying the existing health problems and increasing the burden of medical care. In recent years, however, it has been found that health care is also an important source of greenhouse gas emissions. Anesthetic gases are greenhouse gases that contribute to global warming, which will produce greenhouse effect by absorbing infrared radiation and react with ozone to destroy the ozone layer. Anesthesia providers have a duty to minimize unnecessary anesthetic gas emissions and lower environmental impact in practice. This paper will mainly discuss the impact of climate change on various aspects of human health, explore the impact mechanism of inhaled anesthetics on climate change, and put forward four solutions for reducing anesthetic gases - reduce, remove, recycle and replace by improving the "3R" principle of waste reduction. Only by changing the way of thinking and corresponding practice to realize the sustainability of anesthesia can we truly fulfill the desire of "do no harm".

Keywords: inhalation anesthetics global warming, ozone depletion human health.

Classification: DDC Code: 551.6 LCC Code: QC881.2.S8

Language: English

London Journals Press

LJP Copyright ID: 392862

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

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Accelerated changes in climate are already affecting human health, multiplying the existing health problems and increasing the burden of medical care. In recent years, however, it has been found that health care is also an important source of greenhouse gas emissions. Anesthetic gases are greenhouse gases that contribute to global warming, which will produce greenhouse effect by absorbing infrared radiation and react with ozone to destroy the ozone layer. Anesthesia providers have a duty to minimize unnecessary anesthetic gas emissions and lower environmental impact in practice. This paper will mainly discuss the impact of climate change on various aspects of human health, explore the impact mechanism of inhaled anesthetics on climate change, and put forward four solutions for reducing anesthetic gases - reduce, remove, recycle and replace by improving the "3R" principle of waste reduction. Only by changing the way of thinking and corresponding practice to realize the sustainability of anesthesia can we truly fulfill the desire of "do no harm".

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Author α σ: The Shengli Clinical Medical College, Fujian Medical University, Fuzhou, Fujian 350001, China. Department of endocrinology, Fujian Provincial Hospital, Fuzhou, Fujian 350001, China. Fujian Provincial Key Laboratory of Medical Analysis, Fujian Academy of Medical Sciences, Fuzhou Fujian, 350001, China.
Correspondence to: Gang Chen, Fujian Provincial Hospital,Fuzhou 350001, China.

I. INTRODUCTION

As an important part of the natural environment for human survival, climate is closely related to human activities. With the development of industry, the combustion of fossil fuels, the use of refrigerants, deforestation, the use of cars and other human activities have increased significantly, resulting in a significant increase in greenhouse gases. Greenhouse gas is any gas that can absorb infrared radiation in the atmosphere, including water vapor, carbon dioxide, methane, nitrogen oxides, chlorofluorocarbons, ozone, etc.

When short wave solar rays enter the atmosphere, about one third of the rays are directly reflected back into space, a small part is absorbed by water vapor, clouds and particles, while most of the rays are absorbed by the earth's surface, and then radiated back to the atmosphere in the form of long wave rays. The greenhouse gases in the atmosphere absorb these radiations to keep the earth warm. This process is referred to as the greenhouse effect. However, excessive greenhouse effect will lead to global warming[1]. According to the report of the World Meteorological Organization, the global mean temperature in 2020 is 1.2±0.1℃ above the 1850–1900 baseline temperature, which places 2020 as one of the three warmest years on record globally, and the mean temperature in the past five and ten years is also the highest on record[2].

Global warming affects human health, global ecosystem stability and even socio-economic development. Although some effects are beneficial, such as increasing crop yield and available water in some areas and reducing mortality caused by cold, in general, scientists believe that most of the effects of climate change on human beings are adverse[3]. The consequences of global warming, such as increased frequency of heat waves, changes in precipitation, sea-level rise, increased extreme weather events (drought, flood, hurricane, wildfire, etc.),the deterioration of air quality and environmental sanitation, have caused great harm to humans and ecosystems[4][5].

Although scholars pay more and more attention to the impact of climate change on health and its coping strategies, the global response to climate change has been muted, and fail to meet the commitment made in the Paris agreement to limit global warming to "far below 2℃"[6]. Climate change still causes millions of deaths every year.

The World Health Organization has recognized it as the number one threat to human health in the 21st century[7]. Therefore, there is an urgent need for all countries to take strong action to address climate change and jointly protect our planet and the health of present and future generations.

In the health care industry, with the increase in the amount of surgery and the use of anesthetics, people began to pay attention to the impact of inhaled anesthetics on the global climate, but their contribution to the climate is largely ignored because they are "medically essential"[8][9]. In the past decade, different authors have discussed the impact of inhalation anesthesia on the environment[8]-[12]. It has been established that all inhaled anesthetics are potent greenhouse gases and can destroy the ozone layer. Yet the solutions that will reduce their impact on the environment have not been clearly formulated. Therefore, this review mainly summarizes the impact of climate change on human health, the effects of anesthetic gases on the global environment, and the measures to reduce these effects, so as to provide suggestions for anesthesiologists' decision-making in anesthesia practice.

II. IMPACT OF GLOBAL WARMING ON HEALTH

Global warming will have a direct or indirect impact on human health. Direct impact is usually caused by extreme weather, such as death or injury caused by heat wave, flood, storm, etc.[3]. The change of disease transmission mode, air pollution, water pollution, fresh water shortage, reduction of food production and population migration caused by climate change will indirectly affect human health and bring infectious, nutritional, psychological and allergic diseases[1].

2.1 Infectious Diseases

Climate is one of the important factors affecting the spread of infectious diseases. The continuous warming of the global climate and the frequent occurrence of extreme climate will directly or indirectly aggravate the spread of most infectious diseases. Temperature is a major factor in the prevalence of vector-borne diseases. It can influence the survival, reproduction and life cycle of pathogens[13], as well as the survival, growth, reproduction and distribution of vectors and their ability to transmit pathogens[14]. Temperature, humidity and precipitation are important climatic factors affecting the incidence and transmission of malaria. Among them, climate warming provides suitable habitat for the vector Anopheles, and promotes the growth and development of them and their pathogens, so as to increase the chance of human infection[15]. Dengue virus and its vector Aedes are also sensitive to climatic conditions, especially temperature. Rising temperature can accelerate the reproduction of dengue virus[16], affect the life cycle, distribution density, range, and behavior of mosquitoes, which will lead to the epidemic of dengue fever, but the temperature above a certain threshold will reduce the incidence of dengue fever[13][17].

Higher temperatures and changes in rainfall can affect water and food-borne diseases, which is likewise the reason for the significant increase in diarrhea cases. Algae and plankton provide a habitat for Vibrio cholerae. When the sea water warms or becomes eutrophicated, marine phytoplankton multiply in large numbers (such as red tide caused by algae flooding), which will be conducive to the outbreak of cholera[13][18][19].

Similarly, the increase in temperature within a certain range will also accelerate the reproduction speed of Schistosoma japonicum, Salmonella, Escherichia coli, Shigella and typhoid bacilli[13][16]. If rainfall increases and floods break out, the water flow containing pathogens is more likely to pollute drinking water and irrigation water, greatly increasing human exposure, which often occurs in developing countries with insufficient infrastructure[14][18]. In arid areas, waterborne pathogens are concentrated in the only water, will

also increase water and food-borne diseases[13][20]. As the WHO said, rainfall will affect the transportation and transmission of infectious substances, while temperature will affect their growth and survival[3].

In addition, transmission of diseases such as plague, rabbit fever, yellow fever, Kala Azar, Lyme disease, West Nile disease, tick-borne encephalitis and hantavirus lung syndrome may also be affected by climate change[13][14][16][21]. It is worth mentioning that although the incidence of extreme weather events is low, the impact on infectious diseases is fierce. For example, the famous El Nino phenomenon will lead to the outbreak of malaria, dengue fever, cholera, avian influenza, hantavirus, Rift Valley fever, plague and other diseases[13][14][17][22].

2.2 Respiratory, cardiovascular and neurological system

The increase of temperature and CO_2 concentration will affect the growth of plants and prolong the pollen season, thereby generating more pollens with enhanced allergenicity[23]-[26]. The thunderstorm will gather pollen grains and provoke the release of a large number of respirable allergic particles after they rupture, which is conducive to penetrate deeper respiratory tract[25][27][28]. Warming in winter will increase mite growth and spore formation[28].

Climate warming, increased precipitation, floods and tsunamis will lead to environmental humidity and mold growth[25][26][28]. Smoke, particulate matter and ozone produced by wildfire and sandstorm are all sources of air pollution [25][26][29]. Exposure to these allergens such as pollen, mold and particles will induce more severe asthma and allergic rhinitis[24]-[28]. Exposure to more and more allergens may also make people that do not have allergies develop allergic symptoms[26]. Ozone is generated by photochemical reaction of oxygen in the atmosphere in the presence of ultraviolet and precursor pollutants (nitrogen oxides and volatile organic compounds), which is closely related to high temperature, drought and forest fire[26][29].

Exposure to pollutants such as ozone and particulate matter can induce airway inflammation, reduce lung function, increase the morbidity and mortality of respiratory diseases such as asthma, respiratory tract infections, chronic obstructive pulmonary disease, lung cancer and so on[25][27][29], especially in children and elderly people[26]. Heat causes dehydration of the body and disrupts lung perfusion, which can increase the number of deaths and acute morbidity among respiratory patients[25][27].

Extreme heat can rapidly increase airway resistance and trigger asthma symptoms by stimulating thermosensitive bronchopulmonary C-fiber nerves[28]. Extreme heat, air pollution and air allergens act synergistically to cause excessive mortality and hospital admissions for respiratory allergic respiratory diseases[28].

In the context of global warming, cardiovascular disease accounts for the largest proportion of heat induced mortality, and coronary heart disease is the main cause of death[30]. Some studies have found that the relationship between temperature and cardiovascular disease mortality is U-shaped, meaning that too low or too high temperature will both increase the risk of death[31]-[33], and the mortality even doubled to tripled under extreme high temperature[31]. Moreover, some categories of population are more vulnerable to the adverse effects of climate changes, such as elderly, those suffering from chronic vascular diseases, and low socio - economic conditions[33]. At high temperature, due to the need of heat dissipation, the body will activate sweat glands, expand blood vessels and increase skin blood flow, resulting in increased cardiac output, accelerated heart rate and increased burden on the heart[31][33]. During decompensation, high body temperature leads to systemic inflammatory response and oxidative stress, damages the structure and function of vascular endothelium and produces cytotoxic effects, which will lead to acute coronary syndrome, trigger arrhythmia and even heart failure[31]. In addition, dehydration may result in increases in the counts of platelets, red blood cells cholesterol levels and blood viscosity, promote, thrombosis, which can easily lead to atherosclerosis, coronary heart disease and thromboembolic diseases, and also increase the risk of ischemic stroke[30][33]-[35]. Electrolyte and

acid-base imbalance caused by high temperature is also considered as triggers of acute cardiovascular events[33]. Exposure to air pollutants (O_3, PM) will also increase plasma viscosity and heart rate, which is positively correlated with the morbidity and mortality of coronary artery syndrome, hypertension, arrhythmia, and cerebrovascular events[29][33][35].

The rise of global temperature increases the probability of environmental heatstroke. It is reported that 100% of patients with heatstroke presented with acute neurological symptoms, and 23.3% suffered convalescent or long-term neurological sequelae(prolonged coma, quadriplegia, ataxia, dysarthria and cognitive impairment)[35][36]. Elevated temperature will limit the storage of energy and oxygen, increase the number of free radicals and toxic substances, increase oxidative stress, damage mitochondria, destroy microvascular integrity, and induce neuronal apoptosis and necrosis, which may be the mechanism of stroke pathogenesis and aggravation[29][35]. The damage of high temperature to neurons leads to serious neurological dysfunction and exacerbates the course of neurodegenerative diseases such as dementia, Alzheimer's disease and Parkinson's disease[35]. Besides increasing the morbidity and mortality of ischemic stroke, air pollution will increase the likelihood of dementia and Alzheimer's disease through a variety of pathophysiological mechanisms[35].

2.3 Endocrine and Metabolic Diseases

Studies have shown that by controlling other relevant variables, there is a positive correlation between high temperature and the prevalence of obesity, and the impact of temperature on obesity is stronger than that of most physical activities, and almost the same as that of age and population density[37]. Temperature rise and extreme weather events may increase the morbidity and mortality of diabetes. Diabetics are more likely to experience dehydration, heatstroke and cardiovascular events than non diabetics[38]-[40], which may be related to their impaired thermoregulation mechanism and the use of certain drugs[41]. It is worth mentioning that extreme weather can bring negative influence on the stability and efficacy of insulin, the metabolic control of patients, as well as on access to healthcare, threatening the medical security for the vulnerable group of diabetes[38]-[41].

There are a large number of mitochondria containing uncoupling protein-1 (UCP-1) in brown adipose tissue(BAT) of the human body.

Uncoupling protein-1 can convert the energy generated by glucose and fat decomposition into heat energy instead of ATP, thus increasing energy consumption[42]. The lipids used in BAT will in turn increase the influx of glucose to skeletal muscles, thereby improving insulin sensitivity[40]. Under various stimuli such as cold exposure or sympathetic nerve stimulation, adipocytes expressing UCP-1 are developed in white adipose tissue, which are called beige adipocytes with thermogenic capacity[42][43]. Cold exposure can activate BAT, supplement beige adipocytes, increase thermogenic gene expression, and then improve energy consumption through adaptive thermogenesis to maintain core body temperature[43]. While long term heat exposure will lead to a decrease in the activity of brown and/or beige adipose tissue, reduce energy consumption and thermogenesis, and reduce insulin sensitivity[43]. On the other hand, the adverse effects of climate on agriculture lead to poor grain harvests and rising prices of healthy food, prompting people to consume relatively cheap, high-fat, high-sugar junk food, which are all possible causes of obesity, diabetes, and metabolic syndrome due to global warming[32][38][39][44]. Dehydration caused by global warming may stimulate the production of vasopressin and endogenous fructose. They can not only reduce water loss, but also stimulate fat accumulation and increase blood glucose, thus increasing the risk of these diseases[45]. Extreme climate leads to displacement, poor living conditions and scarcity of resources, resulting in the expansion of slums. This is also directly associated with the increased risk of obesity and diabetes[38].

In fact, the obesity epidemic will influence global warming in turn[37]. Obese patients may increase energy consumption in diet, transportation and

medical treatment, such as taking more cars, eating more processed food and using more medical resources, resulting in more greenhouse gases[44]. Obesity may increase the risk of many other diseases, such as type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, stroke and several cancers[44]. It also serves as a risk factor for metabolic syndrome[46].

In addition, air pollutants activate various cellular pathways and change gene expression, which may lead to decreased insulin sensitivity, increased adipose tissue deposition and β cell dysfunction, increasing incidence rate and prevalence of diabetes mellitus[41].

2.4 Skin Diseases and Eye Diseases

The increase in ultraviolet radiation caused by the depletion of the ozone layer due to greenhouse gases damages two organs that are directly exposed to sunlight, eyes and skin, which can cause sunburn, accelerate skin aging, and increase the morbidity of skin cancer, cataract and snow blindness[3][5][14][47][48]. According to relevant studies, diseases such as cancer of the cornea and conjunctiva, pterygium, macular degeneration, acute photokeratitis and photoconjunctivitis, climatic droplet keratopathy are also related to UVR irradiation[3][49]. Studies have shown that rising temperatures and ultraviolet have a synergistic effect, which will enhance the carcinogenic effects of ultraviolet[14][47][48][50].

Incidence rate of vitreous adenoviral conjunctivitis, fungal keratitis, pseudomonas keratitis, posterior vitreous detachment and retinal detachment may increase when the temperature rises[49]. Higher temperature is beneficial to the growth and reproduction of pathogens and the colonization of that on human skin, increasing the morbidity of skin infections, especially bacteria such as Staphylococcus, Streptococcus and intestinal bacteria, etc.[14][47].

Some infectious diseases caused by climate change also have clinical manifestations on the skin, such as dengue fever, cercarial dermatitis, hand-foot-and-mouth disease, Lyme disease, dracunculiasis and so on[14][48]. After hurricanes, floods, tsunamis and other disasters, the most common skin diseases are skin infections, which can be caused by various pathogens, even some rare pathogens[14]. High allergen counts and strong allergenicity will exacerbate dermatitis and pruritus in patients with atopic eczema[14]. It also exacerbates the exposure and duration of allergic conjunctivitis[49]. Global warming has also led to alterations in plants and animals, resulting in the increased incidence rate of contact dermatitis[14][24].

2.5 Mental Health

In recent years, people mainly pay attention to the impact of climate on physical health, but rarely focus on mental health. Diseases, death, migration, displacement, food insecurity and economic losses as a result of climate change and extreme climate will cause psychological panic, anxiety, sadness, loss, avoidance, emotional disorder, difficulty in concentrating, acute stress disorder, etc.[5][51][52][53]. The incidence of post-traumatic stress disorder and depression in climate related victims is higher than that in ordinary people, and there is a significant increase in suicidal ideation and suicide action among the victims[51]-[53]. Mental illness was considered to be most closely associated with death during a heat wave[51]. Studies suggest that in hot and dry weather, the morbidity, mortality and hospitalization rate of mental illness are higher. The reason may be that heat waves will exacerbate underlying mental illness and behavioral disorders[53]. The number of hospitalized patients with mania was positively correlated with temperature [16]. Depression and suicide rates are also linked to high temperature and air pollution. Extreme high temperature affects the work efficiency of workers, and they are prone to suffer dehydration, heatstroke, fatigue, work injury, kidney disease, etc.[4][51][54].

These factors will lead to psychological problems, socio-economic problems and impact physical and mental health. Climate change will also affect public health[51]. It's believed that as temperatures rise, acts of violence,crime and aggression occur more frequently[53][55]. Competition for limited resources will cause social instability and affect national and international security, which will bring about adverse mental health[51].

2.6 Other

The most direct impact of heat waves is the increase in morbidity and mortality of heat-related diseases (heat cramp, heat syncope, heat exhaustion, heatstroke)[45][56], especially for some vulnerable groups such as children, elderly, chronic patients, mental patients[56][57][58]. Under high temperature environment, human body temperature regulation disorder and excessive heat accumulation in the body will contribute to tissue damage and dysfunction of various organs and systems. Mild manifestations include dizziness, headache, thirst, sweating, panic, weakness, nausea, vomiting, etc.If not handled in time, it will develop into severe heatstroke, manifested with high fever, delirium, coma, seizures, water and electrolyte disorders and multiorgan failure including heart failure, ARDS, Liver failure and acute kidney injury, which can be life-threatening[35][36][56][58]. Rising temperature has resulted in an increase in patients with various kidney diseases, including acute kidney injury, chronic kidney disease, kidney stones and urinary tract infection[58][59][60]. Acute kidney injury is a frequent manifestation of heatstroke.

Repeated acute kidney injury can develop into chronic kidney disease, which mainly occurs in laborers who are often subjected to extreme heat conditions[58][59]. In addition, acute febrile diseases from vector-borne diseases, diarrheal and rodent-borne diseases caused by extreme weather are also well-recognized causes of acute renal injury[59]. Heat stress and dehydration predispose to urinary concentration and low urine volumes, increase the concentration of calcium and uric acid, and the acidity of urine, thus increasing the risk of kidney stones and urinary tract infection[58][59][60]. Climate change and extreme weather such as flood and drought will affect agricultural production and food transportation, resulting in food shortage and insecurity, and eventually causing malnutrition and stunting[38][52]. Insufficient intake of macronutrients and micronutrients will also affect the development of the immune system, leading to secondary immunosuppression in children[52]. Exposure to ultraviolet radiation directly or indirectly inhibits cell-mediated immune

to secondary immunosuppression in children[52]. Exposure to ultraviolet radiation directly or indirectly inhibits cell-mediated immune responses through various mechanisms, which can reduce vaccine efficacy and increase the morbidity of tumors and infections, but also reduce the incidence of allergic reactions and some autoimmune diseases[3][52][61].

III. EFFECTS OF INHALED ANESTHETICS ON GLOBAL CLIMATE

At present, commonly used inhalation anesthetics include volatile liquids and gases. The former, such as halothane, isoflurane, enflurane, sevoflurane and desflurane, are halogenated organic compounds, which are evaporated and transported to patients through anesthesia machines. Desflurane and sevoflurane have the fastest onset and offset speed, and are gradually replacing isoflurane and halothane. The latter, such as N_2O, can make people laugh, also known as “laughing gas”. It has potent analgesic effect and slight anesthetic effect. It is often combined with other general anesthetics and can be used in surgery and dentistry[8][10][62]. Inhalation anesthetics may exert anesthetic effects by acting on different ion channels, prolonging the activity of inhibitory postsynaptic channels, inhibiting the activity of excitatory synaptic channels, to inhibit the transmission of nerve impulses[63]. These anesthetic gases are mainly discharged through the respiratory tract in their original form and rarely metabolized in the body. Most of the time, they will be discharged into the atmosphere and remain in the atmosphere for a long time[8][9][62]. With the wide use of inhalant anesthetics, it is found that they have potential harm to the global climate. The main impact is their contribution to tropospheric greenhouse effect and stratospheric ozone depletion[10].

3.1 Absorption of Infrared Radiation

Volatile anesthetics(VAs) and N_2O are recognized greenhouse gases[8]-[11]. They will also absorb long wave infrared radiation from the surface, raising the temperature of the surface and troposphere. Radiation forcing refers to the net radiation energy obtained by the earth system due to the

change of some factors (the balance between incident solar radiation and outgoing infrared radiation)[9][64]. For example, the increase of carbon dioxide concentration can increase the radiation energy obtained by the earth, which is called as positive forcing, leading to a warming[64].

Each gas absorbs infrared radiation in its own specific wavelength range, so their radiative forcing is different[9]. Radiative forcing is used to quantitatively compare the intensity of different factors in causing climate change[64]. Although the concentration of halogenated organic compounds in the atmosphere is one millionth of carbon dioxide, their total radiation forcing is about 1/6, approximately 11% of the total radiative forcing[65].

This may be explained by their strong absorption capacity in the infrared region of the electromagnetic spectrum, which is the vital spectral region where the earth emits radiation into the space to cool itself, called "atmospheric window"[11][66]. Naturally occurring gases such as CO_2 and H_2O absorb less radiation in the "atmospheric window", which makes VAs a strong greenhouse gas[67]. At present, N_2O accounts for about 6% of the total radiation forcing[8][10]. In order to more accurately express their impact on climate, many scholars calculate their radiation efficiency and global warming potential (GWP) through formulas. GWP is a measure of the contribution of a given mass of greenhouse gas to global warming over a specified time period[9].

This is a relative scale used to compares the contribution of the gas in question to that of the same mass of carbon dioxide[9]. For example, the GWP_{20} of a gas is 100, which means that its warming potential in 20 years is equivalent to 100 times that of CO_2 in the same mass. Hospitals can simply multiply the mass of discharged gas by GWP to calculate the carbon dioxide equivalent of the gas and know the impact of emitted anesthetic gas on climate[66]. Sulbaek Andersen et al.[11][66][68] calculated and corrected for many times that the GWP_{100} of isoflurane, desflurane, sevoflurane, halothane and enflurane were 510, 2540, 130, 50 and 680 respectively, and estimated that the annual impact of global inhaled anesthetic emissions on climate was equivalent to 4.4 million tons of carbon dioxide based on the assumption that 200 million anesthetic operations were performed in the world every year, which is comparable with that of the CO_2 emissions from one coal-fired power plant or approximately 1 million passenger cars. Under comparable and common clinical conditions, the potential impact of desflurane on global warming is greater than that of other VAs[9]. According to the fifth assessment report of the Intergovernmental Panel on climate change (IPCC), the GWP_{100} of N_2O is 264.8[64]. Due to the phasing out of CFC emissions by the Montreal Protocol, N_2O has exceeded CFC-12 and become the third largest source of greenhouse gas emissions, second only to carbon dioxide and methane[64]. Therefore, regardless of the fact that its GWP value is not high, it contributes greatly to climate warming[62].

3.2 Depletion of Ozone Layer

The stratospheric ozone layer can absorb the short wave ultraviolet rays in the sunlight to shields life on the earth from the harmful ultraviolet(UV) radiation. Inhalant anesthetics can be carried up into the stratosphere by the upward-moving air currents and broken down by the UV to form free radicals that can consume and destroy the ozone layer through chemical reaction[8]. Moreover, the recycling of the free radicals allows one that to destroy 10^3-10^5 ozone molecules before it is converted to a less-reactive molecule[69]. Chlorine atoms and bromine atoms decomposed by chlorine-containing anesthetics such as isoflurane, enflurane and halothane (also containing bromine atoms), as well as nitrogen oxides decomposed by N_2O are all ozone depleting substances[69], while sevoflurane and desflurane only contain fluorine atoms that may not participate in the destruction of ozone[65][66][70].

Researchers frequently use ozone depletion potential (ODP) to reflect the ability of gas to destroy ozone, and compare the effectiveness of gas in destroying ozone with that of CFC-11 of the same quality[66][69][71]. Similarly, we can estimate the impact of actual emissions on ozone by computing ODP-weighted emissions (i.e. the ODP multiplied by gas emissions)[69]. Sulbaek Andersen et al.[66] calculated the ODP of halothane,

isoflurane and enflurane as 0.4, 0.01 and 0.01, and Ravishankara et al.[71] calculated the ODP of N_2O as 0.017. The contribution of bromine to ozone depletion is 35-80 times that of chlorine[72], so halothane is the most destructive to ozone.

However, the use of halothane has been reduced and is now widely used only in some developing countries[10][66]. The contribution of halothane to the total stratospheric ozone depletion is approximately 1%, and that of enflurane and isoflurane is 0.02%[62][72]. Although the ODP value of N_2O is not the highest, the ODP-weighted emission of N_2O is the largest as the consumption volumes of N_2O far exceed those of the other anesthetic gases[8][10][62][69], so it is considered the most important ozone depleting substance. The influence of these inhaled anesthetics on ozone depletion is of increasing importance because of decreasing CFCs globally.

3.3 Atmospheric Lifetime of Inhaled Anesthetics

Another important determinant in assessing the contribution of gases to ozone depletion and the greenhouse effect is the atmospheric lifetime of gases. The atmospheric lifetime of gas refers to the mean residence time before the gas is removed by chemical reaction with radicals, by photolysis, and by wet or dry deposition[72].

Langbein et al.[72] estimated that the tropospheric lifetime of volatile anesthetics is 4.0 to 21.4 years and the stratospheric lifetime is more than 100 years from observations of hydroxyl radicals reaction kinetics and UV absorption spectra. According to the data of the World Meteorological Organization, the atmospheric lifetime of desflurane, sevoflurane, isoflurane, halothane, enflurane and N_2O are 14.1, 1.9, 3.5, 1, 4.42 and 123 years[73]. Tropospheric lifetime determines the amount of gas entering the stratosphere, thus determining the extent of its destruction of ozone.

It was derived that up to 20% of the anaesthetics may enter the stratosphere and hence contribute to halogen loading[72]. With regard to the greenhouse effect, tropospheric lifetime can adjust the average concentration level of anesthetic gases that affect the infrared radiation balance of the earth[72]. As time goes by, the anesthetic gas gradually decays, resulting in a gradual decrease in the warming potential[66][67].

Therefore, the long-lived greenhouse gases in the atmosphere have a long-term impact on the climate. Desflurane not only has high GWP value, but also has the longest atmospheric lifetime among VAs, leading to a great and prolonged impact on the environment[67]. As well, N_2O has an almost constant impact on climate because of its long lifetime. This becomes even more pronounced when we consider carbon dioxide equivalent, since desflurane and N_2O are used in much higher concentrations than other anesthetics[67]. Timur et al.[67] called VAs with short lifetime as flow pollutants, considering that if the diurnal emission remains constant, the pollution created will remain constant at the maximum value. While N_2O is called stock pollutants, and the pollution will accumulate with ongoing emission. Because of the continuous use of VAs, they suggested using GWP_1 to help anesthesiologists understand its real impact on the climate.

In addition, other aspects of the whole life cycle of inhaled anesthetics can also produce greenhouse effects, such as carbon dioxide produced by the extraction of natural resources, drug production, transportation, usage and disposal[12], but the proportion is small.

IV. SOLUTIONS

The healthcare industry has become one of the main causes of global warming, accounting for 5% of global greenhouse gas emissions[74]. The waste generated in the operating room accounts for one third of the total waste of the hospital, and the anesthetic gas inhaled alone constitute 5% of hospital greenhouse gas emissions[74][75][76]. If this situation continues, public health will be at risk and will directly lead to the burden of medical care. Hospitals have the responsibility to take immediate action to avoid the significant effect of climate change and integrate sustainability into medical practice. The three basic principles of waste minimization are Reduce, Reuse and Recycle, which will also be the basis of the scheme to reduce operating room waste. Yoan kagoma et

al.[77] believed that two more Rs should be added: Rethink and Research. Timur et al.[78] also proposed modified 3R approach adapted to inhalational anesthetics: Reduce, Refine, and Replace. In this article, we also formulate a strategy for the sustainable development of inhaled anesthetics, improving 3R to 4R: Reduce, Remove, Recycle and Replace.

4.1 Reduce

As we all know, desflurane and N_2O have a significant and long-term impact on the environment. Therefore, their use should be reduced or avoided as far as possible, unless there is a clinical reason to prefer them[12][65][67][74]-[76]. N_2O is often used as a carrier gas for VAs because it can reduce the necessary minimum alveolar concentration of other concomitantly used anesthetic gases[10]. Compared with the use of volatile drugs alone, when adding N_2O, a smaller amount of VAs is required to achieve the same level of anesthesia, and the patient can recover more prompt from general anesthesia[10], but at the same time it will increase the emission of N_2O.

Ryan and Nielsen's research shows that[9], using N_2O as carrier gas significantly increases the impact of sevoflurane and isoflurane, but decreases the impact of desflurane on global warming within 20 years. However, after 100 years, this improvement will be offset by the long lifetime of N_2O, eventually contributing environmental harm. Therefore, try to refrain from delivering N_2O as carrier gas.

Reasonable and effective management of fresh gas flow (FGF) can reduce the waste and pollution of anesthetic gas while achieving the same effect on the patient[79]. There is no doubt that the closed-circuit anesthesia system can maximize the use of fresh anesthetic gas, reduce the use of anesthetic gas by 80% to 90%[8], and hence eliminate virtually all of the environmental contamination. However, the conditions required for closed-circuit anesthesia such as injection of liquid anesthetic, tightly monitoring of gas concentration and evaluation of anesthetic machine volume are more challenging, making it impractical in modern practice[79]. For that reason, so-called "low flow anesthesia" (defined as less than 1L/min) is commonly used now, which can not only reduce the use of anesthetics[78] -[80], but also maintain the temperature and humidity in the breathing circuit, and increase mucociliary clearance[80]. However, because the increase in the requirement for CO_2 absorbent and its concomitant footprint at very low flow rates, there is a need to balance the environmental impact of anesthetic use and energy costs associated with absorbent use[9][79]. Nevertheless, it is unlikely to offset the benefits of reducing volatile drug and N_2O emissions[12][76]. For now, based on the research results of Ryan and Nielsen[9], reducing FGF to 2L/min with sevoflurane (the lowest value to prevent the production of nephrotoxic compound A) and reducing FGF to 0.5 to 1L/min with desflurane and isoflurane would be the best approximations of ideal FGF rates. However, subsequent studies in humans have failed to demonstrate a significant impact on renal function, in addition, the emergence of new carbon dioxide absorbers such as calcium hydroxide and lithium hydroxide may no longer produce any quantifiable levels of compound A, which may allow better acceptance of lower FGF of sevoflurane in the near future[9][74][79]. Therefore, it is recommended to use minimal FGF rates in combination with modern CO_2 absorbers[78].

In fact, the flow is not constant throughout the anesthesia process, and the management of FGF is different at each stage. Feldman[79] provided management strategies during anesthesia induction, intubation, maintenance and emergence, which can truly and effectively obtain the effect of "minimum flow anesthesia". It is worth noting that the inhaled oxygen concentration and exhaled anesthetic gas concentration must be monitored at all times to ensure the safe implementation of these strategies, and the workload may make it difficult for anesthesiologists to adhere to the idea of low flow anesthesia. The development of the automated control of end-tidal anaesthetic gases can reduce the need for anesthesiologists to continually monitor and change gas concentration, significantly decrease volatile agent consumption, and hence bring economic

and environmental benefits, which will increase anesthesiologists' compliance and participation in low flow anesthesia[81].

Besides, anesthetic techniques and the anesthesia machine delivery system will also lead to the leakage and waste of anesthetic gas.

Anesthesiologists can employ the following anesthetic practices to minimize environmental contamination: use appropriate face mask, endotracheal tube and laryngeal mask airway cuff, and reduce the gas flow during the introduction of mask; carefully fill the vaporizer of anesthesia machine to reduce overflow; turn off the flow control valve and vaporizer in time after anesthesia; check of all connections along the anesthesia circuit and at the machine[10].

4.2 Remove

At present, various technologies have been developed to remove organic pollutants from waste gas stream, namely adsorption, absorption, cryogenic condensation, membrane technology, and the first three have been proved to be applicable for removing VAs[82]. Among them, adsorption is by far the most extensively investigated method. VAs can be removed by using adsorbents with strong affinity for anesthetic molecules. Among promising adsorbents, activated carbon, zeolite and metal organic framework have the potential to adsorb and capture VAs[65][82]-[85]. Many chemists have continuously changed the composition, morphology, structure and pore size of these adsorbents to improve their adsorption capacity[82][84]. Compared with VAs, N_2O is usually difficult to be adsorbed[86], and researchers are also looking for suitable adsorbents to reduce N_2O emissions[87]-[89]. The captured anesthetic is not really removed, and the adsorbed anesthetic molecules can be removed from the adsorbent's inner surface via high temperature, low pressure or vacuum and purge gas flow, which is called desorption[82]. Desorption can not only regenerate and recycle the adsorbent to save the cost, but also conduce to the recovery or further processing of anesthetic gas[82][85]. Water absorption of anesthetic gas is also a method, but it is laborious and risks gas evaporation into the atmosphere[90], which may be used when conditions are limited. Other experts have described the technology of cryogenic condensation[86] - using a cold fractionator to selectively condense nitrous oxide and halogenated anesthetics from waste anesthetic gas, and a compressor, a low-flow scavenging system and an intelligent anesthetic waste gas collection unit are used to improve its efficiency and feasibility.

The real removal of anesthetic gas is to destroy anesthetic gas through pyrolysis, catalytic reaction and photochemical reaction. Numerous methods have been proposed for the abatement of N_2O, including thermal decomposition, catalytic oxidation, catalytic reduction, direct catalytic decomposition, photocatalytic technology[91]-[94].

There are also many studies on various catalysts (metals, metal oxides, zeolite molecular sieves, etc.)[92][93][95]-[97]. Among these approaches, direct catalytic decomposition is quite promising because of its superiority in the simple achievement, high decomposition efficiency, low production of nitrogen oxides and environmental friendliness[93]. Japan has developed a system for treating waste anesthetic gas, Anesclean, which can collect volatile anesthetic from waste anesthetic gas and immediately decompose nitrous oxide (N_2O) into N_2 and O_2[98]. According to the technology of Japan, the Swedish company developed and installed a device for simply destroying N_2O in the hospital, called Anesclean SW[94], whose principle is to directly decompose N_2O with heated catalyst. After continuous updating, the new generation can destroy about 98% of the collected gas, and has the advantages of small volume, flexibility, lower energy demand and lower price. Kuroki et al.[91] investigated a system for removing high concentration N_2O by using nonthermal plasma along with an adsorbent, which had the advantages of significant reduction in overall size and total cost and without nitrogen oxides formation when compared to a conventional catalytic reduction or thermal plasma system. At present, there is a new photochemical anesthesia exhaust gas destruction system[99], which can destroy halogenated anesthetics and nitrous oxide through direct photolysis by ultraviolet light or free radicals

reaction to prevent them from leaking into the atmosphere. The system is efficient and economical for removing halogenated anesthetics, but is expensive and inefficient for removing N_2O, so modifications of this current system are necessary to improve its removal efficiency of N_2O. Various methods have their own advantages and disadvantages, so appropriate methods can be selected in combination with the conditions of the hospital.

4.3 Recycle

As mentioned above, VAs can be desorbed under certain conditions after being captured by adsorbents. The trapped halogenated agents could then be reprocessed by steam extraction or fractional distillation for reuse[8][65][85]. The low cost of producing N_2O and the high cost of recycling it may make destruction more suitable for it. Blue-Zone Technology of Canada has developed a filter canister system - Deltasorb. The proprietary silica zeolite in the canister can selectively capture VAs before they are discharged into the air. Then VAs collected in the canisters are recovered through sophisticated desorption and distillation devices, and finally processed into low-cost anesthetics for resale[10][74][82], so as to prolong the life cycle of anesthetics[62]. In a five-year trial, the Deltasorb system was installed in 21 operating rooms in Toronto and prevented 634 tons of carbon dioxide equivalent emissions from entering the atmosphere[82]. But there are still some shortcomings need to be overcome. It can only trap VAs, but allows N_2O to pass through unabated[82], which may be solved by working in conjunction with the system that destroys N_2O.

When the relative humidity is high, the adsorption of water vapor by silica zeolite will displace the adsorbed anesthetic[82]. Apart from that, the system is quite labor-intensive because saturated canister must be collected and new canister must be installed regularly[82][100].

Moreover, the U.S. FDA has yet to grant approval to use salvaged anaesthetic agents for clinical purposes[74], thus alternative solutions would be to use the recovered VAs to produce other fluorinated products or decompose them[82]. This technology has just started and more work needs to be done to determine its sustainability. And it is required to promote it to more operating rooms, after all, reducing the emission of anesthetics is necessary.

One other company – Anesthetic Gas Reclamation Inc. in the United States has created a cryogenic condensation Anesthetic Gas Reclamation (AGR) system[100] to cool the VAs in the waste gas stream to a saturated liquid. It has demonstrated workable for separating and reclaiming exhaled VAs, but hasn't undergone trials in hospitals.

When it is paired with the Dynamic Gas Scavenging System(DGSS), 99% of the anesthetic gas can be collected and reused without chemical alterations in the process[10][100]. DGSS is a scavenging system designed by Vanderbilt University Medical Center[101]. It is activated only when the patient exhales and used anesthetic appears[12],which can reduce vacuum pump duty cycle and decrease energy cost[101].Moreover, it can collect and generate a concentrated stream of waste anesthetic, reduce the dilution of anesthetic gas by air, and facilitate the subsequent condensation process[101].

Although the anesthetic recovery technology is still in a fledging period and the "carbon cost" in the process has not been systematically evaluated, it is very promising. If the recovered anesthetic can be applied to clinical practice in the future, it will be a win-win situation for environmental and economic sustainability.

4.4 Replace

Technologies other than inhalation anesthetics, such as intravenous anesthesia and regional anesthesia, would be least harmful to the climate[12][65][74][76]. Evaluated in the whole life cycle, the greenhouse effect of total intravenous anesthesia (TIVA) with propofol is 4 orders of magnitude lower than that of inhaled anesthetics[12]. Nevertheless, a potential disadvantage of TIVA is that a large amount of unused propofol is wasted[12][76], and these unmetabolized propofol may have harmful influences on aquatic and terrestrial ecosystems, mainly owing to its high persistence,

bioaccumulation and toxicity[65][102][103]. Compared with intravenous anesthesia, regional anesthesia seems an obvious choice to become the "green" anesthesia[102]. Most regional anesthetics use neuraxial or peripheral nerve block anesthesia along with intravenous sedation, thus reducing the use and waste of inhaled anesthetics gases[104].

Other studies have shown that regional anesthesia can bring nursing benefits, including reducing patients' adverse anesthetic reactions, earlier and improved rehabilitation, faster time to discharge, etc.[104]. However, not all surgical operations are suitable for regional anesthesia. Anesthesiologists should choose anesthesia techniques that are beneficial to both patients and environment according to the patient's condition. In some cases, it may be feasible to combine the two anesthesia techniques to reduce the consumption of harmful anesthetics. Xenon is a naturally occurring atmospheric trace gas manufactured from liquefied air, which is a byproduct of pure oxygen production[62][105]. It can exert an anesthetic effect by inhibiting cell membrane calcium pump and blocking N-methyl-D-aspartate(NMDA) receptor and acetylcholine receptor[62][106]. Xenon has many properties of an ideal anesthetic gas, including: non-inflammable and non-explosive; rapid induction of anesthesia; quick recovery from anesthesia; stronger anesthetic and analgesic effects compared to N_2O; low toxicity, devoid of teratogenicity, mutagenicity or carcinogenicity; neuroprotective effect; little effect on cardiovascular and other systems; the potential to protect organ grafts from ischemia-reperfusion injury; hemodynamic stability[8][62][105][106].

Moreover, its impact on the global climate has not been found and hence can be used as a substitute for halogenated compounds and N_2O. However, the production of xenon requires high cost and high energy[105]. Only by using closed-circuit system or adsorption separation technology to reclaim and reuse gas can it become an economically feasible method[8][62][106][107]. However, these require high-tech anesthesia workstation and anesthesia delivery system, which can not be widely used at present.

Therefore, when it is clinically feasible, utilizing other anesthesia methods instead of inhalation anesthesia can reduce environmental contamination. In spite of this, there are still some uncertainties that need to be further studied and considered, such as life cycle assessment of regional anesthesia, other environmental impacts of intravenous anesthetics, xenon recovery technology and so on.

V. CONCLUSION

Medical care can cope with the health burden brought by climate change, but it can also cause climate change and threaten human health. If global health care is a country, it will be the fifth largest carbon emitter on earth[65]. Substantive action is urgently needed to avoid the significant impact of climate change. Anesthesiologists, as professionals, have the obligation to take the lead in applying appropriate strategies and new technologies to clinical practice, reduce the harmful impact on the environment, improve the sustainability of anesthesia, and obtain the synergistic benefits of health, environment and economy. At the same time, researchers should continue to evaluate and research the uncertainty in this field and constantly update the decision-making scheme. Of course, all this needs the support of government policies and funds. As a direct consequence of the COVID-19 pandemic, greenhouse gas emissions are expected to be reduced by 8% in 2020. This may be an opportunity for the government to implement policies to mitigate climate change while restarting and restructuring the economy and rebuilding the public health system, so as to reduce the harm of the two crises to the world[6]. It is time for the whole world to unite to address the critical challenges of global health, and to promote green development of the medical industry.

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Superiority of Surgical Management over Conservative Management in Management of Chronic Pancreatitis – Case report of Classical Representation

Dr. V.R Santhosh , Dr. Hubert Cyril Lourdes Rozario , Dr. Venkatesh Mahadevan & Dr. S Rajenderan

ABSTRACT

Chronic pancreatitis is a inflammatory disease with multiple aetiologies. In this condition, there will be persistent inflammation and irreversible fibrosis associated with atrophy of the pancreatic parenchyma. Alcohol consumption is the most important cause, however multiple aetiologies chronic duct obstruction, trauma, pancreas divisum, cystic dystrophy, autoimmune pancreatitis, tropical pancreatitis, and hereditary pancreatitis. In up to 20% of cases clear cut cause cannot be identified and it will be considered as idiopathic pancreatitis.

Aim: The aim of the study is to demonstrate the Surgical Management also referred as Freys Procedure still has better success in the management of chronic pancreatitis than Conservative Management also referred as Celiac Plexus block.

Keywords: chronic pancreatitis, freys, celiac plexus, lateral pancreatico-jejunostomy, immunoglobulin's.

Classification: DDC Code: 179.7 LCC Code: R724

Language: English

London Journals Press

LJP Copyright ID: 392863

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

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Dr. V.R Santhosh[α], Dr. Hubert Cyril Lourdes Rozario[σ] , Dr. Venkatesh Mahadevan[ρ] & Dr. S Rajenderan[Ω]

ABSTRACT

Chronic pancreatitis is a inflammatory disease with multiple aetiologies. In this condition, there will be persistent inflammation and irreversible fibrosis associated with atrophy of the pancreatic parenchyma. Alcohol consumption is the most important cause, however multiple aetiologies chronic duct obstruction, trauma, pancreas divisum, cystic dystrophy, autoimmune pancreatitis, tropical pancreatitis, and hereditary pancreatitis. In up to 20% of cases clear cut cause cannot be identified and it will be considered as idiopathic pancreatitis.

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Author α: Junior Resident, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India. ORCID – 0000-0001-9917-5801.
σ: Junior Resident, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India. ORCID – 0000-0001-7889-2086.
ρ: Assistant Professor, Department of Surgical Gastroenterology, Sree Balaji Medical College & Hospital, Tamil Nadu, India.
Ω: Head of Department, Department of Surgical Gastroenterology, Sree Balaji Medical College & Hospital, Tamil Nadu, India.

I. INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease in which there is irreversible destruction of pancreatic tissue. Its clinical course is characterized by severe pain, and in later stage exocrine and endocrine pancreatic insufficiency. It's frequently complicated by attacks of acute pancreatitis, which are responsible for the recurrent pain. The incidence is 100-200/100000 population. The disease is more frequent in men.

II. MATERIAL AND METHOD

Patient is a 20 Years Male came to the Surgical Gastro Enterology OPD with features of Chronic Pancreatitis.

III. RESULT

The Outcome of the surgery still holds better in a case of chronic pancreatitis as the patient improved and the pain reduced improving the quality of the patients life than conservative management like celiac plexus block.

IV. CONCLUSION

To conclude that the Surgical Management – Frey's procedure still has good success in a case of chronic pancreatitis with failure of other lines of management.

V. CASE REPORT

A 20 y male presented with complaints of upper abdominal pain for 5 years duration , pain in intermittent in nature, increasing in severity for 2

days. Patient also gives c/o nausea and vomiting 2 episodes / day for 2 days (non-bilious). Patient is known case of pancreatitis (multiple duct calculi). Patient had undergone multiple coeliac plexus block which has failed to relieve the pain. Patient has No comorbidities such as Diabetes, Systemic hypertension, Asthma and Epilepsy. Patient is on mixed diet and no H/o Alcohol consumption. No relevant family history.

On Examination: Patient is thin built and moderately nourished.

Per Abdomen Examination: Soft, Bowel sound - present, Tenderness presented over the epigastrium. No guarding or rigidity.

Serum Amylase and Lipase: 114 and 325 respectively

CT abdomen: Showed dilated main pancreatic duct with multiple duct calculi.

Magnetic Resonant Cholangio Pancreaticogram: Main pancreatic duct appears irregularly dilated measuring 9mm.Head, Body, Tail – atrophic. Parenchymal calcification noted.

Initially patient was evaluated and attempted for celiac plexus block under USG guidance, transient pain relief was achieved only for 36 hours post procedure.

Patient evaluated, pre-anaesthetic fitness obtained and planned for Frey's procedure.

Histopathology: Sections shows distorted pancreatic parenchyma with inter and intralobular fibrosis. Interlobular fibrosis is dense with thick bands of collagen and sparse lymphatic infiltrate.

Histopathological Impression: Chronic Calcific Pancreatitis

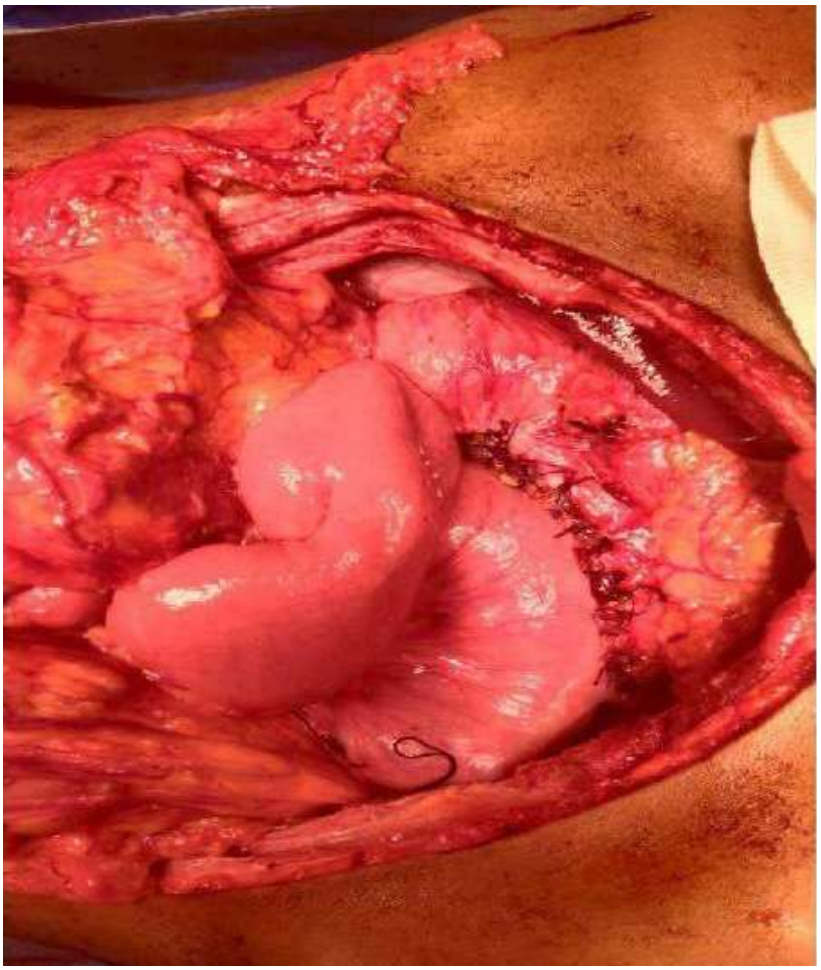


Figure 1.1: Pancreaatico Jenjunostomy

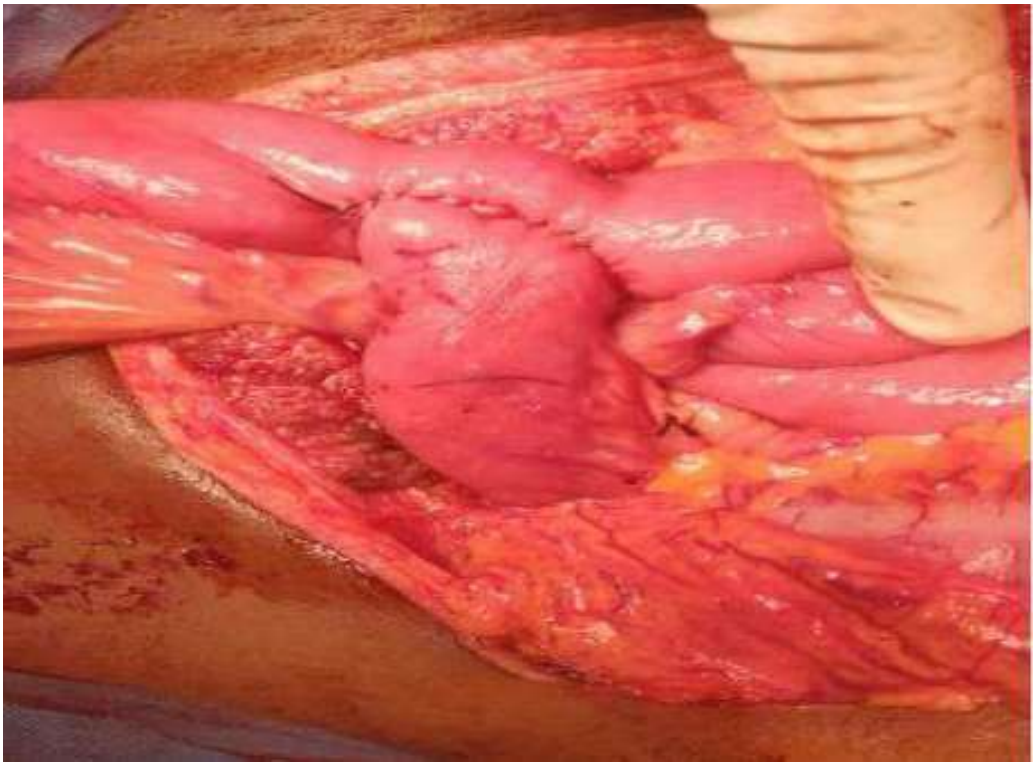


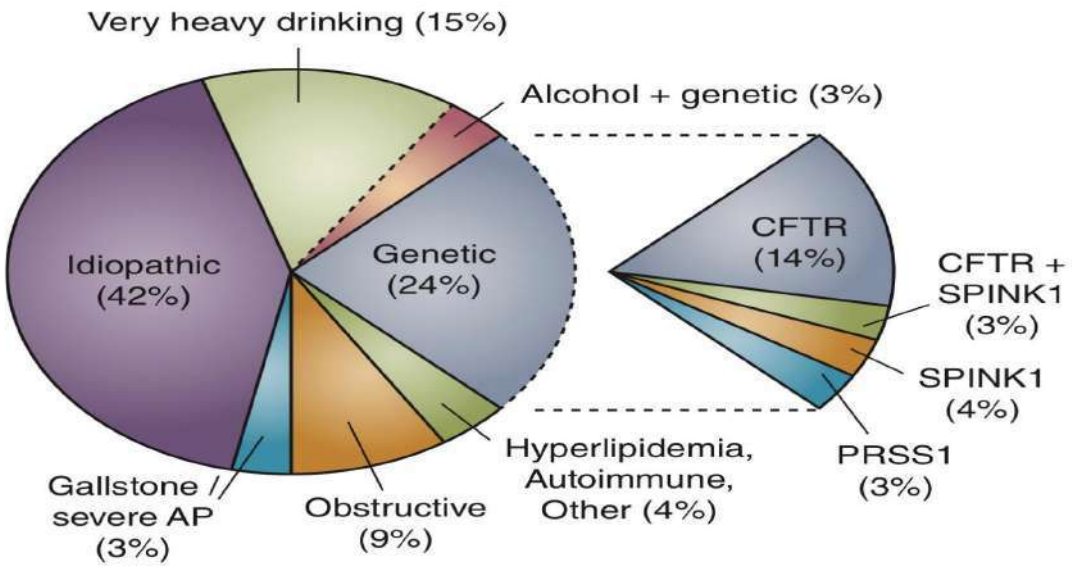
Figure 1.2: Jejuno-Jejunostomy

VI. DISCUSSION

Chronic pancreatitis is a chronic inflammatory disease with multifactorial aetiologies, variable in presentation and challenge to manage and treat. The Various aetiology include Genetic causes, Alcohol, Hyperlipidaemia, Hyperparathyroidism.

The TIGAR-O classification categorizes the chronic pancreatitis into Idiopathic, genetic, Autoimmune, Obstructive and recurrent and severe acute pancreatitis. These various aetiologies are well illustrated in Table 1.1

Table 1.1 - Actiologies of Chronic Pancreatitis



The chronic pancreatitis in young age is uncommon. There will be multiple histopathological features like Interacinar fibrosis, acinar atrophy, interlobular fibrosis, stromal inflammation, ductal distortion. A radiological investigation assists in areas such as diagnosis, evaluation of severity of disease, detection of complications, and assistance in determining treatment options. CT and MRI are the major imaging techniques to help in diagnosing pancreatitis and now Endoscopic Ultrasound has become major modality in evaluation and management of chronic pancreatitis.

The presentation of the chronic pancreatitis will be pain, majorly due to ductal hypertension which is due to strictures, stones or retroperitoneal inflammation with the persistent neural involvement. The patient's quality of life and social function is affected.

It is always important to assess the baseline of pain along with it should be assessed with quality of life and disability of the patient.

In past majority of the pain was thought to be caused by the pancreatic duct obstruction there are many pathologies involved. Pain management starts with the medical therapy which involves abstinence from tobacco and alcohol. Patients are started with opioid management. Other medical options to reduce the pain include pancreatic enzymes, octreotide, antioxidants. In case of autoimmune pancreatitis, the patient should be evaluated for immunoglobulin's G4. In such cases the corticosteroid therapy should be started. The patients who do not respond to medical therapy should be started on other types of management which includes endoscopy, nerve block and surgery.

The patient here underwent initial coeliac plexus block which was failure to the underlying ductal stones which was obstructing the pancreatic duct. The success rate of coeliac plexus block in chronic pancreatitis is around 55-60% (Gress et al).

The major step in treating chronic pancreatitis is the endoscopy therapy plays an important role in treatment of chronic pancreatitis associated with pain.

The indications for surgery in chronic pancreatitis are intractable pain, symptomatic local complication, unsuccessful endoscopic management and suspicion of malignancy. The procedure done for the patient was Freys procedure which is lateral pancreatico-jejunostomy (Figure 1.1) with partial excision of the pancreatic head. It combines both pancreatic duct drainage procedures with resection & Anastomosis surgery (Figure 1.2). The Roux loop is anastomosed to the opened duct and to the edges of the pancreatic defect left by the resection of inflammatory mass in the head. Post-surgery the patient pain reduced and the quality of the life has been improved. The patient has to be frequently evaluated for any endocrine dysfunction like diabetes.

VII. CONCLUSION

The management of the patients with chronic pancreatitis should start with medical therapy but in view of the multiple coeliac plexus block failure and the duct obstruction, the surgery is an appropriate option and it has been shown to improve the quality of life and reduced the pain.

Uncommon Presentations of Umbilical Swelling Across Different Age Groups – A Single Institution Case Series

Anand J, Hubert Cyril Lourdes Rozario, Pugazharasan M & Kuberan K

ABSTRACT

Umbilical hernia occurs due to bulge of the intra-abdominal structures through a defect in the abdominal wall around the umbilicus. Umbilical hernia is a ventral hernia with umbilicus as its centre. Umbilical hernia repair is one of the common surgeries performed routinely for umbilical and para umbilical hernia. Of all the repairs for umbilical hernia, On-lay mesh repair is most commonly performed in adults in our centre.

Keywords: umbilical hernia, paediatric hernia, exomphalos, para umbilical hernia.

Classification: DDC Code: 617.559059 LCC Code: RD621

Language: English

London Journals Press

LJP Copyright ID: 392864

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

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Anand J[α], Hubert Cyril Lourdes Rozario[σ], Pugazharasan M[ρ] & Kuberan K[Ω]

ABSTRACT

Umbilical hernia occurs due to bulge of the intra-abdominal structures through a defect in the abdominal wall around the umbilicus. Umbilical hernia is a ventral hernia with umbilicus as its centre. Umbilical hernia repair is one of the common surgeries performed routinely for umbilical and para umbilical hernia. Of all the repairs for umbilical hernia, On-lay mesh repair is most commonly performed in adults in our centre.

Keywords: umbilical hernia, paediatric hernia, exomphalos, para umbilical hernia.

Author α: Junior Resident, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India. ORCID – 0000-0002-0120-8538
σ: Junior Resident, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India. ORCID – 0000-0001-7889-2086
ρ: Assistant Professor, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India.
Ω: Professor, Department of General Surgery, Sree Balaji Medical College & Hospital, Tamil Nadu, India.

I. INTRODUCTION

Umbilical Hernia can occur at any age. In New-born's it is called exomphalos, usually associated with weakness of abdominal musculature. In infants and children it occurs due to Umbilical sepsis which weakens the umbilical scar. In adults it is not true Umbilical hernia, it is a Para umbilical hernia that occurs either above, below or to the side of the Umbilicus through linea Alba.

In about 90% of cases, increased intra- abdominal pressure is the main reason for umbilical hernia. There are many risk factors like weight lifting, older age, multiparous women, older age, malignancy, chronic cough, bronchial asthma, chronic lung conditions, ascites, prostatism, obesity and chronic use of steroids [1,2].

The hernia sac may contain omentum, colon, and small bowel. Umbilical hernias can also progress to incarceration due to comparatively small fascial defect size to that of large sac and also can be due too mental or bowel adhesions to the hernia sac [3]. Diagnosis can be made by proper history taking and physical examination and with the help of ultrasound to know the defect size, contents and to rule out obstruction.

AIM: The aim of this case series is to emphasise and discuss umbilical swelling presenting across different age groups coexisting with other diseases or presenting with complications and management of umbilical hernia under given circumstances.

CASE 1

A 58year old male patient came with complaints of swelling in the umbilical region for 15 years associated with pain for 1 year.

On examination: A swelling of 5*4 cms was present over the umbilicus (Figure1.1) which was smooth with well-defined borders. Additionally there was another swelling of 6*5cms was palpable in left lumbar region which was smooth with ill-defined margins. Cough impulse was present and the swelling was reducible manually for both the swellings.

Investigations: USG abdomen revealed a defect of approximately 2.6 cms in umbilical region with bowel and omentum as its content. The other findings were a cystic collection of 10*8.2cm in left lumbar region and cholelithiasis. Contrast

enhanced CT scan was done to obtain further information on the suspicious cystic lesion which revealed mesenteric cyst of 10.5*7*9 cms adjacent to third part of duodenum.

Patient was planned on mesenteric cyst excision with umbilical Hernioplasty. Intraoperatively a cyst of 10.5*7*9 cms was found loosely adhered to the mesentery, cyst was excised in Toto and was sent for HPE and On-lay mesh repair was done for umbilical hernia.

Postoperative period was uneventful and as patient's general condition improved he was discharged on post-operative day 7.

Histopathology: reports confirmed the mesenteric cyst.

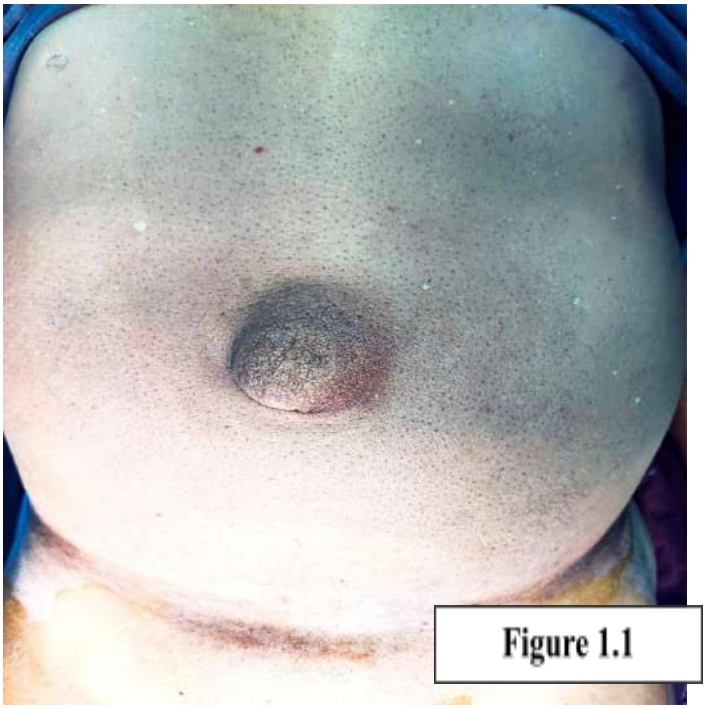

Figure 1.1

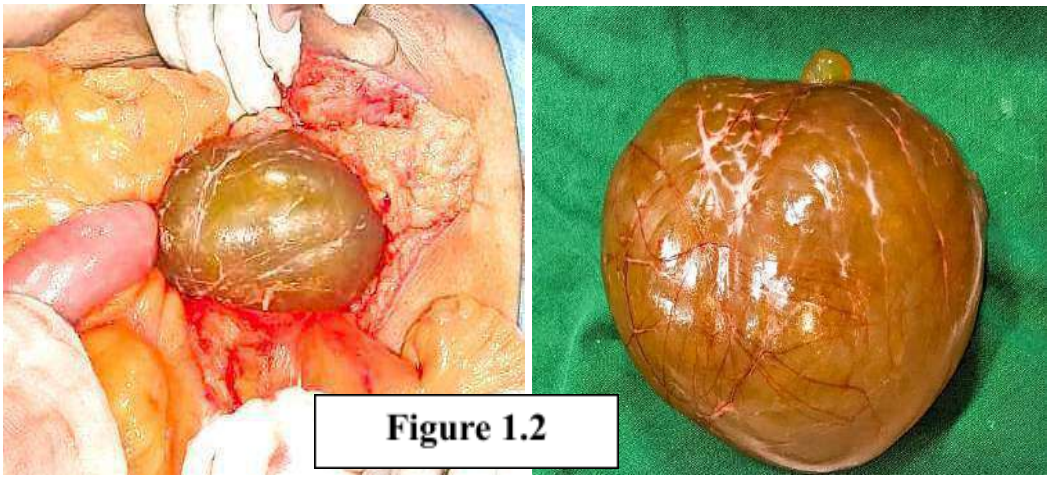

Figure 1.2

CASE 2

A 48 years old male patients came with complaints of swelling and pain in the umbilical region for 6 months followed by increase in intensity of pain and vomiting for 1 day and obstipation for 1 day.

On examination: The abdomen was distended, tense and a swelling around the umbilicus of 3*3 cms noted (Figure 1.3) which was tender, warm and irreducible manually and spontaneously.

Investigations: The ultrasound abdomen revealed a defect measuring 2 cms in the umbilical region

with bowel as its content; the herniated bowel loop was dilated with peri enteric fluid collection noted. Since the physical examination and ultrasound abdomen pointed towards the Strangulation contents of umbilical hernia, patient was taken up for emergency exploratory laparotomy with defect closed with modified Smead Jones technique and On-Lay mesh repair.

Intraoperatively jejunal loop approximately 4 cm was found to be the content and since it was viable the contents were pushed in and On-lay mesh repair was done. Postoperative period was uneventful and as patient's general condition improved he was discharged on post-operative day 7.

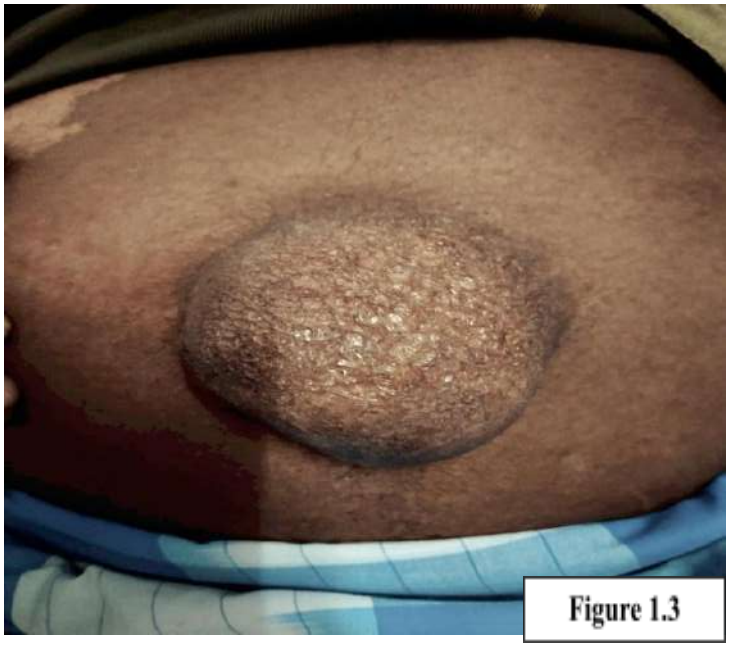

Figure 1.3

CASE 3

A 2 year old male child was brought by his parents with complaints of swelling over the umbilicus since birth, non-progressive in nature, associated with increased in size while coughing / crying and size decrease on lying down.

On examination: A swelling of 2*3cms present over the umbilical region (Figure1.4), reducible manually; cough impulse could not be elicited.

Investigations: USG abdomen revealed a defect of 3*3cms in infraumbilical region with omentum as its content.

Anatomical repair was done by reducing the sac and trimming off excessive sac and rectus was closed vertically with modified Smead Jones technique, post-operative period was uneventful and the child was started on adequate analgesics and antibiotics. As the general condition of the child was improved he was discharged on Post-operative day 5.

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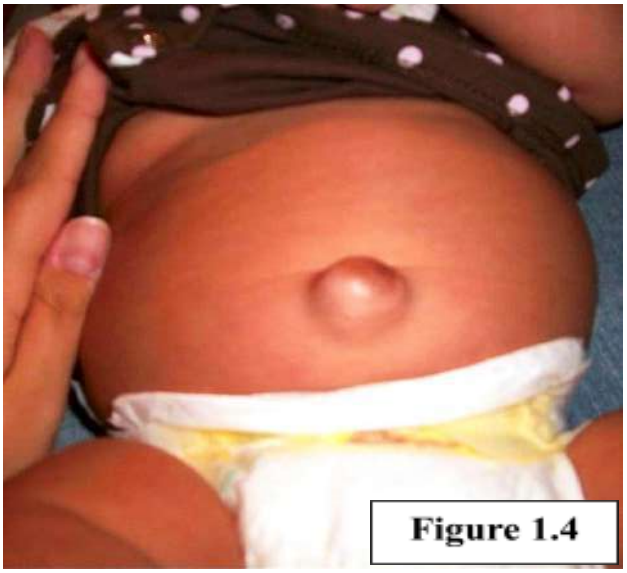

Figure 1.4

CASE 4

A female patient of 26 years old was admitted with history of pain abdomen on and off for 1 month, vomiting on and off 2 episodes per day for 5 days bilious in nature.

On examination: A swelling of 2*3cms present in infraumbilical region, manually reducible and cough impulse present. Borders are well defined; surface is smooth with soft in consistency.

Investigation: USG abdomen revealed a defect of 2*2 cms in infraumbilical region and cholelithiasis

Laparoscopic cholecystectomy was done to begin with. Infraumbilical 10mm port was inserted via open method. After Cholecystectomy and active evacuation of pneumoperitoneum anatomical repair for umbilical hernia was done. Postoperatively period was uneventful. Adequate IV analgesics and antibiotics were given. As her general condition improved patient was discharged on Post-operative day 5.

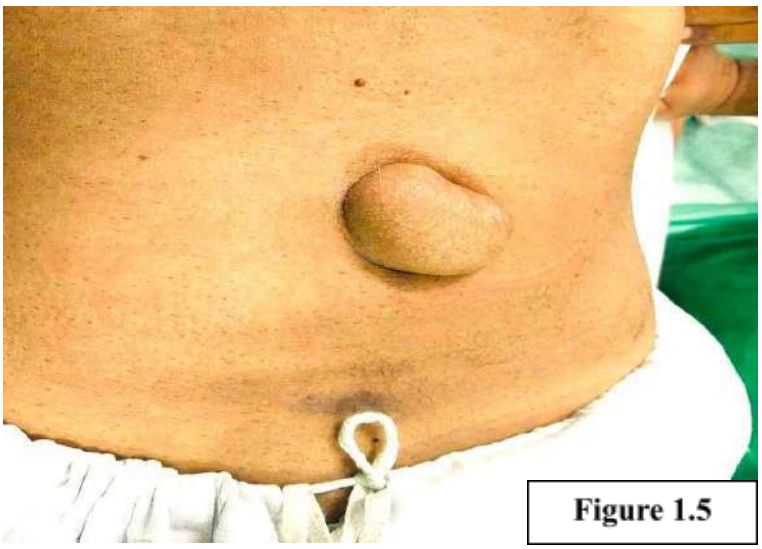

Figure 1.5

II. DISCUSSION

The incidence of umbilical hernias in adult's ranges from 10% to 25% [4]. Women is affected 3 to 5 times more frequently than men [5]. Most of these hernias are smaller than 5cm in diameter but can also present with fascial defect of 10 to 15 cm. Most often these hernia sacs contain small bowel, omentum or colon. In one of the study it was described that the presence of either omentum alone or omentum with large or small bowel was seen in 60% of patients and large bowel alone and small bowel alone was found in 7% and 4% patients respectively [6]. In one of the cases discussed above umbilical hernia presented with mesenteric cyst which is rare.

The Incidence of mesenteric cyst varies from 1 per 100,000 to 250,000 admissions [7]. However it was found incidentally while evaluating for umbilical hernia. In the other case the patient presented with umbilical hernia which progressed to obstruction. Umbilical hernia strangulation is a most serious complication that occurs if loop of small bowel is its content and they present with irreducible, painful umbilical swelling with skin changes over the swelling and along with signs of intestinal obstruction.

In these cases umbilical hernia repair is done but however resection of bowel is decided intraoperatively depending on its viability. Umbilical hernia can occur in infants and is more common (6 to 10 times) in black infants and low birth weight female infants and around 60-80% premature infants also present with umbilical hernia [8].

Umbilical Hernia repair of the infants have low rate of complications, so the repair is usually postponed, more over spontaneous closure of majority of umbilical hernias occurs within 2 years [8].

In few of the studies it is recommended that any umbilical defects of 1.5 cm or more in children of 2 years of age and above, hernia repair can be done because there is minimal chance of spontaneous closure [10, 11].

More often patients with umbilical hernia can present with coexisting cholelithiasis, Prevalence of umbilical hernia with cholelithiasis is 10.5% [12-14]. The common risk factor that links both the condition is obesity. Nowadays both umbilical hernia repair and laparoscopic cholecystectomy are done simultaneously.

Although Para-umbilical hernia repair done along with laparoscopic cholecystectomy can take longer time for surgery, and risk of increased blood loss. It has advantages of single hospital stay, single anaesthesia exposure, easy return to work, and cost effective for the patient.

III. CONCLUSION

An umbilical or Para umbilical swelling presented umbilical hernia should be ruled our first following other differential diagnosis like Mesenteric cyst.

Repair in umbilical hernia should be considered at the time of presentation, if untreated it can produce life threatening consequences like strangulation, incarceration or spontaneous rupture. Surgery is advised only for symptomatic patients and the standard treatment for umbilical hernia in adults is mesh repair.

After repair the prognosis is usually good, however it can recur. Even after elective umbilical hernia repair in patients with type II diabetes, hyperlipidaemia, and in retroviral positive patients there are high chances of recurrence. The increased rates of recurrence in patients are associated with BMI>30 kg/m², poor wound healing, repeated wound infection and uncontrolled Type II Diabetes.

Umbilical hernias can occur again more commonly in patients who fail to modify their life style.

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Apoptosis Induction of Ganoderic Acid-A by Downregulating MiR-125b and miR-365a-3p in Nalm-6 cells

Simin Taheri, Parisa Tande, Faezeh Mortazavie, Farahnaz Zare, Fatemeh Asadian & Gholmhossein Tamaddon

Shiraz university of medical Sciences

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is the most common leukemia in children, which is associated with a high relapse rate despite prevalent therapies. Ganoderic acid-A (GAA) is one of the bioactive compounds of Ganoderma lucidum, which possesses potential antileukemic properties.

Objective: This study aimed to investigate the effect of the GAA extract on the expression of microRNA and the apoptosis induction in the cell line.

Methods: In this case-control study, NALM-6 Cells were treated with the GAA extract and L-asparaginase separately. The cell viability and apoptosis rates were examined using MTT and flow cytometry, respectively. Moreover, the effect of the GAA on the expression of miR-125b and miR-365a-3p, in comparison to L-asparaginase, was studied using RT-PCR.

Keywords: ganoderic acid-a, ganoderma lucidum, NALM-6, miR125b, miR365a-3.p

Classification: DDC Code: 616.99419 LCC Code: RC643

Language: English

London Journals Press

LJP Copyright ID: 392865

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

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Simin Taheri[α], Parisa Tande[σ], Faezeh Mortazavie[ρ], Farahnaz Zare[Ↄ] & Fatemeh Asadian[¥] , Gholmhossein Tamaddon[§]

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is the most common leukemia in children, which is associated with a high relapse rate despite prevalent therapies. Ganoderic acid-A (GAA) is one of the bioactive compounds of Ganoderma lucidum, which possesses potential antileukemic properties.

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Result: The GAA extract inhibited the cell growth in a dose- and time-dependent manner. Moreover, the GAA extract significantly induced apoptosis compared to L-asparaginase (P= 0.0021 vs. P=0.0112). The results showed that the treatment of Nalm-6 cells with GAA significantly reduced the expression of miR-125b (P<0.0001) and miR-365a-3p (P=0.0001). Furthermore, it was demonstrated that the downregulation of miR-125b and miR-365a-3p was surprisingly higher in the GA-treated Nalm-6 cells than in L-asparaginase-treated Nalm-6 cells.

Conclusion: According to the findings, the GAA extract has antileukemic effects and can be used as a promising agent with fewer side effects in all treatments.

Keywords: ganoderic acid-a, ganoderma lucidum, NALM-6, miR125b, miR365a-3.p

Author α σ ρ: MSc of Hematology and Blood bank, Division of Hematology and Blood bank, Department of Laboratory Sciences, School of Paramedical Sciences, Shiraz university of medical Sciences, Shiraz,Iran

Ↄ: MSc of Biotechnology, Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

¥: MD, Pathologist, Division of Hematology and Blood bank, Department of Laboratory Sciences, School of Paramedical Sciences, Shiraz university of medical Sciences, Shiraz,Iran

§: PhD of Hematology and Blood bank, Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

I. INTRODUCTION

B-cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) is a type of hematologic malignancy in children 2 to 10 years [1, 2]. Although antileukemic therapies such as L-asparaginase lead to complete remission in more than 85% of patients, about half of the cases relapse with an unfavorable prognosis [3, 4]. Moreover, the adverse side-effects of treatments are of great concern for patients and reduce their life expectancy [5], hence, looking for treatment regimens with further effects and fewer cytotoxic

effects is of paramount importance. *Ganoderma lucidum* (GL) is locally known as Reishi and lingzi and has long been used to prevent and treat various diseases [6-9]. Medical studies have documented a wide range of biological functions (e.g., antitumor) for GL [10, 11]. One of the main compounds of GL is ganoderic acid (GA) [12]. Recent studies have indicated that GA increases apoptosis in cancer cells by altering miRNA expression [13-15].

MicroRNAs (miRNA or miR) are single-stranded, non-coding endogenous RNAs having negative regulatory effect on the target gene expression, which reduce the level of the target protein by binding to the 3′-UTR region of mRNA. Investigating the miRNAs expression level is helpful in the diagnosis, prognosis, and treatment of hematologic malignancies [16, 17].

In this regard, miR-125-5p (miR-125b) is one of the first known miRs whose expression has been altered in different cancers; hence, it has been extensively studied [18]. Depending on the type of cancer, it can act as an oncogene or suppressor tumor. In BCP-ALL, AML, and MDS, it induces tumors associated with a dismal prognosis [19-21].

The miR-365a-3p gene is a newly-found microRNA, whose expression pattern and biological role depend on the type of cancer [22].

In leukemia [23], pancreatic cancer [24], and hepatocellular carcinoma [25], its expression is increased; however, it plays the role of a tumor suppressor in breast cancer [26], melanoma[27], and ovarian cancer[28]. Studies have revealed an increase in the expression of miR-365a-3p and miR-125-5p in patients with ALL [23]. We selected these two microRNAs according to previous studies and with regard to the role of miR-365a-3p and miR-125-5p in leukemogenesis. By increasing apoptosis rate and changing the miRNAs expression level, GAA seems to have a strong cytotoxic effect on Nalm-6 cells related to the previous treatment of ALL. Accordingly, this study aimed to investigate the effect of treatment with the GAA extract on the apoptosis rate and the expression level of miR-365a-3p and miR-125-5p compared to L-asparaginase in the Nalm-6 cell line.

II. MATERIALS AND METHODS

2.1 Reagents

This case-control study was approved by the Ethics Committee of the Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1399.838). The B-cell precursor leukemia (Nalm-6) cell line was purchased from the American Type Culture Collection (ATCC; Gaithersburg, Maryland, USA). All cell culture materials and reagents were purchased from the Gibco Life Technologies (Waltham, MA) and Sigma-Aldrich (Munich, Germany). The GAA extract was obtained from the Sigma Aldrich Company (St. Louis, MO, USA) and was prepared in DMSO. L-Asparaginase powder vial 10000 IU (Zydus Cadila Company, India) was prepared in PBS.

2.2 Cell culture

NALM-6 was cultured in the RPMI-1640 medium supplemented with 10% fetal bovine serum and 100 U/ml penicillin-streptomycin and 2mM glutamine in a humidified 5% CO2 incubator at 37°C under standard cell culture conditions. The culture medium was changed according to the standard techniques, and the cells were passaged when they achieved 80% confluency. The Trypan blue exclusion method was used to assess cell viability.

2.3 MTT assay

The antiproliferative effects of the GAA extract on the B-ALL cell line, Nalm-6, were first evaluated. In short, 2×10^4 cells/well in 150µL growth medium were seeded in 96-well plates (cells in the logarithmic growth phase). The cells were treated with appropriate amounts of the GAA extract stock solution to reach the concentrations of 25, 50, 100, 200, and 400 µg/ml. The untreated cells were defined as the control group. After the treatment, the cells were incubated under cell culture conditions for 24, 48, and 72 hours. Then the MTT solution (5 mg/ml) was added and incubated for an additional 4 hours. After incubation, supernatants were removed, and the

remaining water-insoluble formazan crystals were dissolved in 150 µl dimethyl sulfoxide (DMSO) for 10 min by shaking gently. Finally, the optical density was measured at 570 nm wavelength using a Stat Fax 2100 microplate photometer (Stat Fax 2100, SKU: 8036-10-0020, USA). IC50 was calculated as the concentration of compounds, causing a 50% inhibition of cell viability. At least three independent experiments were performed in quadruplicate. DMSO was used to prepare GAA and bring it to the desired concentrations. Given the consecutive dilutions of the initial stock, the DMSO concentration was <0.01; hence, there was no need to control DMSO.

2.4 Flow cytometry

To determine the early and late apoptotic populations in the Nalm6 cell-line induced by the GAA treatment, we performed flow cytometry using Annexin-V/PI double staining kit (BD Biosciences, San Jose, CA). Moreover, the standard L-asparaginase treatment was used to compare the effect of GAA on Nalm-6 cells. To perform this test, the Nalm-6 cells in the logarithmic phase were inoculated into 24-well plates and treated with GAA and L-asparaginase separately for 48h. Then the treated cells were collected after centrifugation at 3000 rpm for 10 min and were washed twice with PBS. Afterward, the cells were resuspended in 100 µl of a binding buffer, and 5 µl of Annexin-V was then added to the cell suspension incubated for 15 min at room temperature in dark. The cells were rinsed and resuspended in 200 µl of the binding buffer. In the next ohase, 5 µl of PI was added before reading the values by flow cytometry. Annexin-V positive and PI-negative cells were considered to be in the early apoptotic phase, and the cells with Annexin-V and PI-positive were considered to undergo late apoptosis. The reaction of Annexin V-FITC and PI binding was analyzed quantitatively by using a FACScalibur flow cytometer (BD Biosciences) and FlowJo software (TreeStar LLC).

2.5 RNA extraction

Total RNA was isolated 48 h after the treatment with GAA extract and L-Asparaginase using TRIzol reagent (Thermo Fisher Scientific, MA). RNA quality was assessed with regard to 260/280 and 260/230 ratios by NanoDrop spectro-photometer (Thermo Scientific NanoDrop2000, Finland), and the extracted RNA was stored at -80 ˚C.

2.6 cDNA synthesis and real-time PCR

According to the manufacturer's protocol, specific cDNAs of the selected miRNA were synthesized by using Parsgenom RTreagent Kit (Pars genome, Iran). First, the poly-A tail was added to miRNAs with polyA polymerase at 37 °C. Then RT-enzyme, reaction buffer, and miR-specific primers for cDNA synthesis were mixed with RNA polyA tail (Table 1). Finally, they were incubated at 45 °C for 60 min and inactivated at 85 ºC for 1 min. Subsequently, Real Time-PCR was performed to analyze the cDNAs using Parsgenome Kit.

Table 1: The primer sequences used for real-time polymerase chain reaction assay

miRNAs	Sequence
miR-125b	5´ UCCCUGAGACCCUAACUUGUGA 3´
miR-365a-3P	5´ UAAUGCCCCUAAAAAUCCUUAU3´

2.7 Real Time-PCR assay

To evaluate the expression of miR-125b and miR-365a-3p genes, we calculated the quantitative real-time polymerase chain reaction (qRT-PCR) in a Rotor-Gene Q system (Qiagen, Hilden, USA). The qRT-PCR was run under the following thermal cycling conditions: initial denaturation at 95 ˚C for 15 min followed by 45 cycles of 95˚C for 30 sec, 63˚C for 30 sec, and 72 ˚C for 30 sec. All the qRT-PCR reactions were performed in triplicate. A melting curve analysis was applied to verify the specificity of the products, and the values of the relative quantification were calculated based on the $2^{-\Delta\Delta}$Ct

relative expression formula. Additionally, the U6 rRNA gene was used as an internal control.

2.8 Statistical analysis

For the primary selection of miRNAs to be included in this study, in addition to some information extracted from past studies, the characteristics for the selected miRNAs, including target genes, the underlying cell process, the expression or non-expression of miR in cancerous cells, the function of the selected miRNAs as oncomiR, were evaluated by programs such as Targetscan, miRanda, and MiRTARbase.

All experiments were repeated at least three times and were expressed as mean ± SEM. Statistical significance was assessed by GraphPad Prism 8.0.2 (GraphPad Software, Inc., La Jolla, CA, USA) using the SPSS software version 19.0 (IBM Corp.). The student's t-test analyzed the difference between the two groups. The significance level was set to be P <0.05.

III. RESULTS

3.1 Effect of GAA on cell viability

The cytotoxic effects of different concentrations of the GAA extract (25, 50, 100, 200, and 400 µg/ml) on NALM-6 cells were assessed using the MTT assay after three different time points, namely 24, 48, and 72h. According to the results, GAA could inhibit the growth of NALM-6 cells both in time- and dose-dependent manners. We determined the optimal concentration of GAA by investigating its IC-50. In this study, the Graph Pad software was used to calculate IC50. The IC50 of the GAA extract in NALM-6 cell lines after 48 h of incubation was approximately 130 µg/ml. Accordingly, we used 130 µg/ml of GAA after 48 hours for all subsequent experiments. The data are not presented for 24 and 72h.

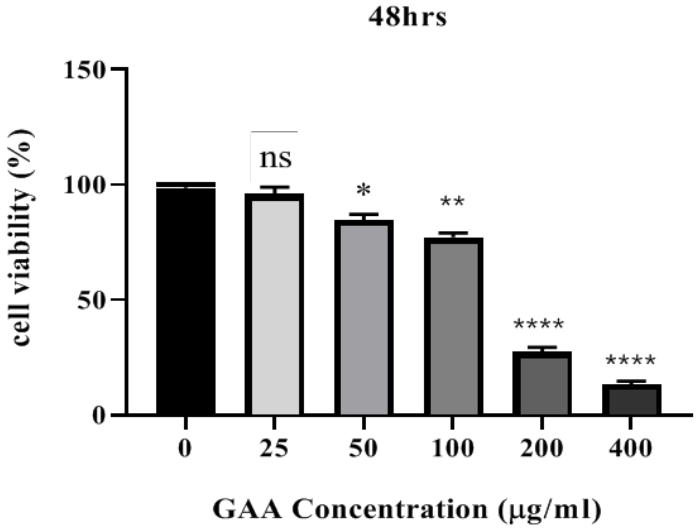
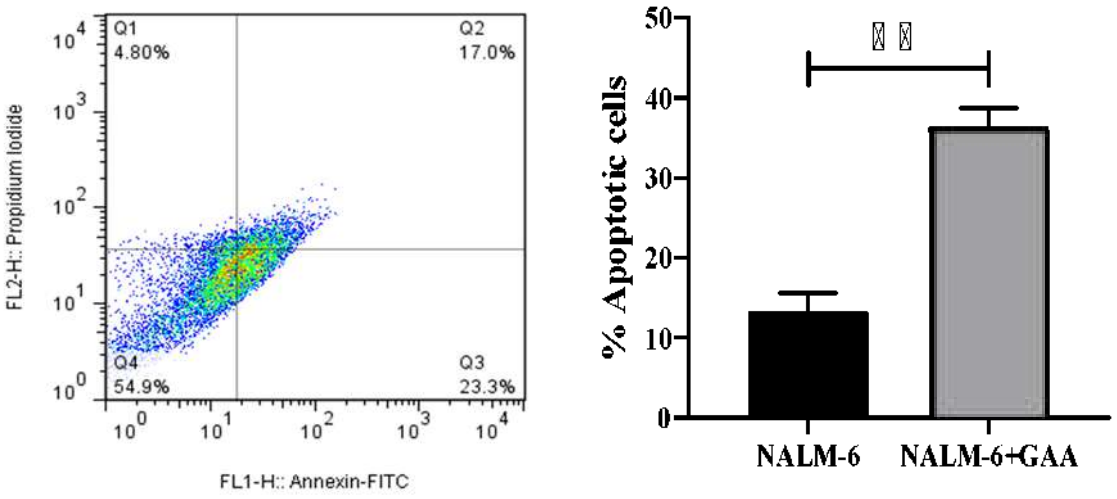


Figure 1: Effects of GAA treatment on NALM-6 at concentrations (25, 50, 100, 200 and 400 µg / ml) and evaluation of cell viability after 48 hours of MTT incubation. (* P <0.05, ** P <0.01, and ** P <0.0001)

3.2 Induction of apoptosis in BCP-ALL cell-lines by GAA extract

Nalm6 cells were incubated with 130 µg/ml GAA for 48 hours. As shown in Figure 2-A, GAA illustrated a significant percentage of early and late-stage apoptotic cells after 48-hour treatment that was 40.3%. According to Figure 2-B, the percentage of apoptosis of GAA-treated cells was impressively increased compared to untreated cells.

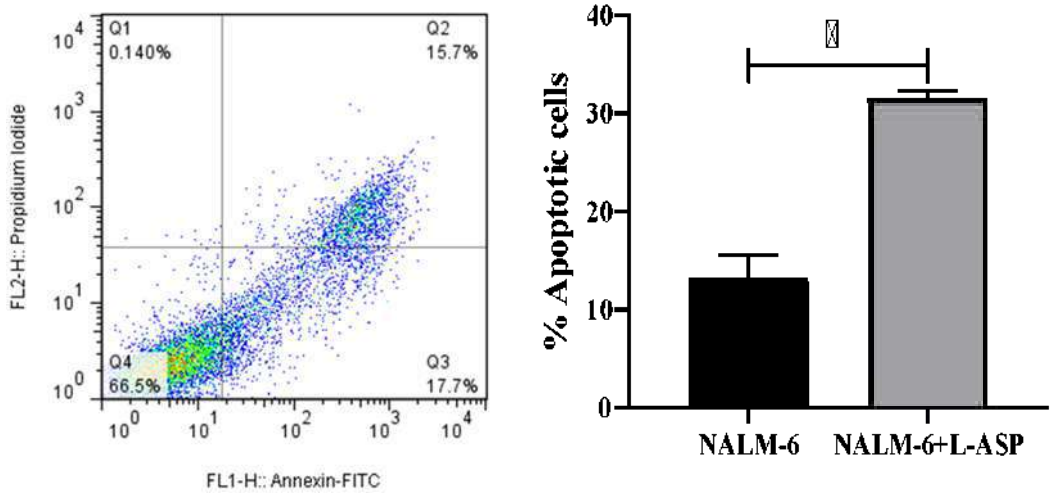


A B

Figure 2: Apoptotic assay after 48 hours (A) Flow cytometric images Q1, Q2, Q3, and Q4 show necrosis cells, late apoptosis, primary apoptosis, and living cells, respectively. (B) The percentage of apoptotic cells in GAA treatment compared to untreated (P = 0.0021)

3.3 Comparing apoptosis in cells treated with GAA extract and L-Asparaginase

Nalm6 cells were incubated with 8 µM L-Asparaginase for 48h. As shown in Figure 3, the percentage of apoptosis in the NALM-6 cells treated with L-Asparaginase (L-ASP) was approximately 33.4%. In contrast, the apoptosis rate in the GAA-treated cells was 40.3%. Compared with the L-ASP treated cells, more extensive apoptosis was observed for the cells treated with GAA (130 µg/mL) after 48h, indicating the lower cytotoxic effect of L-Asparaginase in acute lymphoblastic leukemia cell-lines relative to GAA.

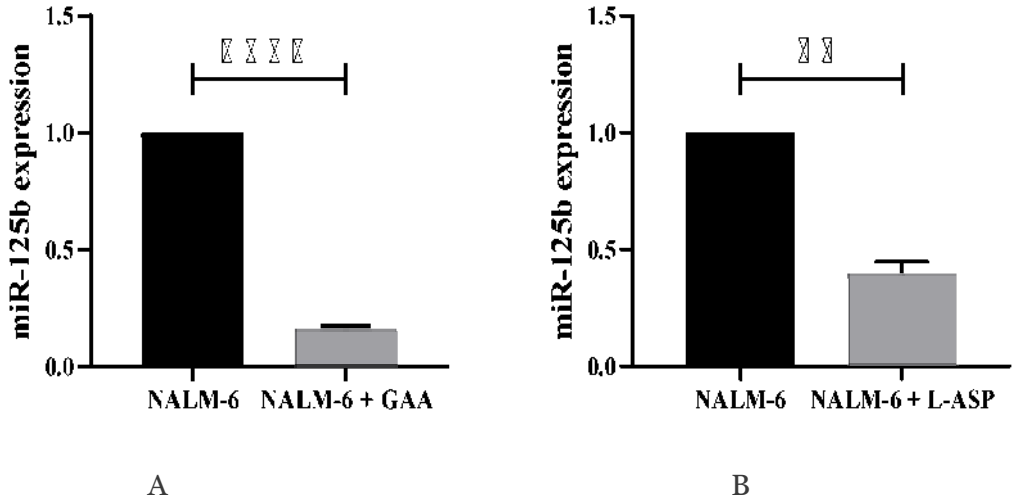


A B

Figure 3: Apoptotic assay after 48 hours (A) Flow cytometric images Q1, Q2, Q3, and Q4 show necrosis cells, late apoptosis, primary apoptosis, and living cells, respectively. (B) The percentage of apoptotic cells in L-ASP (8 µM) treatment compared to untreated (P =0.0121)

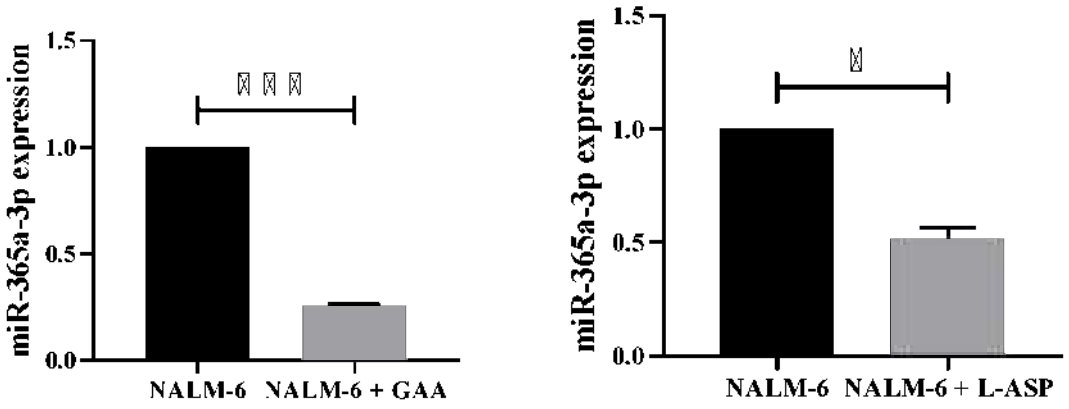
3.4 Effect of GAA on the expression of miR-125b and miR-365a-3p

Following the real-time PCR results, miR-125b (median fold-change of expression [FC] = 0.135, *P*< 0.0001) and miR-365a-3p ([FC] = 0.252, *P* = 0.0001) significantly decreased in the GAA-treated Nalm6 cells compared with untreated Nalm6 cells. Moreover, miR-125b (median fold-change of expression [FC]=0.206, P=0.0023) and miR-365a-3p ([FC] = 0.514, P = 0.0459) significantly decreased in L-asparginase -treated Nalm6 cells compared with untreated Nalm6 cells (Figure 4, 5). On the other hand, the expressions of miR-125b and miR-365a-3p significantly reduced in the GAA-treated Nalm6 cells compared to the L-asparginase-treated Nalm6 cells. The results are presented as mean ± SD for the three independent experiments in triplicate.



A B

Figure 4: Comparison of expression changes of miR-125b in NALM6 cells treated with GAA, L-ASP, and untreated (**P<0.01,****P<0.0001)



A B

Figure 5: Comparison of expression changes of miR-365a-3p in NALM6 cells treated with GAA, L-ASP, and untreated (*P < 0.05, *** P<0.001)

IV. DISCUSSION

In recent years, remarkable progress have been observed in treating acute lymphoblastic leukemia, which has led to substantial outcomes and improvements for the patients. Nonetheless, the exclusive toxicities resulting from anti-leukemic therapeutic regimens with no early intervention are life-threatening. Accordingly, this study highlights the advances in novel therapies for acute lymphoblastic leukemia and supportive

supplements. Recently, herbal compounds have been considered for their anti-cancer properties [29, 30].

The GAA extract is a triterpenoid compound from *Ganoderma lucidum*, having impressive antitumor activities in various cancer cells [31].

The present study revealed the promising antileukemic impacts on B cell precursor-acute lymphoblastic leukemia cells applied by the GAA extract. Much experimental evidence previously investigated different biological activities of this herbal extract, including the antioxidant effect, apoptosis induction, and metastasis inhibition with low toxicity or no side effects [13-15].

However, this is the first report exhibiting the antiproliferative impact of GAA in comparison to the antileukemic agent, L-asparaginase, and its effect on the expression of miR-365a-3p and miR-125-5p in BCP-ALL cell-lines.

The present findings suggest that the GAA extract suppress the growth of Nalm-6 cells and reduces cell viability (Figure1). For this purpose, five different concentrations of the GAA extract (25,50,100,200 and 400 µg/ml) were selected based on the previous studies and their effects on Nalm-6 cells at three different times (namely 24, 48, and 72 hours) were evaluated. It was found that GAA plays a role in reducing cell viability both in time- and dose-dependent manners. Due to the low rate of cell viability after 24h and its high rate after 72h, the subsequent experiments were performed 48h later. The IC50 of the GAA extract was determined to be 130 µg/ml.

Moreover, in vitro treatment with 130 µg / ml, GAA effectively reduces the viability of Nalm-6 cells after 48 hours. Therefore, GAA maybe exerts a cytotoxic activity by inducing apoptosis in the BCP-ALL cells.

Apoptosis is a process involved in cell death, and many researchers have considered this process as an underlying mechanism in preventing the proliferation of malignant tumor cells [32].

Numerous studies have examined the effect of the GL ingredients on the apoptosis induction in the acute lymphoblastic leukemia cell lines [8, 33]. In this study, among other components of *Ganoderma lucidum*, we selected GA as a potential factor inhibiting leukemic cell proliferation. The results indicated that the apoptosis rate of Nalm-6 cells after being exposed to GAA was about 40.3% (Figure 2.A); however, the percentage of apoptosis in the L- asparaginase -treated cells was 33.4% (Figure 3.A). L-ASP is a substantial component of chemoth- erapeutic regimens. However, the side-effects attributed to this drug have affected its therapeutic outcomes.

Virtually, the findings illustrate a noticeable difference between the apoptosis rates in the GAA-treated and L-ASP-treated cells, implying that the GAA extracts significantly suppress cell proliferation and induce apoptosis compared to L-asparaginase. A study examined apoptosis induced by plant compounds, including cinnamon, ginger, and green tea in the Nalm-6 cells. It showed that cinnamon and green tea did not significantly differ in the apoptosis rate compared to the untreated cells. Ginger-induced apoptosis on Nalm-6 cells was about 37% [34].

Compared to this study, our findings showed that the percentage of GAA-induced apoptosis in Nalm-6 cells was higher than the percentage of ginger apoptosis, even though the amount of ginger was higher than GAA. Since the role of GAA in apoptosis induction and mechanism of action as well as its actual target in BCP-ALL are unexplored. Further experiments are required to determine the mechanism by which GAA exerts its inhibitory effect on BCP-ALL cells via apoptosis induction.

We predicted that the apoptosis induction in Nalm-6 cells by GAA might be due to the altered expression of miRNAs (miRNA or miR). In this study, the expressions of miR-125-5p and miR-365a-3p in cells treated to GAA and L-asparaginase were compared with the untreated Nalm-6 cells for the first time. Interestingly, the exposure of Nalm-6 cells to GAA significantly reduced miR-125-5p and miR-365a-3p expression. According to the existing evidence, miRNAs regulates various cellular processes, the most important of which are apoptosis, proliferation, and differentiation [18]. Over the last decade, researchers have conducted numerous studies on the effect of miRNAs in the

diagnosis and follow-ups, assessed the risk of leukemia relapse, and suggested that miRNAs can be used as a predictive biomarker [35].

It is worth noting that miR-125-5p (miR-125b) is one of the first detected miRNAs, including two subtypes of miR-125b-1 and miR-125b-2. MiR-125b-1 is involved in several common chromosomal abnormalities, including t (11; 14) leading to BCP-ALL or Acute myeloblastic leukemia (AML), and miR-125b-2 is elevated in trisomy 21 patients associated with AML7 [36].

Moreover, miR-125b acts as an oncomir or tumor suppressor in malignant cells [37]. Many studies have demonstrated that the expression impairment of miR-125-5p is markedly related to the reduction of apoptosis and promotion of cell proliferation in hematological malignancies [38].

Although the possible mechanism of miR-125b in the induction of tumor genesis has not yet been detected, several potential mechanisms may explain the effects of miR-125-5p dysregulation on cellular processes in leukemic cells: (1) Promoting cell proliferation via PI3K/AKT/ERK signaling pathway[39], (2) Blocking the differentiation of pre-B by targeting MAP3K11 activity, (3) Reducing cell death by targeting P53 tumor suppressor function with decreased mRNA and protein levels, and (4) Inhibiting apoptosis by increasing impressive anti-apoptosis factors Bcl-2 and c-myc and decreasing pro-apoptosis factors BAK1 and Caspase-3 [39]. A study also exhibited that the high levels of miR-125-5p expression were associated with increased relapse and death in acute myeloblastic leukemia patients [40]. The regulation of miR-125-5p expression seems to be one of the therapeutic targets. In our study, GAA downregulated the expression of miR-125-5p in Nalm-6 cells compared to the control cells, as determined by qRT-PCR (Figure 4.A). However, the L-asparaginase had less effect on reducing miR-125b expression (Figure 4.B) (median fold-change of expression [FC] = 0.135, $P<0.0001$ vs [FC] = 0.206, $P=0.0023$ for GAA and L-ASP, respectively). MiR-125b, which plays a critical role in cancer progression, may be a key target of GAA for its chemopreventive activity in ALL. To the best of our knowledge, this is the first study evaluating the expression of miR-125-5p in Nalm-6 cells treated with GAA. The observations in a study on human leukemia cells demonstrated that GL induced mitochondrial Permeability and apoptosis mediated by Bcl-2 down-regulation, Bax translocation, mitochondrial cytochrome c-release, and caspase-3 activation [40]. It was speculated that miR-125 might be associated with the increased expression of anti-apoptotic protein Bcl-2 in pre-B-cell acute lymphoblastic leukemia.

Accordingly, GAA can inhibit Bcl-2 by downregulating oncogenic miR-125b. This is, while the mechanisms involved in the regulation of this miRNA have not yet been elucidated.

Interestingly, similar to miR-125b, a decrease in the miR-365a-3p expression was observed in the acute lymphoblastic leukemia cell lines. In this study, the expression of miR-365a-3p in GAA-treated and L-Asparaginase-treated Nalm6 cell lines was followed by quantitative RT-PCR. Our findings indicated that the expression of the miR-365a-3p decreased after treating the Nalm-6 cells with GAA extract compared to untreated Nalm-6 cells (Figure 5.A). When the Nalm-6 cells are treated with L-asparaginase, they express less downregulation than those treated with GAA (Figure 5.B) ([FC] = 0.252, P = 0.0001 vs [FC] = 0.514, P = 0.0459 for GAA and L-ASP, respectively). Previous studies have documented that the miR-365 expression increased in several malignant tumor cells. [41] A study revealed the higher levels of miR-365 in exosomes derived from imatinib-resistant CML cells compared to sensitive cells, which was caused by inhibiting the expression of pro-apoptotic protein BAX and cleaved Caspase-3 in the sensitive CML cells [42]. In another study, proapoptotic BCL2 associated X (BAX) was one of the downstream targets of onco-miR-365, which up regulation miR-365 suppressed BAX protein level in cells of cutaneous squamous cell carcinoma (CSCC) which downregulation BAX finally caused tumor cells resistant to apoptosis and CSCC expansion [43]. These findings were consistent with those of the present study, suggesting that miR-365 acts as an oncogene as such miR-365 may promote tumor cells by suppressing the apoptotic pathway (Figure 6).

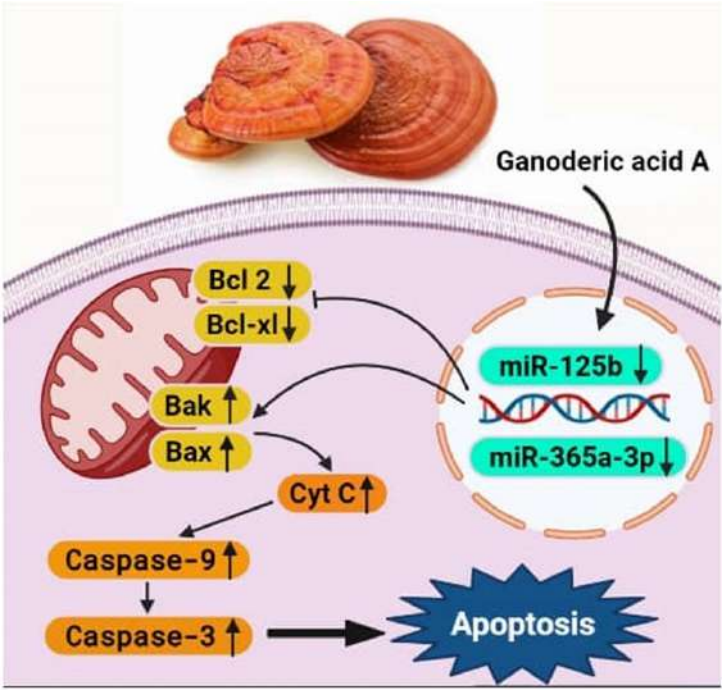


Figure 6: Induction of apoptosis by ganodric acid Treatment with ganodric acid reduced the expression of miR-125b and miR-365a-3p and thus increased apoptosis

Furthermore, in some cancer cells, miR-365 plays the role of a tumor suppressor. Since our study was the first study evaluating the miR-365 expression and the inhibitory effect of GAA on the microRNA expression in Nalm-6 cells, the action mechanism of GAA in reducing miR-365 expression is not yet known.

V. CONCLUSION

The present study illustrates the strong cytotoxic effect of the GAA on acute lymphoblastic leukemia cell lines caused by inducing apoptosis. Moreover, the findings also indicate that GAA alters the expression of miR-125-5p and miR-365a-3p. The findings confirm the similar effect of L-Asparaginase on the Nalm-6 cell line.

Accordingly, the GAA can be used as a combination with fewer side effects in treating acute lymphoblastic leukemia. However, further studies are recommended to delve into this issue.

Authors' contributions

GT and FA carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. ST and FM, provide assistance in the design of the study, coordinated and carried out all the experiments and participated in manuscript preparation. PT and FZ, provided assistance for all experiments. All authors have read and approved the content of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the Diagnostic Laboratory Sciences and Technology Research Center (DLSTRC) for their support.

Conflict of Interest

None declared.

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Cerebrovascular Events in High Altitude: Role of Inherited Prothrombotic Factors

Dr. Saurabh Dawra

INTRODUCTION

Stay at high altitude may predispose to thrombotic cerebrovascular disorders. The role of inherited procoagulant states in predisposing to these events has not been well studied in the Indian subcontinent. With increasing role of Indian soldiers at these heights for long periods and development of adventure tourism in our country, there is a need to study this aspect to establish a basis for risk profile assessment and screening tools for primary prevention of high altitude related strokes and other cerebrovascular events.

Keywords: NA

Classification: DDC Code: 338.479172981 LCC Code: G155.C35

Language: English

London Journals Press

LJP Copyright ID: 392866

London Journal of Medical and Health Research

Volume 22 | Issue 8 | Compilation 1.0

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Dr. Saurabh Dawra

I. INTRODUCTION

Stay at high altitude may predispose to thrombotic cerebrovascular disorders. The role of inherited procoagulant states in predisposing to these events has not been well studied in the Indian subcontinent. With increasing role of Indian soldiers at these heights for long periods and development of adventure tourism in our country, there is a need to study this aspect to establish a basis for risk profile assessment and screening tools for primary prevention of high altitude related strokes and other cerebrovascular events.

II. MATERIALS AND METHODS

All cases of acute onset focal neurological deficit suggestive of stroke/Transient ischemic attack (TIA)/Intracerebral bleed developed at High Altitude (Ht >9000ft above means sea level), referred for management at a tertiary care Neurology centre during the period Jun 2009 to Jul 2011 were included for study. Patients with past history of stroke/TIA, hypertension, dyslipidemia, coronary artery disease, valvular heart disease (congenital/rheumatic), peripheral arterial disease, diabetes mellitus (DM), malignancy or drug abuse were excluded. After complete clinical evaluation to confirm the diagnosis, patients were subjected to investigations based on a standard protocol including complete blood counts, lipid profile, blood glucose levels, renal and liver function tests, ECG, chest radiograph and echocardiography.

Coagulogram including prothrombin time, activated Partial Thromboplastin time (aPTT) and serum fibrinogen levels were done. Tests for prothrombotic states like platelet aggregation test, protein C & S assay, Anti thrombin III (AT III) assay, Factor V Leiden, antiphospholipid antibodies (APLA) and Serum homocysteine levels was done. Statistical analysis using chi square test and Fisher's exact test was carried out.

III. RESULTS

A total of 66 patients were included in the study. This included 65 males and 01 female. The mean age of patients was 34.2 (± 7.376) yrs (Range 20-51yrs). Most of the patients were young, considering the usual age of soldiers posted at this altitude. Mean duration of stay at HAA was 9 months (range 2wks – 36mths). The vascular events noted included stroke (arterial and venous thrombosis), TIA and intracerebral haemorrhage.

There was no seasonal variation noted in the incidence of the high altitude related cerebrovascular events. Maximum events (36.4%) occurred at altitude more than 18,000 ft. The mean altitude of stay was 15,467 ft (SD ± 3317.36) and ranged from 10,300 ft – 22,000 ft. The altitude wise occurrence of cases is depicted in table 1. The mean duration of stay was 9.89 months and ranged from 0.33 months to 36 months (SD ± 7.00 months).

Total number of cerebrovascular events was 66 which included arterial stroke in 26, venous stroke in 26 and 02 patients suffered from intracerebral haemorrhage. Ten patients had TIA with normal MRI brain and 01 patient had spontaneous subdural haematoma.

A total of 26 patients had an arterial infarct (15 of them under 40yrs of age). Out of these 26 patients, 14 had Left Middle cerebral artery (MCA) infarct (01 patient had extensive Lt MCA + ICA infarct) and 07 patients had Right MCA infarct, 05 had lacunar infarcts and 03 had bilateral non specific ischemic changes. Of the 26 patients who had venous infarcts, 20 patients had associated parenchymal lesion while 06 patients suffered from cerebral venous thrombosis without any parenchymal involvement.

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Mean haemoglobin level was 15.14 (SD ± 1.63) g/dl (range 12.4 – 18.8). Average hematocrit (hct) was 45.20 (SD ± 3.15). Platelet count showed mean of 3,00,000/ul (SD±.71). Co-existing pulmonary thromboembolism occurred in one patient of arterial stroke. Echocardiography was normal in all except the patient with co-existing pulmonary thromboembolism.

IV. PROCOAGULANT WORK UP

Prothrombin time and aPTT was normal in all patients. Out of 66, 55 pts (84%) had one or more underlying inherited procoagulant state. Hyper-homocysteinemia (34) and Protein S deficiency (34) were the commonest defects. Details are tabulated in Table #. Sixteen out of 27 patients with arterial stroke had Protein S deficiency, 13 had hyperhomocysteinemia, 06 had protein C deficiency and 02 had factor V leiden mutation.

Venous strokes were noted in 26 patients with hyperhomocysteinemia in 17, Protein S deficiency in 16 and Protein C deficiency in 4 patients. Antithrombin III deficiency, Lupus anticoagulant, Anti-Cardiolipin antibodies IgM and IgG were not detected in any patient.

V. DISCUSSION

In this study of 66 consecutive patients with cerebrovascular events at high-altitude, despite low baseline risk for such events, we assessed the nature of vascular involvement and underlying hypercoagulable state. Classical risk factors for vascular events like hypertension, DM, dyslipidemia and prior vascular events were excluded in these patients. Altitude of more than 9000ft was defined as HAA as per existing regulations in the Indian Army. Mean duration of stay prior to onset of neurological event was 9 mths and in 40% of patients, the onset was within 6 mths, which is the usual period of stay at altitudes above 15000ft. Eighty percent of events occurred within 1yr of stay which needs to be set as upper limit of tenure at these altitudes. Arterial thrombosis was the commonest cerebrovascular events noted followed by venous thrombosis.

Patients developing venous thrombosis were younger compared to those who had arterial stroke, although statistically insignificant, likely due to atherosclerosis being basic underlying defect in arterial strokes which gets frequent with ageing.

Inherited procoagulant state was detected in 55 (84%) patients. Commonest defects noted were hyperhomocysteinemia and protein S deficiency in both arterial and venous thrombosis. Factor V Leiden mutation was noted in 3 cases, all having arterial strokes.

Similar frequency of underlying inherited procoagulant state was seen in patients with venous thrombosis and those with arterial stroke.

Compared to earlier studies from this region,(1-6) we noted higher frequency of inherited procoagulant states. Erythrocytosis or other classical risk factors for vascular thrombosis were not noted in these patients.

To the best of our knowledge, this is the largest Indian study evaluating the frequency of inherited procoagulant states in young patients with high altitude related cerebrovascular events. (1-6) The Strengths of this study were the sample size, assessment of clinical risk profile and procoagulant state in all cases. A study population, with low risk profile, having increased frequency of cerebrovascular events, was good subset to study the frequency and impact of inherited procoagulant risk factors in these events.

Limitations of this study were its restricted study population involving young males, who were not evaluated for underlying procoagulant state before induction to HAA. There is no data available in the unaffected control population in the same region of these procoagulant factors. Role of exposure to low ambient temperatures and hypoxia in HAA in induction/activation of these procoagulant defects needs further evaluation with a prospective study.

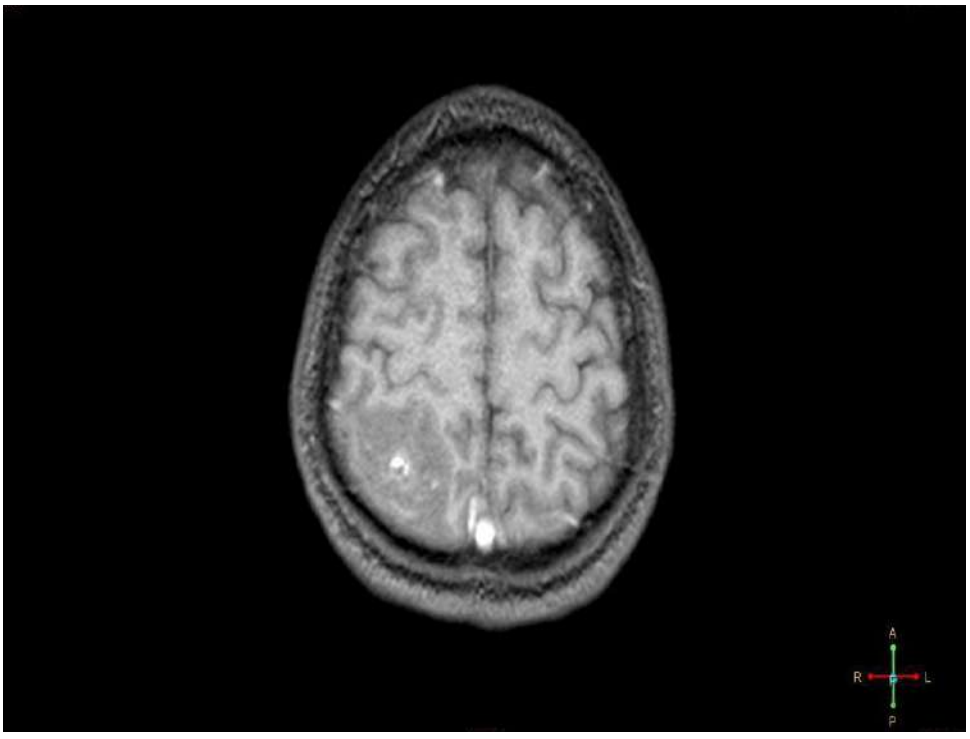
This study highlights the high incidence of cerebrovascular thrombotic events with its devastating effects in otherwise healthy young soldiers posted at HAA. Various inherited procoagulant states noted in these patients may have a significant role to play in pathogenesis of

these events when exposed to HAA, which can only be shown in a prospective study with a healthy control group from the same region. A larger study with a suitable design can address this issue. Pre-induction screening of the inductees to HAA regarding procoagulant states in them may help in risk-stratifying and institution of prophylactic measures like anti-platelets and anticoagulants and decreasing the duration of exposure to these altitudes in high risk cases.

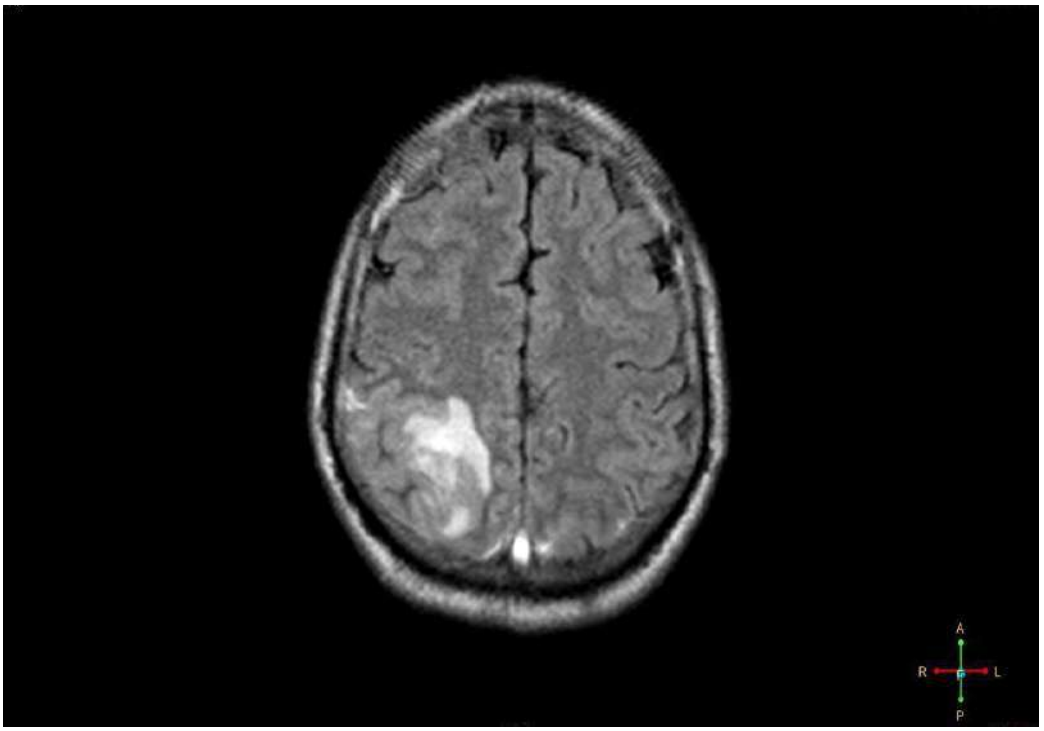
Table 3: Demographic profile of patients with stroke at high altitude area

Characteristics	Patients
Number of patients	66
Age (Years) Mean Range	34.24 21 – 51
Sex Male Female	65 01
Past history of stroke/TIA	00
Family history of Stroke/TIA	00
Duration of stay at high altitude before onset of symptoms Mean Range	 09 months 15 days – 36 months
Altitude of stay Mean Range	 15,467 ft 10,300 – 22,000 ft

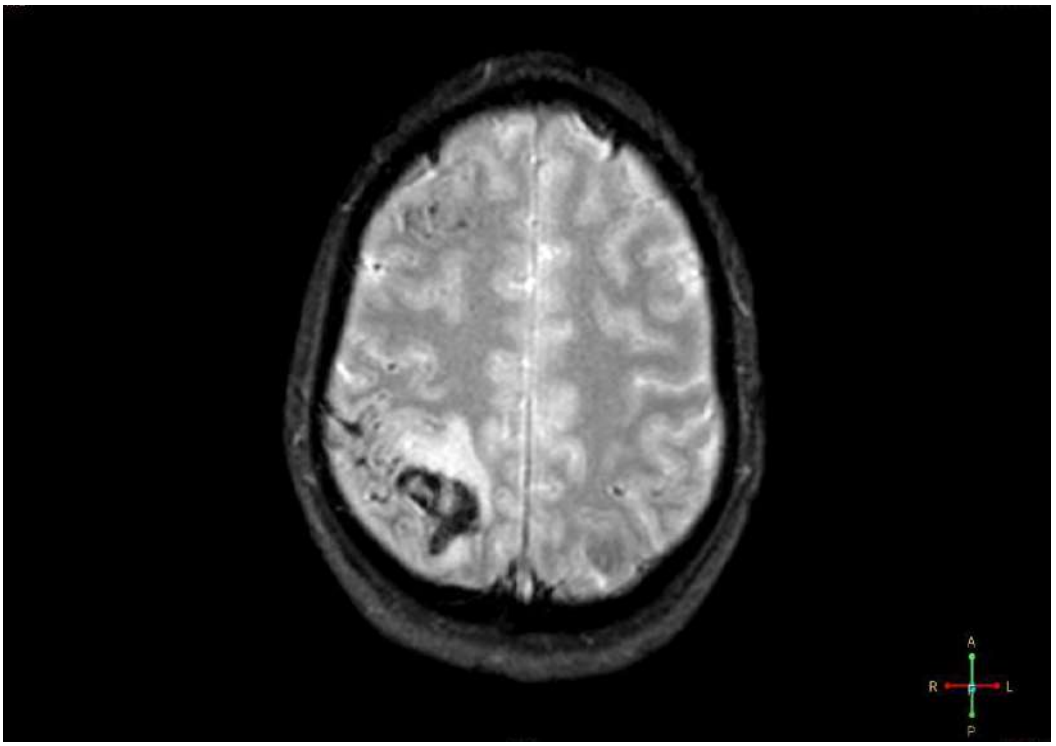
T1 Axial image showing hyperintensity in superior sagittal sinus with a hypointense lesion in the Rt parietal region suggestive of haemorrhagic foci



Fluid attenuated inversion recovery(Flair) Axial image showing hyperintensity in superior sagittal sinus with a hypointense lesion in the Rt parietal region suggestive of haemorrhagic foci



Gradient T2 Fast field echo imaging(FFE) showing blooming on gradient images suggestive of haemorrhage



Magnetic resonance(MR) Venogram showing irregularity, narrowing and absence of flow in the superior sagittal sinus suggestive of superior sagittal sinus thrombosis

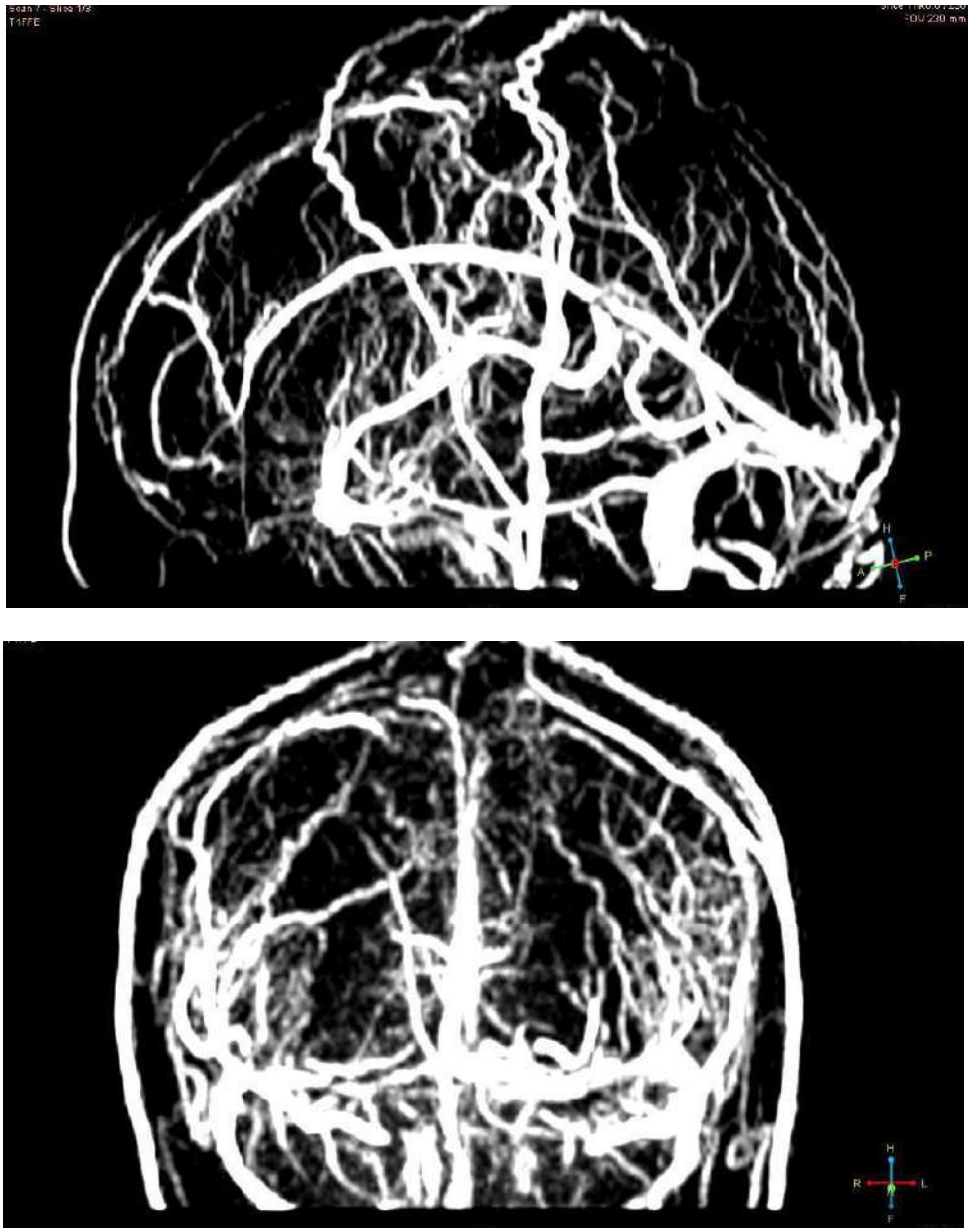


Table 01: Altitude wise distribution of cases of cerebrovascular events in HAA

Height (ft above MSL)	Number of patients	Percentage (%)
> 18,000	24	36.37
15,000 – 17,999	14	21.21
13,000 – 14,999	08	12.12
11,000 – 12,999	20	30.30
9,000 – 10,999	00	00

Table No. 2: Inherited procoagulant state and Cerebrovascular events at HAA

Procoagulant state	Arterial strokes (N=27)	Venous strokes (N=26)	TIA (N=10)	ICH (N=2)	SDH (N=1)	Total (N=66)	P value
Hyper Homocysteinemia (H) only	01	03	01	00	00	05	
Protein C deficiency only (C)	01	00	03	02	00	06	
Protein S deficiency only (S)	06	04	02	00	00	12	
H+C	02	02	03	00	00	07	
H+S	07	10	00	00	00	17	
H+C+S	03	02	00	00	00	05	
Factor V Leiden	02	00	01	00	00	03	
No defect	05	05	00	00	01	11	
Total	27	26	10	02	01	66	

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